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

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

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

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

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

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

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

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

**EONS’ strategic goals**

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

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

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

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

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

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

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

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

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

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

Methods: We have carried out an observational study at baseline and longitudinally in the PREMIDEM-Valencia study including 1094 participants (696 women) at high cardiovascular risk aged 67.5±6 years. We prospectively analyzed cancer incidence as a secondary outcome in this study. Lifestyle, clinical and biochemical variables were assessed by standardized methods. DNA was isolated from blood and the selected polymorphisms were determined.

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

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

Clinical trial identification: ISRCTN35739639.

Legal entity responsible for the study: University of Valencia.
Funding: Instituto de Salud Carlos III.
Disclosure: All authors have declared no conflicts of interest.
Background: Some genetic variants of the MTHFR gene with the increased risk of breast cancer in a high cardiovascular risk population

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

Results: We detected 21 new cases of prostate cancer from 2003 to 2014, representing 1.9% of all cancers and 5.3% of all cancer in men. The analysis of the risk of prostate cancer in the variants described was carried out grouping the carriers of the allele less frequent. The allelic frequency of the rs1476413 was 0.219 for not affected participants while it was 0.148 in the cases. The crude OR was 0.33 (95%CI 0.13-0.83) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment (by age, intervention and smoking habit). For the rs1476405, the allelic frequency was 0.380 for not affected participants while it was 0.295 in the cases. The crude OR was 0.43 (95%CI 0.19-0.97) p = 0.041 for the rs641403 was the allelic frequency was 0.380 for not affected participants while it was 0.295 in the cases. The crude OR was 0.39 (95%CI 0.17-0.87) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment.

Conclusions: The rs1476413, rs1801131, rs4846052 and rs541003 of the MTHFR gene were protective against the development of prostate cancer in a high cardiovascular risk population.

Clinical trial identification: ISRCTN35796395.

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

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

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Background: Breast cancer is second leading cause of cancer-related deaths in women, supporting the need for the detection of novel prognostic biomarkers for risk stratification. There is growing body of evidence showing the association of common genetic variants on chromosome 9p21 with an increased risk of developing different tumors and metabolic disorders. Here we investigated the association of a genetic variant in CDKN2A on chromosome 9p21 with an increased risk of developing different tumors and metabolic disorders.

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

Results: We detected 21 new cases of prostate cancer from 2003 to 2014, representing 1.9% of all cancers and 5.3% of all cancer in men. The analysis of the risk of prostate cancer in the variants described was carried out grouping the carriers of the allele less frequent. The allelic frequency of the rs1476413 was 0.219 for not affected participants while it was 0.148 in the cases. The crude OR was 0.33 (95%CI 0.13-0.83) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment (by age, intervention and smoking habit). For the rs1476405, the allelic frequency was 0.380 for not affected participants while it was 0.295 in the cases. The crude OR was 0.43 (95%CI 0.19-0.97) p = 0.041 for the rs641403 was the allelic frequency was 0.380 for not affected participants while it was 0.295 in the cases. The crude OR was 0.39 (95%CI 0.17-0.87) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment.

Conclusions: The rs1476413, rs1801131, rs4846052 and rs541003 of the MTHFR gene were protective against the development of prostate cancer in a high cardiovascular risk population.

Clinical trial identification: ISRCTN35796395.

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

Results: In this study, we are trying to disclose the mechanism of PXR activation and functional dynamics by TIP60 dependent acetylation. We found the sites of interaction as LBD of PXR with NR box of TIP60 and thus TIP60 mediated subcellular dynamics of PXR. Also, we have found TIP60 mediated the acetylation site of PXR at lysine 170. This novel complex is independent of ligand and does not form a complex with RXR. Also, this complex does not activate ligand dependent PXR target genes. Interestingly, PXR augments TIP60 acetylation on histones. We further discovered TIP60-PXR complex promotes cell migration and adhesion 0.390 for not affected participants while it was 0.295 in the cases. The crude OR was 0.43 (95%CI 0.19-0.97) p = 0.041 for the rs641403 was the allelic frequency was 0.380 for not affected participants while it was 0.295 in the cases. The crude OR was 0.39 (95%CI 0.17-0.87) p = 0.021 and OR 0.39 (95%CI 0.17-0.88) p = 0.023 after adjustment.

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

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

Funding: ICMR.

Disclosure: The author has declared no conflicts of interest.

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

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

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

Results: We identified that SIRT3 expression is downregulated in patients with HCC and high GLUT1 (glucose metabolism index) and Ki67 (proliferation index) expression. In addition, analysis of Cancer Imaging Archive data (TCGA) revealed a negative correlation between GLUT1 and SIRT3 mRNA expression and also HIF1a and SIRT3 mRNA expression. There was also a negative correlation between Ki67 and SIRT3 mRNA expression. After sorafenib treatment, SIRT3 protein expression was highly downregulated in various HCC cell lines (HepG2/Hep3B/Kin-1/Huh7). These cells altered their therapeutic resistance to sorafenib via SIRT3 modulation through a 2 dimensional (D)/3D cell culture system.

Conclusions: Taken together, our results show that SIRT3 acts as a tumor suppressor and plays an important role in therapy resistance for HCC. Legal entity responsible for the study: Division of Life Sciences.

Funding: The National Research Foundation of Korea (Seoul, Korea, Grant Nos. NRF-2015R1A1A01057737, NRF-2018R1C1B603894). Disclosure: All authors have declared no conflicts of interest.
Background: Colorectal cancer is the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed in 2012. It is also one of the most common cancers in China, with nearly 200,000 people dying annually as a result of colorectal cancer. Prediction and intervention of colorectal cancer risk would save millions of lives worldwide. The purpose of this study is to provide a simple, effective and economic method to help people predict and intervene in colorectal cancer risk.

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

Results: The analysis showed that CBC, CMP, lipids and urinalysis data can significantly distinguish healthy individuals from colorectal cancer patients and those data can be used to build colorectal cancer risk prediction models. The predicting accuracy was 96.1% and the clinical verification rate was 93.7%. Top parameters were selected through the discriminant analysis and logistic analysis. Some parameters, such as red cell distribution width, red cell count, leukocyte percentage and age are positively correlated with colorectal cancer risk, and others, such as albumin, platelet count, hematocrit and platelet distribution width are negatively correlated with colorectal cancer risk.

Conclusions: This research shows that the routine blood and urine test results can be used to predict colorectal cancer risks and the accuracy of the prediction is over 99%. The research would provide an effective, convenient and economical method to help people predict and intervene in colorectal cancer risk.

Legal entity responsible for the study: Fuyang No.2 Hospital and Beijing Yiwang Data Technology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

13P Measuring the efficiency of cancer care in Europe

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

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

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

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

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

Funding: Bristol-Myers Squibb.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

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

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

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

Results: We evaluated clinical and histopathologic features of monoclonal and biclonal uterine carcinosarcomas. Monoclonal tumours showed worse prospects than the biclonal ones 1-year overall survival - 20% vs 37% (p = 0.0878). In all cases (100%) of monoclonal tumours the average length of full remission was three times shorter than in cases of biclonal tumours.
**Background:** The bromodomain and extraterminal (BET) family of proteins are chromatin regulators that promote the transcription of several important cell identity genes. BET inhibitors have shown promise in various pre-clinical cancer models as BET inhibition abrogates the transcription of several key oncogenes in a cell type-specific manner. Hence, the purpose of this study was to determine the anticancer activity of the novel BET inhibitor ODM-207 in ER+ breast cancer models and to look for cancer-associated signaling pathways suppressed by BET inhibitors.

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

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

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

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

**Funding:** Orion Corporation, Orion Pharma.


**16P**

**16P**

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

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Orion Corporation, Orion Pharma. Espoo, Finland, Auriene Discovery Technologies Limited, Bangalore, India, Abo Akademi University. University of Turku, Turku, Finland

**Background:** HER2 positive breast cancer associated with metabolic switch

**Table:** Comparison of monoclonal and biclonal carcinosarcomas

<table>
<thead>
<tr>
<th>Clinical and morphological features</th>
<th>Monoclonal tumours</th>
<th>Biclonal tumours</th>
<th>p</th>
<th>≤</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours invades the serosa of the corpus uteri, %</td>
<td>100</td>
<td>50</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>80%</td>
<td>0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Average size of the tumour (cm³)</td>
<td>1305.8</td>
<td>131.5</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Length of full remission</td>
<td>7.75</td>
<td>24.6</td>
<td>&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

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

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

**Results:** In breast cancer with HER2 overexpression nuclear staining was present in immunohistochemistry. The comparative transcriptomic reanalysis of GEO datasets performed on trastuzumab resistant cell lines and sensitive cell lines revealed that in trastuzumab resistant cell lines the reprogramming of cell metabolism takes place. The most common disturbances were detected in the expression of genes involved in the lipid metabolism, glycosylation and vitamin A metabolism. Moreover, among 308 genes upregulated in trastuzumab resistant breast cancer cells the 216 genes were directly bound/regulated by BRG1 ATPase - the core subunit of SWI/SNF chromatin remodeling complex which is known regulator of metabolism related genes. Among 151 downregulated genes 67 were directly targeted by BRG1. Similarly, the another SWI/SNF ATPase (BRM) – directly targeted 151 of 308 upregulated and 12 of 151 downregulated genes. These results strongly suggested the direct regulation or interdependence of HER2 and SWI/SNF complex.

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

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

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

**Disclosure:** All authors have declared no conflicts of interest.

**18P**

**18P**

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


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

**Methods:** We analysed the sensitivity using MTT proliferation assay to the PARP-inhibitor niraparib used alone or in combination with either S-Rustouracil (SFU), irinotecan (active metabolite SN38) or oxaliplatin in a panel of 9 KRAS (HCT15, LSVO), LS1034, SW1116, SW948, HCT116, SW480) or BRAF (WID) mutated CRCs, from the four CMS clusters. Combination index analysis was performed in order to evaluate the synergism between niraparib and the chemotherapeutics. Further characterization of sensitive cell lines was performed using western blot, cell cycle and apoptosis analyses.

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

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

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

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Clinical trial identification: JSCRCTN35739639

Legal entity responsible for the study: University of Valencia.

Funding: Instituto de Salud Carlos III.

Disclosure: All authors have declared no conflicts of interest.

21P Cisplatin in NIPEC or HIPEC?
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Scientific Laboratory of Cancer Chemoprevention and Oncopharmacology, N.N. Petrov National Medical Research Center of Oncology, St. Petersburg, Russian Federation

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

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

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

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

Legal entity responsible for the study: Vladimir Bespalov.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

22P Matrix metalloproteinase-mediated regulation of programmed-death ligand in the human head and neck squamous cell carcinoma microenvironment
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Background: Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is a devastating malignancy with a poor prognosis. According to recent clinical studies, tumour growth can be effectively reduced and survival can be improved by blocking the programmed death receptor 1 (PD-1)-programmed death-ligand 1 (PD-L1) pathway. However, anti-PD-1 treatment is beneficial only for certain patients. Therefore, the mechanisms controlling PD-L1 expression warrant further investigation in order to provide a better understanding of the predicting efficacy of and optimising anti-PD-1 therapy, alone or in combination.

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

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

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

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Trametinib synergizes with desamethasone in KRAS-mutant myeloma cell lines through modulation of NDRG1 and induction of apoptosis

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

Methods: Sensitivity to Tr and Dex was determined via CellTiter-Blue (CTB) assay in the KRAS-mutant myeloma cell lines (MM1s): MM1R (Dex-resistant) & MM1S (Dex-sensitive). Apoptosis and cell cycle were evaluated by flow cytometry. Reverse phase protein array (RPPA) was employed for quantitative analysis of 60 proteins and validated by Western blotting.

Results: CTB assay demonstrated a dose-dependent reduction in cell proliferation with Tr and Dex individually in MM1S, while MM1R was resistant to both treatments. Tr/Dex demonstrated synergistic cytotoxicity in MM1S using CTB and annexin V staining. An accumulation of sub-G1 cells was observed during cell cycle analysis in MM1S, confirming increased cell death. These effects were accompanied by activation of pro-apoptotic proteins, such as cleaved PARP and increased BIM. RPPA revealed the following phospho-proteins were downregulated with Tr/Dex in MM1S compared to MM1R: FAK S412, FAK S397, NDRG1 and 4EBP1. Changes in phospho-NDRG1 were statistically significant (P < 0.001; 2-way ANOVA). This was confirmed by Western blotting, where expression levels were downregulated by Tr/Dex in MM1S but unaffected in the resistant cell line MM1R.

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

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

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

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

Methods: We assessed the expression and activation of TGF-β and AXL in a panel of human CRC cell lines (HCT116, SW480, LOVO, LIM1215 and Westby) by Western blot (WB) and Real time PCR. We tested the sensitivity of Galunisertib (LY2120976), a TGF-βR1 inhibitor, in HCT116 and LOVO cells the treatment by using MTT, soft agar colony formation, cell invasion and wound healing assays. To study the correlation between these two pathways, we generated stable LOVO short hairpin RNA (shRNA)-sh-AXL cells, in which AXL expression was decreased, and stimulated both parental and shAXL LOVO cells with TGF-β.

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

Conclusions: In HCT116 and LOVO cells, TGF-β mediated cell migration, invasion and soft agar colony growth formation were significantly inhibited by Galunisertib treatment. Furthermore, a functional potential cross talk between TGF-β induced signaling and AXL could be formed on pM8 activation. In this respect, combined treatments with Galunisertib and AXL inhibitors are ongoing to evaluate their anti-mutator effects in CRC cells.

Legal entity responsible for the study: Department of Medicina di Prevenzione, Università degli Studi della Campania Luigi Vanvitelli.

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Disclosure: All authors have declared no conflicts of interest.

Isform-specific AKT inhibition differentially affects cell functions in pancreatic adenocarcinoma

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

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

Results: 939 proteins were identified with a false discovery rate (FDR) lower than 1%. Proteome pairwise comparisons were performed with the cells lines. The specific silencing of each isoform lead to differential protein expression profiles, although KEGG pathway analysis tools revealed that many of the pathways altered were common. Individual silencing of any AKT isoform caused an inhibition of glycosylation and a subsequent increase of mitochondrial activity, as seen by fluorescent mitochondrial staining. AKT silencing increased gemcitabine sensitivity for all isoforms. AKT1 and AKT2 increased 5-FU sensitivity, while AKT3 had a comparable value. Western Blot demonstrated an increase in mTOR expression after AKT1 and AKT2 silencing. p-EIF4B expression was decreased after AKT2 and AKT3 silencing. No differences were observed in ERK expression.

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

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Disclosure: All authors have declared no conflicts of interest.

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

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

Methods: Tumor and blood samples were obtained from 20 patients with primary RCC immediately after surgical resection. Blood samples were collected from 10 HD. Tumors were harvested into RPMI1640 medium (Gibco) and processed within 4 h. TIL isolation was performed under modified protocol [Baldan 2015]. Isolated TIL and PBMC were prepared for flow cytometry. Cells were double stained with anti-CD45
Cluster analysis of protein-coding genes based on GO-terms (on biological processes, cellular components, and molecular functions. Among 15521 genes and tumor suppressor genes are more closely related physically, than noncancer-related genes. The aim of this study was to carry out clustering protein genes based on GO-terms and determine cluster structure and oncogene positions on it.

**Conclusions:** GO-terms and determine cluster structure and oncogene positions on it.

**Clinical trial identification:** KCRB11022016.

**Legal entity responsible for the study:** Ministry of Health.

**Funding:** Kidney Cancer Research Bureau.

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 27P**

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<td>RCC, before surgery</td>
<td>180 days</td>
<td>after surgery</td>
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</table>

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

**Disclosure:** All authors have declared no conflicts of interest.

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**28P Oncogenes analysis using GO-based clustering**

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

**Methods:** List of protein-coding genes was obtained with biomaRt Bioconductor package. ClusterProfiler Bioconductor package was used to get gene ontology data of the related genes. The aim of this study was to carry out clustering protein genes based on GO-terms and determine cluster structure and oncogene positions on it.

**Clinical trial identification:** KCRB11022016.

**Legal entity responsible for the study:** Ministry of Health.

**Funding:** Kidney Cancer Research Bureau.

**Disclosure:** All authors have declared no conflicts of interest.

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

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

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

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

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

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

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

**Disclosure:** All authors have declared no conflicts of interest.

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

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

**Methods:** We established KD6 over expression cell lines (MCF7-C6) from MCF-7 by stably transfected CDK6 expression vector. We also established Ribociclib-resistant cell lines (RIBR) after long-term culture under the condition of sufficient doses of Ribociclib from estrogen deprivation-resistant cell lines (EDR) which established from MCF-7 cultured with steroid depleted medium as aromatase inhibitor resistance models. We further established RBBR (R) cell lines from RBBR by long-term cultured without Ribociclib.

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

**Conclusions:** Ribociclib sensitivity was proportional to the expression levels of p21, suggesting that p21 levels might be the monitoring marker for the CDK4/6 inhibitors resistance in breast cancer.
New molecular targets for prevention and treatment of ATL are urgently needed. We described lymphocytes induced by human T-cell leukemia virus (HTLV) that have poor outcomes.

Background: We used flow cytometry, Western immunoblotting, quantitative RT-PCR, and caspase-dependent and -independent cell death in ATL cells, suggesting a novel therapeutic strategy for patients with this fatal disease.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

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

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

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

Results: Among a panel of human CRC cell lines, three with acquired resistance to cetuximab (SW48-CR, GEO-CR and CACO-2-CR) were highly sensitive to the Astragalus compound. The treatment with this compound determines a transition to an epithelial phenotype in all three cell lines with reduction of vimentin and an increase of E-cadherin expression. Moreover, Astragalus treatment determines an induction of apoptosis and a significant increase in cell death in SW48-CR, GEO-CR and Caco-2-CR cells, but not in the parental cell lines. These findings were confirmed by western blot assay with activation of caspase cascade only in cetuximab-resistant cells. Moreover, the antiproliferative effect of Astragalus compound on cetuximab-resistant cells is mediated by the inhibition of Akt/mTOR signaling pathway. In particular, western blot analyses have shown a significant reduction in the expression of 4-E-BP1 and p-4EBP1 in cetuximab-resistant cell lines following Astragalus treatment.

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

Legal entity responsible for the study: Hiroo Kuroki.


Disclosure: All authors have declared no conflicts of interest.

Multiple myeloma metal levels and proteasome activity

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

Methods: The study was performed on MM cell lines MM.1S and L363. Chymotrypsin-like (CT-like) proteasome activity is the primary measure of the degrada-

Disclosure: All authors have declared no conflicts of interest.
subunit were measured and evaluated based on a cumulative inhibition of PS and β5i CT-like sites. Metal content analysis of MM.1S and L363 cells was performed by total reflection X-ray fluorescence spectrometer.

Results: The metal content analysis demonstrated rigorous imbalances for calcium, phosphorus and potassium, moderate to no imbalances for iron and zinc accompanied by 65% MM.1S (34% L363) reduction of CT-like activity under bortezomib. However, under SAH treatment, a decrease in the concentration of phosphorus and potassium was accompanied by minor to no change of iron and zinc levels and an increase of calcium. As metals may positively correlate or be antagonistic to one another, we evaluated the correlations between metals and proteasome activity.

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

Legal entity responsible for the study: AG Hematology.

Funding: Wilhelm Sander Foundation.

Disclosure: All authors have declared no conflicts of interest.

36P A translational drug-screening tool for interrogating the effect of anti-TGF-β therapy on fibroblast activity and the desmoplastic reaction

N. Nissen, N. Willumsen, N. Gudmann, S. Rannow, M. Karsdal, D. Leeming, J. Sand

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

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

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

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

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

Funding: Nordic Bioscience A/S.


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

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

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

Results: Erblin demonstrate selectively high sensitivity to OSCC01 cells (R/M HNSCC) in comparison with other cell lines. Erblin has sub-0.1 μM growth inhibitory activities in vitro against OSCC01 cells as well as marked in vivo activities at 0.1–0.5 mg/kg against OLC01 cells xenografts. Inducible TUBB3 correlates with lower sensitivity to erblin in HNSCC cells and xenograft tumors.

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

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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


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

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

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

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

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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


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

Methods: ITGBL1 coding sequence was PCR amplified from cDNA and cloned into pcDNA3 vector. Transwell system was used to obtain two ovarian cancer cell lines: OAW42/ITGBL1 (+) and SKOV3/ITGBL1 (+) with overexpression of ITGBL1. Control cell lines were obtained by transduction with empty vector. A Matrigel cell invasion assay was performed using 24-well transwell inserts (coated with fibronectin and matrigel). Crystal violet staining of invaded cells was performed, then the dye was solubilized with 10% acetic acid and the absorbance was measured at a wavelength of 595 nm.

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

Conclusions: Our results indicate that ITGBL1 may increase ovarian cancer cell inva-
sion rate. Along with our previous reported results that overexpression of ITGBL1 may
increase migration, decrease adhesion [3] and has no effect on proliferation rate [4], these results suggest that ITGB1I may play an important role in ovarian cancer progression enabling easier spreading of the cells within peritoneal cavity.


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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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Background: The study of circulating tumor cells (CTCs) has rapidly increased in the last decade, as this entity of cells is implicated in cancer prognosis and progression. CTCs constitute a non-homogeneous population of cells, with a histologic ability. The present study tested the gene expression profile of genes involved in bone, liver, lung and brain metastasis. These samples were at stage III and IV, and CTCs were 6.7±2.5/3 ml. For pleura and skin, overexpression was observed in samples with higher CTCs number (8.1±1.3/ml) than in prostate and ovarian cancer, respectively. Markers correlated with liver metastasis were expressed higher in breast and ovarian samples at stage IV. The majority of breast and prostate cancer samples also expressed markers correlated with bone metastasis, while squamous and ovarian cancer samples expressed genes involved in brain metastatosis. By contrast, samples with lower CTCs exhibited expression in markers correlated with metastasis to lung (5.8±2.3/ml), involving breast, prostate and ovarian cancer.

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

Disclosure: Has not received any funding.

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

Results: Targets of overexpressed miRNAs miR-18, miR-23, miR-29, miR-150, miR-181, miR-221/222 and miR-372/373 were found in transcript of CDH1 gene encoding E-cadherin. Transcripts of genes P11R and JAM5 encoding junctional adhesion molecules CAM-A and JAM-C carry targets of miRNAs miR-23, miR-29, miR-155, miR-181 and miR-221/222. Binding sites for miRNAs miR-23 and miR-150 were revealed in transcripts of TJP1 and TJP2 genes encoding tight junction proteins ZO-1 and ZO-2.

Conclusions: Our study showed that inhibition of VEGFA and its receptor VEGFR1 to control downstream signaling may provide a promising therapeutic target for the treatment of tumors.

Legal entity responsible for the study: Academic Group.

Funding: National Natural Science of Foundation.

Disclosure: All authors have declared no conflicts of interest.

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

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

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

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

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

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

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

Disclosure: The author has declared no conflicts of interest.

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

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

Methods: 1. Cell migration ability was measured using Transwell assay. 2. Protein expression was analyzed by western blot. 3. Mouse model detects peritoneal metastasis of gastric cancer cells. 4. Affymetrix scanner 3000 was used to analyse the microarray of gastric cancer cells. And the Bevacizumab could inhibit peritoneal metastatic nodules. We further found the migration of MGC-803 was increased with VEGFA stimulation, mainly through VEGFR1 but not VEGFR2.

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

Legal entity responsible for the study: Shanghai Jiao Tong University, Shanghai, China.


Disclosure: All authors have declared no conflicts of interest.
Background: Temozolomide (TMZ) is a main drug for chemotherapy of glioblastoma multiforme (GBM). During the treatment, both GBM tumour and surrounding normal brain are exposed to the drug, and its effects on the normal brain tissue are not investigated. Survival and invasion of GBM cells depend not only on their characteristics but also on the structure of extracellular matrix (ECM) of brain tissue, which consists mainly of glycosylated molecules such as proteoglycans (PGs) and glycosaminoglycans (GAGs). Here, we aimed to investigate the effects of TMZ on PGs and GAGs expression in normal brain tissue.

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

Results: Treatment with TMZ had almost no effects on the overall transcriptional activity of the PGs core proteins in normal brain tissue but resulted in a 2-fold increase of GAGs content (both heparin sulfates and chondroitin sulfates). Different TMZ-based drugs demonstrated different effects on the PGs core proteins expression - treatment with some of them resulted in significant decrease in syndecan-1, glypican-1, perlecian and lumican expression.

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

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

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

Disclosure: All authors have declared no conflicts of interest.

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

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

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

Legal entity responsible for the study: University of Valencia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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

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

Conclusions: 5-fluorouracil up-regulated exosomal PD-L1 which induced apoptosis of T cells and caused immunosuppression in gastric cancer patients. Legal entity responsible for the study: Academic Group. Funding: National Natural Science Foundation of China. Disclosure: All authors have declared no conflicts of interest.

Methods: Thrombocytosis and leukocytosis are associated with poor prognosis, suggesting a role for these leukocyte subsets in the complex interplay of immune regulation in cancer, and may influence clinical decision-making.

Results: Both thrombocytosis and leukocytosis were observed during treatment of breast, ovarian, colorectal and head and neck cancers, which may indicate the need for further investigation.

Conclusions: Thrombocytosis and leukocytosis are associated with poor prognosis, suggesting a role for these leukocyte subsets in the complex interplay of immune regulation in cancer, and may influence clinical decision-making.

Legal entity responsible for the study: National Cancer Institute. Funding: National Cancer Institute. Disclosure: All authors have declared no conflicts of interest.
47P

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

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Background: Our previous studies have reported that the secretomes of umbilical cord- and adipose-derived mesenchymal stem cells (MSCs) affected the stemness properties of human breast CSCs (BCSCs). However, little is known about specific factors in MSC secretomes, particularly those from human exfoliated deciduous teeth, which involved in tumor aggressiveness such as stemness and proliferation of CSCs. This study aimed to evaluate the stemness and proliferation of human BCSCs after supplementation with heated secretomes of stem cells from human exfoliated deciduous teeth (SHED) to activate latent TGF-beta1.

Methods: To collect SHED conditioned medium (SHED-CM) containing secretomes, SHED were grown in serum-free a-MEM for 24 and 48 hours, respectively. SHED-CM 24-h was then heated at 80°C for 10 min. Human BCSCs (ALDH+) cultured in DMEM-F12 were supplemented with 50% (v/v) non-heated SHED-CM 24- and 48-h, as well as with heated SHED-CM 24-h followed by 72-h incubation. Control was BCSCs supplemented with non-heated 50% (v/v) a-MEM/DMEM-F12. Following the supplementation, we measured the mRNA expression of TGF-beta1 receptor (TIRI), as well as stemness genes ALDH1A1 and OCT4 of BCSCs using qRT-PCR. BCSC proliferation was determined using trypan blue dye.

Results: This study demonstrates that relative mRNA expression levels of TIRI, OCT4 and ALDH1A1 in BCSCs supplemented with non-heated SHED-CM 24- and 48-h were increased compared to their control. Interestingly, the increase of TIRI, OCT4 and ALDH1A1 expressions after TGF-beta1 heat activation was significantly higher than in non-heated SHED-CM. Conversely, BCSC proliferation was significantly reduced after supplemented with non-heated SHED-CM 24- and 48-h, but drastically increased higher than control when treated with heated SHED-CM 24-h, suggesting the involvement of other factors in SHED-CM that restrain TGF-beta1 signaling and suppress cell proliferation.

Conclusions: Heated SHED secretomes contained activated TGF-beta1 that increased the expression of stemness genes, OCT4 and ALDH1A1, as well as proliferation of human BCSCs (ALDH+) via TGF-beta1 paracrine signaling.

Legal entity responsible for the study: Septelina Inawati Wanandi.

Disclosure: All authors have declared no conflicts of interest.

48P

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


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

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

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

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

Legal entity responsible for the study: Tetsuya Kokabu.

Disclosure: All authors have declared no conflicts of interest.

49P

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

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

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

Results: Administration of the anti-L1CAM antibody was well tolerated with no signs of acute local or systemic intolerance observed. In cynomolgus monkey, specific binding was observed in kidney tubules and Kupffer’s cells of the liver, while no binding was observed in the central nervous system, peripheral nerves, or any other tissues. Conclusions: Administration of L1CAM antibody was well tolerated and the observed tissue distribution was consistent with the known expression profile of L1CAM. These data support the safety of anti-L1CAM therapy using an antibody approach.

Legal entity responsible for the study: Elthera AG.

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

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

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

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

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

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

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

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

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57PD Tumor mutational burden and prognosis across pan-cancers

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


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


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

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

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


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

B. Holt¹, D. Micklem¹, A. Brown¹, M. Yule¹, J. Lorens²
¹BerGenBio ASA, Bergen, Norway, ²Department of Biomedicine, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway

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

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

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

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

**Results:**

For HPV+ patients by anatomic site, the proportion of HPV+ was higher (14%) and cervical (38%). The mutational landscape of each cohort was distinct, regardless of HPV status. Higher median TMB was associated with HPV+ tumors. The proportion of HPV+ was higher (14%) and cervical (38%). The mutational landscape of each cohort was similar, regardless of HPV status. Higher median TMB was associated with HPV+ tumors. The proportion of HPV+ was higher (14%) and cervical (38%). The mutational landscape of each cohort was different, regardless of HPV status. Higher median TMB was associated with HPV+ tumors.

**Conclusions:** The mutational landscape of HPV+ tumors was different from HPV- tumors, with HPV- tumors having higher median TMB. These findings suggest that HPV status is an important factor in determining the mutational landscape and TMB in squamous cell carcinomas.

**Table 68P**

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>% HPV+</th>
<th>Median TMB (Interquartile Range)</th>
<th>% TMB</th>
<th>% TMB &gt; 10</th>
<th>% TMB &gt; 20</th>
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<tbody>
<tr>
<td>Anogenital (n = 1213)</td>
<td>76</td>
<td>5 (6–10)</td>
<td>17</td>
<td>5</td>
<td></td>
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<tr>
<td>Head and Neck (n = 1843)</td>
<td>36</td>
<td>4.5 (4–5)</td>
<td>15</td>
<td>5</td>
<td></td>
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<tr>
<td>Esophageal (n = 416)</td>
<td>6</td>
<td>5 (4–6)</td>
<td>13</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lung (n = 3977)</td>
<td>5</td>
<td>9 (8–11)</td>
<td>43</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Skin (n = 422)</td>
<td>8</td>
<td>40 (69–99)</td>
<td>68</td>
<td>62</td>
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</tr>
</tbody>
</table>

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**Funding:** Foundation Medicine, Inc.

**Disclosure:** M. Monteson, E.S. Sokol: Employee: Foundation Medicine, Inc. L.A. Albacker, G.M. Frampton, V.A. Miller, J.S. Ross, S.M. Ali: Employee and stock owner-ship: Foundation Medicine, Inc. All other authors have declared no conflicts of interest.
Methods: In CheckMate 026, TMB was assessed by WES on formalin-fixed, paraffin-embedded tumor samples and matched blood from 312 patients with NSCLC (Carbone et al. NEJM 2017). Data from each sample were aligned to a reference human genome. Two additional patient cohorts treated with nivolumab (development set S) using multivariate analysis methods were also enrolled. TMB scores were compared with data from 710 NSCLC samples in The Cancer Genome Atlas (TCGA) dataset. We examined the concordance of TMB estimates using several mutation filtering schemes, with and without matched germline controls.

Results: TMB scores including synonymous, indel, frameshift, and nonsense mutations (all mutations) were used to identify patients showing primary resistance to APD1. The proportions of patients in A, B, and C were 41:43:32 in S, 23:18:17 in V1, and 30:35:35 in V2. In a comparison with the historical control group (S), the good prognosis group (C) had significantly elevated risk of gefitinib primary resistance and shorter OS compared with controls. In a comparison with V1, the treatment effects in S were significant for OS (P = 0.043). Additionally, statistically significant association between short leukocyte RTL and shorter OS still existed among the EGFR mutant patients with gefitinib treatment (HR = 1.65, 95% CI: 1.28-2.12, P = 0.006). Finally, our most significant association when comparing MPM to controls was for rs2071304 (OR = 0.60; 95% CI: 0.45-0.81; p = 0.0007). Intriguingly, this variant was also strongly associated with significantly higher mortality compared to patients with SPM. Based on the evidence that the immune system plays a role in regulating melanoma progression we explored whether germline genetic variants controlling the expression of immunomodulatory genes (immunomodulatory quantitative trait loci, eQTLs) discmrged risk of MPM compared to patients with SPM or healthy controls.

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

Legal entity responsible for the study: Tomas Kirchhoff.

Funding: NIH.

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

Background: For the first time, we report the identification of a novel biomarker of advanced lung adenocarcinoma.

Methods: In this study, three hundred and sixty-nine patients with stage IIIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. All patients were treated with gefitinib orally at a daily dose of 250 mg as first-line monotherapy. Leukocyte RTL of each patient was measured using quantitative polymerase chain reaction (qPCR) protocol on an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems) and calculated according to Cawthon’s formula. Differences in patients’ characteristics were calculated by Pearson’s χ² tests or Student’s t test. Cox proportional hazard regression analyses were used to calculate univariate and multivariate hazard ratios (HRs). Survival differences were examined using the log-rank test. Two-sided P < 0.05 indicated a significant difference.

Results: Among 369 patients, EGFR mutations were positive in 181 patients (49.1%). Compared to long RTL, short Leukocyte RTL was significantly associated with poor prognosis in all patients after gefitinib treatment (overall survival: 12.9 months vs. 17.8 months, P = 1.2 × 10^-4; progression free survival: 7.8 months vs. 13.0 months, P = 0.043). Additionally, statistically significant association between short leukocyte RTL and shorter OS still existed among the EGFR mutant patients with gefitinib treatment (HR = 1.65, 95% CI: 1.28-2.12, P = 0.006). Besides EGFR mutation status, short RTL also contributed to significantly elevated risk of gefitinib primary resistance (HR = 1.50, 95% CI: 1.05-2.15, P = 0.027). Conclusion: Our results highlight the potential of leukocyte RTL as a novel biomarker in advanced lung adenocarcinoma treated with EGFR-TKIs and the possibility of patient-tailored decisions based on leukocyte RTL.
Gene embedding: A novel machine learning approach to identify gene candidates related to immunotherapeutic responsiveness

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

Methods: TCGA RNAseqV2 level 3 RSEM normalized read counts (January 2016) were downloaded from the Broad Institute TCGA GDAC Firehose. A shallow neural network, aka embedding layers for samples and genes, were trained using log2-transformed data. Neighbors closeness were evaluated by euclidean distance. The model was kept blind from any additional information, including cancer types, protein-protein interactions and gene ontologies.

Results: Gene expressions of 13,085 samples from 36 cancer types were embedded into 50-dimension space, while cancer types were learnt by the model without supervision. Immunotherpay responders and non-responders were stimulated from melanoma (SMMC) and lung squamous cell carcinoma (LUSC) data, and hepatocellular carcinoma-prostate cancer data respectively. 9 genes (TNR18R5, CLEC19A, FCN1, CD8B, SLA2, IL3RA, CTLA4, GZMH), 3 (CD101, LOC154761, RNF152) genes, and 6 (MUC13A, MUC1, PDCD1, GFI1, S1ST, SRBDP3) genes were found to be closely related neighbors with PD-L1, PD-L1, and CTLA-4 respectively in responders but not in non-responders. All neighbors were neither co-expressed in SMMC/LUSC dataset nor indicated as interacting partners on existing databases (BioGRID, MINT, iReWeb, STRING, HPRD and Reactome). 88.8% genes were evidenced as either directly related to checkpoint proteins and/or T cells activation in literature. Further evaluation of the role of identified targets in immune checkpoint blockade therapy would be warranted. Conclusion: Gene embedding identified potential biomarker candidates for immune checkpoint blockade therapy by TCGA data mining and demonstrated the utility of gene embedding learned from big gene expression dataset as a powerful tool to uncover gene relationships that may not be discovered otherwise without prior knowledge on functional interactions.

Legal entity responsible for the study: Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong.

Funding: Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China.

Disclosure: All authors have declared no conflicts of interest.

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

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Background: Rare genetic variants in DPYD increase toxicity and screening for them prevents serious complications by upfront reduction in 5FU dose; however, most patients with severe toxicities do not have a rare mutation. We have previously shown that 2 common DPYD variants were associated with toxicity in patients with advanced colorectal cancer treated on COIN & COIN-B (abstract 3509, ASCO 2013): Cys29Arg (rs4810265 [Minor Allele Frequency (MAF) = 0.21] and Val732Ile (rs1011660) [MAF = 0.04]. We have now genotyped 4 rare variants using the same cohort.

Methods: Blood samples were available from 2183 patients treated with first line oxaliplatin 5FU ± cetuximab. We assayed IVS1+1G>A [rs9182390], Asp949Val [rs7379769], Ly229053 [rs45590337] and Ser534Ala [rs1801158] using KASPar. Primary endpoint was dose reduction or delay in chemotherapy in the first 12 weeks of treatment due to any toxicity except neutropathy. Secondary endpoints were grade ≥2 for neutropenia, lethargy, Nausea & Vomiting (N&V), diarrhea, stomatitis, Hand-foot Syndrome (HFS) and infection.

Results: Two rare variants were associated with toxicity (OR (95% CI)): Asp949Val with neutropenia 3.2 (1.2-8.2) P = 0.019, N&V 3.4 (1.5-7.7) P = 0.002, diarrhea 4.6 (2.1-10.1) P < 0.001 and infection 5.9 (1.3-24.2) P = 0.042; IVS1+1G>A with lethargy 3.9 (1.9-9.4) P = 0.002, diarrhea 4.4 (1.7-11.0) P = 0.002, stomatitis 4.6 (1.7-12.6) P = 0.003, HFS 5.8 (1.2-21.8) P = 0.021 and infection 19.2 (5.0-73.8) P < 0.001. MAF was 0.007 and 0.005, respectively. The effect on toxicity for our 2 common variants was not as marked (OR (95% CI)): Cys29Arg 0.8 (0.7-1.0) P = 0.008 (protective) and Val732Ile 1.6 (1.1-2.1) P = 0.006 for the primary endpoint.

Conclusions: We have validated 2 mutations, Asp949Val and IVS1+1G>A, as predictors for 5FU toxicity in a large cohort of patients and recommend they should be screened for. Our data suggest that common DPYD variants are also associated with toxicity but not to the same level seen with rare ones. While the presence of a single common variant is not an indication for dose modification, the presence of multiple variants in a patient might be. Further work is needed to establish what combinations of common DPYD variants would necessitate 5FU dose alteration.

Legal entity responsible for the study: CARDiff University and MRC CTU.

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Disclosure: T.S. Maughan, J.P. Cheadle: Part funded by an unrestricted research grant from Merck Serono. All other authors have declared no conflicts of interest.

Table: 75P

<table>
<thead>
<tr>
<th>Gene fusion</th>
<th>Cancer type</th>
<th>IHC</th>
<th>Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1</td>
<td>PM3 xenon10-NTRK1 xenon8</td>
<td>Colorectal cancer</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>IRF2BP2 xenon1-NTRK1 xenon8</td>
<td>Postate cancer</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>PRDX1 xenon5-NTRK1 xenon12</td>
<td>Lung adenocarcinoma</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>LMNA xenon2-NTRK1 xenon11</td>
<td>Filtricosarcoma</td>
<td>Positive</td>
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<td>TPR xenon21-NTRK1 xenon 9</td>
<td>Colon cancer</td>
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<td></td>
<td>PM3 xenon10-NTRK1 xenon8</td>
<td>Colon cancer</td>
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<td>AMOTL2 xenon6-NTRK1 xenon12</td>
<td>Squamous cell</td>
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<td>Squamous cell</td>
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<td>Small cell lung cancer</td>
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<td></td>
<td>AKAP13 xenon3-NTRK3 xenon14</td>
<td>Lung adenocarcinoma</td>
<td>NA</td>
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</table>
Conclusions: This study revealed NTRK fusions in approximately 0.3% of Chinese solid tumor pts for the first time. The NTRK gene fusions more commonly occurred in NSCLC (0.3%) and CRC (1.4%), but may occur with other metastatic alterations such as EGFR-drivenactivations. NGS panel sequencing showed the advantage of detect- ing NTRK fusion and providing structure information of partners which could potentially guide more precise treatment options.

Legal entity responsible for the study: OrigMed.

Funding: Has not received any funding.

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

Background: In a randomized, 3-arm, phase 2 trial of lenvatinib (LEN), everolimus (EVE), or LEN+EVE in patients with metastatic renal cell carcinoma the median progression-free survival (PFS) of LEN+EVE improved median progression-free survival (PFS) with compare with EVE (hazard ratio [HR] 0.46; 95% confidence interval [CI] 0.24–0.88; P = 0.001) or LEN (HR 0.66; 95% CI 0.39–1.10; P = 0.211) (Motzer et al. Lancet Oncol 2015). We present biomarker analyses from this study.

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

Results: Serum samples from 145 pts (LEN+EVE, n = 49; LEN, n = 50; EVE, n = 46) were analyzed. HGF, MIG, IL-18BP, IL-18, and ANG-2 concentrations demonstrated the strongest correlation with PFS and were selected for the CBS analysis. Associations with PFS are summarized in the table. In the LEN+EVE arm, median PFS for pts with high (≥3–) vs low (<3–) HGF was 20 vs 15.5 months, respectively (HR 0.28; P = 0.002), whereas no significant difference between high vs low lowCox values was seen in the EVE arm (3.6 vs 5.5 months, HR 1.02; P = 0.951). Median PFS differed significantly between treatment arms for pts with high CBS (LEN+EVE vs EVE, 20.1 vs 13.6 months; P < 0.001), but not for pts with low CBS (LEN vs EVE+EVE, 3.6 vs 5.5 months; P = 0.329).

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

Clinical trial identification: NCT01136733.

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Legal entity responsible for the study: Eisai Inc.

Funding: Eisai Inc.


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

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

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

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

Legal entity responsible for the study: Hoke J. Grabsch.

Funding: Pathological Society of Great Britain and Ireland, Kanagawa Cancer Center. Disclosure: All authors have declared no conflicts of interest.

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

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

Results: 777260 (1%) samples in this series harbored KF. Patients (pts) with KF+ tumors had a median age of 53 years vs. 56 years in the overall population. The TMB in KF+ cases was 3.51 mut/Mb vs. 4.39 mut/Mb for all cases. KF were found in 55 lung (71%) and 22 (29%) non-lung samples. Of KF+ cases, 71% were non-small cell lung cancer, and the remainder were sarcoma (3%), breast cancer (4%), thyroid (4%), cancer of unknown primary (4%), pancreatic (3%), colorectal (3%) and others (1%).
OFK1+ non-lung cases, 39% had BRAF fusions, 30% had ALK fusions, 26% had RET fusions, and 4% had ROS1 fusions. One OFK1+ sarcoma pt received matched targeted therapy with ALK inhibitors including ceritinib and crizotinib. More recently, in 2017, the frequency of the latter is a challenge for clinical investigation. As such, innovative solutions such as basket trial for kinase inhibitors are needed, which may be feasible in an integrated cancer care system with high patient volume.

Legal entity responsible for the study: Ankar Parikh.

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

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

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

Methods: DNA extracted from FFPE tumor tissue underwnt whole-genome shotgun library construction and hybridization-based capture, followed by sequencing using Illumina HiSeq 4000. Sequence data were processed using a proprietary analysis pipeline to identify sub substitutions, indels, copy number alterations, genomic rearrangements, microsatellite instability (MSI), and tumor mutational burden (TMB) in 334 genes.

Results: Clinical validity was demonstrated by establishing statistical non-inferiority between CGP and the respective approved CDx, e.g. cobas EGFR and BRAF mutation testing. ALK rearrangements with FISH and IHC, ERBB2 amplification with FISH, and others. For analytical validity, concordance with an orthogonal NGS platform was 94.6% for substitutions and indels, and within-assy reproducibility had positive percent agreement (PPA) of 99.4%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6%. TMB was analytically validated via concordance with whole-exome sequencing. For the first 616 patients (25% non-small cell lung cancer) assayed in clinical care, 6.6% of cases had TMB exceeding 20 mut/Mb, with 25% of others. For analytical validity, concordance with an orthogonal NGS platform was 94.6% .

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

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

Funding: Foundation Medicine, Inc.


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

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Background: SET deregulation is an alteration that determines poor outcome in metastatic CRC. However, the role of SET in CRC progression and its potential clinical impact in early-stage CRC patients still remain to be investigated.

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

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

Conclusions: Of importance, our results indicate that SET could serve to anticipate undesirable relapses in stage II CRC patients and define a subgroup of early stage CRC patients that could benefit by the use of SET antagonists or PI3K-Akt activating drugs such as FTY720 in anticancer protocols.

Legal entity responsible for the study: Fundacion Jimenez Diaz.

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Disclosure: All authors have declared no conflicts of interest.

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

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

Methods: 384 patients with stage IIB or IV lung adenocarcinoma were recruited between January 2009 and June 2013. Patients were treated with gefitinib orally at a daily dose of 250 mg as 1st-line monotherapy. MDM4 rs4245793 A>G genotypes were determined using MassArray system. Dual lucerase reporter gene assays evaluated the function of MDM4 rs4245793 genetic variant in lung adenocarcinoma cell lines A549 and H1299. The differences of patient clinical characteristics were calculated by student’s t test or χ2 test. Survival differences were examined by log-rank test. Multivariate Cox regression analysis assessed prognostic factors for PFS or OS. Two-sided P < 0.05 indicated a significant difference.

Results: Among 384 patients, EGFR mutations were positive in 181 patients (47.1%). Median progression-free survival (PFS) and overall survival (OS) for all patients with the rs4245793 QA genotype were significantly longer than that of the AA carriers (PFS: 22.9 vs. 10.9 months, P < 0.001; OS: 27.3 vs. 16.5 months, P = 0.003). Notably, in the EGFR mutation-positive subgroup, individuals with MDM4 rs4245793 QA genotype showed 14.1 months prolonged PFS (28.8 months vs. 14.7 months, P = 0.022) and 12.2 months prolonged OS (31.4 months vs. 19.2 months, P = 0.047) compared to the AA group. Reporter gene assays showed that the rs4245793 QA allele leads to significantly increased MDM4 expression in lung adenocarcinoma cells compared to the AA allele (P < 0.05).

Conclusions: MDM4 rs4245793 QA genotypes may act as prognostic biomarker for patients’ survival to gefitinib therapy and offer help to individualized treatment in lung adenocarcinoma patients with EGFR mutations.

Legal entity responsible for the study: Nusha Zhang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
not respond to these drugs that are costly and can lead to substantial toxicity. Therefore, there is an urgent need for biomarkers that can identify patients that will respond to these therapies.

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

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

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

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

Funding: MSD.

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

### Table: 83P

<table>
<thead>
<tr>
<th>Pre-specified subgroup</th>
<th>Patients/events in OS, PFS, ORR, respectively</th>
<th>OS Hazard ratio [&lt;1 favours OP (P value)]</th>
<th>PFS Hazard ratio [&lt;1 favours OP (P value)]</th>
<th>ORR Odds ratio [&gt;1 favours OP (P value)]</th>
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<tr>
<td>Overall population</td>
<td>525/381, 449, 72</td>
<td>0.80 (0.026)*</td>
<td>0.84 (0.065)</td>
<td>1.68 (0.057)</td>
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<td>Evaluate for genetics</td>
<td>400/284, 342, 57</td>
<td>0.80 (0.065)*</td>
<td>0.87 (0.214)</td>
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<td>ATM IHC status³</td>
<td>+ve</td>
<td>0.79 (0.076)</td>
<td>0.96 (0.737)</td>
<td>1.06 (0.870)</td>
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<tr>
<td></td>
<td>-ve</td>
<td>0.72 (0.292)</td>
<td>0.61 (0.081)</td>
<td>3.41 (0.082)</td>
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<td>ATM IHC null</td>
<td>Not null</td>
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<td>0.89 (0.315)</td>
<td>1.25 (0.551)</td>
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<td>Null</td>
<td>0.55 (0.426)</td>
<td>0.28 (0.090)</td>
<td>6.46 (0.141)</td>
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<tr>
<td>ATM</td>
<td>Wt</td>
<td>0.80 (0.062)</td>
<td>0.86 (0.175)</td>
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<td>0.83 (0.803)</td>
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<td>ATM/BRCA</td>
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<td>0.94 (0.008)</td>
<td>1.11 (0.795)</td>
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<td>HRR</td>
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<td>1.05 (0.003)</td>
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<td>ARID1a</td>
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<td>TP53</td>
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<td>L0H score</td>
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<td>&gt;6</td>
<td>0.62 (0.175)</td>
<td>0.71 (0.246)</td>
<td>0.84 (1.00)</td>
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</table>

Olaparib plus paclitaxel sensitivity in biomarker subgroups of gastric cancer


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

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

Results: Efficacy in the genetics evaluable population (n = 400) was broadly consistent with the overall GOLD population (n = 525) for each outcome investigated. ATM-negative patients by IHC had better prognosis independent of treatment. No statistically significant associations with clinical outcomes were identified (Table). Post-hoc exploratory analyses indicated good prognosis (OS) in pts with an ATM mutation, and poor prognosis in pts with CDH1, FGFR2 or KRAS mutations.
Background: Almost one third of carriers of hepatitis B virus (HBV) world-wide are in China and more than 80% hepatocellular carcinoma (HCC) in China are associated with HBV infection. So early detection of HCC in HBV-infected patients is necessary. In the present study, we aimed to develop a diagnostic model by combining protein induced by Vitamin K absence or antagonist-II (PIVKA-II) and α-fetoprotein (AFP) for HBV-related HCC.

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

Results: The training cohort consisted of 199 participants, 908 with HBV-related HCC, 289 with chronic hepatitis B, 314 with HBV-related cirrhosis, and 508 healthy controls. The validation cohort comprised 655 participants, 289 with HBV-related HCC, 113 with chronic hepatitis B, 98 with HBV-related cirrhosis, and 155 healthy controls. Levels of PIVKA-II in serum were significantly higher in HBV-related HCC than all controls. ROC curves showed the optimum diagnostic cutoff for PIVKA-II was 44.18 mAU/mL (area under curve [AUC], 0.907 [95% CI 0.892-0.922], sensitivity 81.13%, and specificity 94.97% in the training cohort; 0.909 [0.883-0.934], 79.02%, and 95.46% in the validation cohort). PIVKA-II maintained diagnostic accuracy for patients with HBV-related HCC who were AFP negative. A model combined PIVKA-II, AFP, age, gender and liver cirrhosis improved diagnostic accuracy for HBV-related HCC versus all controls compared with either test alone (0.951 [0.929-0.973] in the training cohort; 0.954 [0.945-0.962] in the validation cohort).

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

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

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Background: Gastric cancer (GC), is a leading cause of cancer-related death, is a heterogeneous disease where survival depends on factors such as biological differences, MSI status, EBV status, region, ethnicity and patterns of care. The biological context for immune responsiveness and resistance in the clinical are only now starting emerge. Although GC has similar levels of PD-L1 expression and CTC expression to lung cancer, the approvals and success of immunotherapy in GC to date has been mixed.

Methods: We explored 2 randomized MetMAb trials (Ph1 Study YO13832 and Ph2 Study YO28252) in combination with mFOLFOX6 in metastatic HER2-negative and MET-positive GC. We used Study 1 (n = 146) to uncover novel GC biology using Nanostring based gene expression analysis and Study 2 (n = 70) to confirm the findings. Late Stage GC. (Stage IV biopsies) GC from the Study 1 and 2 were compared against early stage GC (Stage I, II and III) in resections from the ACRG GC dataset.

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

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

A clinical trial identification: YO28322: NCT01662869 YO28252: NCT01590719

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

Funding: Hoffmann-La Roche, Genentech.

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

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


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

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

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

Conclusions: We demonstrate a strong prognostic potential of ctDNA in bladder cancer at time of DX, suggesting a potential role for ctDNA in the staging of bladder cancer. Furthermore, we show ctDNA is detected in all patients with disease recurrence after
Role of AR-V7 and AR-FL in resistance to hormonal therapy in mCRPC: independent actors or reciprocal drivers? A translational study by Meet-Uvo group

M. Del Re 1, S. Crucitta 1, A. Sbrana 2, E. Rofi 3, F. Paolieri 3, L. Galli 4, A. Falcone 3, J. Eshleman 9

Background: The androgen receptor splice variant 7 (AR-V7) is strongly associated with resistance to hormonal therapy (HT) in castration-resistant prostate cancer (CRPC), although it is not implemented in clinical practice as a biomarker. The AR-full length (AR-FL) is also overexpressed in CRPC but its role has yet to be clarified. The aim of the present work was to investigate the role of AR-V7 and AR-FL as predictors of resistance to HT in plasma-derived exosomal RNA. Methods: 6 mL of blood were collected in EDTA tubes before the start of abiraterone/ enzalutamide; blood was centrifuged and plasma stored at -80°C until analysis. Exosomes isolation and RNA extraction were performed using the exoNeyse kit (Qiagen) as per manufacturer instructions. The analysis of AR-FL and AR-V7 were performed by digital droplet PCR using the One-Step RT-ddPCR kit (BioRad). The absolute target concentration as copies/ml in samples was calculated by diluting PCR QuantitaSoft and statistical analyses were performed by SPSS v.24.

Results: 52 patients (pts) were enrolled, AR-FL was detected in all pts (median: 700 copies/ml), while 15 subjects (28.8%) were AR-V7+ (median: 310 copies/ml) at baseline. The amount of AR-FL was significantly higher in pts AR-V7+ vs AR-V7− (6700 vs 490 copies/ml, p < 0.001). Median PFS and OS were longer in AR-V7− vs AR-V7+ pts (median PFS 25 vs 4 mo, p < 0.001; median OS 38 vs 9 mo, p < 0.001). A ROC curve was calculated for AR-FL in the overall population and 950 copies/ml was identified as cut-off value. Pts were then stratified across this value and it was found that PFS was 22 mo in pts with <950 AR-FL copies/ml vs 4 mo in pts with ≥950 copies/ml (p < 0.0003). In 12/15 AR-V7+ pts the AR-FL expression was >950 copies/ml while in 3/15 AR-V7− pts, AR-FL expression was <950 copies/ml; however, their PFS reflected the AR-V7+ better than AR-FL status, being, respectively 6, 10, 4 mo. No other clinical variables were correlated with worse PFS at the univariate analysis (i.e. Gleason score ≥7, age). Conclusions: This study demonstrates that resistance to HT may be predicted by AR-V7, making it a clinically relevant biomarker. AR-FL over-expression may contribute to hormone resistance although AR-V7 plays a primary role. Legal entity responsible for the study: Romano Danesi. Funding: University of Pisa. Disclosure: All authors have declared no conflicts of interest.

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

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Background: Brain metastases (BM) are the most common intracranial tumors affecting about 8–10% of all cancer patients. Morphology and immunohistochemical staining are two common approaches used to identify the primary sites of BM samples, but morphological fail to identify poorly differentiated tumors and IHC markers usually lack specificity. About 30 to 14% of BM patients still present with unknown primary site. A 90-gene assay, proposed in our previous study, is an RNA-based gene expression test to identify the tissue of origin in poorly differentiated and undifferentiated tumors. This study aims to evaluate the performance of the 90-gene assay in determining the primary sites for BM samples. Methods: The sequence-based gene expression profiles of 708 primary brain tumors (PBT) collected from The Cancer Genome Atlas database were performed by a 90-gene expression signature, with a similarity score for each of 21 tumor types. We used Optimal Binning algorithm to generate a threshold for separating PBT from BM. Eighteen PBT samples from Fudan University Shanghai Cancer Center were analyzed to substantiate reliability of the threshold. In addition, the performance of the 90-gene assay for identifying the tissue of origin was validated in a cohort of 48 BM samples with known origin from The First Affiliated Hospital, Zhejiang University. For each BM sample, the tumor type with the highest similarity score was considered tissue of origin. When a sample was diagnosed as PBT but the similarity score below the threshold, the second prediction was considered as primary site. Results: A threshold of the similarity score, 70, was identified to discriminate PBT from BM (PBT: ≥ 70, BM: < 70) with an accuracy of 99.9% (703/708). Eighteen PBT and 44 BM were performed by the 90-gene assay. The results of 18 PBT samples matched reference diagnosis with a concordance rate of 100% and all similarity scores were above 70. Of 44 BM samples, the 90-gene assay accurately predicted primary sites in 89% (39/44, 95%CI: 0.75-0.96) of the cases. Conclusions: The 90-gene assay showed promising discriminatory ability to separate PBT from BM and identify the primary site of BM. Our findings demonstrated the potential that 90-gene assay can serve as a powerful tool for accurately identifying the tissue of origin for BM samples. Legal entity responsible for the study: Yulong Zheng. Funding: Has not received any funding. Disclosure: Y. Sun, C. Chen, L. Chen, J. Zhu: Employment: Canhelp Genomics Co. Ltd. Q. Xu: Employment, stock ownership: Canhelp Genomics Co. Ltd. All other authors have declared no conflicts of interest.
Background: Microsatellite instability (MSI) has been approved as the first pan-cancer biomarker in immune checkpoint inhibitors (ICI) therapies. The tumor tissues of most metastatic gastrointestinal cancer patients before ICI therapies were collected. Profiling for improved prognosis prediction in muscle-invasive bladder cancer patients

Methods: The new microsatellite biomarkers were selected by screening 160 extra-colonic cancers can be increased by at least 2-fold over current MSI systems making MSI classification highly accurate and robust. The MSI and IHC results were obtained from the Colon Cancer Family Registry. DNA samples are being tested for MSI using two pan-cancer systems: Promega’s MSI Analysis System version 1.2 and the improved prototype Pan-Cancer MSI System. Mutations in mismatch repair (MMR) and BRAF genes were tested, as well as MMR expression by IHC.

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

Legal entity responsible for the study: Promega Corporation.

Funding: Promega Corporation.


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

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

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

Results: bMSI showed 87.5% accuracy to predict the MMR/MSI status from tissue specimens in the training cohort, and 93.2% sensitivity in the validation cohort. bMSI-H patients had 34.4% objective response rate (ORR) and 45.7% disease control rate (DCR), which were comparable to the dMMR of historical FFPE specimens (33.3% and 47.6% respectively). However, 57.7% pMMR patients were classified as bMSI-H and showed similar ORR (27%) and DCR (40%) and progress-free survival to those of dMMR patients. Furthermore, 17% bMSI-H patients with high bMSI scores (larger than or equal to 28) showed 66.7% ORR and 100% DCR. Finally, 91.7% patients with controlled diseases over 6 months showed decreasing bMSI scores, and 69% patients with progressive diseases showed increasing bMSI scores during therapies.

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

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

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

Disclosure: H. Qin, D. Wang, S. Cai, Y. Bai, Z. Xie: Employee: 3D Medicines Inc. L. Xiong: Employee, stock holder, chairman: 3D Medicines Inc. F. Li: Employee and stock holder: 3D Medicines Inc. All other authors have declared no conflicts of interest.
proportion of PD-L1(+) cells across the whole tissue, which were negatively and posi-
tively correlated with cancer-specific death respectively. This method was used to
replace TNM stages I to 3 while retaining the original stage 4 stratification. Testing for
survival curves differences showed that this combined system yielded a higher prognos-
tic value (Chi-square=41.5, p-value=5.0×10^-9) than the standalone TNM staging system
(Chi-square=34.9, p-value=1.2×10^-7).

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

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

Funding: Definiens AG.

Disclosure: N. Brieu, G. Schmidt: Fully employed: Definiens AG, a subsidiary of
Medimmune and AstraZeneca. C.G. Gavriel: PhD student at the University of St
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at the University of St Andrews; Secondary PhD supervisor of C. Gavriel; funded by
Definiens AG. P.D. Caie: Senior research fellow at the University of St Andrews;
Primary PhD supervisor of C. Gavriel; funded by Definiens AG.

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


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Background: The Epitopes-HPV02 single arm phase II study (NCT01240284) demon-
strated the efficacy of Docetaxel, Cisplatin and 5FU as first line chemotherapy (CT) for
advanced squamous cell carcinoma of the anal canal (SCCA), with a 1-year progress-
ion-free survival rate of 47% (Kim, Lancet Oncol 2018 in press). We previously
reported the validity of HPV ctDNA detection and its prognostic value in localized
SCCA (Cabel, Clin Cancer Res 2018 in press). This ancillary study aims to report the impact of
HPV ctDNA detection in patients enrolled in the Epitopes-HPV02 trial.

Methods: Per protocol, serum samples (1 ml) were collected twice: before CT and, in
non-progressive patients, at CT discontinuation which occurred after 5 months on CT.
HPV16 ctDNA was quantified by ddPCR at both time points and correlated with pro-
gnostic value (Chisquare=41.5, p-value=5.0×10^-9) than the standalone TNM staging system
(Chisquare=34.9, p-value=1.2×10^-7).

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

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

Funding: Definiens AG.

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

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

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

Methods: 100 patients (pts) with mixed solid tumors received single-agent P (anti-PD-
1) 200 mg IV Q 3 weeks in the investigator-initiated Phase II trial (INSPIRE study,
NCT02644369). Germine whole exome sequencing (WES) of peripheral blood mono-
nuclear cells was analyzed using the Illumina HiSeq2500 platform. Consensus HLA class I alleles were predicted from WES using HALAnimer and HLAViewer. Using uni-

Table: 95P

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>A<em>01 and A</em>02 (n = 7)</th>
<th>A<em>01 and no A</em>02 (n = 13)</th>
<th>A<em>02 and no A</em>01 (n = 49)</th>
<th>Neither A<em>01 nor A</em>02 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45(7%)</td>
<td>2(15%)</td>
<td>11(22%)</td>
<td>3(10%)</td>
<td></td>
</tr>
</tbody>
</table>

Table Fisher exact p-value=0.0503

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

Clinical trial identification: Trial protocol number: NCT02644369.

Legal entity responsible for the study: Lillian Siu.

Funding: Merck.

Disclosure: P. Bedard: Research funding: Bristol-Myers Squibb, Sanofi, AstraZeneca,
Genentech/Roche, Servier, GlaxoSmithKline, Novartis, SignalChem, PTC Therapeutics, Nektar, Merck, Seattle Genetics. A. Sprefico: Support for clinical trials: Merck, Novartis, BMS. A. Razak: Research funding: Merck, BMS, Pfizer, Karyopharm,
Deciphera, Eli Lilly, Boehringer, Boston Biomedical, Roche, Novartis and Genentech; Consultancy: Eli Lilly, Eisai, Boehringer Ingelheim, Merck. P. Ohashi: Consultancy/ advisory: Symphogen Inc., Providence Pharmaceuticals, Inc., Baxter US Inc., Lion Biotechnologies, Inc. T. Pugh: Honoraria: Merck, Prosigna, Chrysalis Biomedical Advisors, Consulting, DynaCare Research, Funding: Boehringer Ingelheim; Patents, royalties; other intellectual property: Hybrid-capture sequencing for determining immune cell clonality, combined hybrid-capture DNA sequencing for disease detec-
tion. L. Siu: Advisory board and funding for clinical trials: Merck. All other authors have declared no conflicts of interest.
**Background:** AXL expression promotes tumor growth, angiogenesis, epithelial to mesenchymal transition (EMT), resistance to CT and targeted agents. AXL is over-expressed in CRC. We aimed to evaluate AXL expression in mCRC pts and to correlate it with clinical outcomes.

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

**Results:** AXL staining positively in 20/177 samples with different intensity: 1 week, 3 moderate, 2 intense. In RAS WT cohort 9/102 cases (9%) were positive while in RAS mutant 11/75 (15%). Tumor stroma was assessable in 166 samples. AXL expression was high (moderate + intense) in 47/96 (49%) RAS WT and in 28/70 (40%) RAS mutant cases. No significant correlation was found between AXL expression and clinico-pathological features. In RAS WT cohort, AXL positive pts had a significantly worse median OS (14.8 m [95% CI 12.5-17.2] vs 19.3 m [95% CI 17.3-21.7] p = 0.004), than AXL negative. In RAS mutant KPS 11/75 (15%).

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

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

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

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

**Disclosure:** All authors have declared no conflicts of interest.

| Table: 96P |

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median OS (months - CI95%)</th>
<th>Median PFS (months - CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AXL expression in tumor</td>
<td>AXL expression in stroma</td>
</tr>
<tr>
<td>N (tumor) / N (stroma)</td>
<td>AXL positive</td>
<td>AXL negative</td>
</tr>
<tr>
<td>Overall population</td>
<td>20.1 (12.8-27.4)</td>
<td>36.5 (30.6-42.3)</td>
</tr>
<tr>
<td>RAS WT (CT + cetuximab)</td>
<td>230 (0.0-63.3)</td>
<td>39.8 (30.2-49.4)</td>
</tr>
<tr>
<td>RAS mutant (CT + anti-angiogenic)</td>
<td>20.1 (10.6-29.6)</td>
<td>30.2 (18.4-42.0)</td>
</tr>
</tbody>
</table>

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

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

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

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

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

**Clinical trial identification:** NCT01972217.

**Legal entity responsible for the study:** AstraZeneca.

**Funding:** AstraZeneca.


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Annals of Oncology

Identification of a highly suppressive Treg subset associated to immunotherapy response


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Background: Cancer immunotherapy, particularly monovalent antibodies against immune checkpoint inhibitors, has shown surprising efficacy in several types of advanced incurable tumors, including malignant melanoma. Tregs, a subset of lymphocytes involved in immune-surveillance and self-tolerance, are usually increased in mela-noma patients. Lymphocytes are particularly rich in FKBP15, the intracellular receptor for FK506 and rapamycin. Melanoma aberrantly expresses this immunophosphitin, which supports cancer resistance and invasion. Recently, our group has shown that melanoma interaction with immune cells, through PD-L1/PD1, generated the splicing of FKBP5 gene inducing a lower molecular weight form (FKBP51+). In both melanoma and lymphocyte. Aim of this study is to assess the role of Treg FKBP51+ as a biomarker of response to anti-PD1 drugs.

Methods: Treg FKBP51+ were measured in peripheral blood by flow cytometry. To date, we have outcomes of 11 patients. For 6 patients, we have collected from 4 up to 16 blood samples, before each anti-PD1 administration, with a total of 80 sample analysis. The Tregs were generated by purified CD4+ T lymphocytes from normal donor, stimulated with CD3+CD28+ beads. The suppressive capacity was assessed according to the parameters CD25+K6+ and p70S6K+.

Results: In 5 responder patients, Treg FKBP51+ was 1.2-4.8%; in 5 non-responders, the count was 0.04-0.8%. Interestingly, a patient with count 0.72% developed autoimmunity. The count is inversely related to the prevalence. FR was 0.67 (0.59, 0.74).

Conclusions: Our data reinforce the hypothesis that melanoma patients that benefit from immunotherapy are recognizable by an expansion of a Treg subset which plays a central role in tumor immune evasion. This Treg subset is marked by FKBP51+, a splicing protein isoform generated by triggering of surface antigens (PD-L1, PD1) abundantly expressed on highly suppressive Tregs.

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

Disclosure: All authors have declared no conflicts of interest.

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


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

Methods: Objective response rate (ORR) in biomarker positive patients is the product of ORR in all patients and the fraction of responding patients who are biomarker positive (FR+). FR+ depends on FR, the prevalence of a biomarker. Consistent individual biomarker ORR prevalence curves and 95% credible intervals overlapped substantially with each other, consistent with indistinguishable areas under the receiver operating characteristics curve (AUROC) for PD-L1, TMB and GEP in this pan tumor population. Thus, although PD-L1 or GEP identify populations only partially overlapping with that of TMB, the predictive ability is similar for all 3 biomarkers.

Table: 99P

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>ORR @ 60% Prevalence</th>
<th>ORR @ 30% Prevalence</th>
<th>ORR @ 10% Prevalence</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>15.5 (12.9, 19.0)</td>
<td>21.5 (15.8, 27.4)</td>
<td>33.6 (22.3, 45.7)</td>
<td>0.69 (0.63, 0.76)</td>
</tr>
<tr>
<td>GEP</td>
<td>17.5 (14.1, 21.2)</td>
<td>24.8 (19.2, 30.1)</td>
<td>33.5 (24.2, 44.1)</td>
<td>0.76 (0.70, 0.82)</td>
</tr>
<tr>
<td>TMB</td>
<td>150 (117, 186)</td>
<td>21.5 (15.7, 27.7)</td>
<td>35.9 (24.0, 40.9)</td>
<td>0.67 (0.59, 0.74)</td>
</tr>
</tbody>
</table>

C = Credible interval for ORR and confidence interval for AUROC

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

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

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


99P Comparison of OncoBEAM and NGS methods to detect plasma EGFR T790M mutations at progression of NSCLC

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Background: Various methods have been employed to detect plasma EGFR mutations in patients with non-small cell lung cancer patients (NSCLC). Therefore, we evaluated the performance of digital PCR and next generation sequencing (NGS) to detect the T790M EGFR mutation in prospectively collected patient samples. Paired plasma samples from patients (CIRCAN cohort) that progressed on first-line EGFR TKI therapy were compared using two platforms: OncoBEAM166 EGFR (Sysmex Inostics) and NGS (Illumina), utilizing the 36g oncology panel (Swiss Biosciences).

Methods: 196 stage 4 NSCLC patients with EGFR alteration under TKI were included from various center. Blood was collected in a routine setting, when physician noted...
changes in CT scans that were suspicious of progression. CDNA analysis is recommended in front line in this setting in France. Replica plasma samples were analysed using OncoBEAM and NGS. The thresholds for calling EGFR plasma mutations were 0.5% and 0.02% for NGS and OncoBEAM, respectively and were validated using cDNA reference standards (Horizon Discovery).

**Results:** OncoBEAM detected the p.T790M mutation in 36/196 patients (18.3%), whereas NGS detected T790M in 20/196 patients (10.2%). The agreement of NGS vs OncoBEAM for T790M detection was 55.6%. The p.T790M-positive samples detected by OncoBEAM but missed by NGS were all found to have low mutant allelic fractions (under 0.3%). With regard to sensitizing EGFR mutations, 28/36 OncoBEAM T790M+ patients had accompanying EGFR mutations, whereas all 20/20 NGS T790M+ samples showed absence of sensitizing mutations. In contrast to OncoBEAM, NGS testing revealed other somatic alterations including ERBB2 amplification, and mutations in TP53.

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

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

**Funding:** Symex Innomics / AstraZeneca.

**Disclosure:** C. Tissot, P.-J. Souquet: Membership on pharmacovigilance board. F. S. Jones, D. Edelstein: Symex Innomics. S. Couraud: AstraZeneca, Roche, MSD, Novartis, BMS, Boehringer Ingelheim, Chugai, Pfizer, Lilly, Merck, I. P. Payer: Membership on BMS, Advisory Board. AstraZeneca, Z. Xu: Sophia Genetics. All other authors have declared no conflicts of interest.

**101P**

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

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

**Methods:** Whole transcriptomic sequencing (RNA-Seq; ~200M reads/tumor) was performed across 1,467 unselected clinical cases (NantiHealth; Culver City, CA), with breast, colon, lung and sarcoma reflecting the most common tumor types assessed. To reflect the extremes of age, patients age < 25 and ≥ 80 were compared to the remainder of the cohort. PD-L1 expression was compared across these age-based subsets, along with CTLA4, TGFβ, FOXP3, LAG3 and TIM3 levels were observed (P < 0.001 for each). No significant differences in IDO, LAG3 or TIM3 were observed in this younger cohort. Older patients had no significant differences in checkpoint molecule expression; curiously, a nonsignificant trend towards increased expression of PD-L1, FOXP3 and LAG3 was observed in the small subset of patients age ≥ 85. No differences in TMB were observed by age. Expression and TMB in each decade of age will be reported.

**Conclusions:** In pediatric and adolescent and young adult (AYA) patients, lower expression of multiple immune checkpoint molecules may have implications for immune combinatorial strategies. An opposing trend was seen in octogenarians and expression of multiple immune checkpoint molecules may have implications for patient selection.

Legal entity responsible for the study: Omar Hamid.

**Funding:** Has not received any funding.

**Disclosure:** O. Hamid: Consultant: Amgen, Novartis, Roche, BMS, Merck; Speaker: BMS, Genentech, Novartis, Amgen; Contracted research (for institution): AstraZeneca, BMS, Celldex, Genentech, Immunocore, Incyte, Merck, Merck-Serono, MedImmune, Novartis, Pfizer, Ritan, Roche, C. Steo, S. Reddy. Employee and stockholder: NantOomics LLC. S.K. Pa: Consultant: Pfizer, Inc., Novartis, Ave Pharmaceuticalcs, Inc., Myriad Genetics, Genentech, Inc., Exelixis, Bristol-Myers Squibb Company, Astellas Pharma Inc.; Research/grant supporter: Medivation, Inc.; Honoraria: Novartis, Medivation, Inc., and Astellas Pharma, Inc. All other authors have declared no conflicts of interest.

**103P**

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

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

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

Quantitative RT-PCR was performed on all samples treated with crizotinib, 73.9% (17/23) developed acquired resistance, and 13.04% (3/23) had primary resistance. Using the specimens at the baseline, there was 1 (33.3%) patient with BCL2L11 loss (BIM deletion polymorphism), 1 (33.3%) patient with PTEN mutation, and 1 (33.3%) patient with KIT mutation. Median PFS was significantly shorter in patients with primary resistance than those with acquired resistance (2.3 vs. 14.5 months, P = 0.001).

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

Legal entity responsible for the study: Quxia Zhang.

**Funding:** Has not received any funding.

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**103P**

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

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**Background:** In gastric cancer (GC) there is a need for therapeutic targets/biomarkers beyond HER2 and PD-L1. Claudin 18.2 (CLDN18.2) is a promising target. In healthy tissue, CLDN18.2 is confined to gastric mucosa tight junctions; however, upon malignant transformation, perturbations in cell polarity lead to exposure of CLDN18.2 on the surface of GC cells. In a randomized clinical study (FAST; NCT01600083), patients with CLDN18.2-positive advanced GC and gastrointestinal junction (GEJ) cancers treated with EOX and zolotuzumab (an anti-CLDN18.2 monoclonal antibody) had prolonged survival compared with EOX alone. The CLDN18.2, HER2, and PD-L1 prevalence in global GC/GEJ tissue samples were assessed in this study.

**Methods:** FFPE GC/GEJ tissue samples were stained using antibodies against CLDN18.2, HER2, and PD-L1. IHC assays were run on an automated platform, HER2 amplification was determined by HER2 CISH. Stained samples were evaluated by a trained pathologist using established scoring criteria.

**Results:** A total of 298 GC/GEJ tissue samples (North America, n = 100; Asia, n = 100; Europe, n = 98) were assessed. 148 (50%) were histologically classified as intestinal, 123 (41%) diffuse, 18 (6%) mixed, and 9 (3%) other. In American samples, intestinal histology was the most prevalent; diffuse and intestinal were similar within Asian and European samples. Of the 286 evaluable samples, 30% (n = 86/286) were CLDN18.2+ (± weak), 27% (n = 79/291) were HER2+ and 26% (n = 75/288) were PD-L1+ .

**Conclusions:** CLDN18.2 was found globally to be a high prevalence target in GC/GEJ cancer with limited overlap with HER2. In light of the clinical activity observed for zolotuzumab, CLDN18.2 may serve as a therapeutic target for a large subgroup of patients with GC/GEJ cancer.

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**Legal entity responsible for the study:** Astellas Pharma, Inc.

**Funding:** Astellas Pharma, Inc.

**Disclosure:** D. Moran, A. Arozullah: Employee: Astellas. All other authors have declared no conflicts of interest.
Epigenetic markers in circulating cell-free DNA for detection of early stage colorectal cancer

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Background: The detection of early stage colorectal cancer (CRC) significantly improves chances of a cure and is a key factor in reducing CRC mortality rates. Colonoscopy is currently the gold standard for CRC diagnosis, but a somewhat troublesome and invasive procedure makes its acceptance not high in the general public as a screening tool. Epigenetic silencing of tumor-related genes by promoter methylation is common in CRC, but no biomarker has been proven to be individually of sufficient sensitivity or specificity in routine clinical practice. Objective: To identify a tumor-derived methylated gene in the serum of stage IIA CRC and assessed their diagnostic potentials for early stage of colorectal cancer.

Methods: In this prospective study, DNA methylation levels were measured by quantitative methylation-specific PCR. Seven genes were screened in an exploratory set of case-control serum samples. Promising methylation markers were selected and verified in the serum of a test set comprising 60 stage IIA CRC and 60 age-gender-matched healthy controls. Receiver operating characteristic curve (ROC) was constructed for assessment of assay performance.

Results: Serum methylation levels of TAC1, EYA4 and SST were significantly higher in stage IIA patients as compared to healthy controls (all P < 0.001, Mann-Whitney U-test). Area under the receiver operating curve (AUC) using serum methylation of TAC1 and EYA4 was 0.78 (95% confidence interval (CI), 0.68-0.85) and 0.73 (95% CI, 0.64-0.82), respectively. At a specificity of 85%, the assay sensitivity of TAC1 and EYA4 was 58.3% and 43.3%, respectively. Combination of serum methylation levels of EYA4 and SST improved the assay sensitivity to 52.5%. With TAC1 and SST being investigated in tumor DNA as well, we noticed that methylation of both genes in the same serum DNA always mirrored that of tumor DNA, exhibiting 100% concordance.

Conclusions: Serum methylation levels of TAC1, EYA4 and SST might be useful for minimally invasive detection of early stage of colorectal cancer. Validation study in larger and independent cohorts is necessary.

Legal entity responsible for the study: Singapore General Hospital.

Funding: National Medical Research Council, Singapore.

Disclosure: All authors have declared no conflicts of interest.

Detection and clearance of RET variants in plasma cell free DNA (cfDNA) from patients (pts) treated with LOXO-292


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Background: LOXO-292 is a novel, highly-selective, small molecule inhibitor of RET currently in clinical development (Phase 1, NCT03157128) for pts with advanced cancers harboring oncogenic RET alterations (e.g. non-small cell lung cancer [NSCLC], medullary thyroid cancer [MTC], papillary thyroid cancer [PTC], etc.). Here, we update data previously presented at ASCO 2018 on modulation of RET variant allele frequencies (AF) in plasma cfDNA with LOXO-292 therapy.

Methods: Blood was collected pretreatment, after 15 days of treatment, and at each restaging for cfDNA analysis by next-generation sequencing (NGS, Guardant).

Results: As of 4/21/18, 82 pts were enrolled (38 RET fusion NSCLC, 29 RET mutated MSCC, 9 RET expression PTC, 9 RET fusion pancreatic cancer and 4 others) to 8 dose cohorts (20mg QD240mg BID), and 343 plasma samples were collected. Here we report on 65 pts with plasma NGS results available. Of 62 pts enrolled based on a RET variant detected in a tumor sample, concordant RET alterations were detected in 41 (66%) of the corresponding pretreatment plasma samples, including 19/30 (63%) pts with RET-fusion positive plasma NGS results. Of 62 pts enrolled based on a RET variant detected in a tumor sample, concordant RET alterations were detected in 41 (66%) of the corresponding pretreatment plasma samples, including 19/30 (63%) pts with RET-fusion positive plasma NGS results. In RET alteration-negative pre-treatment samples, peak AF for other detected alterations was generally low (0.28% median), suggesting low tumor DNA shed into plasma. Of 34 pts with a detectable pre-treatment plasma RET alteration and day 15 plasma NGS, RET alteration AF decreased by a median of 96%, with complete clearance in 15 pts (44%). Day 15 plasma clearance was observed at multiple doses, and was more common in RET fusion-positive (67%) than RET-mutant (8%) pts. Data for additional pts will be updated at the time of presentation.

Conclusions: The rapid clearance of RET variants from plasma cfDNA on LOXO-292 supports its observed clinical activity across a range of doses, tumor types and RET alterations. NGS of plasma cfDNA can detect a range of targetable RET variants, though tumor genotyping remains critical if the initial plasma NGS is negative. Serial plasma genotyping warrants continued study as an early pharmacodynamic marker for novel targeted therapies.

Clinical trial identification: NCT03157128.

Legal entity responsible for the study: LOXO Oncology Inc.

Funding: LOXO Oncology Inc.


A prediction panel with DNA methylation biomarkers for lung adenocarcinoma

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Background: Lung adenocarcinoma accounts for more than 40% of lung cancer incidence. Thus, it is urgent to identify early-stage related markers. In this study, the effectiveness of CpG methylation on predicting lung adenocarcinoma was investigated.

Methods: In total, 1,170 patients with lung adenocarcinoma from four independent databases were included. One medical center was sorted into validation cohorts by a 75%:25% ratio. In the discovery phase, recursive feature elimination was performed to evaluate the importance of selected CpGs to classification model. In the validation phase, four candidate CpGs were validated using two cohorts (n = 382 and n = 10). To explore the potential biological function of selected CpGs, GO enrichment analysis was performed using the Database for Davidson version 6.8.

Results: After the selection of CpGs by the K-Means Clustering algorithm, 62 CpGs showed great different methylation profiles between lung adenocarcinomas and adja- cent nonmalignant lung tissue (p < 0.05). Among these selected CpGs, 95.16% were hypermethylated in the malignant samples comparing to only 4.84% were hypomethylated. With the evaluation of recursive feature elimination, four CpGs corresponding to H0X9A, KRTAP8-1, CCND1, and TULP2 were highlighted as candidate predictors in the training phase. The performance of these four candidate CpGs were validated in two validation cohorts (p < 0.01). These disparate hypermethylated genes were significantly enriched in GO biological processes including negative regulation of transcription from DNA polymerase II promoter, DNAtemplated transcription, while the hypomethylated gene was obviously enriched with the terms including adenylyl cyclase-activating G-protein coupled receptor signaling pathway. The direction of methylation did not affect the enrichments for our CpG sites.

Conclusions: A four-CpG-based signature, including HOX9A, KRTAP8-1, CCND1 and TULP2, is useful for the prediction of lung adenocarcinoma. Legal entity responsible for the study: Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University.

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Disclosure: All authors have declared no conflicts of interest.

A novel genomic classifier for early stage colorectal cancer patients

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Background: Identifying patients at risk of relapse in early colorectal cancer (CRC) stages is an unmet clinical need. Due to the limitations of clinicopathological variables in predicting individual risk of recurrence in CRC patients, genomic information has
increasingly gained prominence as a potential method for patient stratification. We have previously shown that Myosin Vb (MYO5B) expression alone or in combination with the expression of its adapter protein RAB8A shows strong prognostic value in early CRC patients.

**Background:** Immune checkpoint inhibitors have remarkably improved the natural history of patients (pts) with non-small cell lung cancer (NSCLC), with improved clinical responses and overall survival compared to standard therapy. However, over 80% of unselected NSCLC pts do not respond, highlighting the need of theranostic biomarkers. In previous reports, our results confirmed the association of baseline plasma albumin concentration with an elevated platelet activation, further supported by a 2-fold increase in soluble CD40 ligand was elevated in pts with reduced PFS, probably in relation with an elevated platelet activation, further supported by a 2-fold increase in plasma concentration of baseline platelet-derived growth factors (PDGFs) in these pts.

**Conclusions:** Our study identifies promising, predictive, immune-related biomarkers in NSCLC pts treated with PD-1 blockade.

**Funding:** Fondation de France, 3Department of Oncology, Institut Curie, Paris, France

**Legal entity responsible for the study:** Molecular Disease Mechanisms Group.

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 109P**

<table>
<thead>
<tr>
<th>Tumor subcohort</th>
<th>% of edPOLE mt (n/N)</th>
<th>Clinical and molecular profile of edPOLE mt pts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole cohort</strong></td>
<td>3.6 (9/245)</td>
<td>pMMR: 100% (9/9)</td>
</tr>
<tr>
<td>EC Endometrioid adenocarcinomas</td>
<td>Other histologies</td>
<td>6 (4/49) 13 (4/31) 0 (0/18)</td>
</tr>
<tr>
<td>CRC BRAF/KRAS/NRAS wt</td>
<td>p.V600E BRAF mt</td>
<td>2.6 (5/196) 0 (0/30) 0 (0/30)</td>
</tr>
<tr>
<td>Non p.V600E BRAF mt</td>
<td>Codons 12 or 13 KRAS</td>
<td>6 (3/49) 5 (1/20)</td>
</tr>
<tr>
<td>mt Non codons 12 or</td>
<td>13 KRAS mt Multiple</td>
<td>286 POLE 1 codon</td>
</tr>
<tr>
<td></td>
<td>BRAF/KRAS/NRAS mt</td>
<td>459 POLE</td>
</tr>
</tbody>
</table>

**Conclusions:** Our screening strategy identified edPOLEmt in 13% of endometrioid ADK and 2.6% of CRC. Pts selection on clinicopathological (histology for EC, young age, left colon or rectum), and molecular criterias (pMMR, unusual BRAF/KRAS/ NRAS mt) seem to increase the proportion of edPOLEmt. The use of these criteria in practice could help select patients for edPOLE screening. Additional clinicopathological and molecular data will be shown.

**Legal entity responsible for the study:** Anaïs Pujals.

**Disclosure:** All authors have declared no conflicts of interest.
Immune prognostic index (IPI) and hyper-progressive disease (HPD) in patients (pts) exposed to targeted agents (TAs) in phase I trials (Ph1T): Can lessons from immune checkpoint inhibitors (ICIs) be translated to other scenarios?

Methods: In pts enrolled in Ph1T with TAs.

Results: Median OS was 7.9 m [6.7-10], significantly different as per IPI score (IPI0 18 m [7.8-27.8] vs. 3.8 m [2.2-5.3]; p<0.001). Importantly, in pts with PD at first restaging and g2 mutations. Kaplan-Meyer survival curves were plotted and p-values computed.

Conclusions: We confirm, as reported in literature, that baseline LDH serum levels are inversely associated with response probability. It’s reasonable to jointly consider age and ECOG, which give a significant contribution to model performance. The developed algorithm, once validated on an independent prospective series, might be a base to guide physicians in clinical practice to better plan ICI therapy tailored on pts characteristics.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

111P Combination of baseline LDH, performance status and age to identify solid tumor patients with higher probability of response to anti-PD1 and PD-L1 monoclonal antibodies

Background: The advent of immune check point inhibitors (ICIs) has improved prognosis of various cancers. To better select responding patients (pts) and for a more accurate management of economic resources, biological and biochemical factors have been investigated. To date, no predictive biomarkers have been validated. The aim of this study is to identify manageable and routinely detectable parameters to use in clinical practice to select pts with higher change of response to ICIs.

Methods: 271 consecutive metastatic solid tumor pts treated in our Institute from 2013 to 2017 with ICIs were evaluated for baseline LDH serum level, ECOG score, age, type of ICIs, number of metastatic sites, histology and sex. A training and validation set were used to build and test models, respectively. Variables’ effects were assessed through odds ratio estimates (OR) and area under the receive operating characteristic curves (AUC), from univariate and multivariate logistic regression models. The validated estimates were used to develop an Excel algorithm to calculate probabilities of response.

Results: As best response, 55.4% of pts achieved disease control and 44.7% had progressive disease. On the training set, LDH, age and ECOG showed a significant OR (p < 0.001, 0.009, 0.042, respectively) and were combined in a multivariate model with an AUC of 0.771 (95%CI: 0.701-0.842). These results were statistically validated on the validation set (AUC: 0.685, 95%CI: 0.569-0.801). By fitting the validated model on all pts, the 3 variables retained a significant OR and a satisfactory cross-validated AUC.

Conclusions: We confirm, as reported in literature, that baseline LDH serum levels are inversely associated with response probability. It’s reasonable to jointly consider age and ECOG, which give a significant contribution to model performance. The developed algorithm, once validated on an independent prospective series, might be a base to guide physicians in clinical practice to better plan ICI therapy tailored on pts characteristics.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

111P Circulating exosomal integrin αv/β5 predicts liver metastasis and prognosis in human colorectal cancer

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Background: Ever since the “seed-and-soil” hypothesis, the mechanism of cancer metastatic organosperm is still an unresolved mystery. In colorectal cancer (CRC), there is still no robust metastasis predictive biomarkers for distant organ metastasis, which is the most common cause of deaths. In spite of the function of exosome in RNA and...
protein delivery, its clinical significance in CRC metastasis remains uncertain. Here, we evaluated the potential role of serum exosome integrin in CRC metastasis.

**Methods:** Tissue integrin α5β1 was quantified by quantitative reverse-transcription PCR in 31 pairs of primary CRC and corresponding matched liver metastasis (LM), with non-LM as control. Serum exosomal integrin α5β1 was accessed by ELISA in 126 CRC patients with LM and 166 CRC patients without, as well as when LM was diagnosed in these 166 patients in exploratory cohort. In prospective validation cohort, serum exosomal integrin α5β1 was investigated in 135 initially diagnosed CRC patients without metastasis. CRC-associated metastasis mouse models were established to verify the role of serum exosomal integrin α5β1.

**Results:** Integrin α5β1 level in LM was significantly increased compared with that in non-LM, which was correlated with its expression in primary CRC. Serum exosomal integrin α5β1 was significantly increased in CRC patients with LM than those without, in a TNM stage-dependent manner. Moreover, it was found that serum exosomal integrin α5β1 in CRC patients was significantly upregulated when LM occurred and associated with unfavorable survival. In validation cohort, increased serum exosomal integrin α5β1 indicated higher risk of LM and unfavorable prognosis. Serum exosomal integrin α5β1 was significantly increased in mice with LM compared with controls.

**Conclusions:** Our clinical and animal model data indicate that increased levels of serum integrin α5β1 associate with CRC LM and unfavorable survival. These results suggested that circulating integrin α5β1 could be a promising non-invasive predictor for CRC LM and prognosis.

**Legal entity responsible for the study:** Xi’an Jiaotong University.

**Funding:** NSF.

**Disclosure:** All authors have declared no conflicts of interest.

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**114P** Circulating and tumor-associated caspase-4: A novel diagnostic and prognostic biomarker for non-small cell lung cancer patients?

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**Background:** Late diagnosis limits therapeutic options and survival rate of non-small cell lung cancer (NSCLC) patients. Therefore, the identification of biomarkers represents an urgent need.

**Methods:** A highly sensitive and specific ELISA test was developed to identify/quantify a novel/selected diagnostic biomarker for NSCLC patients, caspase-4, which was detected into the plasma and tissues of NSCLC patients. This test was validated by using plasma from 125 NSCLC patients and 79 healthy (non-pathological) subjects. Caspase-4 quantification was also assessed in the lung tumor mass of 98 paired-matched NSCLC patients compared to 10 non-tumor lung tissues (i.e. tuberculosis).

**Results:** Circulating caspase-4 was detected in both healthy and NSCLC patients; however, at different range values: 2.603–3.372 ng/ml for NSCLC patients (95% CI) compared to 0.3994–0.6219 ng/ml for healthy subjects (95% CI). The sensitivity of the test ranged from 97.07% to 100%; the specificity was 88.1% with a positive predictive value of 92.54%, accuracy of 95.19% and AUC of 0.981. Tissue levels of caspase-4 in the tumor mass showed that 72 (72.7%) out of 99 patients were positive. More importantly, higher levels (cut-off value = 0.307 ng/ml) of caspase-4 in the tumor mass were associated to reduced overall survival (median 0.92 years) compared to NSCLC patients with lower levels (median 3.02 years).

**Conclusions:** We report for the first time caspase-4 as a novel diagnostic and prognostic biomarker, opening new therapeutic perspectives for NSCLC patients.

**Legal entity responsible for the study:** ImmunePharma srl.

**Funding:** ImmunePharma srl.

**Disclosure:** All authors have declared no conflicts of interest.

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**116P** Genomic characteristics of standardized uptake value of 18F-fluorodeoxy-glucose positron emission tomography in breast cancer

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**Background:** Standardized uptake value (SUV), an indicator of the glucose uptake degree in 18F-fluorodeoxy-glucose positron emission tomography (FDG-PET), has been used as a prognostic factor in various malignant tumors. The aim of this study is to identify a molecular signature reflecting prognostic SUV characteristics in breast cancer (BCR).

**Methods:** We sought to identify a molecular signature associated with SUV by a gene expression profiling using a dataset obtained from 60 BCRs who underwent preoperative FDG-PET. The prognostic value of the signature was verified in three BCR cohorts including TCGA dataset (n = 1,616). Various statistical methods, including log-rank and Cox regression analyses, were applied to estimate an association between the signature and BCR prognosis. To compare somatic variants between two patient subgroups divided by the signature, we obtained predefined gene sets involved in oncogenic or metastatic pathways and estimated a difference of their mutation frequencies between subgroups in the TCGA cohort.

**Results:** By a gene expression profiling, we defined a signature, namely SUV signature, consisting of 723 genes significantly associated with SUV (Pearson correlation test, |r| > 0.35, p < 0.001). The patient subgroups classified by the signature (i.e., SUV-high-cluster and SUV-low-cluster) were significantly similar with patient classification by SUV [Fisher exact test, odds ratio 8.02, 95% confidence interval (CI) = 2.45-29.3, p < 0.001]. When estimating prognostic value of the SUV signature in three cohorts, the signature showed a strong prediction ability (log-rank tests, each p < 0.05) and an independent clinical utility (multivariate Cox regression model, hazard ratio = 1.51, 95% CI = 1.07-2.22, p = 0.01) in BCR prognosis. Gene network and mutation analyses revealed that a signaling defined by TP53-FOXN1 and its downstream effectors involved in glycolysis-glucagonogenesis might be important mediators in FDG-PET operation.

**Conclusions:** Our results uncover genomic and metabolomic characteristics of glucose uptake captured by FDG-PET, supporting an understanding of glucose metabolism as well as a poor prognosis in BCR patients with high SUV.

**Legal entity responsible for the study:** Korea Research Institute of Bioscience and Biotechnology Gananam Severance Hospital.

**Funding:** Korea Research Institute of Bioscience and Biotechnology.

**Disclosure:** All authors have declared no conflicts of interest.

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**117P** Characterization of PD-L1, CD8, CD3, CD68 and PanCK in tumor microenvironment of GI tract tumors with respect to patients’ mismatch repair deficiency and anti-PD-1 treatment outcome using SPlex IHC and whole slide image analysis

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**Background:** Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. However, not all patients with mismatch repair deficiency respond to the PD-1 blockade treatment. To understand the different responses, we evaluated tumor
Exhaustion of platelet kinetics and its implication in post-resection HCC recurrence

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Background: Platelet activation and the release of various growth factors from platelet micro-environment such as PD-L1 expression in relationship with tumor infiltrating immune cells.

Methods: FL multiplex IHC for PD-L1, CD8, CD3, CD68, and pan-cytokeratin (panCK) on Benchmark ULTRA instrument stained 54 pre-pembrolizumab treatment patient resection and biopsy specimens including pancreatic, colorectal and cholangiocarcinoma. 17 are mismatch-repair proficient (13 PD, 3 SD and 1 CR) and 37 deficient (5 PD, 10 SD, 9 CR, and 13 PR).

Results: Random forest modelling, logistic regression and Relief feature selection followed by quadrant discriminant analysis were used to assess the relationship of multiple IHC reads in relationship to anti-PD-1 treatment responses. Different groupings were used, e.g. PR + CR vs. SD and PD, and PR + CR + SD vs. PD. Fraction of PD-L1+ macrophages and fraction of PD-L1+ ‘helper’ cells in tumor regions, stroma, and epithelial tumor were identified most important features. Mps IHC achieves 89% accuracy over 70% with mismatch repair status alone.

Conclusions: Multiplex IHC together with automated image analysis provides a tool to evaluate multiple biomarkers and their special relationships in the tumor micro-environment. In a cohort of 54 patient specimens, exploratory analysis of multiple IHC data suggests that the knowledge of PD-L1 expression on various immune cells phenotype aids in better predicting response to anti-PD-1 therapy compared to mismatch repair status alone.

Legal entity responsible for the study: Roche Diagnostics/VENTANA Medical Systems, Inc.

Funding: Roche Diagnostics/VENTANA Medical Systems, Inc.

**121P** LungBEAM: A prospective multicenter trial to monitor EGFR mutations using BEAMing technology in stage IV NSCLC patients


**Background:** Liquid biopsy is a promising approach to improve the management of NSCLC patients, as it offers a minimally-invasive alternative to tumor tissue testing, and enables timely monitoring of patients on therapy. The goal of the present study was to evaluate the clinical value of longitudinal testing of EGFR mutation status in plasma of tissue EGFR mutation-positive NSCLC patients during first-line EGFR TKI therapy across 19 Spanish hospitals to: 1) determine the timing of T790M mutation emergence and 2) monitor EGFR mutation levels in plasma during first-line EGFR TKI therapy with respect to radiological progression.

**Methods:** Blood samples from 109 therapy-naïve advanced NSCLC patients were collected at baseline and monthly throughout EGFR TKI standard therapy. Results from OncoBEAM EGFR mutation were performed by Sysmex in Hamburg, and compared to those obtained by the EGFR tissue testing obtained at the referring hospital. The times at which T790M were first detected in blood were compared to the date of progression as determined by radiological imaging in standard clinical practice.

**Results:** At baseline, the initial positive percent agreement (PPA) for EGFR mutation status in 78 out of 109 patients enrolled in this study was 71.6%. From a total of 60 patients out of 89 who completed the study showing either clinical or radiological progression, 20 patients (33.3%) showed presence of the T790M mutation in plasma during follow-up. In 13 of these patients plasma T790M positivity was detected an average of 34 weeks prior to radiological progression. Furthermore, the clearance of EGFR mutations in plasma at 8 weeks after initiation of EGFR TKI was a favorable indicator for PFS (37.3 weeks with clearance vs 25.5 weeks in patients without clearance). Patients showing EGFR mutation clearance at 8 weeks had an average baseline MAF of 3.6%, whereas patients with detectable mutations at 8 weeks showed an average baseline value of 15% MAF.

**Conclusions:** Overall, these results show high PPA of plasma and tissue EGFR mutation status at baseline. Early EGFR mutation clearance may be predictive of response to first-line EGFR TKI therapy. Plasma detection of T790M mutation anticipates clinical progression.

**Clinical trial identification:** SYS-ONC-2015-01.

**Legal entity responsible for the study:** Sysmex Inostics GmbH.

**Funding:** Sysmex Inostics GmbH.

**Disclosure:** All authors have declared no conflicts of interest.

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**122P** Immune checkpoints and liver resection after neoadjuvant chemotherapy including bevacizumab in patients with colorectal liver metastases

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**Background:** Liver resection after neoadjuvant chemotherapy including bevacizumab offers the possibility of cure in patients with colorectal liver metastases. The clinical value of immune checkpoint expression as prognostic biomarker is unclear.

**Methods:** Expression analyses of IDO-1, PD-L1 and CTLA-4 were performed by immunohistochemistry in resected colorectal liver metastases in patients who underwent liver resection after neoadjuvant chemotherapy including bevacizumab (2005–2011). Association of expression of immune checkpoints in tumor cells and immune cells with response, RFS and OS was investigated.

**Results:** One hundred forty-six patients were enrolled (88 [60.3%] male/58 [39.7%] female, median age 63.0 years [31.0–80.4]). High expression of CTLA-4 in tumor cells was associated with shorter OS (median OS 48.2 months versus not reached, HR 2.04, P = 0.028). High expression of IDO-1 and PD-L1 in immune cells was associated with longer OS (not reached versus 47.1 months, HR 0.43, P = 0.016 and not reached versus 47.1 months, HR 0.41, P = 0.037). Results of IDO-1 remained significant in multivariable analysis (HR 0.29, P = 0.086). Low expression of CTLA-4 in tumor cells was associated with better histologic response (26 major, 19 partial, 18 none versus 14 major, 23 partial, 30 none, P = 0.032). No association of expression was found with RFS and radiologic response.

**Conclusions:** The clinical meaning of immune checkpoint expression and its association with response and survival were dependent on the expressing cell types. IDO-1 and CTLA-4 may be new prognostic and/or predictive biomarkers in patients with colorectal liver metastases. The role of immune checkpoint inhibitors in a multidisciplinary treatment approach remains to be elucidated.

**Legal entity responsible for the study:** Stefan Sterenborg.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**123P** Gene expression (GE)-based biomarkers associated with nivolumab response in a real-life cohort of patients with metastatic non-small cell lung cancer (mNSCLC)

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**Background:** Robust and versatile biomarkers are urgently needed to identify cancer pts who are likely to benefit from immune checkpoint inhibitors (ICI). The Tumor Inflammation Signature (TIS) is an 18-gene signature measuring the suppressed adaptive immune response necessary for pts clinical benefit from ICI (Ayers, J Clin Invest 2017). This retrospective study evaluated the performance of TIS and additional GE signatures assessing pathways associated with immune evasion in mNSCLC pts, treated with nivolumab as per label (2nd line), in two French cancer centers.

**Methods:** RNA from primary FFPE tumor samples from 77 immunotherapy-naive mNSCLC pts, treated with nivolumab monotherapy, was profiled with a β-version of the NanoString® nCard 360 GE panel, which includes the TIS and other tumor and immune biology signatures. The statistical analysis treated associations of GE and clinical response.

**Results:** In the whole cohort analysis, samples from pts who experienced clinical benefit showed an “inflamed” phenotype. Specifically, TIS was significantly higher in the responder group compared to non-responders (p = 0.005, non-adjusted). A similar association was observed for myeloid and macrophage scores (p = 0.001 and p = 0.002, respectively) as well as for PD1C31 (PD1), CD274 (PDL1) and CTLA4 (p = 0.05, 0.001, 0.02, resp.). In a subtype analysis, squamous carcinomas showed a less inflamed phenotype than adenocarcinomas but had elevated proliferation, glycolysis and hypoxia scores, as well as increased ARG1 and NOS2. In contrast, in the independent subtype analysis, both TIS and additional immune signatures remained associated with clinical response.

**Conclusions:** TIS and other immune signatures predicted response to nivolumab single agent in a real-life cohort of pts, in both adenocarcinoma and squamous mNSCLC. Thus, assessing GE patterns can give insight into different immune evasion operat- ing at the single patient level. Additional analyses of this cohort, evaluating the
Table: 124P

<table>
<thead>
<tr>
<th>RAS wt</th>
<th>RAS mut</th>
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<tbody>
<tr>
<td>low miR-21 (n = 166)</td>
<td>high miR-21 (n = 167)</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>OS (months)</td>
</tr>
<tr>
<td>10.6 vs. 10.3</td>
<td>35.8 vs. 25.9</td>
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<tr>
<td>p = 0.3</td>
<td>p = 0.005</td>
</tr>
<tr>
<td>10.1 vs. 9.9</td>
<td>24.5 vs. 23.8</td>
</tr>
<tr>
<td>p = 0.3</td>
<td>p = 0.4</td>
</tr>
<tr>
<td>85. vs. 12.2</td>
<td>202 vs. 26.0</td>
</tr>
<tr>
<td>p = 0.04</td>
<td>p = 0.0</td>
</tr>
</tbody>
</table>

Conclusions: Along with RAS status, miR-21 expression level may be a promising predictive biomarker for anti-EGFR therapy.
Simultaneous identification and profiling of tumor-specific T cells by mass cytometry

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Background: immunoSCAPE leverages the high-dimensional immune profiling capabilities of mass cytometry combined with a unique technology for the identification of antigen-specific T-cells to support the development of immunotherapy strategies in cancer and immune-related diseases. In cancer, there is now strong evidence that immunotherapy-mediated tumor rejection can rely on tumor-specific (neoadjuvant-specific) CD8+ T-cells. Consequently, the discovery of neoantigens becomes valuable for personalized cancer immunotherapies. Although in silico pipelines exist, that are capable of predicting non-synonymous mutations potentially gaining rise to tumor-specific neoantigens, it is not clear how accurate these methods are in identifying immunogenic and therapeutically relevant epitopes, since T-cell epitope usage can be influenced by many factors. Moreover, analysis of T-cells in cancer patients is challenging as it requires detecting rare antigen-specific T-cell populations in samples that are usually limited in volume and availability.

Methods: By applying cytometry by time of flight in conjunction with combinatorial peptide–MHC tetramer staining and high-performance dimensional analysis tools, we are able to map broadly MHC-I-class I epitope with a high sensitivity for rare antigen-specific T-cells and perform concurrently in-depth characterization of these cells.

Results: We will show here the application of this technology in the context of immunotherapy, through the example of a murine in vivo tumor model responsive to checkpoint blockade inhibitors, as well as through the analysis of different human cancer samples.

Conclusions: Together, by providing insights into the nature of neoantigen-specific T-cells, immunoSCAPE’s unique target discovery and high-dimensional immune profiling platform is a valuable tool for the development of novel diagnostic biomarkers and therapeutic strategies at different stages of drug development.

Legal entity responsible for the study: A*STAR / Singapore Immunology Network and immunoSCAPE.

Funding: immunoSCAPE.

Disclosure: E. Newell: Board director and shareholder: immunoSCAPE. Pte. Ltd. All other authors have declared no conflicts of interest.

Over-expression of S100B protein as a serum marker of brain metastasis in non-small cell lung cancer and its prognostic value

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Background: Validated serum biomarkers for patients suffering from non-small cell lung cancer (NSCLC) brain metastasis are urgently needed for early diagnosis, treatment monitoring, and prognostic classification in daily clinical practice and trials. Serum S100B was reported to be a marker of leaky blood-brain barrier (BBB), which was often caused by brain tumors. This study aimed to investigate the role of S100B and S100B antibody in the early detection of NSCLC brain metastasis and the prognostic significance.

Methods: 100 patients with NSCLC brain metastasis, 50 patients of stage IV NSCLC without brain metastasis, and 50 patients with cerebrovascular diseases were enrolled in this prospective study. S100B and S100B antibody were measured in serum samples of all patients before and after treatment by ELISA, and the correlations with brain metastasis were assessed by ANOVA. Kaplan-Meier survival analyses and COX regression were used to unveil the prognostic significance.

Results: The results showed that serum S100B correlated significantly with NSCLC brain metastasis (p < 0.001), but not S100B antibody (p > 0.05). When evaluated by the ROC curve, at the cut-off point 13.83 pg/ml, the sensitivity and specificity were 94% and 93%, respectively (AUC = 0.938, p < 0.001). The PFS and OS of NSCLC patients with brain metastasis were significantly shorter in the patients with high levels of serum S100B. In addition, S100B was an independent prognostic factor.

Conclusions: In conclusion, serum S100B was a sensitive and specific marker for early detection of brain metastasis in NSCLC and could be used as a surveillance tool for prognostic evaluation.

Legal entity responsible for the study: Affiliated Cancer Hospital of Zhengzhou University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Pre-diagnostic measurements of high-sensitive C-reactive protein and risk of prostate cancer: The PROCA-life study

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Background: Inflammation may promote prostate cancer development, which can be characterized by elevated circulating levels of inflammation markers, such as high-sensitive C-reactive protein (hs-CRP). Whether pre-diagnostic measurements of hs-CRP are associated with prostate cancer remains unknown.

Methods: In the Prostate Cancer Study throughout lifetime (PROCA-life), a total of 11,064 initially healthy men, who participated in the Tromsø Study between 1994 and 2008,
were included. Pre-diagnostic hs-CRP was assessed and height and weight were measured at study entry. During a mean follow-up time of 14.2 years, a total of 459 men developed histological verified prostate cancer and detailed medical and histological records were obtained.

Results: At study entry, the cohort participants had a mean age of 60.5, mean level of hs-CRP of 2.18 mg/l and a mean body mass index (BMI) of 25.8 kg/m². The 459 prostate cancer cases identified had a mean age at diagnosis of 72.0 years. Among normal weight men (BMI < 25 kg/m²), we observed a positive linear relationship between pre-diagnostic hs-CRP levels and prostate cancer risk after adjustments, both when using single and repeated measurements of hs-CRP, with hazard ratio 1.09 (95% CI 1.01-1.16), respectively. This relationship was not present in the overweight (BMI 25-30 kg/m²) or obese (BMI >30 kg/m²) group.

Conclusions: Our study supports the hypothesis that inflammation may play a role in prostate cancer development, but this association may vary by body composition.

Legal entity responsible for the study: University of Tromsø.

Disclosure: All authors have declared no conflicts of interest.

130P
Training and validation of a gene expression signature for microsatellite instability
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Background: Clinical response to cancer immunotherapy can be predicted from two biologically distinct variables: tumor foreignness, manifested in some tumors as deficient DNA mismatch repair (dMMR)/microsatellite instability (MSI), typically measured by qPCR or IHC, and anti-tumor immunity, typically measured by gene expression signatures or IHC. Clinical benefit should be more accurately predicted by the combination of the two variables than by either alone, but measuring both variables requires multi- and clinical assays. Here, we investigate the ability of gene expression alone to provide a surrogate measure of both tumor foreignness and immunogenicity, empowering a single assay to measure both axes of predictive biology. In addition, we explore the relationships between tumor foreignness and immunogenicity in both dMMR and MMR-proficient (pMMR) tumors.

Methods: Using TCGA datasets from colon, esophageal, stomach and uterine cancers, we trained two algorithms predicting hypermutation: the first detecting loss of expression of mismatch repair genes (MLH1, MSH2, MSH6 and PMS2) and the second identifying expression patterns shared by hypermutated tumors across these four cancer types. A final algorithm synthesizes the two above algorithms into a single score. For independent validation, we evaluated 60 colorectal cancer (CRC) FFPE samples, 30 dMMR and 30 pMMR as previously identified by IHC, and a cohort of 10 MSI and 5 MSI endometrial and neuroendocrine tumors with the NanoString nCounter® platform.

Results: We show that our algorithms successfully predicted hypermutation phenotypes and MMR status in TCGA training data and in the independent CRC and endometrial datasets analyzed with NanoString, with an AUROC of 0.94. Additionally, we demonstrate that higher mutational burden is linked to a heightened tumor immune environment as shown by adaptive immune gene signatures.

Conclusions: Gene expression proves to be a powerful predictor of microsatellite instability and hypermutation in cancers where dMMR subtypes are known to exist. This discovery raises the possibility that a gene expression algorithm measuring both hypermutation and immune activity may be advantageous in predicting response to checkpoint inhibitors in these cancer types.

Legal entity responsible for the study: NanoString Technologies.

Funding: NanoString Technologies.


131P
Development and analytical validation of a plasma-based tumor mutational burden (TMB) score from next-generation sequencing panels
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Background: The advantages of plasma-based tumor mutational burden (TMB) include non-invasive, real-time assessment of mutational load, without the limitations of insufficient tissue. However, at low levels of tumor DNA shedding, TMB may be underestimated if a fraction of the genomic alterations is below assay limit of detection. Currently available blood TMB panels report a 1% tumor content limit of detection, which would result in about half of all clinical plasma samples (based on > 30,000 patients) with unvaluable TMB. Hence, clinically effective blood-based diagnostics must be highly sensitive and account for tumor shedding. Here, we present a comprehensive cDNA-based TMB using a 500-gene (GuardantOMNI) and a 73-gene (Guardant360) panel.

Methods: We developed a statistical model to calculate TMB on plasma samples with low cell-free circulating tumor DNA (ctDNA) content. Theoretical panel performance was assessed in silico by subsampling mutations from whole exome sequencing (WS) to the Guardant panel space (2Mb for GuardantOMNI and 200Kb for Guardant360) from 9,104 TCGA samples and 30 lung cancer samples with published immunotherapy outcomes. Sensitivity was evaluated using 50 serially diluted cDNA specimens. Analytical validation was performed against tissue-based WES TMB using matched plasma and tissue samples across multiple tumor types.

Results: High correlation was observed between TMB called on the Guardant panel and WS mutations from the TCGA dataset (τ = 0.99 with GuardantOMNI, τ = 0.92 with Guardant360). Subsetting WS from clinical outcome cohorts to each panel recapitulated the association with PFS on immunotherapy (HR = 0.41 with GuardantOMNI, HR = 0.27 with Guardant360). The sensitivity of detection was assessed down to 0.3% tumor content and 5ng ctDNA input. Lastly, we show high quantitative concordance between matched plasma and tissue WS samples for both GuardantOMNI and Guardant360.

Conclusions: We describe a plasma-based TMB score that correlates with tissue-derived TMB at tumor fractions down to 0.3%, enabling TMB calculation on > 70% of all clinical samples. Accurate reporting of TMB from a plasma sample has the potential to accelerate clinical trial enrollment and improve outcomes.

Legal entity responsible for the study: Guardant Health, Inc.

Funding: Guardant Health, Inc.


132P
Carbohydrate antigen 19-9 and apolipoprotein A2 Isoform as early detection biomarkers for pancreatic cancer: A prospective evaluation by the EPIC study
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Background: This study prospectively evaluated the performance of an apoprotein A2 isoform (ApoA2-ATQ/AT) in combination with carbohydrate antigen 19-9 (CA19-9) as early detection biomarkers for pancreatic cancer.

Methods: Using ELISA, we measured CA19-9 and ApoA2-ATQ/AT in plasma samples collected ≤60 months before diagnosis from 159 pancreatic cancer patients and 217 matched controls within the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort. The diagnostic sensitivity, specificity, and C-statistics were calculated for risk scores by strata of the time before diagnosis.

Results: The C-statistics of CA19-9 and CA19-9 + ApoA2-ATQ/AT for distinguishing pancreatic cancer patients from cancer-free individuals were 0.87 and 0.68, respectively, for samples taken ≤6 months before diagnosis, and 0.74 and 0.72, respectively, for samples taken >6 to 18 months before diagnosis. The joint diagnostic model using CA19-9 + ApoA2-ATQ/AT showed significantly improved diagnostic discrimination in samples taken ≤18 months before diagnosis. Before diagnosis, the specificity of CA19-9 + ApoA2-ATQ/AT was 98%, while the sensitivities of CA19-9 + ApoA2-ATQ/AT were 57%, 36%, and 43%, respectively, and those of CA19-9 alone were 30%, 29%, and 36%, respectively. This joint model also showed significantly improved C-statistics for the diagnostic discrimination of samples taken >6 to 18 months (0.80 for CA19-9 + ApoA2-ATQ/AT, 0.74 for CA19-9, p = 0.004) and >18 months (0.8 for CA19-9 + ApoA2-ATQ/AT, 0.78 for CA19-9, p = 0.003) before diagnosis.

Conclusions: Compared to CA19-9 alone, CA19-9 + ApoA2-ATQ/AT showed improved diagnostic discrimination for early detection ≤18 months before diagnosis. This plasma biomarker panel may provide a useful first measure for detecting pancreatic cancer prior to imaging. We have reported those results on behalf of the EPIC Europe.

Legal entity responsible for the study: National Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Sarcopenia is associated with poor prognosis in cancer pts and inflammation has been recognized as a hallmark of cancer. In this study, we investigated the synergistic effect of sarcopenia and inflammation on survival in advanced stage cancer pts treated with IO.

Methods: We performed a retrospective analysis of 98 pts treated on IO-based phase 1 clinical trials at Winship Cancer Institute of Emory University from 2009-2017. CT images at mid L3 were obtained at baseline. Skeletal muscle density was obtained using SliceOmatic v5.0 by Tomovision and converted to skeletal muscle index (SMI) by dividing by height². We defined sarcopenia as SMI <39. Neutrophil-to-lymphocyte ratio (NLR) was obtained at baseline and used as a surrogate of inflammation. Pts were categorized based on recursive partitioning methods into three groups: (1) low NLR, (2) high NLR without sarcopenia, (3) high NLR with sarcopenia. Overall survival (OS) and progression-free survival (PFS) were measured from date of first dose of IO to date of death or clinical or radiographic progression, respectively. Multivariable analysis and diagnosis methods related thereto”; Research funding: Novartis, Astellas Pharma, Celgene, Bayer, Stem CentRx, Regeneron, AstraZeneca/MedImmune; Travel, accommodations: EMD Serono, Pfizer, and AstraZeneca. T.K. has received lecture fees from AstraZeneca, Bayer, and Takeda; Travel, accommodations: EMD Serono, Pfizer, and AstraZeneca. T.K. Owoникoko: Consulting/advisory role: Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, and MedImmune; Intellectual property of the following: “Overcoming acquired resistance to chemotherapy treatments through suppression of STAT3” and “Selective chemotherapy treatments and diagnostic methods related thereto”; Research funding: Novartis, Astellas Pharma, Celgene, Bayer, AtoMedentRx, Regeneron, AstraZeneca/MedImmune, Abbvie, G1 Therapeutics, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Conclusions: Sarcopenia may have a synergistic effect with inflammation on decreasing survival in pts treated with IO. Prospective validation of the impact of body composition parameters on survival and whether adipose tissue plays a role in the relationship may be warranted. Equal contribution: MAB, DJM, JMS.

Table: 133P Univariable analysis (UVA) and MVA† of inflammation and sarcopenia with survival

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>HR (CI)</th>
<th>p-value</th>
<th>N</th>
<th>HR (CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group 1: NLR &lt;2.9</td>
<td>243 (10.3, 44.8)</td>
<td>36 – –</td>
<td>36 – –</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2: NLR ≥2.9, SMI ≥39</td>
<td>94 (5.5, NA)</td>
<td>33 2.65 (1.22-5.72) 0.013*</td>
<td>33 2.08 (0.90-4.77) 0.085</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group 3: NLR ≥2.9, SMI &lt;39</td>
<td>3.8 (2.8, 5.9)</td>
<td>21 8.40 (3.47-20.31) &lt;0.001*</td>
<td>21 7.93 (3.19-19.73) &lt;0.001*</td>
<td></td>
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<tr>
<td>PFS</td>
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<tr>
<td>Group 1: NLR &lt;2.9</td>
<td>4 (2.5, 5.4)</td>
<td>36 – –</td>
<td>36 – –</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2: NLR ≥2.9, SMI ≥39</td>
<td>2.8 (1.6, 4.1)</td>
<td>33 1.62 (0.95-2.79) 0.078</td>
<td>33 1.35 (0.77-2.39) 0.298</td>
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</tr>
<tr>
<td>Group 3: NLR ≥2.9, SMI &lt;39</td>
<td>1.6 (1.2, 1.8)</td>
<td>21 4.16 (2.26-6.76) &lt;0.001*</td>
<td>21 4.37 (2.26-8.48) &lt;0.001*</td>
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</tbody>
</table>

*The multivariable model was built by controlling for gender, checkpoint indication, # of previous treatment lines, royal marden hospital (RMH) risk group, age, ECOG PS, race, # of metastatic sites, and histology. *statistical significance at alpha < 0.05.

134P Prediction of irAEs in ipilimumab-treated melanoma patients based on serum autoantibodies

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Background: Checkpoint inhibition is an effective treatment in patients with meta-

stasis melanoma (MM). T cell activation can induce tumor rejection but also possibly severe autoimmune side effects (irAE). Autoantibody biomarkers from serum have potential to predict irAEs such as an ipilimumab-induced colitis.

Methods: We use a cancer immunotherapy array consisting of 850 human protein anti-

gens from 4 classes: 1. Tumor-associated antigens (TAA), 2. cancer pathway proteins, 3. autoimmunome antigens, 4. cytokines/interleukins. Protein antigens were covalently coupled to magnetic beads and serum AAs were analyzed by Luminesex FlexMap 3D. First, we screened pre-immunotherapy sera from 142 patients with MM (Heidelberg Cohort: 82 ipilimumab (Ipi) treated; 11 Ipi/Nivolumab (Nivo); 40 Pembrolizumab (Pembro), 119 healthy controls (HC)). In this cohort, 41.9% (n = 59) experienced irAEs of any grade and 7% (n = 10) had colitis of grade 3 or 4. In a second study, 200 MM patients from 5 European sites (53 Ipi/Nivo; 111 Pembro, 100 HC) were ana-

lyzed. 25.6% (n = 42) had grade 3 or 4 irAEs, 12.8% (n = 21) had diarrhea or colitis of any grade and 9.8% (n = 16) had grade 3 or 4 colitis.

Results: 40 different AAs were significantly more prevalent in MM compared to HC including NY-ESO, NY-ESO 2 and other TAs, cytokines, and nuclear proteins. Significant correlations of AAs were seen in Ipi-treated patients who experienced irAEs, both in mono- but also in combination therapy, allowing to dichotomize MM in risk groups. Also different sets of AAs were seen in Pembro-treated patients with irAEs. The protein antigens represent a variety of biological processes: they are involved in melanoma progression including transcription factors or components of the E3 ubiquitin ligase complex, cytokeratins, and proteins involved in cell adhesion.

Conclusions: In MM, screening of AAs prior to start of Checkpoint inhibition holds potential to predict for irAEs such as colitis. As irAEs are especially frequent in Ipi-

based treatment regimes, AAs presented here may serve as useful biomarkers for a risk-based treatment decision.

Legal entity responsible for the study: Jessica C. Hassel and Protagen AG.

Funding: Protagen AG.
Combined tumor-based BRCA/TP53 mutation testing in ovarian cancer

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Background: Somatic or germline BRCA mutations remain the best predictive biomarker for PARP inhibitor benefit and > 95% of high grade serous ovarian cancers (HGSOC) have BRCAm or TP53m mutation. Combined BRCA/TP53 tumor testing may provide the advantages of i) rapid results, ii) identification of somatic BRCAm, and iii) indirect evidence of the 2nd hit event, i.e. loss of heterozygosity (LOH).

Methods: Between 1/1/2016 and 1/2/2018 182 pts with HGOC underwent BRCA/ TP53 testing with a capture NGS panel and were oriented to a germline BRCA/ TP53 testing via a dedicated genetics consultation. The ratio of allelic fractions (AF) for BRCAm/TP53m was calculated to estimate the proportion of cells carrying the BRCAm and derive LOH.

Results: At the time of data cut-off, gBRCA results were available for 125/182, and still pending for 61. 15/125 (12%) demonstrated a deleterious (DEL) BRCA1m (N = 12) or gBRCA2m (N = 5). Tumor testing was performed on 182 with a median testing turn-around time of 16 days (range 7-539 days). Twenty-seven (15%) were non-contributive. Among 155 contributive tumor samples, 31 DEL BRCAm (21%) were identified. All gBRCAm (15/15) were identified on tumor testing including one large re-arrangement. 16 additional DEL BRCA1m or BRCA2m were detected: 10 somatic BRCAm in pts with confirmed wild-type (WT) germline status, and 6 among pts with pending germline results. Median TP53m AF was 0.48 (range 0.012-0.92) confirming a huge variability in tumor cellularity among samples. Among gBRCAm cases, ratio AF BRCAm/TP53m was always $\geq 1$ confirming germline origin and suggesting LOH. AF BRCA1m/TP53m was lower among known sBRCAm cancers (median AF (BRCA1m/TP53m) 0.11) but always $\geq 0.8$ suggesting acquired BRCA1 mutation was present and associated with LOH. For 3 gBRCA WT samples with $\leq 10$% tumor cellularity and very low DEL BRCA1m AF (0.04, 0.04 and 0.03), TP53m AF were also $< 0.05$, thus validating the somatic BRCAm.

Conclusions: Combined BRCA/TP53 tumor testing is fast, sensitive and identifies somatic BRCA mutations. In addition, information on TP53 AF is useful to validate $\leq 10$% neoplastic cells, identify somatic BRCA1m in low cellularity samples and provides indirect evidence for LOH as the 2nd hit.

Legal entity responsible for the study: Alexandra Leary.

Funding: Has not received any funding.

Background: PIK3CA is mutated in up to 20% of HER2 positive breast cancers, contributes to HER-2 therapy resistance and may be predictive of response to PI3K inhibition therapy. PIK3CA mutations in breast cancer occur primarily at hotspots E545K at a large proportion of a cohort of patients with HER2 therapy resistant advanced breast cancer, is the isoform encoded by the PIK3CA gene. The aim of this study was to assess PIK3CA mutation status in matched tumour and plasma samples pre copanlisib treatment and to monitor PIK3CA mutation concentration changes in plasma over the course of PIK3 inhibition therapy. Methods: For 12 patients with advanced HER2 positive, breast cancer treated on a clinical trial of copanlisib and trastuzumab, we prospectively examined serial plasma samples to quantify the PIK3CA hotspot mutations in circulating tumour DNA by droplet digital PCR (ddPCR). Samples were pre-treatment, then every two weeks on treatment and immediately after radiological disease progression. Archival formalin fixed paraffin embedded (FFPE) primary tumour tissue were examined using MassArray to detect PIK3CA mutation. Results: PIK3CA mutations were detected in 6/12 (50%) archival FFPE primary tumours; either an exon 9 (n = 2) or exon 20 (n = 4), all of which were also oestrogen receptor positive and had at least one prior line of anti Her2 therapy in the advanced cancer setting. There were 106 plasma samples included in the mutation analysis. PIK3CA mutation (H1047R or E454K) >500copies/ml were detected in 66% (70/106) of the samples. Of the six tumour samples that had no PIK3CA mutation detected, three had >5000copies/ ml (range: 0-25,900copies/ml) of mutated PIK3CA detected in serial plasma samples. Variations in plasma DNA mutation levels over time were found in all 12 patients. Conclusions: Our data demonstrate that PIK3CA mutation is detectable in the plasma of a large proportion of a cohort of patients with HER2 therapy resistant advanced breast cancer, is potentially a more meaningful representation of current mutation status than archival primary tumour tissue given discordance and levels of mutation fluctuate with PIK3 inhibition combined with trastuzumab.

Legal entity responsible for the study: Cancer Trials Ireland.

Funding: Bayer Pharmaceuticals.

Disclosure: B. Hennessey: Research funding: Bayer Pharmaceuticals. All other authors have declared no conflicts of interest.
**Background:** Clinical studies have established TMB, a measurement of mutations in the tumor genome, as a predictive biomarker for clinical efficacy of immune checkpoint inhibitors (ICIs). There is a lack of standardization for TMB estimation and reporting, which is critical for ensuring consistency for clinical implementation. An international collaboration organized by Friends of Cancer Research (Friends) and the QuIP (Quantitative Imaging Pathology Initiative GmbH) (QuIP) is establishing recommendations for achieving consistency in TMB estimation and reporting.

**Methods:** Friends and QuIP are using complementary TMB harmonization approaches. Friends will conduct in silico analyses where TCGA data will be compared between TMB estimates derived from whole exome sequencing (WES) and commercial targeted panel gene sets, followed by the use of patient-derived tumor cell lines to establish a universal reference standard for the alignment of panel-derived estimates. QuIP will compare TMB estimates from selected tissue (NSCLC) and other solid tumors using a WES-derived reference standard with commercial next-generation sequencing panels and lab-developed tests at several German academic institutions. These data will inform consistency of TMB estimation, assay comparability, and TMB cut-off values for potential clinical use.

**Results:** Preliminary data indicate several components influence TMB estimation: pre-analytical factors (eg, input material quality/quantity), sequencing parameters (eg, enrichment technologies), library preparation, bioinformatics (eg, filtering of germline variants), FFPE-induced deamination artifacts, mutation types, and clonal vs subclonal events. Analyses of panel size and composition suggest that larger panels may make more reliable TMB estimation and that the panel should include actionable targets, genes associated with mutagenesis (eg, microsatellite instability), and potential negative predictors of response (eg, mutated JAK2, JAK1/2, PTEN).

**Conclusions:** The Friends and QuIP collaboration will establish recommendations for reliable and reproducible TMB measurement to ensure consistent identification of patients who are likely to respond to ICIs.

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**Funding:** Bristol-Myers Squibb.

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**DNA damaging agents and immunotherapy in NSCLC: Is there a STING in the tale?**

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**Background:** In NSCLC patients, several clinical trials are testing the efficacy of DNA damage response inhibitors (DDR) and chemotherapy in combination with anti-PD1/L1 drugs. DDR activator antitumor immune responses in cancer through release of cytokine DNA leading to STING activation, stimulation of neo-antigens and release of pro-inflammatory cytokines. Our group has previously demonstrated a strong correlation between STING and immune activation, showing that tumors with high STING score have the highest levels of targetable immune markers.

**Methods:** We analyzed mRNA and protein expression of immune and EMT genes in the lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC) TCGA NSCLC and in a panel of NSCLC cell lines, correlating them with the presence of somatic mutations in DDR genes. Contemporary, we treated NSCLC cell lines in vitro with cisplatin and various DDRi combinations, including PARP/ATR/ATM/WEE-inhibitors, to determine the effect on DNA damage and immune markers expression (western blot and RPPA analysis).

**Results:** In both TCGA cohorts, immune markers mRNA expression clustered together and were positively correlated with EMT genes. In the LUAD cohort, high expression of CD274 (PDL1) was associated with high levels of other immune suppressive markers (LAG3, IDO1, and CD274). Notably, expression of STING pathway mediators (TBK1 and TMEF173) and mesenchymal markers (TWIST1/2, SNA1, SMO, and TGFBR1) were positively related with CD274. Moreover, we found that mutations in DDR-related genes TP53, BRCA1, and FANCM were correlated with higher levels of targetable immune suppressive markers (LAG3, IDO1, and CD274) and the mesenchymal marker, TWIST1, but lower levels of TMEM173. Finally, in vitro treatment with DDRi and cisplatin increased DNA damage, as demonstrated by increased p-H2AX, and proportionally upregulated PDL1 and STING in some cell lines. Our findings provide rationale to combine DNA damaging agents with immunotherapy drugs targeting immune suppressive markers in NSCLC. From our data, expression of EMT genes and deleterious mutations in DDR genes represent the best candidates to select patients that can benefit from these combinations.

**Legal entity responsible for the study:** MD Anderson Cancer Center.

**Funding:** AstraZeneca.

**Disclosure:** All authors have declared no conflicts of interest.
prognostic significance across the different molecular subtypes of advanced breast cancer.

Methods: The study population included 219 trastuzumab-treated women with advanced breast cancer who had been found to have HER2-positive disease by local testing. For all tumors, central testing for HER2 was performed and cyclin D1 (CCND1) gene amplification and mRNA and protein expression were assessed by FISH, qRT-PCR and IHC, respectively.

Results: Only 134 of the 219 patients (61.2%) were HER2-positive (HER2 gene amplification and/or pS 3+ HER2 protein expression). After a median follow-up of 136.0 months, 105 HER2-positive patients (78.4%) and 76 HER2-negative patients (89.4%) had died, while 80.0% of the former and 87.1% of the latter had disease progression. Median PFS was 14.0 months for HER2-positive and 8.9 months for HER2-negative patients, while median survival was 48.1 months and 35.0 months, respectively. Cyclin D1 mRNA expression was higher in patients with positive ER/PR. Cyclin D1 (as assessed by FISH, qRT-PCR, IHC) and HER2 did not reach significance in terms of PFS or survival either in the entire study population or in HER2-positive patients. In the HER2-negative subgroup, negative cyclin D1 protein expression was associated with higher risk of progression (HR = 1.66, 95% CI 1.01–2.72, Wald’s p = 0.045), while in the novo metastatic patients, the risk of progression was higher for patients with non-amplified CCND1 tumors (HR = 2.00, 95% CI 1.03–3.90, p = 0.041).

Conclusions: Aberrant activation of the cyclin D1-mediated pathway appears to reduce the risk of progression in HER2-negative tumors, but not in HER2-positive ones. If our results are validated by larger prospective trials, further evaluation of the cyclin D1-mediated pathway might identify prognostic and therapeutic implications in patients with advanced breast cancer.

Legal entity responsible for the study: Heletoff Cooperative Oncology Group (HeCoOG).

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Disclosure: G. Moutouzou, C. Christodoulou, P. Papakostas: Honoraria: Roche; Advisory role, travel: Roche. G. Luradici: Honoraria: Roche. A. Kourats, G. Fountoulakis: Advisory role: Roche. E. Ziais: Advisory role, travel, honoraria: Roche; Research funding: Roche/Genentech. All other authors have declared no conflicts of interest.

Expression of TK1 and CDK9 in plasma-derived exosomes is associated with clinical response to CDK4/6 inhibitors in breast cancer

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) improve PFS in advanced breast cancer receiving palbociclib/ribociclib in association with hormonal therapy. Three out of plasma were taken at the beginning of treatment (baseline) and at the first clinical evaluation (after 3 months). Objective responses were defined following the RECIST criteria v.1.1. RNA from plasma-derived exosomes was extracted by the ExoNeasy kit (Qiagen) and analysed for the expression of thymidine kinase 1 (TK1), CDK 4, 6 and 9 by digital droplet PCR (BioRad). Mann-Whitney test was applied.

Results: Thirty-four metastatic breast cancer patients were prospectively enrolled in this study. The comparison of mRNA levels of TK1, CDK4, 6 and 9 between baseline and the first clinical evaluation was available in 22 patients treated with letrozole/anastrozole + palbociclib + ribociclib and 22 patients given fulvestrant + palbociclib. 18 patients had newly diagnosed advanced breast cancer while 16 patients received >1 line of treatment. Objective responses were: (2.9%), CR, (4.11%), PR, 16 (47.1%) SD and 13 (38.2%) PD. The comparison of changes in the expression between TK1, CDK 4, 6 and 9 at baseline compared to first evaluation was statistically significant for TK1 (PR +SD vs. PD p = 0.009), CDK4 (PR +SD vs. PD p = 0.020), CDK9 (PR +SD vs. PD p = 0.047) and CDK9 (PR +SH vs. PD p = 0.008). The univariate analysis didn’t find any significant correlation between patients clinical variable and PFS (i.e. type of hormonal treatment, the line of treatment, performance and menopausal status, visceral metastasis, bone only metastasis, number of metastasis, previous hormonal or lines of chemotherapy received).

Conclusions: Exosomal expression of CDK4, CDK6 and in particular of TK1 and CDK9 may be useful to early identify patients who are likely to respond to CDK4/6i.

Legal entity responsible for the study: Romano Danesi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

146P HER2 amplification is associated with higher tumor mutation burden in breast cancer

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Background: ErbB family consists of four transmembrane proteins (ErbB1/EGFR/ HER1, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4) and plays a prominent role in the process of cell growth. Previous studies suggested that ErbB gene driven non- small-cell-cancer exhibited a suppressive immunity with lower tumor mutation burden (TMB) level. HER2 gene amplification (HER2+) is a well-known poor prognosis predictor in breast cancer and anti-HER2 target therapy has significantly improved the clinical prognosis of HER2+ patients. However, the association between HER2 gene alteration and TMB in breast cancer is still unclear.

Methods: Whole-genome sequencing data and clinical data of 366 breast tumors from The Cancer Genome Atlas (TCGA) and next generation sequencing (NGS) data of 335 breast tumors from clinical dataset were analyzed to explore the association between HER2 gene alteration and TMB. TMB was defined as total number of somatic non-synonymous mutations in coding region.

Results: 20.5% (75/366) of breast tumors in TCGA cohort and 20.3% (68/335) in clinical cohort harbored HER2 amplification. HER2 amplification was significantly associated with higher TMB in both TCGA cohort (P = 0.010) and clinical cohort (P = 0.008). HER2 somatic alteration occurred in 3.7% (12/336) of breast tumors in TCGA cohort and 7.2% (24/335) in clinical cohort. HER2 somatic alteration was also associated with higher TMB level in TCGA cohort (P = 0.016), but no association was observed in clinical cohort (P = 0.339). In addition, hormonal receptor (HR) + HER2 breast tumors exhibited the lowest TMB level compared with HR + HER2 (P = 0.001), HR-HER2 + (P = 0.052) and triple negative breast cancer (P = 0.000). Patients with low TMB level tended to have a better overall survival than patients with higher TMB level (median, 216.6 vs. 112.0 months; HR, 0.572; 95% CI 0.31–3.05; P = 0.067).

Conclusions: HER2 amplification is associated with higher TMB in breast cancer. These findings may assist the selection of breast cancer patients likely to benefit from immunotherapy.

Legal entity responsible for the study: Yongmei Yin and Shaqing Zhou.

Funding: National Natural Science Foundation of China.

Disclosure: All authors have declared no conflicts of interest.

147P Application of CRISPR/Cas9 system for identification of genes involved in the regulation of pancreatic cancer cells platinum sensitivity

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Background: Pancreatic cancer (PC) is an aggressive disease with high lethality rate due to multiple resistance mechanisms. We used in vitro CRISPR/Cas9 genetic dropout screening to identify genes involved in the regulation of PC, cell line sensitivity to platinum chemotherapy drugs.

Methods: We used two sgRNA libraries: 1) enriched for genes regulating cell cycle and nuclear proteins genes (CG, 50,000 sgRNA targeting 4,716 genes); 2) genome-wide (GW, 90,860 sgRNA targeting 18,164 genes). We performed screens in Mia PaCa-2 cells expressing doxycycline-inducible Cas9. Cells were treated with established IC50 of oxaliplatin (1 uM) or cisplatin (3 uM) for 9 cell divisions (12 days). Genomic DNA was extracted and sgRNA-containing regions were amplified and barcoded by PCR for further analysis by NGS. Statistical analysis for sgRNA enrichment or depletion was performed using R package comparing cells treated with the drugs vs. vehicle in the presence of Cas9/doxycycline.

Results: We identified 755 genes which significantly changed in cisplatin or oxaliplatin-treated cells (FDR 95%; p < 0.05). Candidate genes (n = 130) were further selected if at least 2 sgRNA per gene showed more than 2-fold change vs. vehicle. Among the 130 genes, 16 were known platinum sensitivity regulators involved in the double stranded break DNA repair pathway; 11 genes were positive platinum sensitivity regulators as their inactivation reduced sensitivity; 119 genes were negative platinum sensitivity regulators as their inactivation increased sensitivity. Gene Ontology analysis of the 130 candidate genes allowed us to identify regulators of cell cycle (n = 46), DNA replication and repair (n = 43), cellular compromise (n = 15), cellular assembly and organization (n = 35) and cell morphology (n = 48). Analysis of protein–protein interaction network showed that the majority of the hits (n = 74) are directly involved into cell cycle regulation and DNA repair processes.

Conclusions: We identified 130 candidate genes potentially involved in the modulation of platinum resistance most of which are regulating the cell cycle and DNA repair which is in keeping with the known DNA damaging mechanisms of action of platinum chemotherapy.

Legal entity responsible for the study: Kazan Federal University.
Annals of Oncology


148P Elevated 70kDa heat shock protein (hsp70) and autophagy levels in peripheral blood mononuclear cells (PBMCs) in women with a malignant breast mass

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Background: PBMCs respond to adverse physiological conditions to maximize survival and to alleviate the threat. Hsp70 is produced to maintain protein function and actuates an immune response. Autophagy is induced to provide sufficient nutrients in response to accelerated gene activation. We tested the hypothesis that PBMCs respond to the presence of a malignant breast mass by increasing production of hsp70 and manifesting a higher level of autophagy.

Methods: In this pilot study seventy women had their breast mass evaluated by mammogram and/or breast ultrasound. A core biopsy and surgery was performed as indicated. PBMCs were isolated from peripheral blood, lysed and intracellular levels of hsp70 and p62 (a measure of autophagy) were quantitated by ELISA. Extracellular hsp70 in plasma was also measured. Differences in lab measurements between women with a diagnosis of a benign or malignant breast mass were determined. All assays were performed by personnel blinded to the clinical data.

Results: A breast malignancy was diagnosed in 42 women while 28 had a benign lesion. Plasma hsp70 levels were higher in women with a malignant lesion (p = 0.03). PBMCs from 46 women were available for analysis. Mean hsp70 levels were higher in PBMCs from 38 women with a malignant lesion than in 8 women with a benign breast mass (p = 0.04). The PBMC p62 levels were higher in women with a benign breast lesion than in those with a malignant breast lesion (p = 0.0001). Since p62 is inversely related to the level of autophagy this indicates that autophagy is higher in PBMCs from women with a malignant breast lesion. There was no difference in the concentration of hsp70 or p62 between women with different histological types or stage of breast cancer.

Conclusions: Detection of elevated levels of hsp70 and autophagy in PBMCs, and higher plasma hsp70 levels, may differentiate between women with a malignant or benign breast lesion. Further studies on a larger sample are needed to confirm if the levels of autophagy and hsp70 induction in PBMCs may be of value in the preoperative triage of women with a breast mass.

Legal entity responsible for the study: Weill Cornell Medicine.

Funding: Weill Cornell Medicine.

Disclosure: All authors have declared no conflicts of interest.

148P Only estrogen receptor “positive” is not enough to predict the prognosis of breast cancer running head: Revisiting estrogen positive tumors in 8th AJCC staging era

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Background: In 2018, biomarkers including estrogen receptor (ER) status were incorporated in the 8th AJCC staging system. ER expression levels were not considered in those changes. We hypothesized that the levels of ER expression could affect the prognosis of breast cancer. The risk for patients with weakly ER-positive breast cancer should not be underestimated.

Methods: A retrospective review was conducted to identify all female patients with invasive breast cancer between 2003 and 2012. ER negative (group I), weakly ER-positive (group II), and strongly ER-positive (group III) were defined as Altered total scores of 0-2, 3-5, and 6-8, respectively. We examined a multigene panel, designated the BCT score, which is a newly developed prognostic model for predicting the risk of a distant metastasis.

Results: Among the 4,494 patients enrolled in this study, 1,310 (28.5%), 361 (7.9%), and 3,277 (66.2%) were categorized as group I, II, and III, respectively. Median FUT duration was 57.8 months. Compared to group III, patients in group II were younger, had larger tumors, and were also more likely to have PB-negative tumors, HER-2 amplification, high Ki-67, and high nuclear grade. Between group II and III, there was a significant difference in OS (P = 0.0764, 0.09, and 0.10, respectively). After adjusting for additional factors that may affect OS, the HR for OS showed higher in group II than in group III. The baseline median BCT score indicated that lower ER expression was associated with significantly higher BCT score (P < 0.0001) and significantly more likely to have high risk group (P < 0.0001) relative to higher levels of ER expression group.

Conclusions: ER expression levels affect the prognosis of breast cancer. The risk for patients with weakly ER-positive breast cancer should not be underestimated.

Legal entity responsible for the study: Institutional Review Board (IRB) of Samsung Medical Center in Seoul, Korea (IRB number: 2017-06-130).

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Disclosure: All authors have declared no conflicts of interest.

ClinAdv

151P Recurrent and metastatic carcinomas of the lacrimal gland: High frequency of ERBB2 driven disease

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Background: Lacrimal gland carcinomas (LGC) are uncommon primary malignancies that have a propensity to recur locally but rarely undergo metastasis. We performed comprehensive genomic profiling (CGP) on a series of 12 LGC to uncover genomic alterations (GA) that could possibly be used to design novel routes to targeted and immunotherapies for these rare neoplasms.

Methods: From a series of 158,360 clinically advanced cancer cases, FFPE tissue samples from 12 cases of LGC underwent CGP to find base substitutions, short indels, copy number changes and gene fusions. Microsatellite instability (MSI) was determined on 114 loci and tumornur mutational burden (TMB) was determined on 1.1 Mb of sequenced DNA and reported as mutations (mut) per megabase (Mb).

Results: The 12 LGC patients ranged in age from 34 to 76 years (median 61 years) and 67% of the patients were male. The LGC included 7 (58%) adenocarcinomas, 2 (17%) squamous cell carcinomas, 2 (17%) adeno-cystic carcinomas and 1 (8%) undifferentiated carcinomas. There were 1 (8%) grade 1, 3 (25%) grade 2 and 3 (25%) grade 3 tumors. 2 (17%) of LGC were stage III and 10 (83%) were stage IV at the time of sequencing. There were an average number of 4.25 GA per tumor. Three (25%) of the LGC featured ERBB2(HER2) gene amplification. One (33%) of the 3 ERBB2amplified
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Background: Improving the outcome for patients diagnosed with Cancer of Unknown Primary (CUP) is an unmet clinical need where survival is usually less than 1 year. Molecular characterisation of the disease may have diagnostic and therapeutic implications. The circulating tumour DNA test - Guardant 360™ is designed to detect gene alterations with a range of clinical utility.

Methods: Twenty-five patients were referred to Sarah Cannon Research Institute for ctDNA analysis. The panel covers all NCCN somatic mutations. Digital Sequencing Platform technology, exome sequencing and targeted amplicon sequencing allowed sequencing of targeted regions at very low DNA concentrations. Variants of unknown significance (VUS) were also measured. All patients were discussed at our institutional Genomics Review Board.

Results: Twenty-five patients (14 female; 11 male) were recruited from 24 August 2017 to 17 April 2018. Median age was 67 years (range 27-76). Main sites of disease were: lymph nodes (8); pleura (8); liver (6); bone (3) and adrenal glands (2). The median turnaround time (TAT) from sample collection to report was 10 days (range 6-15). Seventeen patients (68%) had potentially actionable mutations; 4 patients had no significant mutations detected: 1 post resection; 2 responding to chemotherapy; and 1 sampled prior to commencing chemotherapy. Genetic alterations detected included: BRAF V600E, KRAS, FGFR3, MYC, KIT, PIK3CA and HER2. Twelve patients had ≥ 3 somatic mutations (including variants of uncertain significance (VUS)); ≥ 6 mutations were found in 5% of the patients.

Conclusions: ctDNA is feasible with an acceptable TAT and the identification of significant potentially actionable targets. Targetable mutations were detected including BRAF V600E; KRAS; FGFR3; MYC; KIT; PIK3CA and HER2. Twelve patients had ≥ 3 somatic mutations (including variants of uncertain significance (VUS)); ≥ 6 mutations were found in 5% of the patients.

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

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Disclosure: I. Fauli. Employee: Guardant Health. All other authors have declared no conflicts of interest.

153P Reproducibility of the mRECIST criteria for the assessment of HCC treated by anti-VEGFR therapy: Impact of readers’ expertise

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Background: The reproducibility of the mRECIST criteria for the assessment of HCC treated by anti-VEGFR therapy is unknown. The purpose of this study was to evaluate the inter-reader variability and its sources in the mRECIST assessment of treatment response for HCC treated by anti-VEGFR drugs.

Methods: A subset of 41 advanced HCC tumours in 24 patients treated by anti-VEGFR drugs were selected from a phase II/III nalsed study (the original study). These data were retrospectively reviewed according to mRECIST criteria by one mRECIST expert at the time of the original study. The precision of measurements among the 3 non-experts and between the expert and the 3 non-experts were nalysed by assessing bias and standard deviation (SD) using the Bland-Altman method. The agreement of readers’ responses was assessed using the Kappa statistic. The causes of discrepancies were nalysed.

Results: Among the 3 non-experts, SD of measurements ranged (24.9%, 36.3%) and the Kappa coefficients were moderate (0.41 [0.28, 0.53]). SD in measurements of expert versus non-experts ranged (33.2%, 41.3%). Two patients had no difference in tumour size measurement at mRECIST. The main cause of discrepancy at declaring PD came from the complexity of HCC enhancement patterns and the poor deinition of tumour boundaries. Discrepancies at detecting PR came from the reader variability at selecting only the viable part or the entire liver tumor.

Conclusions: When used by mRECIST non-experts to assess the subvacular effect induced on HCC by anti-VEGFR therapy, mRECIST appears to lack reproducibility. It is therefore important when using mRECIST to require specific training to reduce readers’ variability.

Legal entity responsible for the study: Median Technologies.

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Disclosure: H. Beaumont, N. Faye, C. Klifa. Employee: Median Technologies. All other authors have declared no conicts of interest.

154P PD-L1 expression pattern in large cell neuroendocrine carcinoma of the lung

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Background: Large cell neuroendocrine carcinomas of the lung (LCNECs) are rare neoplasms with limited therapeutics options. Pathological diagnostic of LCNEC is morphologically based, may be difficult and needs immunohistochemical (IHC) analysis. Immune checkpoint inhibitors targeting tumoral and immune cells interaction have changed the NSCLC treatment but few data are available on LCNECs immune environment and particularly the expression of PD-L1 on both tumour and immune infiltrating (IC) cells. The objective of the present study is to determine the expression and pattern of PD-L1 staining in a cohort of LCNECs patients.

Methods: Clinical files and tumors biopsies of patients (pts) with a LCNEC diagnosed between 01.01.2014 and 31.12.2016 were retrospectively collected (GPPC-03-2017). All histological samples were centrally reviewed by six pathologists, according to the latest WHO 2015 classification. LCNEC was confirmed and PD-L1 expression was determined both in TC and IC, using the anti-PD-L1 antibody 22C3 (kit and automated Dako). PD-L1 expression was scored on TC as the percentage of PD-L1 positive cells (0 to 100%). PD-L1 expression on IC was determined as follows: IC: positive IC representing < 1% of the tumor surface; IC: positive IC representing ≥ 1% but < 5% of the tumor surface; IC: positive IC representing ≥ 5% but < 10% of the tumor surface; and IC: positive IC representing ≥ 10% of the tumor surface.

Results: 86pts were initially included in the study, 28 (32%) were excluded for non-LCNEC diagnosis. Among the 58 pts with LCNEC, five (9%) had a composite LCNEC with a NSCLC component. The mean age of the population was 65 years, mainly men (86%) and former or current heavy smokers (93%). PD-L1 was positive on TC for only 12% of the samples, while 76% of the samples showed PD-L1 positive, with respectively 18 (35%) IC3, 8 (14%) IC2, and 13(25%) IC1.

Conclusions: LCNEC display a particular PD-L1 expression pattern, different from NSCLC and from SCLC and may suggest a potential effectiveness of therapeutic anti-PD-L1 antibodies, this hypothesis have to be addressed in clinical trial.

Legal entity responsible for the study: GPPC.
155P Inter-rater reliability of programmed death ligand 1 (PD-L1) scoring using the VENTANA PD-L1 (SP263) assay in non-small cell lung cancer (NSCLC)

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Background: The VENTANA PD-L1 (SP263) assay has been developed as a companion diagnostic for anti-PD-L1 immune checkpoint inhibitors. Here we investigate assay inter-rater reliability, applied to PD-L1 scoring of tumour (TC) and immune cell (IC) infiltrates in NSCLC.

Methods: Six expert European pulmonary pathologists independently scored 200 NSCLC samples stained using the VENTANA PD-L1 (SP263) assay. Archival, conventionally-sourced formalin-fixed paraffin-embedded specimens were selected to represent the dynamic range of PD-L1 expression. Each pathologist scored the proportion of TCs expressing PD-L1 (TM score), tumour-associated IC population as a percentage of total tumour area (PIC value), and percentage of ICs expressing PD-L1 (IC score). Scores were analysed using intra-class correlation coefficient (ICC) and patient classification using Fleiss’ Kappa.

Results: Inter-rater results were available for 3 pathologists and 180 cases. TM scoring between pathologists showed strong pair-wise correlations between individuals (R²=0.90) with an ICC >0.95. Pair-wise and overall agreement was >85% for TC >1% and >93% for TC >20%, TC ≥25%, and TC ≥50%. Fleiss’ Kappa showed substantial agreement for TC ≥1% and excellent agreement for TC ≥20%, TC ≥25%, and TC ≥50%. There were systematic and substantial differences in PIC values and IC scores between pathologists with poor pair-wise correlations. ICC indicated poor reliability for both PC score (0.36) and PIC values (0.044). Fleiss’ Kappa showed poor agreement for IC ≥25% (0.185).

Conclusions: Assessment of TM score in NSCLC was highly reproducible using the VENTANA PD-L1 (SP263) assay, building confidence in the accuracy of this assay in patient selection for anti-PD-L1 therapy. However, expert pathologists were unable to reproducibly assess IC score in NSCLC, suggesting assessment methodology is unreliable for this tumour type and assay. This contrasts with urothelial cancer (UC) in which pathologist agreement for PIC values and IC scores was generated as part of UC VENTANA PD-L1 (SP263) IHC assay CE marking and FDA approval. This difference in pathology of the different tumour types requires further investigation.

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Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.


156P Relationship between ring-type dedicated breast PET and tumor-infiltrating lymphocytes in early breast cancer

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Background: FDG uptake on PET is related to biological parameters and prognosis in breast cancer. The predominance of stromal tumor-infiltrating lymphocytes (TILs) in breast cancer is a biomarker for prognosis and pathological complete response after neoadjuvant chemotherapy. However, whether whole-body PET (WBPET) and dedicated breast PET (DbPET) can reflect the amount of TILs is unclear. This study investigated the relationship between TILs and maximum standardized uptake value (SUVmax) in WBPET and ring-type DBPET.

Methods: A total of 125 invasive breast cancers underwent WBPET and ring-type DbPET and resected specimens were pathologically assessed. The impact on SUVmax on the tumor biological parameters and TILs was retrospectively evaluated. SUVmax was classified as high and low relative to the median values (WBPET-SUVmax: 2.2 and DbPET-SUVmax: 6.0).

Results: SUVmax correlated with tumor size, nuclear grade, Ki-67 labeling index, and TILs in both WBPET and DbPET (all P < 0.001). The cut-off values of tumor size, Ki-67 labeling index, and TILs predicting high SUVmax were 20 mm, 20%, and ≥20%, respectively. In multivariate analysis, the predictive factors for high SUVmax were tumor size and Ki-67 labeling index for WBPET and tumor size and TILs for DbPET. A high SUVmax in DbPET was related to high numbers of TILs tumors after propensity score matching analysis; however, WBPET was not (P = 0.007 and P = 0.664, respectively).

Table: 156P Logistic regression analysis for predicting high SUVmax tumor on WBPET and DbPET

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
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<td>HER2 positive</td>
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<td>TILs &gt; 20%</td>
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<td>Histogram_IC-NST</td>
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<td>Ki-67 labeling index &gt; 20%</td>
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<tr>
<td>TILs &gt; 20%</td>
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</tr>
</tbody>
</table>

Conclusions: Unlike WBPET, the SUVmax in ring-type DbPET can represent the immune microenvironment after adjusting for tumor biological factors. DbPET might be a biomarker of pathological response to neoadjuvant chemotherapy and prognosis.

Legal entity responsible for the study: Shinosuke Sasada.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

157P Short-term responders of non-small cell lung cancer patients to EGFR tyrosine kinase inhibitors display high prevalence of TP53 mutations and primary resistance mechanisms

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Background: Non-small cell lung cancer (NSCLC) with activating EGFR mutations in exon 19 and 21 usually responds to EGFR tyrosine kinase inhibitors (TKI), but sometimes the responses can only be maintained for a few months. The underlying mechanisms of such short responses have not been fully elucidated.

Methods: The genomic profiles of sixteen short-term responders (SR) that had progression free survival (PFS) of less than 6 months on the first-generation EGFR TKI were interrogated, in comparison to twelve long-term responders (LR) that had more than 24 months of PFS. All patients were diagnosed with advanced lung adenocarcinoma and harbored EGFR 19del or L858R mutation before treatment. Paired tumor samples collected before treatment and after relapse (or at the last follow-up) were subjected to next-generation sequencing of 416 cancer-relevant genes.

Results: SR patients were significantly younger than LR patients (p < 0.001). 88% of SR patients have TP53 variations compared to 13% in LR patients (p = 0.001), and 37%. SR patients carry EGFR amplification, which is much higher than LR patients (8%).
addition, 12 SR patients (75%) were identified with other potential primary resistance mechanisms in pre-treatment samples, including PTEN loss, RIM deletion polymorphism, amplifications of EGFR, ERBB2, MET, HRAS and AKT2. Comparatively, only 3 LR patients (25%) were detected with EGFR or AKT1 amplification that could possibly exert resistance.

Conclusions: The diversified pre-existing resistance mechanisms in SR patients revealed the complexity of defining treatment strategies even for EGFR sensitive mutations.

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Funding: Has not received any funding.

Disclosure: X. Tong, X. Wu, Y.W. Shao: Employee: Geneseeq Technology Inc. J. Yan: Employee: Nanjing Geneseeq Technology Inc. All other authors have declared no conflicts of interest.

158P Assessment of cfDNA in patients with metastatic colorectal cancer treated with cetuximab monotherapy


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Background: Third line systemic treatment for patients with RAS wild-type metastatic colorectal cancer (mCRC) includes anti-EGFR monoclonal antibodies such as cetuximab. Here, we examined cell-free DNA (cfDNA) to gain insight into mechanisms underlying primary and acquired resistance in patients with mCRC receiving cetuximab.

Methods: 34 patients with RAS wild-type mCRC (KRAS and NRAS exon 2-4) received biweekly cetuximab monotherapy (500mg/m2). cfDNA was isolated from plasma obtained at baseline, after 2 weeks of treatment and during disease progression (PD). E20-20 ng DNA was used for targeted next generation sequencing using the Oncoscan™ Colon cfDNA Assay (14 genes, 242 hotspots). Mutation analysis of tumor tissue was performed according to standard of care, at least including KRAS and NRAS. Outcome was defined as clinical benefit (CB: PD < 8 weeks, n = 21) or no CB (NCB; PD ≥ 8 weeks, n = 13).

Results: Baseline cfDNA concentration correlated with the sum of diameters on CT (p = 0.043) and metabolically active tumor volume on [18F]FDG PET (p < 0.001). In 6/13 (46%) of patients with NCB, mutations in KRAS (n = 3) and BRAF (n = 3) were detected in baseline cfDNA. Two KRAS mutations were detected in cfDNA, but not in tissue. All BRAF mutations in cfDNA were present in tissue, one BRAF mutation in tissue was not detected in cfDNA. In one patient (5%) with CB a polyclonal KRAS mutation was detected in cfDNA, which was not found in tumor tissue. In 9 patients with CB, cfDNA concentrations were measured and decreased from a median of 45 ng/mL (range 13 – 784 ng/mL) at baseline to 19 ng/mL after 2 weeks of treatment (range 9 – 42 ng/mL) (p = 0.008). In patients with CB an enrichment of mutations in genes associated with resistance (KRAS, NRAS and BRAF) was found in 12/17 (70%) at PD compared to baseline. Moreover, in 8/17 (47%) of these patients EGFR mutations in codons coding for the epitope binding site of cetuximab emerged and in 9/17 (53%) multiple mutations in the same gene occurred suggesting the presence of multiple subclones.

Conclusions: A subset of mCRC patients with NCB could be identified based on baseline cfDNA mutations associated with cetuximab resistance. By using cfDNA we can optimize patient selection for cetuximab therapy and elucidate mechanisms of resistance.

Clinical trial identification: NCT02117466.

Legal entity responsible for the study: Erasmus University Medical Center.

Funding: Dutch Cancer Society.

Disclosure: L. Angus: Advisory board: Merck B.V. All other authors have declared no conflicts of interest.

159P Quantifying circulating cell-free DNA as a clinical biomarker


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Background: This is the first comprehensive study on the effect of pre-analytical and demographic parameters that could be a source of variability in the quantification of nuclear and mitochondrial genome circulating DNA (cfDNA and mtDNA) and their respective expression levels.

Methods: We set optimal calculation of the simultaneous quantification of circulating nuclear and mitochondrial genome copy number based on a clinically validated q-PCR method. We report data from a total of 217 subjects, 99 healthy individuals and 118 metastatic colorectal cancer (mCRC) patients. We also investigated the influence of blood storage and collection time on cfDNA concentration from healthy volunteers.

Results: Approximately 26,650 and 3,000-fold more mitochondrial than nuclear genome copies were found in healthy subjects and mCRC patients, respectively. Neither NcirDNA nor McirDNA plasma concentrations depended on age in the healthy and mCRC cohorts taken as a whole. Remarkably however NcirDNA levels were significantly higher in healthy men as compared to women (n = 99; P < 0.010). Men and women did not differ in McirDNA levels. NcirDNA levels increased slightly with age in healthy women, suggesting a potential influence of menopause. A highly significant statistical difference was found between mCRC patients and healthy individuals for NcirDNA (P < 0.001) and McirDNA (P < 0.019). In healthy volunteers, there was a higher level of NcirDNA at 9:00 AM with no food intake.

Conclusions: Nuclear and mitochondrial cirDNA levels do not vary in the same way with regards to blood stability, collection time, and pathological status. Our observations, of pre-analytical, analytical and demographic factors, could serve to set standard operating procedures and to transpose cirDNA analysis into clinical practice in oncology. Guidelines on the preanalytical conditions will be also presented from data from this study and a complete review of the literature.

Legal entity responsible for the study: Alain R. Thierry.

Funding: SIRIC Montpellier Cancer Grant INCA_Inserm_DGOS_12553.

Disclosure: All authors have declared no conflicts of interest.

160P Gene expression profile (GEP) and survival among patients with advanced ovarian cancer


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Background: The ability of T-cell–inflamed GEP (Ayers et al. J Clin Inv. 2017) to predict clinical outcome in ovarian cancer is not fully understood. A retrospective observational study was conducted to evaluate the prognostic value of GEP and its association with programmed death ligand 1 (PD-L1) expression in patients with advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer (OvCa).

Methods: Patients diagnosed as FIGO stages II-IV OvCa from 2004 to 2012 at Aarhus University Hospital and Rigshospitalet, Copenhagen, Denmark, were included. Patients were considered platinum sensitive if treatment-free interval [TFI] was >6 months. PD-L1 was assayed using the 22C3 antibody, and positivity was defined as ≥ 1 stained tumor or immune cells per 100 tumor cells. T-cell–inflamed GEP score was defined as low (< 0.318), intermediate (0.318 < TFI < 0.162), or high (> 0.162). The log-rank test and Cox proportional hazards model were used for survival analyses, adjusting for age, stage, histology, residual tumor, surgery type, performance status, platinum sensitivity, and PD-L1 expression status.

Results: Median age of the 376 patients was 63 years (range, 26-86); 9%, 70%, and 20% were FIGO stages II, III, and IV disease, respectively. Of these patients, 80% had type II histologic type, and 76% were platinum sensitive; 49% had a GEP score of low, 16% had intermediate, and 35% had high. Baseline characteristics between GEP groups were similar; PD-L1 and GEP scores were correlated (Spearman r = 0.71, Kendall tau r = 0.57). Median overall survival (OS) was 43 months (95% CI, 38-49) in all patients and was similar for patients with low GEP (41 months) and intermediate GEP (40 months), compared with patients with high GEP (52 months). There was no significant association between GEP status (intermediate vs high) and OS among all patients (adjusted hazard ratio, 1.00 [95% CI, 0.72-1.38]), by platinum sensitivity or by PD-L1 expression status.

Conclusions: GEP correlated with PD-L1 expression in patients with advanced OvCa, but OS was not significantly different between GEP categories.

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

Funding: Merck & Co., Inc.

163P Predicting survival benefit of cetuximab plus cisplatin in patients with metastatic gastric cancer patients using quantitative proteomics

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Background: Cetuximab plus cisplatin (XP) is a standard treatment for metastatic gastric cancer (mGC). Cetuximab activation requires the enzymes uridine-cytidine kinase 2 (UCCK2) and orotate phosphoribosyltransferase (OPRT). We previously used mass spectrometry to quantify UCCK2 in tumor samples from 5-FU-treated patients with stage III/IV colorectal cancer; UCCK2 protein expression > 319 amol/ug of tumor protein was associated with improved survival. Here, we assessed whether these biomarkers would predict survival among mGC patients treated with XP.

Methods: Archived tumor samples from patients with mGC were microdissected and solubilized for mass spectrometry quantification of 16 protein biomarkers. Kaplan-Meier survival curves were compared using a log-rank test. Multivariable Cox models of survival included clinical covariates and protein biomarkers.

Results: mGC tumor samples from 116 XP-treated patients were analyzed (male: 64%; median age: 55 years). All samples expressed OPRT protein (range: 202–1719 amol/ug), and 114 of 116 expressed UCCK2 (range: 119–933 amol/ug). Patients with UCCK2 expression above the pre-defined cutoff of 319 amol/ug (n = 30) had longer time to progression (TTP): HR (0.60; p = 0.023) than patients below the cutoff. Results for overall survival (OS) were similar (HR: 0.59; p = 0.015). OPRT protein expression > 790 amol/ug (n = 24) was associated with longer TTP (HR: 0.38; p < 0.019) and longer OS (HR: 0.40; p = 0.029). In multivariate analysis, UCCK2 and OPRT remained independent predictors of survival after adjustment for age, gender, ECOG performance status, metastatic sites, and other clinical covariates.

Conclusions: We validated a pre-defined UCCK2 expression cutoff and discovered an OPRT protein cutoff in an XP-treated mGC patient cohort. Patients with tumor expression of UCCK2 and OPRT proteins above quantified thresholds survived longer than patients with lower expression. Mass spectrometric quantitation of these common tumor proteins at diagnostic stage may improve patient selection for XP. Studies to validate these and other chemo predictive biomarkers are ongoing.

Legal entity responsible for the study: NantOncics.

Funding: NantOncics.

Disclosure: D. Yen, E. An, Y. Tian, F. Cecchi, T. Hombrough: Employment: NantOncics. All other authors have declared no conflicts of interest.

163P Accurate measurement of tumor mutation burden in liquid biopsy (tTMB) using a 500 gene panel


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Background: Tumor mutation burden (TMB) has been shown as a new predictive biomarker for immune checkpoint inhibitor in various cancer types. It is typically measured by processing tumor tissue with substantial input which limits its clinical utility in patients with metastatic or unresectable disease. Meanwhile, there is increasing interest in circulating tumor DNA (ctDNA) that act as a noninvasive real-time biomarker for cancer patients. Therefore, here we develop a new next generation sequencing assay that can identify patients with sufficient tumor fraction in plasma and accurately measures the TMB from blood (tTMB).

Methods: Cell free DNA (ctDNA) was extracted from plasma across four original tissue types by different tumor stages. ctDNA Assay was performed with unique molecular identifier (UMI) sequenced on the Illumina platform and analyzed using an internal pipeline for variants down to 0.4%. By integrating the fragment size distribution and droplet digital mutation frequency, we were able to estimate the tumor fraction per plasma sample. A tTMB score was also derived using all the coding variants on a 1.1M panel across 500+ genes. The matched TMB score is derived by the same assay using FFPE tissue.

Results: Our assay has generated sufficient results from 1-4ml plasma for variant detection down to 0.4%. Across four tissue types by various cancer stages, our assay and pipeline yield a variant concordance of 79% between ctDNA and FFPE. Majority of mutations only found in plasma may be associated with clonal hematopoiesis in genes such as TET2, DMBT3 and etc. By combining fragment size distribution and droplet mutation frequency, we were able to estimate tumor fraction in plasma. Tumor fraction in plasma is significantly associated with tumor stage that >50% of metastatic cancers and >25% early stage lung cancers contain high tumor fraction. In patients with at least 1% tumor content, there is high correlation between ctDNA and tTMB measured by plasma and FFPE (R² > 0.92).

Conclusions: We have developed a cfDNA assay to detect somatic variants and determine tTMB with high accuracy and precision with input as low as 10 ng of ctDNA. Our assay yield accurate measurement of tTMB compared to tissue biopsy.

Legal entity responsible for the study: Illumina, Inc.

Funding: Has not received any funding.


164P Circulating tumor DNA and RNA as an exploratory biomarker to evaluate GT0918 in a phase I/II clinical trial in mCRPC patients


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Background: Metastatic castration resistant prostate cancer (mCRPC) is a complex disease with distinct molecular features in relation to genomic instability and selective treatment pressure. Circulating tumor DNA and RNA fragments (ctDNA & ctRNA) found in blood offers the potential of disease diagnosis, monitoring and resistance mechanism interrogation by detecting genomic alterations from tumor. We explored ctDNA & ctRNA-based biomarkers from patient blood to assess their associations with clinical response of GT0918, a potent AR antagonist, in a Phase 1/2 clinical study in mCRPC who progressed after abiraterone or enzalutamide and docetaxel, or cannot tolerate either or both therapies.

Methods: We performed a retrospective analysis of blood samples from mCRPC patients collected at baseline, on- and after study during the trial. A highly sensitive ctDNA- & ctRNA-based NGS assay was developed to detect mutation, copy number gain, fusion and splicing variants. Statistical analyses were performed in R.
Results: 20 blood samples were collected at multiple time points from 8 patients. ctDNA-based variants were detected in all of patients. The most frequent mutations are TP53 (55.0%) and AR (30.9%). Combined mutation rates in PTEN-IDPK-ART and DNA damage repair pathways (BRCA1/BRCA2/ATM) are both 35.9%. Importantly, AR hotspot mutations (W742C, T878A, and S889G) and amplifications are detected in 4 subjects. AR splicing variants (AR-V3, AR-V7) were found in 3 patients by cDNA assay. Interestingly, one AR-V5+ patient became negative during the treatment accompanied by a decrease of other molecular biomarkers including prostate-specific PSAP mutation and ctDNA yield. In contrast, another patient who was AR-V3+ at C4D1, had constantly high AR amplification and increasing ctDNA yield over treatment. Last, as a hallmark of prostate cancer, TMPRSS2-ERG fusion was also detected in 2 patients.

Conclusions: This is a preliminary study to explore genomic alterations in mCRPC in response to GT098 treatment. As a non-invasive assay, the ctDNA & cDNA-based assay was highly sensitive and provided useful molecular insights for monitoring treatment effect and deciphering drug sensitivity & resistance mechanisms.

Clinical trial identification: NCT02862772.

Legal entity responsible for the study: Suzhou Kintor Pharmaceuticals, Inc.

Funding: Suzhou Kintor Pharmaceuticals, Inc.


The frequency of primary cilia, CD8+ tumor infiltrating lymphocytes and PD-1 expression in renal cell carcinoma of clear-cell type

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Background: Primary cilia (PC) is considered to represent a functional homologue of the immune synapse due to morphological and functional similarities in architecture. Both microtubule structures, i.e. primary cilia of cancer-associated fibroblasts and immune synapses between cytotoxic CD8+ tumor infiltrating lymphocytes (TILs) and antigen-presenting or cancer cells, are regularly found in varying amounts in the microenvironment of solid tumors. These could, in fact, represent two sides of the same coin. However, so far both parameters have not been evaluated simultaneously within the same group of patients.

Methods: The presence of PC in cells, programmed cell death protein-1 receptor (PD-1) expression and the frequency of intraepithelial cilia (ITLs) was retrospectively evaluated in tumor tissue blocks of the resected specimens of the kidney in 104 patients with renal cell carcinoma of clear-cell type, 71 males and 33 females, with a median age of 64 years (range 38-82 years). Twenty-eight patients had stage I, 15 stage II, 31 stage III and 30 patients had stage IV tumor. Grade was as follows: grade 1 in 27 patients, grade 2 in 15 patients, grade 3 in 5 patients and grade IV in 30 patients.

Results: The median frequency of PC was 0.0028% (0-0.0465%). The frequency of intraepithelial cilia was negative in 1 patient, <25% in 65, 26-50% in 29 and 26-50% in 11, respectively. The expression of PD-1 was <5% in 52 patients, 5-25% in 34 patients, 25-50% in 13 patients, 51-75% in 4 patients and 75% in 1 patient. During the follow-up, recurrence occurred in 42 patients and 43 patients died. Median PFS was 44% (95% CI: 34-67%) and median OS was 98% (95% CI: 84-117%).

Conclusions: The present study provides the first data on the potential association frequency of PC, PD-1 and ITLs in patients with renal cancer.

Legal entity responsible for the study: MH CZ-DRO (T1H, 0064190).

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Disclosure: All authors have declared no conflicts of interest.

The frequency of primary cilia, CD8+ tumor infiltrating lymphocytes and PD-1 expression in renal cell carcinoma of clear-cell type

Association of MMR protein expression and MMR gene mutations in Chinese colorectal cancer patients

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Background: DNA mismatch repair (MMR) deficiency is a genetic abnormality that has important clinical implications related to therapeutic option, familial cancer risk assessment, and checkpoint inhibitor response. It occurs in approximately 15% of colorectal cancers (CRC). Associations between MMR protein expression, microsatellite instability (MSI), and gene mutations remain under investigation.

Methods: Thirty-one FFPE samples from primary CRC patients (pts) were collected for immunohistochemistry (IHC) assay of MMR proteins, PCR-based MSI assay if available and NGS-based panel assay. Genomic alterations including single base substitutions, short and long insertions/deletions, copy number variations, and gene rearrangements were assessed. MSI status were predicted based from NGS.

Results: Out of 31 sample, 12 CRC were identified as MMR deficiency (dMMR) by IHC including 5 males and 7 females (median age: 66 years), and 19 samples as MMR proficiency (pMMR) including 13 males and 6 females (Median age: 53 years). Eight of the 12 dMMR samples (67%) harbored at least one MMR gene mutations predicted as loss of functions,[11] including nonsense mutations or truncations in MSH2, MSH6 or MLH1. No MMR gene mutation was detected in any of the 19 pMMR samples (p-value<0.001). In addition, 2 BRAF- and 6 KRAS hotspot mutations were detected in dMMR samples, and 8 KRAS, 1 BRAF and 1 NRAS mutations in pMMR samples. NGS based panel MSI algorithm successfully predicted the MSI status of all the 31 samples with 100% concordance with the MMR results. Neither copy number variation nor rearrangement was detected. Five pMMR samples were identified as microsatellite stability (MSS) by PCR, 6 dMMR were high level of microsatellite instability (MSI-H), and the rest were failed due to DNA contents.

Table: Association of MMR protein expression and MMR gene mutations in Chinese colorectal cancer patients

<table>
<thead>
<tr>
<th>n</th>
<th>MMR gene</th>
<th>KRAF mutations</th>
<th>NRAS mutations</th>
<th>BRAF mutations</th>
<th>MSI status</th>
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<tr>
<td></td>
<td>(n, %)</td>
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<td>(n, %)</td>
<td>(n, %)</td>
<td>(n, %)</td>
</tr>
<tr>
<td>dMMR (IHC)</td>
<td>12 (100%)</td>
<td>6 (50%)</td>
<td>0 (0%)</td>
<td>2 (16.7%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>pMMR (IHC)</td>
<td>19 (0%)</td>
<td>8 (42.1%)</td>
<td>1 (5.2%)</td>
<td>1 (5.2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Conclusions: We observed a significant association between MMR deficiency and MMR gene mutations from deep DNA sequencing. The results suggested that CRC pts with MMR gene mutations could be more likely to have dMMR status.

Legal entity responsible for the study: OrgiMed.

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Disclosure: D. Chen, X. Dong, J. Hu, G. Chrm, W. Shi, M. Yao: Employer: OrgiMed. All other authors have declared no conflicts of interest.

Somatic and germline mutations of Chinese gastric cancer patients


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Background: Gastric cancer is a high incidence malignancy in China, but the disease is often diagnosed at an advanced stage with limited therapeutic options and poor prognosis. Unfortunately, limited progress of target and immune therapy has achieved in gastric cancer due to tumor heterogeneity and the lack of effective biomarkers in the clinic. Thus the precise understanding of gastric cancer genomic profiling is urgent for exploring clinical strategy of this malignancy.

Methods: Formalin Fixed Paraffin Embedded (FFPE) samples of 110 Chinese gastric cancer patients were collected for next-generation sequencing (NGS)-based 450 genes
Validation of the MammaTyper®-pathological complete response (pCR)-score as a predictor for response after neoadjuvant chemotherapy (NACT) in patients with early breast cancer (BC)

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Background: Prediction of the response to NACT in early BC (pts) can lead to improved treatment decisions. The MammaTyper® test can be used to predict the probability of pCR after NACT by integrating accurate and reproducible assessment of ERBB2, ER, and MKI67 mRNA into a standardized prediction model (Varga et al. Breast Cancer Research 2017).

Methods: Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor samples of pts with GC1-2 BC, enrolled in the single arm phase II TECHNO trial (Untch et al. JCO 2011) and the randomised phase III PREPARE trial (Untch et al. Ann Oncol. 2011). MammaTyper®, a molecular in vitro diagnostic RT-qPCR test, was used to assess the expression of ERBB2 (HER2), ER (ER), and MKI67 (Ki67) genes from which a predefined continuous score was calculated. The study aimed to validate the MammaTyper® pCR-score for predicting pCR (ypT0 ypN0) after NACT in BC. Pts were classified into a low or high score group according to a predefined cutoff: score ≤ 41 predicts a low probability of pCR, score ≥ 42 predicts a high pCR rate.

Results: A total of 324 pts with available FFPE samples and MammaTyper® measurements were analyzed. The MammaTyper® score was significantly associated with an increased pCR rate (AUC = 0.805, p < 0.001). Similarly, pts with high MammaTyper® score (N = 159) had more frequently pCR compared to pts with low score (N = 165) (30.2% vs 3.0%, respectively; OR = 13.84 [95%CI 3.34-55.86], p < 0.001). In addition, the MammaTyper® pCR-score remained significantly predictive when adjusted for age, nodal status, tumor grade and treatment (OR = 10.90 [95%CI 3.38-35.16], p < 0.001). Within the non-pCR subgroup, pts with low score had a significantly longer disease-free (DFS) and overall (OS) survival compared to pts with high score (DFS HR = 1.59, 95%-CI 1.04-2.44, p = 0.032; OS HR = 2.85, 95%-CI 1.62-5.00, p < 0.001).

Conclusions: The MammaTyper® pCR-score predicts pCR after NACT and seems to improve prognosis additionally to clinical predictors in pts with early BC. Its utility with regard to conventional ER, PR, Ki67 and HER2 has to be analyzed in future studies.

Legal entity responsible for the study: GBG Forschungs GmbH and BioNTech Diagnostics GmbH, Mainz.

Disclosure: P.A. Fasching: Personal fees: Celgene, during the conduct of the study; Grants and personal fees: Novartis; Personal fees: Pfizer, Roche, Teva, outside the submitted work. M. Labie: Personal fees: BioNTech Diagnostics GmbH, outside the submitted work; Employee: BioNTech Diagnostics GmbH; Patent WO 2015/024942 pending, new patent application pending. K. Webster: Grants and non-financial support: BioNTech Diagnostics GmbH, Mainz, Germany, during the conduct of the study; Patent EndoPredict issued. C. Denken: Personal fees: Teva, Novartis, Pfizer, Roche, Amgen, MSD Oncology; Other: Sividon Diagnostics, outside the submitted work. K. Schloßb: Personal fees: BioNTech Diagnostics GmbH, outside the submitted work; Patent WO 2015/024942 pending, new patent application pending. F. Mariné: Personal fees: Roche, AstraZeneca, Pfizer, Tesaro, Novartis, Amgen, PharmMar, GenomicHealth, CureVac, Eisai, outside the submitted work. S. Lohi: Grants: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva, Vifor during the conduct of the study and outside the submitted work. All other authors have declared no conflicts of interest.

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Disclosure: Y. Zheng, Q. Cui, A. Wang, H. Chen, W. Shi, K. Wang, M. Yao: Employee: OrigiMed. All other authors have declared no conflicts of interest.

Selective induction of PD-L1 expression in plasma-derived exosomes by gemcitabine-nab-paclitaxel vs. FOLFIRINOX in pancreatic cancer

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Background: Pancreatic ductal adenocarcinoma (PDAC) is considered a poorly immunogenic tumor and treatment with immune checkpoint inhibitors lacks efficacy in this disease. Recently, the use of immune checkpoint inhibitors with radiation therapy in PDAC has demonstrated synergistic activity. The aim of this study was to evaluate the effect of FOLFIRINOX and GemMnPAC on PD-L1 expression in plasma-derived exosomes of PDAC patients.

Methods: Four ml of plasma were obtained at baseline (before initiation of chemotherapy) and at the time of first radiological evaluation (3 months) from patients undergoing first-line FOLFIRINOX or GemMnPAC chemotherapy. Exosomes and RNA extraction from plasma were performed using the exoNasy kit (Qiagen®, Valencia, CA, USA); PD-L1 expression was evaluated by digital droplet PCR (Bio-Rad®, Hercules, CA, USA).

Results: A total of 22 pancreatic cancer patients were enrolled in this study, 15 (68.2%) were treated with GemMnPAC and 7 (31.9%) with FOLFIRINOX. In the GemMnPAC group one patient had a partial response (PR), 11 patients had stabilization of disease (SD) and 3 progressed (PD). In the FOLFIRINOX group there were 1 RP, 3 SD and 1 PD. Eleven patients treated with GemMnPAC had a significant increase of PD-L1 expression at 3 months vs. baseline. Indeed, the mean PD-L1 copies/ml was 90 at baseline and 170 at 3 months (p = 0.02). On the contrary, in the FOLFIRINOX group, PD-L1 levels were increased in 3 patients and remained stable/decreased in 4 subjects; the mean baseline copies/ml were 70 vs 80 at 3 months (p = 0.4). The selective induction of PD-L1 expression was independent from tumor response.

Conclusions: These pilot data suggest that, due to its ability to increase PD-L1 expression, GemMnPAC regimen may be used as induction-treatment for immunotherapy in pancreatic cancer, either sequentially or concomitantly.

Legal entity responsible for the study: Romano Danesi.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

References:

169P Selective induction of PD-L1 expression in plasma-derived exosomes by gemcitabine-nab-paclitaxel vs. FOLFIRINOX in pancreatic cancer

168P Validation of the MammaTyper®-pathological complete response (pCR)-score as a predictor for response after neoadjuvant chemotherapy (NACT) in patients with early breast cancer (BC)
Background: Tumor heterogeneity is difficult to characterize with tissue biopsies in late stage cancers, in which primary and metastatic tumors may have diverged in their mutational profiles. Assessing the diversity of mutations detected by sequencing circulating tumor DNA (ctDNA) from liquid biopsies can quantify the genetic complexity of tumors shedding DNA into the blood.

Methods: In a prospective, observational study, we obtained pre-treatment plasma samples from 56 subjects with Stage IV small cell lung cancer (SCLC) treated with first-line chemo or chemoradiation therapies. Plasma samples were analyzed with the AVENIO ctDNA Surveillance Kit, a targeted next-generation sequencing panel of 198 kinases. We applied the Shannon and Simpson diversity indices by considering each somatic variant as a species and the number of detected duplex molecules with that mutation as the abundance of that species. Samples were ranked as low tumor heterogeneity if their plasma variant diversity score was below the first tertile of the cohort.

Results: Stage IV SCLC subjects with low tumor heterogeneity evaluated by the Shannon diversity had shorter overall survival (hazard ratio = 1.8; 95% CI 1.3–3.3; log-rank p = 0.004; median survival difference = 4.5 months). Furthermore, subjects with low tumor heterogeneity evaluated by the Gini–Simpson or inverse Simpson diversity index had shorter overall survival (hazard ratio = 1.8; 95% CI 1.3–3.5; log-rank p = 0.033; median survival difference = 4.5 months).

Conclusions: The molecular barcoding scheme in the AVENIO kit allows for each strand of the original double-stranded ctDNA molecule to be tracked. From this reconstructed profile of circulating duplex molecules harboring tumor variants, we derived a tumor heterogeneity measure based on the Shannon and Simpson diversity indices commonly used in ecology. We found that late stage SCLC subjects with low tumor heterogeneity had shorter overall survival, suggesting that highly heterogeneous SCLC tumors may respond better to chemotherapy or radiation. Studies to further validate these findings are ongoing.

Legal entity responsible for the study: Roche Sequencing Solutions, Inc.

Funding: Roche Sequencing Solutions, Inc.

Disclosure: S. Yang, L. Xi, C. Woestmann, S. McNamara, B. Hinzmann, S. Froehler, C. Xu, A. Balasubramanyam, F. P. Adams, B. Wehnl, S. McNamara, B. Hinzmann, S. Froehler, and L. Xi are employees of Roche Sequencing Solutions, Inc. J. Palma, E. T. Wehnl, B. Wehnl, and S. McNamara are employees of Roche Diagnostics GmbH.

17TP MET exon 14 splicing mutation and its correlation with clinicopathological features in subjects with non-small cell lung cancer

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Background: Driver mutations are genomic alterations important for tumor initiation and growth. They are found in genes that control cellular proliferation and long-term survival. MET exon 14 splicing mutation occurs in about 3% of cases of non-small cell lung cancer (NSCLC). It has been recognized as an important biomarker to predict response to MET tyrosine-kinase inhibitor therapy. The aim of this study was to investigate possible connection among the MET exon 14 mutations and genomic as well as clinicopathological features in patients with NSCLC.

Methods: The study was performed among 270 patients (58% males and 42% females; mean age of 57.1 ± 16.48 years) with histologically confirmed diagnosis of NSCLC. The distribution of MET exon 14 splicing mutation was detected using the quantitative real-time polymerase chain reaction restriction fragment length polymorphism assay. RNA was extracted from formalin-fixed paraffin-embedded samples. The study was conducted according to the Declaration of Helsinki, the protocol was reviewed and approved by the institutional Ethics committee and all patients provided written informed consent.

Results: MET exon 14 splicing mutation was detected in 9 patients (3.4%). It was found in 7 adenocarcinomas (18.9%) and in 2 squamous cell carcinomas (3.4%). Most adenocarcinomas occurred in females and non-smokers. Squamous cell carcinoma predominately occurred in male smoking patients. All subjects with MET exon 14 splicing mutation had earlier pathology stage of disease (IA, IB, IIA, IIIB) (31%) and older age (>75 years) (43%). Overall survival (OS) of these patients were statistically longer than in patients with KRAS and EGFR mutations (2.2 vs. 1.3 months and 2.4 vs. 1.8 months).

Conclusions: We found that MET exon 14 splicing mutation occurs at a frequency of 3.4%, in older age, and mostly in early stage of NSCLC. OS of patients harboring MET exon 14 splicing mutation has lasted longer than in patients harboring KRAS and EGFR mutations. Patients with MET exon 14 splicing mutation may respond well to MET tyrosine-kinase inhibitor therapy. Further studies are needed to confirm our results.

Legal entity responsible for the study: Cancer Genomic Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

172P Cancer stem cell markers in pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer deaths in both men and women world-wide. Despite development of scientific, PC remains lethal disease. Recently, cancer stem cells (CSC) of pancreatic cancer that often are resistant to treatment have been identified. Present study aims to investigate the existence and prognostic value of CSC markers in PDAC patients.

Methods: 52 hematoyxin and eosin-stained slides cut from formalin-fixed, paraffin-embedded (FFPE) PDAC tissues were evaluated by a pathologist, and the areas of the slide representing tumor and normal were scored. The samples were analyzed for the presence and differential expression of LGR5, CD44 and CD133 using RT2 Profiler PCR Array Data Analysis (http://www.sabiosciences.com/pcr/arrayanalysis.php) to compare the PCR array analysis results and the characteristics of the tumors and cases.

Results: Of the 52 patients, 29 were men and 23 were women, with an average age of 63 years (range, 26–91 years). All patients underwent pancreaticoduodenectomy (Whipple procedure). The median size of tumors was 2.3 cm (range, 0.5–6.0 cm). Lymphatic, vascular, and perineural invasions were observed in the tumors of 23 (44.2%), 9 (17.3%), and 5 (9.6%) patients, with 2 patients showing concurrent lymphatic, vascular, and perineural invasions. Tumors were classified as stage IA (n = 4), stage IB (n = 11), stage II A (n = 7), stage II B (n = 10), and stage III (n = 22). All surgically resected specimens showed negative (R0) resection margin status. The CD44 was not significantly expressed in eCC tumors compared to normal tissue. LGR5 and CD133 expression level was significantly higher in tumors than in corresponding normal tissues (4.5 fold, P = 0.034; 3.7 fold P = 0.045, respectively). Increased CD133 expression was associated with ampulla vateri tumor localization (P = 0.011). Over expression of LGR5 and CD133 were associated with short overall survival.

Conclusions: Here, we report that CD133 and LGR5 may acts as a functional CSC in the aggressivite of PDAC. Our results suggest that these molecules may serve as a candidate prognostic biomarker and target for new therapies in PDAC.

Legal entity responsible for the study: Ekmel Kay.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

173P Tumor mutation burden assessment on FFPE samples using a targeted next-generation sequencing assay

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Background: Tumor mutation burden (TMB) predicts durable benefit from immune checkpoint blockade in several cancer types. We demonstrate the ability of a targeted panel with fast turn-around time and low input needs to estimate TMB from research samples.

Methods: We developed a single sample analysis workflow to estimate mutation burden (TMB; nonsynonymous mutations/Mb) from FFPE and fresh frozen tumor research samples. The assay utilizes a PCR-based target enrichment strategy with 409 genes and 1.7 Mb of genomic regions. The workflow requires only 10 ng of input DNA and
enables a 2.5-day turn-around time from sample to the final report. Sequencing is performed on high throughput semiconductor sequencing platform to achieve sufficient depth (~500x coverage) and accuracy. The workflow is tumor sample only, with no matched normal sample required, germ-line variants, along with background noise, are removed through filters based on population databases. The assay is research use only for diagnostic procedures.

**Results:** A comparison with whole exome sequencing (WES) on 12 FFPE tumors, where WES was performed on tumors and their matched normal using Agilent’s exome enrichment kit (~150x coverage for tumor; ~100x coverage for normal) on illumina platform and our assay ran on tumors only, showed high correlation (r²=0.83) between TMB estimates by our assay with that from WES. To assess reproducibility, we compared raw somatic mutations/ Mb in library replicates for a cohort of 21 FFPE research samples (19 CRC, 2 Melanoma) and observed high correlation (r²=0.97). Our pipeline identifies mutation signatures consistent with specific mechanisms such as UV and tobacco smoking, as well as ACP injury for FFPE processing.

**Conclusions:** A simple workflow has been developed on the Ion Torrent sequencing platform with an AmpliSeq panel to estimate TMB from FFPE and fresh frozen tumor research samples. This solution will advance research in immuno-oncology.

**Legal entity responsible for the study:** Thermo Fisher Scientific.

**Funding:** Thermo Fisher Scientific.


**175P** Microsatellite instability-high (MSI-H) colorectal cancers with elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) signature represent a target population for immune checkpoint and DNA damage therapies


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**Background:** Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) is a different type of genomic instability in colon cancer (CRC) in contrast to mono- and dinucleotide based instability microsatellite instability (MSI). In this study, we performed comprehensive genomic profiling (CGP) of CRC patients with different EMAST and MSI status to understand their genomic structure, which may help match them with relevant therapies.

**Methods:** 99 formalin-fixed, paraffin-embedded (FFPE) CRC tissues consisting of four subtypes based on their EMAST and MSI status, namely (1) EMAST+ and MSI-high (MSI-H), (2) EMAST+ and microsatellite-stable (MSS), (3) EMAST- and MSI-H, and (4) EMAST- and MSS, were subjected to next-generation sequencing (NGS) with a 440-gene panel to identify mutations and copy number variants (CNVs). Tumor mutational burden (TMB) was determined using mutations detected on exonic regions sequenced and CNV index was calculated to infer genome instability.

**Results:** In line with previous studies, the prevalence of TP53 (17.6%, n = 3) and APC (23.5%; n = 4) mutations was much lower whereas BRAF V600 mutation (41.2%; n = 7) was much higher in the subtype (1) CRCs which had both MSI-H and EMAST signatures. Interestingly, these dual positive tumors had a significant higher TMB and lower CNV index than other subtypes (TMB: (1) vs (2), (3), and (4); 54 vs 19, 25; and CNV index: (1) vs (2), (3), and (4); 3.9 vs 13.7, 9.9, and 17.8; p < 0.014, 0.006, and 0.0003), suggesting there are more likely to benefit from immune checkpoint inhibitors. Notably, ATM and ARID1A genes mutated in a mutually exclusive way in up to 13/17 (76.5%) of tumors with MSI-H and EMAST signatures, which may predict treatment benefit from the PARP inhibitors.

**Conclusions:** MSI-H and EMAST+ CRCs show distinctive genomic features that give them the potential opportunity for checkpoint inhibitors in combination with PARP inhibitors.

**Legal entity responsible for the study:** ACT Genomics.

**Funding:** Has not received any funding.

**Disclosure:** K.T. Tan, S-I. Chen: Shareholder: ACT Genomics. All other authors have declared no conflicts of interest.

**176P** Levels of circulating fibroblast growth factor (FGF) 23 and prognosis of cancer patients with bone metastasis


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**Background:** The FGF signaling network plays a key role in tumorigenesis and is recognized as a potential therapeutic target. FGF23 is predominantly expressed in bone osteocytes and can act as an autocrine, paracrine and/or endocrine growth factor in cancer. In this study, we aimed to assess the role of circulating FGF23 levels in the prognosis of cancer patients with bone metastases.

**Methods:** This study included a cohort of 112 patients with cancer (63% breast;16% prostate) and metastatic bone disease treated with bone targeting agents (BTA), in which serum baseline FGF23 was quantified by ELISA and further dichotomized in two groups (FGF23<60pg/mL and FGF23≥60pg/mL). Cut-off was defined by mean + one standard deviation. The association of FGF23 with overall survival (OS) and with time to skeletal related events (TSRE) was investigated. Time to event outcomes was calculated using the Kaplan-Meier method and tested using univariate/multivariate Cox regression models controlling for established prognostic factors across patients with solid tumors and bone metastases: extra-bone involvement, urinary N-terminal telopeptide (uNTX), presence of bone fractures, and castration.

**Results:** Mean FGF23 was 38.16 ± 26.15 pg/mL (interquartile range [IQR] 19.77-50.72). 16.8% of patients were classified as FGF23≥60pg/mL (n = 19). Baseline characteristics were balanced between groups, except for the median uNTX level, which was higher in the FGF23≥60pg/mL group (84.30 vs 118.02 nmol BCE/mmol creatinine, p = 0.046). Median time from beginning of BTA was similar between groups (1.28 vs 1.10 months, p = 0.161). After a median follow-up of 26.0 months [IQR 13.0-47.0], median OS was 34.4 months in the FGF23≥60pg/mL group and 12.2 months in the FGF23<60pg/mL (multi- variate HR 0.18, 95% CI 0.07 – 0.44, p = 0.001; univariate p = 0.001). As a continuous variable, FGF23 at baseline kept its prognostic association (p = 0.001). Patients with FGF23≥60pg/mL status at baseline had a longer TSRE (13.0 vs 2.0 months, p = 0.04).

**Conclusions:** In this exploratory cohort, patients in the FGF23≥60pg/mL had a longer OS and TSRE. Further studies are warranted to define its role as a prognostic biomarker and as a potential predictor of response to drugs targeting the FGF axis.

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**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

**176P** Clinical significance of RCAS1 and CD3 expression in non-small cell lung cancers in immunotherapy era


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**Background:** Lung cancer is the first cause of cancer related deaths. RCAS1 (Receptor-binding Cancer Antigen expressed on SiSo cells) is a protein that is expressed in different types of cancer and seems to be involved in the process of the tumour cells’ escape from the immune system surveillance (immunoscape). CD3 (Cluster of differentiation CD3), is an antigen that is part of the T cell receptor (TCR) complex on a mature T lymphocyte. Tumor infiltrating lymphocytes (TILs) have been correlated with patients’ survival in several neoplasms.

**Methods:** The aim of this study was to evaluate the clinical importance of RCAS1 and CD3 expression in non-small cell lung cancer (NSCLC). Tissue microarrays of tumor specimens from 112 patients with newly diagnosed NSCLC were constructed. The sections were stained with monoclonal antibodies against RCAS1, Ki-67 and CD3 using immunohistochemistry and they were studied through classical pathological evaluation and computerized image analysis. Correlations among RCAS1, Ki-67 and CD3 expression, clinicopathological variables and survival were analyzed. In all cases p-value ≤ 0.05 was considered significant.

**Results:** 112 patients were included in this study with mean age 63.6 years old and 83% were males. RCAS1 expression was higher in grade III tumors comparing with grade I (p = 0.004) and grade II (p = 0.005) regardless of the histological type and in adenocarcinomas with lymphovascular invasion (p = 0.014). A positive correlation between RCAS1 and Ki-67 levels was observed (p = 0.002). There was an inverse correlation of overall survival with RCAS1 and Ki-67 levels and patients with higher expression of RCAS1 or Ki-67 had a significantly shorter survival. Also, an inverse correlation between RCAS1 expression and the percentage of CD3+ TILs was found. Finally, a positive correlation between the percentage of CD3+ TILs and the patients’ overall survival (p = 0.094) was observed.

**Conclusions:** CD3 expression was negative correlated with RCAS1 and positive with overall survival in patients with NSCLC. RCAS1 could be a useful biomarker indicating tumor aggressiveness and immunoscape of cancer cells. Further studies needed to elucidate the possible role of RCAS1 as a biomarker in immunoscape era.

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**Disclosure:** All authors have declared no conflicts of interest.
Conclusions: The utility of malignant pleural effusion (MPE) as a source of tissue for determining EGFR mutations to guide EGFR TKI therapy in advanced adenocarcinoma of the lung (LUAD) remains unclear. This study compared MPE, plasma and tumor to assess if MPE could be utilized as a source of tissue for EGFR mutational analysis in LUAD patients.

Methods: MPE samples were obtained before chemotherapy, six BC cell lines, and 10 normal breast autopsy samples. Genome-wide DNA methylation profiling of a collection of breast tissues and cell lines were performed. A total of 114 genes that distinguish between high- and low-methylated BC subtypes. Noteworthy are the genes of adenylate cyclases ADCY4, ADCY8 and adenylyl kinase AKAP3. Genes that define the classical cancer suppressor genes between epigenetic subtypes of BC, as their expression is compromised in tumors is not compromised by the presence of normal tissues. With a prognostic analysis aimed to identify a relationship between change in NLR during treatment and OS.

Results: Median follow-up was 17 months. Median OS of pts with baseline NLR <4 was not reached (NR) compared with 17.1 months with NLR >4 (HR 0.29, 95% CI 0.13-0.65, p = 0.003). Pts whose NLR started and remained high after 4-6W of treatment performed significantly worse than those with a change in NLR to <4 at this time point. Further analysis of a larger cohort may strengthen this association and potentially allow early identification of poor-risk pts and an opportunity to escalate treatment.

Legal entity responsible for the study: Andrew Haydon.

Disclosure: All authors have declared no conflicts of interest.

178P comparative study of EGFR mutations detected in malignant pleural effusion, plasma and tumor tissue in patients with adenocarcinoma of the lung

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Background: The utility of malignant pleural effusion (MPE) as a source of tissue for determining EGFR mutations to guide EGFR TKI therapy in advanced adenocarcinoma of the lung (LUAD) remains unclear. This study compared MPE, plasma and tumor as sources of tissue for EGFR mutational analysis in LUAD patients.

179P Prognostic value of change in neutrophil-lymphocyte ratio during treatment with first-line anti-PD1 therapy in metastatic melanoma

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Background: With the advent of immunotherapy, the overall survival (OS) of patients (pts) with advanced melanoma has seen significant improvement. Multiple studies have demonstrated a negative correlation between elevated baseline serum neuropeptide-lymphocyte ratio (NLR) and OS in melanoma and other solid tumours. This retrospective analysis aimed to identify a relationship between change in NLR during treatment and OS.

Methods: 83 consecutive pts with metastatic melanoma who received first-line anti-PD1 immunotherapy (mono or combination therapy) were identified at a single institution between May 2015 and August 2017. NLR was measured at baseline and follow-up 4-6 weeks (4-6W) of therapy, with the result at each time point correlated with OS.

Results: Median follow-up was 17 months. Median OS of pts with baseline NLR <4 was not reached (NR) compared with 17.1 months with NLR >4 (HR 0.29, 95% CI 0.13-0.65, p = 0.003). Pts whose NLR started and remained high after 4-6W of treatment performed significantly worse than those whose NLR fell to <4 at 4-6W (median OS 6.5 months vs NR, HR 0.18, p = 0.028). Survival in the latter group was comparable to those with a baseline NLR <4. NLR was more prognostic at 4-6W (HR 0.17, 95% CI 0.07-0.41, p = 0.000091) than at baseline (HR 0.29, 95% CI 0.18-0.65, p = 0.003). On Cox regression multivariate analysis including age, sex, M-stage, lactate dehydrogenase level, presence of brain and/or liver metastases and NLR at the two time points, NLR >4 at 4-6W was the strongest prognostic factor (HR 0.14, 95% CI 0.06-0.37, p < 0.00005).

Conclusions: NLR is a simple and inexpensive prognostic biomarker in metastatic melanoma. NLR >4 at baseline is associated with a significantly poorer OS. In this cohort, NLR at 4-6W was the strongest predictor of outcome. Persistent elevation of NLR >4 at 4-6W after initiation of treatment was associated with a significantly poorer prognosis than those with a change in NLR to <4 at this time point. Further analysis of a larger cohort may strengthen this association and potentially allow early identification of poor-risk pts and an opportunity to escalate treatment.

Legal entity responsible for the study: Andrew Haydon.

Disclosure: All authors have declared no conflicts of interest.

178P Xmal-RRBS DNA methylation screening resolves breast cancer epigenetic heterogeneity

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Background: Breast cancer (BC) heterogeneity calls for molecular subtyping that would assist in personalized treatment. An advantage of DNA methylation markers is that their detection in tumors is not compromised by the presence of normal tissues. With a perspective to develop methylation-based BC diagnostic markers, we have performed a genome-wide DNA methylation profiling of a collection of breast tissues and cell lines.

Methods: Xmal-RRBS method was used to profile DNA methylation of 170 BC samples obtained before chemotherapy, six BC cell lines, and 10 normal breast autopsy specimens. Unsupervised hierarchical cluster analysis was used to discern intrinsic DNA methylation BC subtypes; clustering uncertainty was assessed with pvclust R package using bootstrap permutation approach.

Results: We have identified 10 epigenetic BC subtypes different in the DNA methylation profiles. Of these, BC cell lines constitute a separate extremely high methylated subtype clustering far from any tissues assessed. In turn, BC tissues are classified into two major epigenetic subtypes, high- and low-methylated at the promoter region of genes. We identified 114 genes that distinguish between high- and low-methylated BC subtypes. Noteworthy are the genes of adenylate cyclases ADCY4, ADCY8 and adenylate cyclase stimulators ADORA2B, ADYA1 proteins; of cell adhesion and extracellular matrix (CDH4, NRXN2, MXRAS, COMP, integrins A8 & A11, ADAM19; potassium channels KCNNH, KCN1, KCNG1, KCNR1, KCNQ1, ATP1A1). More than a third among differentially methylated are homologous genes (VAX2, TLLA, GSK1, IRX1, FOXC2, FOXE3, NKX6-2, VSX1, SOX21, POU4F1) and genes encoding proteins involved in early development and morphogenesis (ZIC1, SPON2, DPPY5, PTO4, TAF4). Expectedly, there is no statistically significant difference in expression of the classical tumor suppressor genes between epigenetic subtypes of BC, as their expression is compromised in tumors is not compromised by the presence of normal tissues. With a perspective to develop methylation-based BC diagnostic markers, we have performed a genome-wide DNA methylation profiling of a collection of breast tissues and cell lines.

179P A serum microRNA expression signature for radiosensitivity of non-small cell lung cancer

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Background: Chemoradiotherapy represents the main treatment for non-small cell lung cancer (NSCLC), especially for the advanced lung cancer. However, the curative effect varies significantly. Many microRNAs are verified to be associated with it and microRNA signature may be a good biomarker to predict the radiosensitivity. Genomic-wide microRNA profiling was analyzed by microarray and validated by qRT-PCR in radio-resistant cell lines and their parent cell lines (A549 and PC9, the corresponding cell lines named A549-R and PC9-R). Then we used colony formation assay to perform the validation by transfecting miRNA mimics into A549 and PC9 for functional verification. Finally, a potential microRNA signature was established by an independent set of non-small cell lung cancer (NSCLC) serum samples and validated by available corresponding formalin-fixed paraffin-embedded tissue (FFPE) samples.

Results: 73 up-regulated and 24 down-regulated miRNAs were found by microarray and 11 up-regulated, 3 down-regulated and 3 non-differentially miRNAs were rechecked by qRT-PCR. A miRNA signature, including miR-1290, miR-2861, miR-25-3p and miR-92a-1-5p was selected for further exploration. Overexpression of miR-1290 and miR-2861 increased the radio resistance of A549 and PC9 while overexpression of miR-25-3p and miR-92a-1-5p reversed the radio resistance of A549-R and PC9-R. The four-miRNAs signature could predict the chemotherapeutic response with high accuracy, 83.4% and 79.5% in both the test (serum samples) and validation (FFPE samples) cohorts respectively.

Conclusions: It is the first report of a miRNA signature for cell lines, serum and tissues. Serum and tissue miRNAs represent novel biomarkers to predict radiotherapy response clinically and may represent potential molecular targets to sensitize resistant cancer.

Legal entity responsible for the study: Shandong Cancer Hospital affiliated to Shandong University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Anti-tNASP antibodies as a diagnostic marker for malignant tumors
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Background: Nuclear Autoantigenic Sperm Protein (NASP), a facilitator of chromatin assembly, is expressed as two splice variants: tNASP, specific for testis and cancer cells, and nNASP, expressed in all somatic cells. Exposure of nNASP to the immune system induces a robust humoral immune response. We suggest that patients with malignancies have a higher level of serum anti-tNASP antibodies than those without malignancies. We hypothesized that detection of anti-tNASP antibodies in serum can be used as a cancer screening test.

Methods: Serum from cancer patients and healthy individuals (negative control) were tested for the presence of antibodies against nNASP using enzyme-linked immunosorbent assay (ELISA) with a recombinant nNASP fragment as bait. A total of 139 serum samples from patients with a known malignancy were tested. These included bladder (11), brain (12), breast (12), endometrial (10), gastrointestinal (10), lung (10), ovarian (10), prostatic (12), skin (10), soft tissue (12), thyroid (10), or urinary (10) malignancy, as well as sera from 10 control patients with no known cancers (negative control).

Results: The majority of samples (56.5%) demonstrated elevated levels of anti-tNASP antibodies compared to negative control: glioblastoma, astrocytoma, colorectal adenocarcinoma, pulmonary adenocarcinoma, laparoscopic ovarian cancer, ovarian serous carcinoma, ovarian adenocarcinoma, bladder urothelial and squamous cell carcinoma, adenocarcinoma of the urinary bladder, prostate adenocarcinoma, and endometrial adenocarcinoma. Samples from patients with melanoma, thyroid, breast carcinomas, and different types of sarcomas demonstrated similar levels of anti-tNASP antibodies as control samples.

Conclusions: Serum anti-tNASP antibody levels are markedly elevated in the majority of cancer patients tested as compared to healthy controls. These data demonstrate that detection of anti-tNASP antibodies is a viable diagnostic approach and has the potential to be used as an early noninvasive screening method for detection of multiple cancers.

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Disclosure: All authors have declared no conflicts of interest.

Neoadjuvant biomarker research study of palbociclib combined with endocrine therapy in estrogen receptor positive/HER2 negative breast cancer: The phase II NeoRHEA trial
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Background: Palbociclib (P) is a CDK4/6 inhibitor used in combination with endocrine therapy (ET) in metastatic estrogen receptor (ER)+/HER2- breast cancer (BC). The role of P in early BC treatment is currently being tested in phase III trials. Biomarkers that help us predict primary resistance to P may lead to better patient selection and thus avoid toxicity and reduce costs. In vitro studies suggest that CDK4 T172 phosphorylation is associated with sensitivity to P and an 11-gene expression signature has been developed that can predict the CDK4 modification profile in breast tumors. In order to identify biomarkers of resistance to P/ET and validate the 11-gene signature, we have launched the NeoRHEA study.

Trial design: Single arm, phase II trial, enrolling patients with ER+/HER2- breast tumors ≥ 15mm, N0-1N1. Subjects will receive 4 months of neoadjuvant P/ET (tamoxifen or fulvestrant or letrozole). Subjects' response to therapy will be evaluated before and after treatment by ultrasound, using WHO criteria. Biopsy samples will be collected at baseline and surgery. Primary objective is to identify biomarkers of resistance to P/ET (defined as stable or progressive disease by ultrasound) using RNA-sequencing of baseline samples. A key secondary objective is to validate the 11-gene signature as a biomarker of resistance to P/ET. Other secondary objectives include: to evaluate the safety of P/ET, to identify biomarkers of resistance to P/ET, defined as residual cancer burden of 3 or high tumour proliferation by the Genomic Grade Index; to understand mechanisms of resistance to P/ET by comparing tumors transcriptome at baseline and at surgery; to assess the role of plasma ctDNA in monitoring response to P/ET. Assuming a resistance rate of 20%-25% and a 10% dropout, 100 subjects are needed to develop a binary predictor. Any biomarker identified will be further validated in other studies e.g. NeoPAL (preliminary agreement in place). Accrual started in July 2017 and 38 patients have been enrolled thus far. The study is expected to be completed in 2019. Trial number is NCT03066621. Study sponsor is Institut Jules Bordet with a research grant from Pfizer.

Clinical trial identification: NCT03066621

Legal entity responsible for the study: Institut Jules Bordet.

Funding: Pfizer.

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Distant disease-free survival (DDFS) according to response category in neoadjuvant endocrine therapy (NET): 6-year analysis in phase III NEOS trial


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Tumor-infiltrating lymphocytes (TILs) as an independent prognostic factor for early HER2+ breast cancer patients treated with adjuvant chemotherapy and trastuzumab in the randomized shortHER trial


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High-dose chemotherapy (HDCT) with hematopoietic stem cell transplantation (HSCT) in high-risk breast cancer (BC) patients with ≥4 involved axillary lymph nodes (ALN): 20-year follow-up of a randomized phase 3 study

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An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients (EORTC QLQ-BC23) - EORTC QLQ-BR45


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Impact of nab-paclitaxel dose reduction on survival of the randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy of weekly nab-paclitaxel (nP) with solvent-based paclitaxel (P) followed by anthracycline/cyclophosphamide for patients with early breast cancer (BC)

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Tumor infiltrating lymphocytes predict benefit from TAC but not from ddAC in triple negative breast cancer in the randomized MATADOR trial (BOOG 2004-04)

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Research-based PAM50 predicts risk of relapse in residual disease after anti-HER2 therapies

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Randomized trial of lisinopril or carvedilol for the prevention of cardiotoxicity in patients with early stage HER2-positive breast cancer receiving trastuzumab

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Real-life utilization of genomic testing for invasive breast cancer patients in Italy and France reduces chemotherapy recommendations

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Background: Oncotype DX® (ODX) is a multigene assay allowing physicians to tailor treatment in HR−, HER2− early-stage breast cancer patients. Clinical validation and utility of ODX have been demonstrated across multiple studies in over 63,000 breast cancer patients worldwide. It provides level 1A evidence and has been incorporated in major international clinical guidelines. A market access program was initiated in 2015 in France and 2016 in Italy to assess real-life test utilization and its impact in current clinical practice.

Methods: The program allows for prospective data collection reflecting real life use of ODX by physicians in various clinical practice settings throughout France and Italy. Patient data were collected through an online dedicated platform including classical pathological and clinical parameters (e.g. histology, tumor grade and size, ER, PR, HER2 and Ki67), patient age, ODX Recurrence Score (RS) Results and recommended treatment both before and after the test results have been reported.

Results: A total of 53 and 19 qualified breast cancer centers, in France and Italy respectively, participated in the program and collected 2632 case reports. Study results demonstrated that ODX is used among a wide variety of patient profiles: 24% N1, 7% Nmic & 69% N0, 11% G1, 64% G2 and 25% of G3, 32% pre-, 8% peri- & 59% are post-menopausal, 34% are 35-50, 52% 51-70 and 13% are older than 70, 13% have Ki67%<10%, 35% Ki67 10-20%, 30% Ki67 20-30% & 18% Ki67>30%, 12% tumor <1cm, 59% 1-2cm and 27% tumor 2.1-5cm. RS distribution is the following: <18 (56%), 18-30 (35%) and >30 (9%). In addition, pre-ODX 60% and 48% patients had a treatment recommendation for chemo-hormonotherapy (CT-HT) in France and Italy respectively. Post-testing, the number of patients recommended CT-HT decreased to 29% and 31% for France and Italy respectively, highlighting that the test reduced unnecessary use of CT and homogenized treatment decisions.

Conclusions: In France and Italy, the use of the ODX test results in an overall reduction in CT recommendations, while also identifying patients more likely to benefit from CT.

Legal entity responsible for the study: Genomic Health SARL.

Funding: Genomic Health SARL.

Disclosure: S. Barni, F. Cognetti: Medical Consultant: Genomic Health. All other authors have declared no conflicts of interest.
Background: Invasive lobular carcinoma (ILC) is the second most common histologic breast cancer subtype and represent approximately 10% of all breast cancers. Despite this high frequency, benefit of adjuvant chemotherapy (CT) in ILC is still unclear.

Methods: Our objective was to investigate the impact of CT on survival in ILC. Patients were retrospectively identified from a cohort of 23,537 patients who underwent primary surgery in 18 French centres between 1990 and 2014. Only ILC, hormone positive, HER2-negative patients who received adjuvant endocrine therapy (ET) were included.

Endpoints were disease-free survival (DFS) and overall survival (OS). A propensity score was used. Ten-year estimates DFS in case-matched patients for propensity score analysis were 90% (95% CI [87%-93.4%]) in the ET + CT group vs. 66% (95% CI [61.4%-71.4%]) with ET alone and 10 year estimates OS were 96% (95% CI [93.8%-98%]) in the ET + CT group vs. 71% (95% CI [66.6%-76.2%]) with ET alone. Regarding subgroup analysis, low-risk patients without CT did not have significant differences in DFS or OS compared to low-risk patients with CT.

Conclusions: Patients receiving adjuvant ET for hormone receptor-positive, HER2-negative ILC could derive significant DFS and OS benefits from CT. Our results highlight that patients with high-risk ILC should not be denied adjuvant CT because of such histologic subtype.

Legal entity responsible for the study: Gilles Houvenaeghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 196P Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 5,252)</th>
<th>Baseline Lymphopenia (n = 158)</th>
<th>No Baseline Lymphopenia (n = 5,094)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (Range)</td>
<td>50 (19-92)</td>
<td>48 (31-77)</td>
</tr>
<tr>
<td>TNM Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2672 (50.9)</td>
<td>81 (51.3)</td>
<td>2591 (50.9)</td>
</tr>
<tr>
<td>II</td>
<td>1890 (36)</td>
<td>53 (33.5)</td>
<td>1837 (36.1)</td>
</tr>
<tr>
<td>III</td>
<td>450 (8.6)</td>
<td>18 (11.4)</td>
<td>432 (8.5)</td>
</tr>
<tr>
<td>Subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+/HER2-</td>
<td>3286 (62.6)</td>
<td>90 (57)</td>
<td>3196 (62.7)</td>
</tr>
<tr>
<td>ER+/HER2+</td>
<td>538 (10.6)</td>
<td>19 (12)</td>
<td>539 (10.6)</td>
</tr>
<tr>
<td>ER-HER2+</td>
<td>496 (9.4)</td>
<td>23 (13.9)</td>
<td>474 (9.3)</td>
</tr>
<tr>
<td>ER-HER2-</td>
<td>912 (17.4)</td>
<td>27 (17.1)</td>
<td>885 (17.4)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>983 (18.7)</td>
<td>124 (78.5)</td>
<td>4145 (81.4)</td>
</tr>
<tr>
<td>No</td>
<td>4269 (81.3)</td>
<td>34 (21.3)</td>
<td>949 (18.6)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2957 (56.3)</td>
<td>69 (43.7)</td>
<td>2226 (43.7)</td>
</tr>
<tr>
<td>No</td>
<td>2295 (43.7)</td>
<td>89 (56.3)</td>
<td>2868 (56.3)</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3755 (71.5)</td>
<td>49 (31)</td>
<td>1448 (28.4)</td>
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<tr>
<td>No</td>
<td>1497 (28.5)</td>
<td>109 (69)</td>
<td>3646 (71.6)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3799 (72.3)</td>
<td>108 (68.4)</td>
<td>3691 (72.5)</td>
</tr>
<tr>
<td>No</td>
<td>1453 (27.7)</td>
<td>50 (31.6)</td>
<td>1403 (27.5)</td>
</tr>
<tr>
<td>HBsAg test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>182 (3.5)</td>
<td>14 (8.9)</td>
<td>168 (3.3)</td>
</tr>
<tr>
<td>Negative</td>
<td>4419 (84.1)</td>
<td>126 (79.7)</td>
<td>4293 (84.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>651 (12.4)</td>
<td>18 (11.4)</td>
<td>633 (12.4)</td>
</tr>
<tr>
<td>Baseline Lymphopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>158 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5094 (97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
EBCT at the Yonsei Cancer Center between 2006 and 2015 were included. Baseline complete blood counts data were collected from electronic medical records system.

Multivariable regression models adjusted for age, stage, neoadjuvant/adjuvant chemotherapy, subtype were used to evaluate associations between baseline absolute lymphocyte count (ALC) and OS/BCSS/DRFS.

Results: A total of 5,785 stage I–III EBCT patients were underwent breast surgery from 2006 to 2015; 533 patients were excluded due to lack of complete data (n = 282) and the diagnosis of second primary cancer (n = 270). Median follow-up duration was 72.73 months (95% confidence interval (CI), 73.85-75.64). Of 5,252 eligible patients, only 159 (3.0%) had baseline lymphopenia (ALC < 1,000/mL). The incidence of baseline lymphopenia was similar among age group, stage, and subtype, but patients with HBsAg (+) showed higher baseline lymphopenia than HBV negative patients (7.7% vs. 2.9%, p < 0.001). In univariate analysis, baseline lymphopenia was significantly associated with poor OS, BCSS and DRFS. In multivariable analysis, baseline lymphopenia predicted lower DRFS HR: 0.502, 95% CI, 0.307-0.820. The prognostic significance of baseline lymphopenia regarding to DRFS was highest in HER2 positive subtype.

Conclusions: Baseline lymphocyte counts predicted distant recurrence in early breast cancer.

Legal entity responsible for the study: Gun Min Kim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

### 197P A propensity score analysis exploring the impact of the addition of adjuvant chemotherapy (aCT) to hormone therapy (aHT) in a multi-center series of resected luminal early stage pure invasive lobular breast cancer (ILC)


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**Background:** Patients (pts) resected for luminal early breast cancer are assigned to receive aCT according to international guidelines based upon clinico-pathological features, regardless of the histotype, given the lack of prospective data for ILC. Thus, the aim of this analysis was to investigate the effect of aCT in a multi-center series of luminal early stage pure ILC.

**Methods:** Clinico-pathological data of consecutive pts affected by luminal pure ILC, undergone surgery between 2000 and 2014, were correlated with disease-free and overall survival (DFS/OS) using a Cox model. A propensity score analysis was performed to evaluate the prognostic impact of aCT. Kaplan-Meier curves were compared with Log-Rank analysis.

**Results:** Data from 576 pts were gathered (median age 58 years (yrs)). At median follow-up of 72 months, 5%-10% DFS and OS were 81.5%/71.8% and 91.8%/80.4%, respectively. Tumor-size according to TNM (T, HR 1.78, 95% CI 0.91-3.49, p = 0.09) and lymph-node (N) status (HR 2.97, 95% CI 1.69-5.19, p < 0.0001) were independent predictors for DFS at multivariate analysis. N status (HR 3.93, 95% CI 1.79-8.70, p = 0.001), K67 (HR 2.66, 95% CI 0.92-7.70, p = 0.072), and age (HR 2.32, 95% CI 1.09-4.93, p = 0.029) were predictors for OS. A significant prognostic effect of aCT upon OS was found after adjusting for T, N, K67, grading and age at diagnosis with the propensity score method, as shown in the table. Particularly, aCT significantly prolongs DFS in pts with T > 2 (p = 0.03) and OS in pts with K67 > 4% (p < 0.0001).

**Table 1: 197P**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Category</th>
<th>5-yr (%)</th>
<th>10-yr (%)</th>
<th>Log-Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>aHT</td>
<td>76.6</td>
<td>54.4</td>
<td>0.08</td>
</tr>
<tr>
<td>DFS</td>
<td>aCT + aHT</td>
<td>85.0</td>
<td>76.4</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>aHT</td>
<td>80.9</td>
<td>55.6</td>
<td>0.001</td>
</tr>
<tr>
<td>OS</td>
<td>aCT + aHT</td>
<td>98.1</td>
<td>95.9</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Despite the retrospective nature of this analysis, the propensity score analysis indicates that pts with luminal ILC may significantly benefit from the addition of aCT to aHT in terms of long-term survival, particularly for larger and more aggressive tumours.

Legal entity responsible for the study: University of Verona.

Funding: University of Verona.

Disclosure: All authors have declared no conflicts of interest.

### 198P Benefit of adjuvant systemic therapies in HR+/- HER2- pTab node-negative breast carcinos


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**Background:** Hormone receptor-positive, HER2-negative, pTab N0 breast cancers (BC) are generally estimated as having a low risk of recurrence after locoregional treatment and adjuvant treatment decisions could be challenging. We examined the impact of endocrine therapy (ET) +/- chemotherapy on outcomes in this population.

**Methods:** A total of 4,788 patients with pTab N0 HR+/- HER2- BC were identified from a large cohort of 22,475 consecutive patients who underwent primary surgery at 15 French centres between 2000 and 2014. Endpoints were disease-free survival (DFS) and overall survival (OS). Analyses of causal effect using propensity scores were realized using a logistic regression including age, tumour size, histology, grade, and lymphovascular invasion (LVI).

**Results:** Of 4,779 patients with pTab HR+ HER2- BC, 846 patients did not receive any adjuvant treatment and 3,933 received ET, among which 251 received chemotherapy. Age ≥70y, ducial histology, high grade and tumour size ≥5mm were independently associated with ET prescription. Age ≥50y, LVI and grade 2, were independently associated with chemotherapy prescription. At a median follow-up of 47.7 months, ET was independently associated with a significant DFS benefit in multivariate analysis (HR: 0.60 (0.41-0.89), p = 0.011) with 5-year estimate DFS of 94% (95% CI 92-96%) without ET vs. 96% (95% CI 95-97%) with ET, while addition of adjuvant chemotherapy was not (HR: 0.90 (0.39-2.09), p = 0.813). These results were supported by the analyses of causal effect using propensity scores (HR: 0.48 [0.28-0.83]; p = 0.009 for ET, and HR: 1.54 [0.11-21.8] p = 0.38 for chemotherapy). OS was not significantly impacted by systemic treatments despite a trend for ET in multivariate (HR: 0.60 [0.36-1.00], p = 0.051) and in propensity score analyses (HR: 0.52 [0.24-1.15]; p = 0.092).

**Conclusions:** Adjuvant endocrine therapy is associated with a survival benefit in pTab N0 HR+/- HER2- BC even with a relatively short follow up. Consistent with current consensus guidelines that do not recommend adjuvant chemotherapy in these tumours, we did not find any benefit of adding chemotherapy to ET. These data provide additional clues to the issue of adjuvant systemic treatments in these tumours.

Legal entity responsible for the study: Gilles Houvenaeghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: The anti-proliferative effect of oral metronomic vinorelbine (mVNB) alone or in combination with endocrine therapy in patients with hormone receptor (HR)-positive HER2-negative breast cancer has been scarcely addressed.

Methods: Postmenopausal women with untreated stage I-III breast cancer were randomized (1:1:1) to receive 3 weeks of dexamethasone (LTZ) 2 mg/day, oral mVNB 50mg 3 days/week or the combination. The 1st objective was to evaluate, within PAM50 Luminal A/B disease, if the anti-proliferative effect of mVNB+LTZ was superior to monotherapy. An anti-proliferative effect was defined as the mean relative decrease of the PAM50 11-gene Proliferation Score in each arm. Secondary objectives included safety and the comparison of the anti-proliferative effect between arms. An unplanned analysis of stromal tumor infiltrating lymphocytes (TILs) was performed. PAM50 analyses were performed using the nCounter<sup>®</sup> based Breast Cancer 360<sup>®</sup> panel.

Results: A total of 61 patients were randomized and 54 paired samples (89%) were analyzed. Main patient characteristics were mean age 67.5 years, tumor size 1.7 cm, stage I (55.7%) and grade 1-2 (90%). Grade 3 toxicities occurred in 3.3% of cases. Most base-line samples were Luminal A (74.1%) or B (22.3%). The anti-proliferative effect of mVNB+LTZ (73.2%) was superior to both monotherapy arms combined (49.9% p = 0.001) and mVNB (19.1% p < 0.001). The anti-proliferative effect of mVNB+LTZ (73.2%) was higher compared to LTZ (65.3%) but did not reach statistical significance (p = 0.328). Stromal TILs (70% at week 3) were observed across arms in 66.6% (mVNB), 59% (LTZ) and 60% (mVNB+LTZ) of the cases. In tumors with ≤10% TILs at baseline, a significant increase in TILs was observed following mVNB+LTZ (paired analysis p = 0.012).

Conclusions: mVNB is well-tolerated and presents antiproliferative activity alone and in combination with LTZ. Further investigation comparing these biological results with other metronomic schedules or drug combinations is warranted. Of note, the increase of TILs observed with the combination opens the possibility of studying this combination with immunotherapy.

Clinical trial identification: NCT02802748.

Legal entity responsible for the study: SOBUT Breast Cancer Research Group.

Funding: Pierre Fabre Médicament.

Disclosure: A. Prat: Consultancy: Pfizer, Eli Lilly, Novartis, Nanostring Technologies; Research funding: Novartis, Nanostring Technologies; Scientific advisory board: OncoLogic Biotech. J.A. Perez Fidalgo: Advisory board: Clingen, Pharmamar, Clovis, Other: Substantiation relationships (speaker) Roche, Pharmamar, AstraZeneca, Ipsen. All other authors have declared no conflicts of interest.

199P Anti-proliferative effect of oral metronomic vinorelbine in PAM50 Luminal/HER2-negative early breast cancer (SOLT1-1501 VENTANA): An open-label, randomized, three-arm, multicenter, window-of-opportunity study

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<sup>1</sup>Medical Oncology, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain, <sup>2</sup>Medical Oncology, Hospital Universitari Ramón y Cajal, Madrid, Spain, <sup>3</sup>Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, <sup>4</sup>Medical Oncology, Complejo Asistencial Universitario de León, León, Spain, <sup>5</sup>Medical Oncology, Hospital Clínico Universitario de La Rioja, Logroño, La Rioja, Spain, <sup>6</sup>Medical Oncology, Fundación Instituto Valenciano de Oncología, Valencia, Spain, <sup>7</sup>Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, <sup>8</sup>Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain, <sup>9</sup>Medical Oncology, Vall d’Hebron University Hospital / Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain, <sup>10</sup>Medical Oncology, Hospital Clínic i Provincial de Barcelona / IDIBAPS / SOLTI Breast Cancer Research Group, Barcelona, Spain, <sup>11</sup>Bioinformatics, IDIBAPS / SOLTI Breast Cancer Research Group, Barcelona, Spain.

Abstract: The role of androgen receptor (AR) as a prognostic marker has been proposed in breast cancer. This study investigated AR status and its clinical significance in breast cancer, especially in triple negative breast cancer (TNBC). We also evaluated discordant AR status during the process of lymph node metastasis, locoregional recurrences (LRR) and distant metastasis.

Methods: From January 2005 to December 2010, we retrospectively reviewed 120 patients including 55 TNBC patients diagnosed as invasive carcinoma with no special type (NST), who were treated at the Kangbuk Samsung Hospital. Tissue microarray was constructed and immunohistochemical expression of AR was performed for 120 invasive carcinomas, NST specimens and matching samples from 28 lymph node metastasis, 2 LRR and 8 distant metastases.

Results: AR expression was found in 35.0% (42/120) of the total patients and 14.5% (8/55) of those diagnosed as TNBC. Positive expression of AR was significantly correlated with smaller tumor size, early T stage, fewer lymph node metastases, early AJCC stage, lower histologic grade, estrogen receptor/progesterone receptor positivity, more luminal A type, less TNBC, longer disease-free survival and overall survival, fewer distant metastasis and no deaths from breast cancer (all P < 0.05). AR was a favorable prognostic marker for disease free survival in univariate analysis (P = 0.041). The discordance rate of AR status between primary and recurrent/metastatic disease was 21.6%.

Conclusions: AR expression was associated with favorable clinicopathological outcomes in the whole study population. AR status can be altered during tumor progression.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

201P The outcomes of early breast cancers utilizing the oncoprotein Dx recurrence score (RS) instead of clinicopathological (CP) factors for prognostic risk assessment: A single institution experience

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<sup>1</sup>OncoClinic Centre, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, <sup>2</sup>Pathology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Abstract: Genomic profiling of hormone receptor positive breast cancer outperforms CP factors in predicting the outcomes. This has led to wider application of genomic testing for risk stratification. This can lead to avoidance of chemotherapy in patients with favorable outcomes.

Methods: Patient with TI, T2, node negative estrogen and or Progesterone receptor positive Her 2 Negative breast cancer, regardless of age, menopausal status, Grade or Ki67 were eligible for risk prediction using the Oncotype DX RS. All patient who had RS were included from March 2012- September 2017. The test was sent out and done in reference laboratory (Genomic Health). The original cut off of Low RS (<18), Intermediate RS18-31 and high RS > 31 was used. Patient with low RS were spared chemotherapy. While those high score received chemotherapy. Intermediate risk was preferably given chemotherapy. The changes in therapy based on RS score were reordered as compared to CP factors (St. Gallen Criteria). The disease free and overall survival was analyzed.

Results: Complete data was available for 141 Patients. Median age was 51 years (30-78). 54% premenopausal. 97% ductal histology. Grade correlated with RS. Grade or Ki67 were eligible for risk prediction using the Oncotype DX RS. All patient who had RS were included from March 2012- September 2017. The test was sent out and done in reference laboratory (Genomic Health). The original cut off of Low RS (<18), Intermediate RS18-31 and high RS > 31 was used. Patient with low RS were spared chemotherapy. While those high score received chemotherapy. Intermediate risk was preferably given chemotherapy. The changes in therapy based on RS score were reordered as compared to CP factors (St. Gallen Criteria). The disease free and overall survival was analyzed.

Conclusions: Our data in a younger group of mainly premenopausal women with early breast cancer is consistent with the published data about the prognostic value of RS. A substantial percentage of these patient can be spared chemotherapy and its related toxicity without adversely affecting the long-term outcomes. Utilizing RS in decision making may potentially be cost effective.

Legal entity responsible for the study: The breast cancer group at KFSH.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

202P Circulating tumor cells as a prognostic marker in non-metastatic breast cancer patients

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Abstract: Still, there is no clinically reliable marker to detect micro-metastasis or breast cancer relapse. This study aimed to evaluate the role of circulating tumor cells (CTCs) as a biomarker in non-metastatic breast cancer patients.

Methods: CTCs quantification was carried out using flow cytometry for 50 breast cancer patients post-operatively on three intervals; before starting, after three cycles and at the end of adjuvant chemotherapy. The relationship between CTCs and other tumor characteristics and outcomes were studied.

Results: The median follow-up duration was 35 months. Before starting adjuvant chemotherapy, CTCs were very rare (cut off point =5) in 36% of the patients and dropped to 20% after finishing chemotherapy (P = 0.04). There was a strong negative correlation (r=-0.89) between change in the CTC levels from baseline till mid-treatment (3 cycles)
Molecular subtyping of breast cancer by dedicated breast PET

Breast Surgery, Hiroshima University Hospital, Hiroshima, Japan

Background: Therapeutic strategies for treating breast cancer differ according to molecular subtype. We investigated whether dedicated breast PET (DbPET), a high-resolution molecular breast imaging device, could stratify breast cancer by subtype.

Methods: We included 390 patients with invasive breast cancer who underwent ring-type DbPET between January 2016 and March 2018. The association between SUVmax and various tumor characteristics such as size, nuclear grade, estrogen receptor (ER) status, human epidermal growth factor receptor 2 (HER2) status, and Ki-67 labeling index, were assessed. Tumor subtypes were classified as luminal A-like, luminal B-like, ER−/HER2+, or triple negative on the basis of the St. Gallen International Expert Consensus.

Results: The median patient age was 57 years, the median tumor size was 1.5 cm, and the median SUVmax on DbPET was 6.9. The number of patients with each subtype was luminal A-like in 113, luminal B-like in 85, ER−/HER2+ in 40, and ER−/HER2− in 12, and triple negative in 40 patients. SUVmax significantly correlated with tumor size (P < 0.001), nuclear grade (P < 0.001), ER status (P = 0.004), HER2 status (P < 0.001), and Ki-67 labeling index (P < 0.001). The median SUVmax values of the luminal A-like, luminal B-like, ER−/HER2+, and triple negative subtypes were 4.6, 8.2, 9.5, 16.1, and 10.4, respectively (Table, all values of P < 0.001 relative to luminal A-like). Thus, DbPET distinguished luminal A-like tumor subtype from other subtypes.

Conclusions: DbPET can be used to classify breast cancer into molecular subtypes, which may help determine the necessity of adjuvant chemotherapy. SUVmax, as assessed on DbPET, may thus contribute to the selection of proper therapeutic strategies in invasive breast cancer.

Legal entity responsible for the study: Hiroshima University Hospital.

Disclosure: All authors have declared no conflicts of interest.

Table: 203P

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Median SUVmax (IQR)</th>
<th>P value referred to luminal A-like</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A-like</td>
<td>4.6 (3.0-6.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Luminal B-like</td>
<td>8.2 (4.9-12.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ER+/HER2+</td>
<td>9.5 (5.5-16.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ER−/HER2+</td>
<td>16.1 (7.5-20.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Triple negative</td>
<td>10.4 (4.2-17.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
accounting for tumour size, nodal status, stage, grade, hormone receptor status, HER2 receptor status, histologic type and year of diagnosis, younger age still predicts for a better outcome (p < 0.001).

Conclusions: Younger women diagnosed with early stage favourable histology breast cancers have a better prognosis compared to older women. This will help in counselling on prognosis and management of younger patients.

Legal entity responsible for the study: Guek Eng Lee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

TNBC universe: A monocentric retrospective analyses of TILs and AR as prognostic markers

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Background: TILs have been proposed as a prognostic biomarker in many tumor types both in the adjuvant and neoadjuvant setting. In TNBC, TILs are present at the highest level and have been demonstrated to be associated with better prognosis. TNBC is a highly diverse group of cancers and subtyping is necessary to better identify patient-tailored therapies. Cluster analysis by gene expression identified 6 TNBC subtypes among which the so-called ‘‘luminal androgen receptor subtype’’.

Methods: We retrospectively collected 160 early stage TNBC consecutively treated at our Institution from 2006 to 2015. Data were obtained for clinicopathological patients’ characteristics. On IHC archive slides we analyzed stromal TILs scored as a continuous variable and androgen receptor’s (AR) percentage and intensity of expression. We performed Cox analyses for DFS and for OS, and we used chi-square and Fisher test to evaluate the correlation between TILs, AR and other clinical variables. To define high vs low TILs, an internal dataset cut-off of 10% was considered.

Results: 150 patients were eligible for IHC analyses of TILs and AR. With a median follow-up of 6.5 years, 41 local and/or distant relapse events were observed and 28 patients died of disease. Interestingly, TILs were found to be significantly associated with nodal status (N0 vs N1-3); grading (G2 vs G3) and Ki-67 (<20% vs ≥20%) (p = 0.007, p = 0.055 and p = 0.002, respectively). AR was also significantly associated with proliferation, specifically AR-positive cases presented mostly with a Ki-67<20% (p = 0.008). Probably due to the paucity of events, no statistically significant association of TILs and AR with either DFS or OS was observed.

Conclusions: TILs are a promising prognostic marker, but still prospective validation is needed to integrate them into clinical practice. Among TNBC, the identification of AR-expressing luminal subtype might provide a targeted therapy chance for a low proliferation TNBC subtype. Larger prospective trials are likely to validate TILs prognostic role and to explore the universe of TNBC subtypes targeted therapies opportunities.

Legal entity responsible for the study: Istituto Clinico Humanitas.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Genomic spectrum of Asian breast cancer based on targeted next-generation sequencing in 150 consecutive primary breast cancer

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Background: Application of next-generation sequencing (NGS) enables to reveal genetic diversity of malignant tumors. Here we report our experience with targeted NGS.

Methods: We conducted in a total of 150 primary breast cancer including 98 (65.3%) patients of the luminal/HER2-negative subtype, 28 (18.7%) patients of the HER2 subtype, and 24 patients of the (16.0%) TNBC subtype. Of the 150 patients, 138 patients had 432 genomic alterations including 306 mutations and 126 aberrant copy number variations (CNV). The most common genetic mutation was PIK3CA mutation (64 patients, 42.7%), followed by TP53 mutation (48 patients, 32.0%), TET2 mutation (26 patients, 17.3%) and ERBB2 mutation (6 patients, 4.0%). Of the 6 patients with ERBB2 mutations, 5 patients were in the luminal/HER2-negative subtype and 1 in the HER2 subtype. When ERBB2 amplification excluded, most common CNV was found in FGFR1 (12 patients, 8.0 %) followed by CCND1 (10 patients, 6.7 %). In 35 ER-positi HER2-negative patients who agreed to receive Oncotype DX assay, 18 patients (48.6%) had PIK3CA mutation. In patients with PIK3CA mutation, 13 (72.2%) had a low RS, and 5 patients (28.8%) had an intermediate RS. A patient with RS of 27, which is recognized as high score by the criteria of TAILORx trial, had co-mutations as PIK3CA H1047R and F35L.

Conclusions: Our data with targeted NGS panel suggested that genomic landscape of Asian breast cancer is in accordance with previous NGS studies with Western women. In addition, our subgroup study with Oncotype DX supports early notion that ER-positive breast cancer patients with PIK3CA mutation show a better prognosis compared with those without PIK3CA mutation.

Legal entity responsible for the study: Chihwan Cha.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

The impact of the 21 gene recurrence score (RS) on chemotheraphy (Chemox) prescribing in hormone receptor (HR) positive, lymph node positive (LN+) early-stage breast cancer (BC) in Ireland: A national, multi-centre, prospective study (CTRIAL16-15-34)

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Background: The 21 gene RS has improved the selection of patients (pts) for Chemox in early BC. Internationally, the RS is used in LN + disease, but has not been reimbursed for this indication in Ireland. We conducted a prospective study to determine the extent to which use of the RS could alter Oncologists’ Chemox recommendations in pts with LN + BC.

Methods: Eligible patients had 1-3 LN+, HR+ HER2- BC. All pts gave written informed consent. Baseline demographics were collected. Questionnaires were completed by a Consultant Oncologist before and after the RS, which examined expectations of tumour chemo-sensitivity, strength of Chemox recommendation and type of planned Chemox. The primary endpoint was the % reduction in pts recommended Chemox (N = 75).

Results: RS was available on 74/75 pts; median age 54 (range 32-78) yrs. Most pts had T1 (43%) / T2 (47%), grade 2 (72%) tumours with 1 LN + (68%). The RS was <11 in 10 (13%), 11-25 in 36 (76%) and >25 in 8 (11%) pts. Access to the RS led to a 27% reduction in Chemox recommendations from 68 (92%) to 48 (65%) pts. This was most notable in pts with 1 LN + (46 vs 24) and 2 LN + (13 vs 7). Access to the RS led to a reduction in physician perception of tumour chemosensitivity and strength of Chemox recommendation (Table). Use of the RS led to a decrease in Anthracycline (A)-Taxane (T) Chemox (50 vs 17 pts) and T-based Chemox (30 vs 21 pts) with a resultant increase in non-A, non-T Chemox (8 vs 10 pts). The use of the RS did not impact on Chemox recommendations in women <49yrs (all got Chemox). The biggest reduction in Chemox occurred in women age 51-70 with LIN + (28 vs 18 pts). Overall, in 47 (64%) cases, Oncologists thought the RS significantly changed their treat-ment recommendations.

Table 208P

<table>
<thead>
<tr>
<th>Physican questionnaires before and after RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How sensitive will the tumour be to Chemox?</td>
</tr>
<tr>
<td>10 (13)</td>
</tr>
<tr>
<td>After RS</td>
</tr>
<tr>
<td>21 (28)</td>
</tr>
<tr>
<td>2. How strongly do you recommend Chemox?</td>
</tr>
<tr>
<td>10 (13)</td>
</tr>
<tr>
<td>After RS</td>
</tr>
<tr>
<td>11 (15)</td>
</tr>
</tbody>
</table>

Continued
Table: 208P

Table: 208P Continued

<table>
<thead>
<tr>
<th></th>
<th>Physician questionnaires before and after R5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not very strongly</td>
</tr>
<tr>
<td></td>
<td>Before R5</td>
</tr>
<tr>
<td>7 (9)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>23 (31)</td>
<td>16 (22)</td>
</tr>
</tbody>
</table>

Conclusions: Broader access to the 21 gene RS could result in a reduction in the use of Chemox in Ireland.

Legal entity responsible for the study: Cancer Trials Ireland.

Funding: Genomic Health Company.

Disclosures: P.G. Morris: Honoraria: Genomic Health Company. All other authors have declared no conflicts of interest.

209P Lymphocyte-predominant breast cancer has a significantly lower ANC and tumor-associated neutrophil consisting tumor microenvironment.

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Background: Lymphocyte-predominant breast cancer (LPBC) is defined as tumors having high TIL levels (>50%). Blood cell counts including absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), percentages of ANC and ALC, and neutrophil-to-lymphocyte ratio (NLR) was obtained from pretreatment laboratory data.

Results: Of 577 tumors, 99 (17.2%) was LPBC, and 478 (82.8%) was non-LPBC. When 5 markers of peripheral blood counts were compared, LPBC had a significantly higher mean ANC than non-LPBC (3.671 vs. 3.336, P = 0.004), but other means were not different. Further, in luminal/HER2-negative breast cancer, mean ANC of LPBC was still higher than that of non-LPBC (P = 0.025), whereas it tended to be higher in LPBC in other subtypes (P = 0.385 in HER2, P = 0.260 in TNBC).

Conclusions: Our results suggest that low peripheral ANC might be linked with LPBC, supporting the hypothesis that systemic immune cell counts might be associated with tumor-immune microenvironment. Further study on an association between peripheral ANC and tumor-associated neutrophil consisting tumor microenvironment is warranted.

Legal entity responsible for the study: The Institutional Review Boards of the Kangnam Severance Hospital, Yonsei University, Seoul, Korea.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

210P Genetic alterations of early-stage breast cancers by next-generation sequencing (NGS)

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Background: Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. Patients diagnosed with early-stage generally have better survival. However, disease-free survival differed significantly for different molecular subtypes. Understanding the genetic alterations of early-stage breast cancer may help to identify patients at high risk for relapse.

Methods: We retrospectively reviewed genetic profiling of 53 early-stage breast cancer samples in our institute. Surgical specimens were analyzed using hybridization capture-based NGS ER-seq method, white blood cells as control, which enables simultaneously assess single-nucleotide variants (SNV), insertions/deletions (indel), rearrangements and somatic copy-number variation (CNV) of 1021 genes.

Results: Fifty-three surgical specimens from 51 female patients with early-stage breast cancer were analyzed, including two bilateral primary breast cancers with different molecular subtypes. There were 29 HR+ /HER2-, 6 HER2+ /HER2+ and 12 TNBC. The median diagnosis age was 43 (range 31-67). In addition to TP53, there were 16 genes carried actionable mutations identified (details in table). The most frequently mutant genes were TP53 and PIK3CA, in all molecular subtypes. Among PIK3CA mutations, the H1047R/L were tested in all subtypes. Other gene alterations were highly heterogeneous in different molecular subtypes. HRAS or KRAS mutation was always identified with other genes. For instance, HRAS/PIK3CA and KRAS/AKT1 concurrent in 2 HR+ /HER2-, KRAS/PIK3CA concurrent in 1 TNBC. Interestingly, for the two bilateral primary breast cancers, one patient had no overlapping mutation in 2 samples within total 6 variants, the other one only had common HER2 CNV in 2 samples within total 13 variants.

Table: 210P

Table: 210P

| Signaling Pathways | Genetic Alterations | HR+/HER2- | HER2+ | HR+/HER2+ | TNBC |<br>12 |
|-------------------|---------------------|-----------|-------|-----------|------|
| p53               | TP53                | 14        | 5     | 4         | 11   |
| PI3K/AKT/mTOR     | PIK3CA              | 12        | 3     | 1         | 3    |
|                   | AKT1                | 6         | -     | -         | -    |
|                   | PTEN                | 3         | -     | -         | -    |
|                   | NFI                 | 1         | -     | -         | -    |
|                   | FLON                | 1         | -     | -         | -    |
|                   | recombination       |           | -     | -         | -    |
|                   | BRCA1(gm)           |           | -     | -         | -    |
|                   | repair              |           | -     | -         | -    |
|                   | BRCA2(gm)           |           | -     | -         | -    |
|                   | BRCA2(sc)           |           | -     | -         | -    |
|                   | ATM(gm)             |           | -     | 1         | -    |
|                   | RX/RAf/MAPK         |           | -     | -         | -    |
|                   | HRAS                | 1         | -     | -         | -    |
|                   | KRAS                | 1         | -     | -         | -    |
|                   | Cell cycle          |           |       |           |      |
|                   | RB1                 |           |       |           |      |
|                   | CCND1               | 1         |       |           |      |
|                   | RIKs                | FGR1      | 1     | -         | -    |
|                   |                    | HER2 CNV  | 4      | 5         | -    |
|                   |                    | EGRF CNV  | 2      | 1         | -    |

Conclusions: Genetic alterations were highly heterogeneous in different molecular subtypes of early-stage breast cancers. And this may contribute to the different relapse risk.

Legal entity responsible for the study: Geneplus-Beijing.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

211P Oncotype Dx results in patients ≤ 40 years: Does age matter? New insights

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Background: The 21-gene recurrence score (RS) predicts the benefit of adjuvant chemotherapy (CT) in ER positive, HER2-negative breast cancer (BC) and has been validated in a population where women under 40 are underrepresented. Young BC pts are more likely to receive adjuvant chemotherapy (CT) in addition to endocrine therapy (ET). Our objective was to assess the RS results in young (≤40 yo) vs older (≥40 yo) pts and evaluate the impact of age on clinical decision making according to RS categories.

Methods: We retrospectively reviewed electronic medical files of all patients with early stage hormone receptor BC for whom RS was available between 2007 and 2017 in 3 specialized cancer centers. We used the Mam-Whitney and Chi-squared tests to assess differences between subgroups. Similarly, we evaluated the association between age groups and treatment, within each ODs category. To determine if age was associated with CT use in the low-risk category, a logistic regression model was constructed.

Results: A total of 1391 pts were included, 336 (24.6%) ≤40 yo and 498 (90.4%) > 40 yo. No statistical differences were found between the younger and older groups in T (p = 0.874), N (p = 0.794), stage (p = 0.188), or grade (p = 0.791). Young patients underwent radical surgery more frequently than their older counterparts (41.5% vs 25.7%, p = 0.041). Statistically significant differences were also observed in ER mean, which was lower in the younger group (80% vs 90%, p < 0.01). The median RS result was significantly higher in the younger group (19 vs 16, p = 0.009). Also, high-risk recurrence score category was significantly more frequent in the younger group (22.6% vs 9.2%, p = 0.009). In the intermediate-risk category there were no differences in the
proportion of patients who received CT according to age groups (p = 0.484). In the low-risk category, 28.0% of patients ≤40 years vs 11.3% of patients >40 years received CT (p = 0.037).

Conclusions: Our results indicate that RS tends to be higher in patients with BC ≤ 40 yo and that the frequency of high-risk RS is significantly higher in the younger group suggesting biological differences between groups. 28% of young patients with low-risk RS from our cohort are overtreated. Based on these results, it should be considered to develop a test adjusted to the age of the patients.

Legal entity responsible for the study: Oncosaul.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 213P

<table>
<thead>
<tr>
<th>Main Tumor Profiles (99 of 107 patients)</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>14&lt;Ki67&lt;20% - G2 - N0</td>
<td>5</td>
<td>33</td>
<td>47</td>
</tr>
<tr>
<td>14&lt;Ki67&lt;20% - G2 - N1</td>
<td>0</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>K67=14% - G2 - N0</td>
<td>6</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>K67=14% - G2 - N1</td>
<td>0</td>
<td>13</td>
<td>65</td>
</tr>
<tr>
<td>K67&gt;20% - G2 - N0</td>
<td>2</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>K67&gt;20% - G2 - N1</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>K67&gt;20% - G3 - N0 - T1</td>
<td>0</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>K67&gt;14%- G1 - N1</td>
<td>5</td>
<td>29</td>
<td>4</td>
</tr>
</tbody>
</table>

G: grade; N0/N1: node negative / positive (1 to 3); T1: tumor size ≤ 20mm

Conclusions: Our study showed that a significant proportion of patients were classified in the intermediate risk group, and most were spared chemotherapy. A specific guidance is needed in this risk group.

Legal entity responsible for the study: Centre Oscar Lambret.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 214P

<table>
<thead>
<tr>
<th>Prosigna risk groups</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
</table>
| G: grade; N0/N1: node negative / positive (1 to 3); T1: tumor size ≤ 20mm

Conclusions: Ki67 is an important predictor for oncotype Dx recurrence score risk groups in early breast cancer

Legal entity responsible for the study: Centre Oscar Lambret.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 215P

<table>
<thead>
<tr>
<th>Prosigna risk groups</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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</table>
| G: grade; N0/N1: node negative / positive (1 to 3); T1: tumor size ≤ 20mm

Conclusions: The gene expression profiling assay OncotypeDx (ODx) prognosticates the risk of estrogen receptor positive (ER+) breast cancer (BC) recurrence and assesses the likely benefit from adjuvant chemotherapy in addition to endocrine therapy. There have been several attempts to develop algorithms that provide similar outcome prediction to the ODx assay with the use of routine clinicopathological characteristics. Ki67 is frequently incorporated into these assessments, although there is no standard cut-off for its use. Method: We retrospectively reviewed the electronic medical records of 330 patients with early stage ER+ BC for whom ODx recurrence score (RS) was available. Patients were diagnosed and treated at two specialized cancer centers between 2014 and 2017. Our objective was to determine the ki67’s median differences between ODx risk groups. We used Spearman rho for the correlation between Ki67 and ODx score and used Kuuskala-Wallis test for compare medians, pairwise comparison for the intergroup relations.

Results: Mean age at diagnosis was 57.42 years (range 28-89). Mean tumor diameter was 15.67 mm. 78.9% were intermediate histologic grade and 9.7% patients had lymph node involvement. Median expression of ER and PR were 90% (5-100) and 70% (0-100), respectively. We assessed the correlation between Ki67 and ODx score, with a Pearson r=0.31, p<0.001. The data showed a directly proportional trend between Ki67 and ODx score. Median Ki67 was 20 (1-100). According to ODx RS, 61.5% of tumors were low-risk, 30.3% were intermediate risk and 8.2% were high risk. Median Ki67 within each category group is as follows: low: 15 (IQR:15), intermediate: 20 (IQR:18) and high: 40 (IQR:35), with a statistically significant difference between medians (p < 0.001). In the Pairwise comparison intergroup the data showed: Low-Intermediate (p < 0.05), Low-High (p < 0.001), Intermediate-High (p < 0.001).

Conclusions: The data showed directly proportional trend between Ki67 and ODx score. In our population there is a statistically significant difference between Ki67 medians according to ODx risk groups.
Background: PAM50 (Prosigna®) identifies a gene-expression profile that categorises early breast cancer (BC) in intrinsic subtypes and gives prognostic estimation based on a 10 year-recurrence risk score (BOR). The purpose of this study was to evaluate the impact of PAM50’s information on adjuvant treatment decisions.

Methods: Prospective collection of BC cases treated in a Cancer Centre in the last 10 months, in which PAM50 was used to define treatment strategy. Demographic, clinic and pathologic characteristics are described. Concordance between immunohistochemistry (IHC) and PAM50 subtypes were assessed as well as therapeutic decision changes according to risk stratification, using blind revision. Categorical variables were compared using chi-square test.

Results: Inclusion of 101 patients, median age of 52 years (34-79 years). Fifty-five patients (54.3%) were premenopausal, 71 (70.3%) had ductal carcinomas, 71 (70.3%) pT1c, 99 (98%) pG2, 72 (71.3%) pN0, ER positive and HER2 negative: Eighty-five (84.2%) had a PR expression above 20% and 63 (62.4%) had a Ki-67 <15%. Overall discordance rate between BC subtypes by IHC and PAM50 was 34%, (p < 0.001). By IHC, 51 (50.5%) were luminal A-like. Forty-seven (92%) remained luminal A with PAM50 (IHC ROR: 20 (60%), intermediate 16 (34%), high 9 (2%)); 10 (8%) changed to luminal B (intermediate ROR: 1 (25%), high 3 (75%)). Of the 50 luminal B-like tumours (49.5%), 20 (40%) remained luminal B (intermediate ROR: 8 (48%), high 12 (60%) and 10 (60%) changed to luminal A (IHC ROR = 18 (60%), intermediate 12 (40%)). Based on PAM50, adjuvant strategy was changed in 28 patients (28%), (p = 0.001): 15 (54%) changed from endocrine therapy (ET) only to chemotherapy (CT) also and 13 (40%) changed from CT and ET to ET only.

Conclusions: PAM50 availability results in 28% change in adjuvant plan with more cases of chemotherapy. The 34% discordance with classic IHC subgroups, especially in luminal B tumours, underlines the need for more accurate tests in this heterogeneous population to define the adequate adjuvant strategy. A longer follow up is important to evaluate the prognostic value of clinical decisions based on genetic signatures.

Legal entity responsible for the study: Breast Department - IPO-Porto.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Significance of receptors expression, mitotic index and Ki67 in breast cancer patients with Nottingham Prognostic Index (NPI) poor prognosis score

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Background: Nottingham Prognostic Index (NPI) is a used prognostic model for breast cancer patients, but new histological prognostic factors are today defined. We evaluated their effect within patients with poor prognosis NPI score.

Methods: We retrospectively selected 351 non-metastatic breast cancer patients with High NPI score (>5.4). They were classified according to surrogate definition of intrinsic subtypes of breast cancer (St Gallen 2015). Several prognostic factors were evaluated. We used log rank test, cox regression model to evaluate the significance of clinic-pathological factors.

Results: Median age of our population was 50 years. They were luminal A in 30%, Luminal B in 43%, HER overexpression in 10% and basal like in 17%. On univariate analysis, menopausal status (HR = 0.32 [0.13-0.76]), endocrine receptors expression (HR = 0.52 [0.27-1.56]), HER2 overexpression (HR = 3.08 [1.94-10.39]), Mitotic index (HR = 1.05 [1.02-1.09]) and obesity (HR = 3.49 [1.27-9.38]) were significant prognostic factors. There was no prognostic value of age (<53 yrs, Kr 67 cut-off of 20% and nodal cancerate. There was a highly significant difference (p < 0.001) in overall survival between the 6 intrinsic subtypes. Five-year overall survival was 95% for Luminal A, 90% for Luminal B, 56% for HER2 and 36% for basal-like. On multivariate analysis receptors expression and intrinsic subtype were significantly associated to survival (p < 0.05).

Conclusions: In NPI aggressive disease, the most important prognostic factors were receptors expression and intrinsic subtype. The elaboration of a histology-matched NPI score could afford better prognostic evaluation of early stage breast cancer.

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Disclosure: All authors have declared no conflicts of interest.
Impact of hormone receptor status in HER2+ early breast cancer: A paradigm shift in the trastuzumab era


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Background: While hormone receptor-positive (HR+) and negative (HR−) HER2+ breast cancers (BC) are thought to be distinct diseases, only few studies have investigated the impact of HR status in the context of trastuzumab (TRZ)-treated BC. We evaluated the impact of HR status on outcomes of HER2+ early BC, before and after generalization of TRZ.

Methods: Patients were identified from a cohort of 23,374 women who underwent primary surgery in 18 centers between 2000 and 2017. Since the year 2005 marked the generalization of TRZ, we conducted distinct analyses in patients treated between 2000 and 2004 and those treated between 2005 and 2017. Impact of HR status analyses were done with censorship of events occurring after 5 years in both cohorts. Proportionality tests included all events.

Results: Of 979 HER2+ patients, 349 were treated between 2000 and 2004 without TRZ, and 621 between 2005 and 2017, with TRZ-based adjuvant chemotherapy. Endocrine therapy was received by 92 and 94% of HR+ patients, respectively. In the first group, HR status impacted disease-free survival (DFS) in univariate analysis (Hazard ratio: 2.44 [1.43-4.19]; p < 0.001, log-rank test). Conversely, HR status did not significantly impact DFS in the cohort with TRZ (Hazard ratio: 1.34 [0.66-2.71]; p = 0.411). Overall survival was also impacted by HR status in the group treated without TRZ (Hazard ratio: 2.49 [1.23-5.40]; p = 0.009), but not in the TRZ group (Hazard ratio: 0.482). These results were maintained in multivariate analysis including age, LV, lymph node involvement, histology, grade and tumor size. Evolution of Hazard ratio over time for cumulative incidence of first recurrence according to HR status in patients without TRZ showed a non-proportionality of risks on metastatic (p = 0.027, AD-test) recurrence, with a decreasing risk for HR+ over time. Conversely, the analysis of cumulative incidence of first recurrence did not show such a trend in patients treated with TRZ, suggesting the proportionality of the risks over time for HR status.

Conclusions: Instead patients treated without TRZ, HR status was no longer determinist of outcomes when patients received TRZ. These observations are supported by the analysis of Hazard ratio’s evolution over time for cumulative incidence of first metastatic recurrence.

Legal entity responsible for the study: Gilles Houvenaghel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

220P Safety profile of subcutaneous trastuzumab in patients with HER2-positive early breast cancer: The HERMIONE non-interventional prospective study


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Background: The HERMIONE study was conducted to assess, in HER2-positive early breast cancer, the safety profile of subcutaneous formulation of trastuzumab (SC T) in real life in France.

Methods: This prospective, multicenter, noninterventional study included 511 patients planned to be treated in both nonadjuvant and adjuvant settings with a follow-up (FU) of 12 months maximum. The safety analyses concerned 505 patients, either naive (40.4%) or non-naive (59.6%) of intravenous trastuzumab (IV T). According to routine practice, patients received concomitant locoregional radiotherapy (68.7%), endocrine therapy (59.9%) and chemotherapy (37.8%). Primary endpoint was the description of systemic and local Adverse Events (AEs) of SC T assessed by NCI CTCAE: Common Toxicity Criteria. AEs included febrile neutropenia (9.2% of SAEs) and pulmonary embolism (6.6%). Main AEs was CHF in 11.5% of patients and related to SC T only in 4.5%. Injection site pain was the main SC T-related AE (9.1% of patients). Few AEs (1.4%) led to SAEs (6.6%). Main AESI was CHF in 11.5% of patients and related to SC T only in 4.5%. Injection site pain was the main SC T-related AE (9.1% of patients). Few AEs (1.4%) led to SAEs (6.6%). Main AESI was CHF in 11.5% of patients and related to SC T only in 4.5%. Injection site pain was the main SC T-related AE (9.1% of patients). Few AEs (1.4%) led to SAEs (6.6%). Main AESI was CHF in 11.5% of patients and related to SC T only in 4.5%. Injection site pain was the main SC T-related AE (9.1% of patients). Few AEs (1.4%) led to SAEs (6.6%). Main AESI was CHF in 11.5% of patients and related to SC T only in 4.5%

Results: Patients were included in 105 sites between January and November 2015. The median age was 58 years. Over the FU period, AEs occurred in 422 patients (83.6%): 92 AEs (3.8%) were grade ≥ 3, 76 (3.1%) were serious, 87 (3.6%) were SAEs and 336 (13.7%) were related to SC T. Most frequent AEs (> 10% of patients) were asthenia, arthralgia, radiation skin injury, myalgia, hot flush and diarrhea. Main grade ≥ 3 events were radiation skin injury (1.8% of patients) and febrile neutrophenia (4.4%). Serious AEs (≥ 3): included febrile neutropenia (9.2% of SAEs) and pulmonary embolism (6.6%). Main AESI was CHF in 11.5% of patients and related to SC T only in 3.5%. Injection site pain was the main SC T-related AE (9.1% of patients). Few AEs (1.4%) led to permanent SC T discontinuation. Only 1 death assessed as not related to SC T (pulmonary thromboembolism) was reported. QoL analyses showed no deterioration of global health status.

Conclusions: The HERMIONE study showed that the safety of SC T (HERCEPTIN®) in a real-life setting is consistent with the known profile, without new safety concerns or QoL deterioration.

Clinical trial identification: NCT02286362.

Editorial acknowledgement: Stéphanie Molsen, Axial.

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

Editorial acknowledgement: Stéphanie Molsen, Axial.

Legal entity responsible for the study: Hoffmann-La Roche.
Background: Fixed-dose adjuvant subcutaneous (s.c.) trastuzumab (T) has been approved in the treatment of early HER2-positive breast cancer (BC), based on the evidence of its non-inferiority to standard intravenous (i.v.) infusion. Few data from real-life are available regarding cardiac toxicities associated with fixed-dose subcutaneous T administration. We conducted a retrospective study in order to compare cardiac toxicity profile of adjuvant fixed-dose s.c.-T and weight-based i.v.-T, according to anthropometric data which takes into account more than simply weight.

Methods: Patients treated with adjuvant T for HER2-positive breast cancer at Humanitas Research Hospital from December 2013 to October 2017 were evaluated. T was administered at a either fixed dose of 600 mg s.c. or 6 mg/kg i.v., respectively. Data regarding previous chemotherapy, Body Mass Index (BMI), and development of cardiotoxicity (in LVEF > 10% points, to a value < 50%) were extracted from medical records. Four BMI classes were considered: underweight (BMI < 18 kg/m²), normal weight (18-24.9 kg/m²), overweight (25-29.9 kg/m²), and obesity (> 30 kg/m²). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).

Results: A total of 260 HER2-positive BC patients receiving adjuvant T were analyzed. Median age was 56 (range, 32-88), median BMI 23.5 (range, 15.8-50.2 kg/sqm). 156 had a normal weight, 196 patients received s.c.-T and 64 (24.62%) i.v.-T. 156 had a normal weight (18-24.9 kg/sqm), overweight (25-29.9), and obesity (> 30). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).

Conclusion: Cardiac toxicity profile of fixed-dose s.c.-T is consistent with that of weight-based i.v.-T in the real-world setting regardless differences in anthropometric data as BMI. Our study confirms safety of subcutaneous T administration, which still represents a valid and more convenient alternative to intravenous administration.

Legal entity responsible for the study: Istituto Clinico Humanitas.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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**Abstracts**

**223P** Real-life data on the cardiac toxicity of adjuvant fixed-dose subcutaneous trastuzumab in HER2-positive breast cancer

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**Background:** Fixed-dose adjuvant subcutaneous (s.c.) trastuzumab (T) has been approved in the treatment of early HER2-positive breast cancer (BC), based on the evidence of its non-inferiority to standard intravenous (i.v.) infusion. Few data from real-life are available regarding cardiac toxicities associated with fixed-dose subcutaneous T administration. We conducted a retrospective study in order to compare cardiac toxicity profile of adjuvant fixed-dose s.c.-T and weight-based i.v.-T, according to anthropometric data which takes into account more than simply weight.

**Methods:** Patients treated with adjuvant T for HER2-positive breast cancer at Humanitas Research Hospital from December 2013 to October 2017 were evaluated. T was administered at a either fixed dose of 600 mg s.c. or 6 mg/kg i.v., respectively. Data regarding previous chemotherapy, Body Mass Index (BMI), and development of cardiotoxicity (in LVEF > 10% points, to a value < 50%) were extracted from medical records. Four BMI classes were considered: underweight (BMI < 18 kg/m²), normal weight (18-24.9 kg/m²), overweight (25-29.9), and obesity (> 30). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).

**Results:** A total of 260 HER2-positive BC patients receiving adjuvant T were analyzed. Median age was 56 (range, 32-88), median BMI 23.5 (range, 15.8-50.2 kg/sqm). 156 had a normal weight, 196 patients received s.c.-T and 64 (24.62%) i.v.-T. 156 had a normal weight (18-24.9 kg/sqm), overweight (25-29.9), and obesity (> 30). All variables were compared with categorical tests (Pearson Chi-squared with Yates correction or Fisher exact test).

**Conclusion:** Cardiac toxicity profile of fixed-dose s.c.-T is consistent with that of weight-based i.v.-T in the real-world setting regardless differences in anthropometric data as BMI. Our study confirms safety of subcutaneous T administration, which still represents a valid and more convenient alternative to intravenous administration.

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**222P** Comprehensive evaluation of the pharmacokinetic profiles of SB3 and reference trastuzumab

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**Background:** SB3 has been approved by the European Commission as a biosimilar reference of trastuzumab (TRZ). Physicochemical and functional studies showed that SB3 was highly similar to TRZ. Here, the pharmacokinetic (PK) results comparing SB3 and TRZ in cynomolgus monkeys, healthy male subjects, and early breast cancer patients are reported.

**Methods:** PK profiles were evaluated in cynomolgus monkeys following intravenous administration of 25 mg/kg of SB3 or TRZ every week for 4 weeks. In healthy male subjects, the PK equivalence between SB3 vs. EU-TRZ, between SB3 vs. US-TRZ, and between EU-TRZ vs. US-TRZ were assessed in a Phase I, 6 mg/kg single dose study.1 The trough concentration was evaluated in a Phase III study of early breast cancer patients receiving either SB3 or EU-TRZ in combination with neoadjuvant chemotherapy.2 Equivalence was to be concluded if the 90% confidence interval (CI) for the ratio of geometric mean squares means (LM3 Means) of the PK parameters were within the standard margins of 80.00% to 125.00%.

**Results:** Maximum concentration Cmax of time to reach Cmax (Tmax), and the area under the concentration-time curve from time zero to 168 hour (AUC0-168) were similar in cynomolgus monkeys treated with SB3 or TRZ. In 108 healthy subjects, the 90% CI for the AUC from time zero to infinity (AUCinf) and Cmax from zero to the last quantifiable concentration (AUC0-inf) and Cmax for all pairwise comparisons were within the pre-defined equivalence margin. The PK population in Phase III study consisted of 313 patients (SB3, n = 161; TRZ = 152). Mean trough concentrations were similar from cycle 3 to 8 of SB3 ranging from 37.71 to 58.80 µg/mL and TRZ ranging from 39.83 to 53.13 µg/mL and the corresponding 90% CIs fell within the pre-defined equivalence margin. The proportion of patients with Cmax,0 to 24 exceeding 20µg/mL was similar between the treatment groups at each cycle.

**Conclusions:** In addition to the non-clinical study in cynomolgus monkeys, similar PK profiles were well demonstrated between SB3 and TRZ in healthy subjects and in early breast cancer patients. Reference 1. Pivot X et al. Clin Ther. 2016, 38:1665-75; 2. Pivot X et al. J Clin Oncol. 2018; 36:968-74.

**Disclosure:** X. Pivot: Principle investigator: Phase III study of SB3; Consultant and honoraria: Samsung Bioepis. S-J. Song: Y.C. Yoon: Employment: Samsung Bioepis. All other authors have declared no conflicts of interest.

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**Table: 222P**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Time period</th>
<th>Single targeting (S)</th>
<th>Dual targeting (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER -</td>
<td>Oct 15-Nov 17, Dec 16-Nov 17</td>
<td>31 (56%)</td>
<td>34 (62%)</td>
</tr>
<tr>
<td>ER +</td>
<td>24 (44%)</td>
<td>21 (38%)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>55</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>37 (67%)</td>
<td>29 (53%)</td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>18 (33%)</td>
<td>26 (47%)</td>
<td></td>
</tr>
<tr>
<td>pCR (n %)</td>
<td>17 (31%)</td>
<td>34 (62%)</td>
<td></td>
</tr>
<tr>
<td>ER +</td>
<td>11 (35%)</td>
<td>17 (50%)</td>
<td></td>
</tr>
<tr>
<td>ER -</td>
<td>6 (25%)</td>
<td>17 (81%)</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>11 (30%)</td>
<td>22 (76%)</td>
<td></td>
</tr>
<tr>
<td>N-</td>
<td>6 (33%)</td>
<td>12 (46%)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** A substantial increase in pCR rates was observed with dual targeting, regardless of ER and nodal status, reproducing the registration trial data in real-world clinical practice. pCR rates were greater in ER negative patients, regardless of regimen. The small subgroup most likely to achieve pCR were ER negative patients treated with TCHP. The proportion of patients with Cmax,0 to 24 exceeding 20µg/mL was similar between the treatment groups at each cycle.

**Disclosure:** R. Burcombe: Honorarium and advisory board: Roche in 2017 for writing an article (BRN) on HER2 directed therapy for MBC. All other authors have declared no conflicts of interest.
**224P** Neoadjuvant trial of nab-paclitaxel and atezolizumab (Atezo), a PD-L1 inhibitor, in patients (pts) with chemo-insensitive triple negative breast cancer (TNBC)

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**Background:** Achieving a residual cancer burden (RCB) 0-1 portends an excellent prognosis for TNBC pts receiving neoadjuvant (NACT) anthracycline (AC) and taxane chemotherapy while pts with high residual disease (RCB II-III) have a 40-80% recurrence risk. The GeparTrio and Aberdeen trials demonstrated that pts with poor response by ultrasound (US) during NACT had pathologic complete response (pCR) rates of 2-9% even if NACT was changed based on US response. Immunotherapy is a promising strategy for chemo-insensitive TNBC, however, given toxicity and potential for long-term morbidity, pt selection is important.

**Methods:** Pts identified as having chemo-insensitive TNBC with AC using US or through previous participation in a separate trial, ARTEMIS, were eligible. To identify pts having a pathological complete response, we used a 2-stage Gehan-type design, which guarantees an overall type I error rate of 0.05. The protocol would continue to accrue if the observed number of positive responses was not less than the expected number. The 1st randomization required a minimum of 12 and a maximum of 20 patients to achieve a 37% estimated true positive fraction (TPF) with a 0.03 type I error with a 95% confidence interval (CI). Using a 2-stage Gehan-type design, if 3+ pt had an RCB 0-1 in the first 19, the protocol would continue to accrue a total of 37 pts to estimate an RCB 0-1 rate for atezolizumab in chemo-insensitive TNBC for future trials. We report the interim analysis of the first 19 pts.

**Results:** 19 pts enrolled from 02/2016–12/2017. One pt received 1 cycle, then withdrew consent. Median age was 54 (range 35-75). Presenting clinical stage was II in 7 pts and III in 12 pts. Final pathology status was: RCB 0-5; RCB 0-1; RCB 1-2 and RCB II-3; RCB 0-1=6/19 (32%). Toxicity included 6 serious adverse events in 3 pts: fever, elevated creatinine and post-surgical pain. Most common toxicities included fatigue, neuropathy, pain, anemia, rash, elevated transaminases, hyperglycemia, nausea and dyspnea. Six pts required atezol to be held and/or discontinued.

**Conclusions:** The combination of nab-paclitaxel and atezol in patients with triple-negative breast cancer (TNBC) is feasible. The combination was well tolerated and resulted in a 32% pathological complete response in the first 19 pts enrolled. Further studies are needed to confirm these results.

**Clinical trial identification:** NCT02530489.

**Legal entity responsible for the study:** Jennifer Litton.

**Funding:** MD Anderson Moonshot Program, Genentech.

**Disclosures:** J.K. Litton: Advisory boards (without personal compensation): AstraZeneca and Pfizer; Research studies: GSK, EMD Serono, Genentech, Pfizer, AstraZeneca, Novartis; CME with upToDate, med learning group, PER guidelines; NIH PIPO and NCCN guidelines. E.A. Mittendorf: Advisory board: Merck and Sellas; AstraZeneca and Pfizer; Research studies: GSK, EMD Serono, Genentech, Pfizer; Funding: University of Texas, MD Anderson.

**225P** Prognostic implications of circulating tumor cells (CTCs) after neoadjuvant chemotherapy for triple negative breast cancer (TNBC)

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**Background:** ARTEMIS (A Randomized, TNBC Enrolling trial to confirm Molecular Imaging Improves Survival) is a randomized trial to determine if precision guided neoadjuvant chemotherapy (NACT) impacts rates of pathologic complete response in the breast and axillary nodes (pCR). We hypothesized that CTCs in peripheral blood at the time of surgery, after completion of NACT, would be prognostic in TNBC.

**Methods:** Venous Blood taken following completion of NACT and immediately prior to surgery was assessed for CTCs as part of two IRB approved studies, ARTEMIS (2014 – 0185/PAT5-1050) and LAB04-0698. CTCs (per 7.5 ml blood) were identified using the CellSearch System (Menarini Silicon Biosystems). Samples with one or more cells having morphologic criteria for malignancy were deemed CTC+. Log-rank test and Cox regression analysis were applied to evaluate associations between CTC+, pCR, and overall survival.

**Results:** pCR was achieved in 24/68 (35%) patients with TNBC. Twenty-four patients (35%) were CTC+. 3-year overall survival was evaluated in 4 groups of patients: pCR- no CTCs (n = 20), pCR-CTC+ (n = 4), non-pCR-no CTCs (n = 24) and non-pCR-CTC+ (n = 20). Three year OS was higher in the pCR-no CTCs cohort (100%), compared to pCR-CTC+ (50%), non-pCR-no CTCs (83%), non-pCR-CTC+ (19%); log rank p < 0.0001. In this data set, the presence of CTCs was associated with significant risk of death at 3 years [hazard ratio of 12.3 (95% CI 3.4-45.4, p = 0.00002)], whereas a favorable, but non-significant trend was noted for pCR [hazard ratio of 0.2 (95% CI 0.0, 1.4, p = 0.11)].

**Conclusions:** The presence of CTCs at the time of surgery after NACT has prognostic significance beyond that of pCR and should be considered in evaluation of patients for adjuvant clinical trials.

**Legal entity responsible for the study:** University of Texas, MD Anderson.

**Funding:** University of Texas, MD Anderson.

**Disclosure:** All authors have declared no conflicts of interest.

**226P** A prediction model for pathological complete response after neoadjuvant chemotherapy of HER2-negative breast cancer patients

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**Background:** Pathological complete response (pCR) is an established surrogate marker for survival in breast cancer (BC) patients treated with neoadjuvant chemotherapy. Prediction of pCR based on clinical information available at biopsy, particularly the biomarkers estrogen receptor (ER), progesterone receptor (PgR) and Ki-67 expression, might assist in the identification of patients who benefit from preoperative chemotherapy. Although biomarker assessment is mostly reported as the percentage of positively stained cells with values from 0 to 100%, cut-off points are used to classify patients into groups. Aim of this study was to examine established cut-off points and to develop a prediction tool estimating a patient’s pCR likelihood obtained from clinical predictors and these biomarkers as assessed during clinical routine or categorically with established or newfound thresholds.

**Methods:** This study included all HER2-negative BC patients from one German institution treated with neoadjuvant chemotherapy from 2002 to 2017, having complete observations (N = 829). Various logistic regression models for predicting pCR which differ from each other by the usage of the biomarkers were set-up: (M1) continuous biomarkers from 0 to 100% as assessed during clinical routine; (M2) categorical (positive/negative) biomarkers with established thresholds, (M3) categorical biomarkers with newfound thresholds. Prediction accuracy (e.g., AUC) was assessed using cross-validation.

**Results:** A total of 163 (19.7%) patients achieved a pCR. The optimal cut-off points for ER, PgR and Ki-67 were 30%, 10% and 35%, respectively. The prediction model M1 with continuous biomarkers was more precise (cross-validated AUC: 0.865) than the prediction models M2 and M3 (both 0.854). The most accurate model M1 had a sensitivity of 0.80 at a specificity of 0.78. Beside these biomarkers, a patient’s likelihood of achieving a pCR depended on age at diagnosis, clinical tumor stage and grading.

**Conclusions:** Using biomarkers as continuous variables yielded more precise predictions than when used categorically. Therapy decisions should base on predicted pCR- probabilities obtained from multivariable prediction models rather than single biomarker values.

**Legal entity responsible for the study:** Erlangen University Hospital, Erlangen.

**Funding:** Has not received any funding.

**Disclosure:** A. Hartmann: Personal fees: AstraZeneca, BMS, MSD; Grants: Biontech, Nanostripping; Personal fees and non-financial support: Roche, Symmes; Grants: Janssen, Cepheid outside the submitted work. P.A. Fasching: Grants and personal fees: Novartis; Personal fees: Pfizer, Roche, Teva, Celgene Grants: Biontech, outside the submitted work. All other authors have declared no conflicts of interest.
Evaluation of the MammaTyper® as a molecular predictor for complete pathological response (cPR) after neoadjuvant chemotherapy (NACT) and outcome in patients with different breast cancer (BC) subtypes


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Background: MbpRcs are morphologically heterogeneous, frequently triple-negative and resistant to chemotherapy. To better understand why MbpRcs are resistant to chemotherapy, we investigated associations between response to NAST and clinical, morphologic, as well as molecular characteristics in a cohort of MbpRcs patients (pts).

Methods: 19 MbpRcs pts were identified from a prospective cohort of 242 triple-negative breast cancer (TNbc) pts treated with anthracycline-based NAST. Histologic subtype of MbpRc was determined by light microscopy. TNbc subtypes were determined using the Vanderbilt gene expression signatures (GES). Residual cancer burden (RCB) was assessed after surgery.

Results: Of the 19 MbpRcs, 37% (7/19) were matrix producing and 63% (12/19) were not. Analysis of GES revealed the following subtype distributions: mesenchymal (M) (32% (6/19)), mesenchymal stem-like (MSL) (11% (2/19)), basal-like 2 (BL2) (32% (6/19)), immunomodulatory (IM) (11% (2/19)), unstable (UNS) (12% (2/ 19)), basal-like 1 (BL1) (5% (1/19)). Fifty-seven percent (47/81) and 39% (54/122) of the matrix producing and non-matrix producing MbpRcs were of the M/MSL subtype, respectively. Twenty-one percent (4/19) of pts had a pathologic complete response (pCR) and 32% (6/19) of pts had a minimal residual disease (RCB-I) following NAST. MbpRcs that were matrix producing or of the M/MSL subtype were associated with worse response to NAST as none (0/11) of the pts with MbpRc that was matrix producing and/or of the M/MSL subtype had a pCR/RCB-I, compared with 50% (4/8) of the remaining pts (p = 0.018).

Table: 228P Associations between response to NAST and clinical, morphological as well as molecular characteristics

<table>
<thead>
<tr>
<th>pCR/RCB-I (n = 4)</th>
<th>RCB-II/III (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>57.3 (42.4-67.2)</td>
</tr>
<tr>
<td>Mean tumor size - cm (SD)</td>
<td>2.6 (1.2)</td>
</tr>
<tr>
<td>Clinical nodal status</td>
<td></td>
</tr>
<tr>
<td>Negative - n (%)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Positive - n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I - n (%)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>II - n (%)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>III - n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
</tr>
<tr>
<td>1 - n (%)</td>
<td>0</td>
</tr>
<tr>
<td>2 - n (%)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>3 - n (%)</td>
<td>3 (21)</td>
</tr>
<tr>
<td>Metaplastic subtype</td>
<td></td>
</tr>
<tr>
<td>Matrix producing - n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Non-matrix producing - n (%)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>TNbc subtype</td>
<td></td>
</tr>
<tr>
<td>M/MSL - n (%)</td>
<td>0</td>
</tr>
<tr>
<td>BL1/2 - n (%)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Other - n (%)</td>
<td>1 (25)</td>
</tr>
</tbody>
</table>

Conclusions: Analysis of GES suggest that MbpRcs are enriched for subtypes less likely to achieve pCR/RCB-I with NAST (BL2, M/MSL). Matrix-producing (light microscopy) and the M/MSL subtypes (GES) appear to be associated with resistance to anthracycline-based NAST in MbpRc.
Background: HER2+ occurs in 15-20% of BC and is associated with worse prognosis. While previous studies reported that NAT-induced HER2 status at diagnosis was IHC 3+ or 3+ confirmed by SISH in 8. N, all diagnostic tumor biopsies and surgical specimens were assessed for IHC. Results: 108 female pts were included (median age 52yo, range 30-82; TNM stage was III in 68, II in 40. Hormone receptor (HR) were positive (ER and PR) in 68. HER2 status at diagnosis was IHC 3+ in 100 pts and IHC 2+ SISH amplified in 8. NAT, chemotherapy (CT) and all pts/ (taxanes (TA)/) IHC 3+ (p < 0.001). pCR rate was 46% after CT+T/P and 39% with CT alone (p = 0.6). With a median follow-up of 55 months, there were 5 disease-free survival (DFS) events; 4 deaths), and 21% and 50% for pts whose residual tumors became HER2 negative (5 years DFS; 4 deaths; p = 0.002, log-rank test). Of the 60 pts with residual invasive tumor at surgery, 52 remained HER2+ and 8 (13.3%) lost HER2+; 5-DFS and 5-OS is 70% and 84%, respectively, for pts whose tumors remained HER2+ (14 DFS events; 8 deaths), and 21% and 50% for pts whose residual tumors became HER2 negative (5 years DFS; 4 deaths; p = 0.002 and <0.001, log-rank test).

Conclusions: We confirmed the negative prognostic impact of NAT-induced HER2 loss on residual tumor leading to worse DFS. Despite the retrospective design and small sample size, these results suggest the importance of retesting HER2 after NAT, to better refine pts prognosis.

Legal entity responsible for the study: José Luis Passos Coelho.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Complete response (CR) to anthracycline-based chemotherapy using magnetic resonance imaging (MRI) predicts high rates of pathologic complete response (pCR) for triple negative breast cancer (TNBC) patients treated preoperatively with anthracycline and taxane-based regimens

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Background: Predictors of pCR to neoadjuvant chemotherapy (NAC) for breast cancers have been studied extensively. We focused on CR to anthracycline-based chemotherapy using MRI for prediction of pCR, in patients treated with NAC with anthracycline and taxane-based regimens.

Methods: Tumor measurements were done at diagnosis, after anthracyclines and at the end of taxanes. pCR was defined as absence of residual invasive foci and no lymph node involvement. Associations of clinicopathologic parameters with pCR were evaluated with the p < 0.05. All test results with a p value of less than 0.05 were considered significant.

Results: A total of 114 TNBC patients were treated with NAC. Median age was 53 (27-77) years. 44 patients (38.6%) had stage II and 67(58.8%) stage III. Mutation of BRCA was detected in 9 patients and variants of uncertain significance in 5. 49 patients (43%) with tumor size by MRI > 50 mm, 49 (43%) with positive results on fine needle aspiration of axilla (FNAA), and 88 (77.2%) with histologic grade III. NAC regimen consisted in 108 patients (94.7%) of 4 cycles of pirarubicin + cyclophosphamide (CP) and in 3 patients (2.6%) 4 cycles of doxorubicin + CP, followed by taxane-based regimens in 43 patients (97.7%) that pCR. CR was MRI occurred in 22 patients (19.3%) after anthracycline-based regimen. At the end of NAC there were 37 patients (32.5%) with CR by MRI. Association of clinicopathologic parameters with pCR were: 62.8% pCR in patients with tumor size ≤ 50mm (p = 0.389), 51.8% in patients with NAC pCR (p = 0.238), 81.4% in grade III tumors (p = 0.0700), 46.5% pCR in patients with CR by MRI after anthracycline-based regimen (p = 0.0001) and 65.1% pCR in patients with CR by MRI before surgery (p = 0.0001). All the patients with CR by MRI after anthracycline-based regimen had a CR by MRI before surgery.

Conclusions: CR by MRI after treatment with anthracyclines could be a clinically useful predictor of pCR in patients with TNBC treated preoperatively with anthracyclines and taxane-based regimens and patients who not reach CR after anthranciles could benefit from improve taxanes regimen.

Legal entity responsible for the study: Luis Antonio Fernandez Morales.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Impact of breast cancer subtype on survival after lumpectomy versus mastectomy for early stage invasive breast cancer

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Background: Randomized clinical trials (RCT) have demonstrated equivalent survival for breast-conserving therapy with radiation (RT) and mastectomy for early-stage breast cancer. Early-stage breast cancer patients who underwent BCT or mastectomy was studied to observe whether outcomes of BCT were achieved in a single institution series, and whether survival differed by surgery type when stratified by breast cancer subtypes.

Methods: Information was obtained from the institutional breast cancer data base with stage I or II breast cancer between 1990 and 2010, who were treated with either BCT or mastectomy and followed for vital status through December 2014. Con proportional hazards modeling was used to compare overall survival (OS) and disease-specific survival (DSS) between BCT and mastectomy groups. Analyses were stratified by breast cancer subtype.

Results: A total of 3486 women fulfilled eligibility criteria. Women undergoing BCT had improved OS and DSS compared with women with mastectomy (adjusted hazard ratio for OS = 0.69, 95% CI = 0.51-0.95, p = 0.023; adjusted hazard ratio for DSS = 0.68, 95%CI = 0.48-0.96, p = 0.029). 10 year overall survival rate in women undergoing BCT was 95.2% in Luminal A, 94.8% in Luminal B, 84.8% in Luminal HER2+, 91.5% in HER2 enriched and 92.1% in Triple negative. 10 year overall survival rate in women with mastectomy was 91.2% in Luminal A, 82.3% in Luminal B, 89.5% in Luminal/HER2, 86.2% in HER2 enriched and 88.4% in Triple negative. The group achieving greatest benefit in OS and DSS with BCT relative to mastectomy were stage II
Survival outcomes of dose dense neoadjuvant and adjuvant chemotherapy in triple-negative breast cancer patients: Indian scenario

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Background: Breast cancer is the most common cancer in Indian women. Triple-negative breast cancer (TNBC) is associated with poor prognosis at any stage of diagnosis. It is an aggressive disease with a 5-year survival rate of 77% compared to 93% for other subtypes. Prevalence of TNBC in India is higher compared to western populations, making it an important target for early detection and treatment. Potential superiority of dose-dense chemotherapy in comparison with conventional regimen has been recently demonstrated in a meta-analysis in 2017 across various subsets of breast cancer. Aim of the study was to analyse survival outcomes in TNBC treated with dose dense chemotherapy at a tertiary care centre in India.

Methods: Retrospective analysis of patients diagnosed with TNBC stage I-III in last 8 years treated with 2 weekly dose dense AG regimen (adriamycin at 60mg/m2 and cyclophosphamide at 600mg/m2 for 4 cycles followed by 2 weekly Paclitaxel at 175mg/m2) with a control group of patients treated with the conventional regimens. Localised advanced breast cancer (LABC) was defined as T>5cm and N2 disease. Kaplan-Meier method and log rank test were used to estimate survival functions.

Results: 97 patients with ER, PR and Her2neu receptor negative status were evaluated. Median age at diagnosis was 44 years (range 26–68 years). 56.7% had stage II disease, 36% stage III and stage I (7%). Disease free survival (DFS) rate at 2 years and 5 years was 90% ≥ 3% and 75% ≥ 5% respectively. Overall survival (OS) rate at 2 years was 82% ± 6%. 24 patients received NACT out of which 12 (50%) patients had pathCR. The DFS rate did not differ significantly between adjuvant and neoadjuvant subgroups. Early breast cancer and LABC subgroups had a statistically significant difference in DFS rates (p=0.0002).

Conclusions: To our knowledge, this is the first study in India to evaluate survival outcomes of dose dense therapy in TNBC. The improved DFS (79%) and OS (82%) in this high risk subgroup are very promising, especially in patients with early disease. We advocate use of dose dense regimen in all patients of TNBC in curative setting.

Legal entity responsible for the study: Manipal Hospital Ethics Committee.

Disclosure: Has not received any funding.

235P Prognostic factors associated with pathological complete response in early breast cancer patients undergoing neoadjuvant chemotherapy: the importance of Ki-67 and molecular subtype

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Background: Ki-67 immunohistochemical determination is a widely used biomarker of cell proliferation in patients (pts) undergoing endocrine treatment for breast BC. The role of Ki-67 in pts undergoing neoadjuvant chemotherapy (NAC) for early BC remains controversial.

Methods: We analyzed retrospectively data on 137 patients undergoing taxane and/or anthracycline, trastuzumab based NAC. Luminal A was documented in 6 pts, Luminal B in 29 pts, Her-2 positive in 30 pts and triple negative breast cancers (TNBC) in 72 pts. Pathological complete response (pCR) was defined as the complete disappearance of the invasive cancer in the breast and absence of tumor in the axillary lymph nodes examined by axillary clearance.

Results: The pCR rate of the entire cohort was 41.6%. At 2 years 92% of pts who attained a pCR were disease free compared to 80% of pts who did not attain a pCR (log rank test p<0.0147). On univariate analysis factors associated with higher pCR included primary tumor size (T1 68% vs. T2 41% vs. T3 or T4 0%, Chi² p<0.00017), nodal disease (NO 49% vs. N1 39% vs. N2 8%, p=0.02948), ER receptor status (negative 65% vs. positive 14%, p<0.00000), PR receptor status (negative 33% vs. positive 17%, p<0.00002), molecular subtype (TNBC 53.4%, HER2-50% and Luminal A+B was 8.5%, p<0.00002), Ki67 (40–55% vs. 15–39% vs. <15%, p=0.01086) and Stage (I 85% vs. IIA 49% vs. IIB 36% vs. III 5%, p<0.00006).

Conclusions: Factors not associated with a higher pCR included age, menopausal status, extranodal spread and lympho-vascular invasion. In a logistic regression model Ki-67 as a continuous variable (p<0.01203) and molecular subtype (p<0.02228) retained its significance; while tumor size, stage of disease, nodal status, ER and PR loss significance.

Legal entity responsible for the study: The Medical Oncology Centre of Rosebank.

Disclosure: Has not received any funding.

SLND is a valuable tool in breast cancer patients with clinically positive axillary nodes. Methods: We conducted a prospective cross-sectional study on breast cancer patients diagnosed at Milad Hospital of Tehran, Iran from June 2014 to February 2015. Biopsy-proven node positive patients who converted to clinically node-negative following NAC and had a successful SLND (more than three identified SLNs) were included in the study. We used a 2 × 2 contingency table to analyze the feasibility of SLNB (sensitivity, specificity, false negative ratio, and accuracy). STATA statistical software (version 13.0, StataCorp LP, Texas, USA) was used for statistical analysis.

Results: Among 52 patients who entered the study, 47 had a successful SLND (more than three identified SLNs) in whom we achieved a sensitivity of 100% (16/16), false-negative rate of 0% (0/21), a negative predictive value of 100% (16/16), and an overall accuracy of 89.4%. Conclusions: SLND seems to be feasible and accurate in clinically lymph node positive breast cancer patients who achieve a clinically negative node status following neoadjuvant chemotherapy.

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

Disclosure: Milad General Hospital - Iran National Social Security Organization.

236P The accuracy of sentinel lymph node biopsy following neoadjuvant chemotherapy in clinically node positive breast cancer patients: A single institution experience

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Background: Sentinel lymph node dissection (SLND) after neoadjuvant chemotherapy (NAC) is of questionable accuracy. In this study we evaluated the feasibility and accuracy of SLND in breast cancer patients with clinically positive axillary nodes.

Methods: Retrospective analysis of patients diagnosed with TNBC stage I-III in the last 8 years treated with 2 weekly dose dense AC regimen (adriamycin at 60mg/m2 and cyclophosphamide at 600mg/m2 for 4 cycles followed by 2 weekly Paclitaxel at 175mg/m2) and a control group of patients treated with the conventional regimen. Localized advanced breast cancer (LABC) was defined as T >5 cm and N2 disease. Kaplan-Meier method and log rank test were used to estimate survival functions.

Results: 97 patients with ER, PR and Her2neu receptor negative status were evaluated. Median age at diagnosis was 44 years (range 26–68 years). 56.7% had stage II disease, 36% stage III and stage I (7%). Disease free survival (DFS) rate at 2 years and 5 years was 90% ≥ 3% and 75% ≥ 5% respectively. Overall survival (OS) rate at 2 years was 82% ± 6%. 24 patients received NACT out of which 12 (50%) patients had pathCR. The DFS rate did not differ significantly between adjuvant and neoadjuvant subgroups. Early breast cancer and LABC subgroups had a statistically significant difference in DFS rates (p=0.0002).

Conclusions: To our knowledge, this is the first study in India to evaluate survival outcomes of dose dense therapy in TNBC. The improved DFS (79%) and OS (82%) in this high risk subgroup are very promising, especially in patients with early disease. We advocate use of dose dense regimen in all patients of TNBC in curative setting.

Legal entity responsible for the study: Manipal Hospital Ethics Committee.

Disclosure: Has not received any funding.

237P Index BRCA1/2 testing under a multidisciplinary program

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Background: Germline BRCA1/2 mutations are the main cause of Hereditary Breast and Ovarian Cancer syndrome (HBOC). Whenever possible, Index testing should be done in a family member with a previous breast or ovarian cancer (affected individuals, AI) and not in non-affected individuals (NAI). In this review we characterize, decisional process and BRCA1/2 mutation detection rate of index testing in AI and NAI.

Methods: Analysis of all consecutive HBOC files registered from November 2000-December 2017. The BRCAPOSO model was applied to affected patients (pts) and the Tyrer-Cuzick model to all non-affected female individuals. Comprehensive BRCA1/2 analysis was done, including MLPA and c.156_157insAlu testing (Machado PM et al, 2007).

Results: 6112 individuals were counseled and 4642 (76%) consented on genetic BRCA1/2 testing: 3420 (56%) index pts and 1222 (20%) family relatives. Index pts: 3361 (98.3%) had a previous cancer diagnosis (AI) and 59 were NAI. Both groups included mostly women (AI 95.2%; NAI 97%). The mean age for NAI was 40.7 years (20-79) and 79% had at least one-first degree relative with breast or ovarian cancer. Testing decision for NAI: either affected relatives were dead (80%), refused testing (15%) or were unreachable (5%). The global BRCA1/2 detection rate for index pts was 10.44%, being higher (13.6%) for NAI index cases, 18 pathogenic variants: 2 BRCA1, 6 BRCA2. The mean pretest BRCA mutation probability (P) for NAI was 10.72% (range
This was 18.5% for those who tested positive and 9.45% for inconclusive results  ($p = 0.05$). The pre-treatment breast cancer risk was 26.69% for all NA cases, being higher for those found to be BRCA1/2 carriers (36.07% vs 28.04%).

**Conclusions:** Our conservative approach allowed for a detection rate in NA1 that compared favorably to affected index pts. Although some groups propose widespread BRCA1/2 screening we suggest that NA1 should be tested as index only if no cancer relatives are available. Despite the small sample size, the BRCA pre-test probability of 10% or higher seems to increase the detection rate in this subgroup.

**Legal entity responsible for the study:** Fatima Vaz.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** BRCA1 and BRCA2 proteins play a central role in DNA repair process. BRCA1/2 germline mutations predispose breast cancer patients to greater acute hematological toxicity. This has implication for primary prophylaxis with G-CSF.

**Methods:** We included women with primary breast cancers treated with (neo)adjuvant chemotherapy and screened for BRCA1/BRCA2 germline mutations in Geneva (Swiss cohort). The primary endpoint was the incidence of febrile neutropenia following the first chemotherapy cycle (C1). Secondary endpoints were the incidence of grade 3-4 neutropenia, grade 4 neutropenia and hospitalization during C1, G-CSF use, and chemotherapy dose reduction during the entire chemotherapy regimen. Long-term toxicities (hematological, cardiac and neuropathy) were assessed in the Swiss cohort and a second cohort of patients from Lyon (French cohort).

**Results:** Overall, 221 patients were assessed for acute hematological toxicity, including 89.8% of BRCA1 (p = 0.005), 14% of BRCA2 (p = 0.863) and 51% of non-carriers. Grade 4 neutropenia was found in 57% of BRCA1 (p = 0.001), 14% of BRCA2 (p = 0.285) and 64% of non-carriers. Grade 4 neutropenia (88%; p = 0.003) and grade 4 neutropenia and hospitalization during C1, G-CSF use, and chemotherapy dose reduction during the entire chemotherapy regimen. There was no difference between the three groups.

**Conclusions:** Our initial approach integrates data on BRCA1/BRCA2 germline mutations and hematological toxicity. This has implication for preoperative prophylaxis with G-CSF.

**Legal entity responsible for the study:** Intidhar Labidi-Galy.

**Funding:** La Fondation Henriette Meyer.

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** PALB2 germ-line mutations in Russian breast cancer patients: Identification of recurrent alleles and analysis of phenotypic characteristics of the tumors

**Methods:** We included women with primary breast cancers treated with neo/adjuvant chemotherapy and screened for PALB2 germline mutations in Moscow (Russian cohort).

**Results:** Among patients with triple-negative breast cancers, PALB2ute mutations (35% vs. 12%, p = 0.038) and secondary endpoints were the incidence of grade 3-4 neutropenia, 64% of BRCA1 carriers and 6% of non-carriers. Among patients with triple-negative breast cancers, PALB2ute mutations (35% vs. 12%, p = 0.038) and grade 4 neutropenia (73% vs. 28%, p = 0.003) and grade 4 neutropenia (69% vs. 13%, p = 0.0011) were significantly more frequent in BRCA1 carriers compared to non-carriers. Among BRCA1 carriers, the majority of patients were likely to have grade 3-4 neutropenia (28% vs. 0.001), and grade 4 neutropenia (69% vs. 13%, p = 0.001) were significantly more frequent in BRCA1 carriers compared to non-carriers. Among BRCA1 carriers, the majority of patients were likely to have grade 3-4 neutropenia (28% vs. 0.001), and grade 4 neutropenia (69% vs. 13%, p = 0.001). None of those having mutations located in the RING domain (6%) compared to non-carriers. For long-term toxicity analysis, 898 patients were included (167 BRCA1, 91 BRCA2 and 640 non-carriers). There was no difference between the three groups.

**Conclusions:** PALB2ute mutations predispose breast cancer patients to greater acute hematological toxicity. This has implication for preoperative prophylaxis with G-CSF.

**Legal entity responsible for the study:** Institute of Fundamental Medicine and Biology, Kazan Volga Region Federal University, Kazan, Russian Federation, *Chemotherapy Department, Kazan Oncology Center, Kazan, Russian Federation, *National Research Cardiovascular Center, Kazan, Russian Federation

**Funding:** Russian Science Foundation.

**Disclosure:** All authors have declared no conflicts of interest.
Lynch syndrome-associated hereditary mutations cause breast and ovarian cancer: Results from Russian Hereditary Oncogenesics project

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Background: Lynch syndrome is a hereditary disease caused by mutations in DNA mismatch repair system (MMR), which includes MLH1, MSH2, MSH6, PMS2, EPCAM genes. Clinical manifestation of the Lynch syndrome is usually colorectal cancer (CRC), endometrial cancer, uterine cancer and kidney cancer. We aimed to analyze occurrence of mutations in MMR system genes in patients with hereditary breast and ovarian cancer.

Methods: We have analyzed 228 samples of blood from patients with hereditary breast (BC) and ovarian cancer (OC) in Tatarstan Regional Cancer Center, Russia. The criteria for inclusion was at least one out of three observations: Young age of manifestation of breast or ovarian cancer (before 30 y.o. for BC and 55 y.o. for OC), first or second-degree relatives with breast or ovarian cancer, primary multiple BC and OC. The libraries for sequencing were prepared using NimBioGen SeqCapEZ Choice (Roche) with custom gene panel followed by sequencing on MSSEQ platform.

Results: Eighty out of 101 (8%) patients with hereditary OC and five out of 127 (4%) patients with hereditary BC carried pathogenic mutation in one of MMR genes. The average age of manifestation of BC and OC in the patients with Lynch syndrome was 54 y.o. in BC and 56 y.o. in OC respectively. Nine women had first and second-degree relatives with either BC, OC, colon or esophageus cancer. The distribution of affected genes in HBOC cohort was as follows: 3 patients with mutation in MSH6 gene, 4 patients with mutation in MSH2 gene, 2 patients with mutation in MSH2 gene, 3 patients with mutation in MLH1 gene. One patient carried mutation in EPCAM gene.

Conclusions: To date, the clinical standard for screening for Lynch syndrome is the Amsterdam criteria II, which are not oriented to the occurrence of OC and BC in patients, as well as to the presence of these cancers in a hereditary history in patients with colorectal cancer. However, our experience shows that patients with signs of hereditary disease can also have the same mutations in the genes of the MMR system, which determine the Lynch syndrome. Thus, impact of Lynch syndrome-associated germline mutation on other types of cancer should be reconsidered and studied in detail.

Legal entity responsible for the study: Tatarstan Cancer Center.

Funding: The work is supported by the Russian Foundation for Basic Research № 18-415-160090 p_a and according to the Russian Government Program of Competitive Growth of Kazan Federal University.

Disclosure: All authors have declared no conflicts of interest.

Impact of deleterious germline BRCA mutations, addition of taxanes and use of adjuvant endocrine therapy (ET) on anti-müllerian hormone (AMH) levels in early breast cancer (BC) patients treated by adjuvant chemotherapy (CT)

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Background: AMH is a promising biomarker of treatment-induced gonadal damage. The impact of carrying a deleterious germline BRCA mutation, adding a taxane to anthracycline-based CT and using adjuvant ET on gonadal function following CT remains unclear. We assessed the influence of these 3 factors on AMH levels before and after adjuvant CT in EBC patients.

Methods: This monocentric retrospective study included consecutive EBC patients aged 50 years treated with adjuvant FEC CT between 2008 and 2016, known germline BRCA status and available plasma samples before and after CT. AMH levels (ng/ml) were assessed before starting CT, 1 year and over 3 year after diagnosis.

Results: 148 patients were included. 35 (24%) patients harbored a deleterious germline BRCA mutation, 127 (86%) received a taxane following FEC CT and 90 (63%) had adjuvant ET after CT. Overall median age was 55 (range 22-40). In the whole cohort, median AMH levels dropped after adjuvant CT (from 1.69 ± 0.06, p < 0.0001) and slightly recovered after 3 years (0.17 ± 0.001). No difference in baseline (1.94 ± 1.66, p = 0.57) and at 3 years (0.25 ± 0.16, p = 0.43) AMH levels were observed between patients with or without a BRCA mutation. Significant lower AMH levels were observed for patients who received a FEC-taxane regimen as compared to those treated with FEC only CT 1 year after diagnosis (0.04 ± 0.022, p = 0.0006), with no difference at 3 years (0.18 ± 0.06, p = 0.47). Patients treated with adjuvant ET had slightly higher AMH levels than those who did not receive ET 1 year after diagnosis (0.12 ± 0.02, p = 0.008) with no difference at 3 years (0.11 ± 0.20, p = 0.22).

Conclusions: Use of adjuvant CT is associated with a significant and durable alteration in ovarian reserve measured by AMH levels. Addition of taxanes to FEC increased CT-induced gonadotoxicity immediately after CT exposure but not for longer follow-up. Carrying a germline BRCA mutation and using adjuvant ET following CT were not associated with additional negative impact on patients’ ovarian reserve after treatment.

Legal entity responsible for the study: Centre Henri Becquerel, Rouen, France.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Lynch syndrome-associated hereditary mutations cause breast and ovarian cancer: Results from Russian Hereditary Oncogenesics project

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Background: The phase III neoadjuvant GeparOcto trial (NCT02123544) randomised patients with triple-negative breast cancer (TNBC) to receive treatment with intensified dose-dense epirubicin (E), paclitaxel (P), and cyclophosphamide (C) (iPdEPC) or weekly paclitaxel/liposomal doxorubicin (PM), plus carboplatin (CB). Data on germline mutational analysis of patients with TNBC and the correlation with pathological complete response (pCR ypT0/is ypN0) were analysed.

Methods: NGS-based germline mutational analysis of BRCA1/2 and further 16 BC predisposition or candidate predisposition genes was carried out in 393 patients (iPdEPC: n = 194, PMCb n = 199). Deleterious (IARC class 4/5) variants were validated by Sanger sequencing. Detection of copy number variations (CNV) was carried out using an in-house CNV detection tool and established open access tools. Validation of CNVs was performed by either multiple ligation-dependent probe amplification or real-time PCR.

Results: Overall, 69 of 393 (17.6%) patients carry pathogenic mutations in the BRCA1/2 genes. In 324 BRCA1/2 negative patients, 39 patients carry mutations in at least one of the 16 further analysed genes (9.3%). Of those, two patients carry two mutations in the same gene (ATM/CHEK2, PALB2/ARC22) and 28 carry mutations in one gene (n = 2 BRAD1, n = 8 BRIP1, n = 9 FANCM, n = 1 BRCA1, n = 8 PALB2, n = 1 RAD50, n = 1 RAD51C). No mutations were found in CDH1, MRE11A, PTEN, RAD15D, STK11, and TP53. Overall patients with a BRCA1/2 mutation had a pCR of 69.4% vs 46.0% without a mutation (p < 0.001). In the iPdEPC group, patients with a BRCA1/2 mutation had a pCR of 64.7% vs 45.0% without a mutation (p = 0.040); in the PMCb arm, patients with a BRCA1/2 mutation had a pCR of 74.3% vs 47.0% without a mutation (p = 0.005).

Conclusions: Our data confirm that BRCA1/2 germline mutations represent a predictive biomarker for the achievement of pCR following neoadjuvant anthracycline-taxane-containing chemotherapy for TNBC.

Clinical trial identification: NCT02123544.

Legal entity responsible for the study: German Breast Group (GBG).

Disclosure: A. Schneeweiss: Honoraria: Roche, Cellgene, AstraZeneca, Novartis, and Pfizer during the past 2 years. C. Hanisch: Consulting or advisory role: Novartis, Roche, Ameen, and Celgene during the past 2 years; Speakers’ bureau: Novartis, Roche, Ameen, Pfizer, and Celgene during the past 2 years. V. Müller: Honoraria: Ameen, AstraZeneca, Daichi Sankyo, Eisai, Pfizer, Novartis, Roche, and Teva during the past two years; Consulting or advisory role: Euxal, Roche, Pfizer, Ameen, Daichi Sankyo, and Eisai during the past 2 years, EU; Travel, accommodation, or other expenses paid or reimbursed: Roche and Pfizer during the past 2 years. K. Luebbe: Consulting or advisory role: Roche and Novartis during the past 2 years. S. Loibl: Honoraria: Pfizer and Roche during the past 2 years (institution); Consulting or advisory role: Novartis, Pfizer, Roche, and SeaGen during the past 2 years (institution); Research project fund- ing: Abbvie, Ameen, AstraZeneca, Celgene Novartis, Pfizer, Roche, SeaGen, Teva, and Vifor during the past 2 years (institution). All other authors have declared no conflicts of interest.
245P  BRCA1/BRCA2 predictive genetic testing in an Irish population: A missed opportunity

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Background: The diagnosis of a BRCA1/2 mutation has significant implications for both patients and their families, with both screening and prophylactic surgical interventions available. Underutilisation of genetic testing services has been reported in other jurisdictions. BRCA1/2 testing is requested in only 29-53% of eligible women and 11-12% of eligible men, represented a missed cancer prevention opportunity. Possible explanations include lack of family disclosure, poor access or lack of awareness of genetic counselling services, or patient preference. We investigated the rates of BRCA1/2 predictive testing in an Irish population.

Methods: We performed a multicentre, retrospective analysis of 63 pedigrees from two Irish tertiary hospitals over a five-year period (2012-2017). By manually examining pedigrees, we identified eligible family members who should receive BRCA1/2 mutation testing as per national guidelines.

Results: A total of 1048 candidates for predictive BRCA1/2 mutation testing were identified. 318 (30.4%) proceeded to BRCA1/2 mutation testing including 215 (37.5%) females and 99 males (21.9%). Uptake of testing favouring women was statistically significant (T = 3.7, p <.0002).

Conclusions: We demonstrate suboptimal uptake of BRCA1/2 mutation testing in the Irish population, particularly among Irish men. Predictive BRCA1/2 testing and subsequent screening/surveillance/prophylactic intervention in mutation carriers can meaningfully impact breast cancer survival. This represents a missed cancer prevention opportunity for Irish society.

Legal entity responsible for the study: Department of Cancer Genetics, St. James’ Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

246P Incidence and survival among young women with stage I-III breast cancer

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Background: De novo Stage IV breast cancer (BC) is increasing in premenopausal women. Less is known about current incidence and survival among these women with Stage I-III BC.

Methods: A total of 1,048 candidates for predictive BRCA1/2 mutation testing were identified. 318 (30.4%) proceeded to BRCA1/2 mutation testing including 215 (37.5%) females and 99 males (21.9%). Uptake of testing favouring women was statistically significant (T = 3.7, p <.0002).

Conclusions: We demonstrate suboptimal uptake of BRCA1/2 mutation testing in the Irish population, particularly among Irish men. Predictive BRCA1/2 testing and subsequent screening/surveillance/prophylactic intervention in mutation carriers can meaningfully impact breast cancer survival. This represents a missed cancer prevention opportunity for Irish society.

Legal entity responsible for the study: Department of Cancer Genetics, St. James’ Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 246P

<table>
<thead>
<tr>
<th>Stage</th>
<th>HR Status</th>
<th>Grade</th>
<th>10-Year Survival % (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age (years)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>20-29</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>30-39</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>40-49</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>50-59</td>
</tr>
<tr>
<td>Any</td>
<td>+</td>
<td></td>
<td>81.2 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>85.4 (0.5)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>89.2 (0.1)</td>
</tr>
<tr>
<td>+</td>
<td>Low</td>
<td></td>
<td>67.7 (2.0)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>73.8 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>54.2 (5.7)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>44.9 (3.9)</td>
</tr>
<tr>
<td>Stage II</td>
<td>+</td>
<td></td>
<td>62.8 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>73.7 (0.7)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>60.1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td>49.2 (1.2)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td>49.8 (0.8)</td>
</tr>
</tbody>
</table>

Conclusions: Among young women, HR + BR is increasing in incidence and associated with reduced survival for those 20-29. Understanding the etiologies underlying these trends may inform strategies directed toward improving outcomes for these women.

Legal entity responsible for the study: University of Iowa.

Funding: United States Centers for Disease Control and Prevention (U01DD001035) and the Nealie Bell Stevens Fund for Breast Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

246P Toxicity and clinical outcomes of partial breast irradiation (PBI) compared to whole breast irradiation (WBI) for early stage breast cancer: A systematic review and meta-analysis

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Background: There is uncertainty about efficacy and toxicity differences between adjuvant PBI and WBI in women with early-stage breast cancer treated with breast conservation.

Methods: We identified randomized trials that compared PBI to WBI in early-stage invasive breast cancer using PubMed. Odds ratios (ORs), 95% confidence intervals are presented.

Table: 246P

<table>
<thead>
<tr>
<th>OR, 95% CI</th>
<th>P value all/subgroup difference</th>
<th>Weighted absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.28 (1.66-3.15)</td>
<td>&lt;0.001</td>
<td>1.47%</td>
</tr>
<tr>
<td>0.64 (0.25-1.62)</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>1.49 (0.88-2.53)</td>
<td>0.14</td>
<td>0.3%</td>
</tr>
<tr>
<td>1.96 (1.20-3.14)</td>
<td>0.97</td>
<td>-0.1%</td>
</tr>
<tr>
<td>0.94 (0.59-1.47)</td>
<td>0.77</td>
<td>-0.1%</td>
</tr>
<tr>
<td>0.85 (0.44-1.63)</td>
<td>0.37</td>
<td>-0.1%</td>
</tr>
<tr>
<td>0.55 (0.41-0.73)</td>
<td>&lt;0.001</td>
<td>-1.6%</td>
</tr>
<tr>
<td>0.71 (0.42-1.20)</td>
<td>0.41</td>
<td>-1.1%</td>
</tr>
<tr>
<td>0.76 (0.61-0.95)</td>
<td>0.02</td>
<td>-1.1%</td>
</tr>
<tr>
<td>0.79 (0.51-1.22)</td>
<td>0.75</td>
<td>-1.1%</td>
</tr>
</tbody>
</table>
Background: Anthracycline and taxane-based (A+T) chemotherapy (CT) is the current standard adjuvant CT for HER2-negative BC patients. However, anthracyclines can be associated with common and long-term toxicities (e.g. cardotoxicity and leukopenia). After a phase III trial demonstrated that docetaxel+cyclophosphamide (TC) was more effective than doxorubicin+cyclophosphamide (AC), the use of TC has increased. Nevertheless, RCTs could not demonstrate that TC is non-inferior to the standard A+T. This is a systematic review and meta-analysis of RCTs comparing A+T versus TC, as adjuvant CT in HER2-negative BC patients.

Methods: A literature search using PubMed, EMBASE, Cochrane, ASCO and SABCS websites was performed up to March 30, 2018, to identify RCTs comparing TC vs A+T as adjuvant CT in HER2-negative BC patients. Disease-free survival (DFS) and overall survival (OS) were assessed. A subgroup analysis of DFS in hormone receptor positive (HR+) and negative (HR-) disease was also performed. Hazard ratios (HR) and 95% confidence intervals (CI) for DFS were extracted from each trial, and a pooled analysis was conducted using the random-effect model. The Higgins’ I-squared Test was used to quantify heterogeneity.

Results: A total of 8 RCTs that randomized 12,741 early BC patients were included. Five RCTs were published as pooled results: ABC trials comprised 3 RCTs, and PlanB 1 RCT. The comparison of TC versus A+T demonstrated a non-significant benefit in favour of A+T for both DFS (HR 1.08, 95% CI 0.96 - 1.20) and OS (HR 1.95, 95% CI 0.90 - 1.22). The magnitude of the benefit of A+T was more pronounced in patients with HR− disease. Grade 3-4 leucopenia (OR: 1.2, 95% CI:1.068-1.348, p = 0.015) and thrombocytopenia (OR: 1.11, 95% CI: 0.95-1.30, p = 0.28) were the most common toxicities in the TC group.

Conclusions: Globally, our results showed that A+T was associated with a slight non-significant improvement in DFS and OS as compared to TC. Nevertheless, in selected patients such as those with HR+ disease, TC may be considered an alternative option to avoid the toxicities of anthracycline-based CT.

Clinical trial identification: CRD42018090962 - PROSPERO register.

Legal entity responsible for the study: Institut Jules Bordet.

Disclosure: All authors have declared no conflicts of interest.
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Background: This study aimed to compare the diagnostic performance of pre-operative evaluation of contrast-enhanced digital mammography (CEDM) and contrast-enhanced magnetic resonance imaging (CEMRI) and to evaluate the effect of each modality to the surgical management in women with breast cancer.

Methods: This single-institution prospective study was approved by the Institutional Review Board and informed consent was obtained from all patients. From November 2016 to October 2017, 84 patients, who were diagnosed as invasive carcinoma (69/84) and ductal carcinoma in situ (DCIS) (15/84) underwent both CEDM and CEMRI, were enrolled. We correlated the imaging findings and surgical management with pathologic results, and compared the diagnostic performance of both modalities in the detection of index and secondary cancers (multifocality and multicentricity), and occult cancer in contralateral breast. We also evaluated whether CEDM or CEMRI made changes in surgical management of the affected breast attributed to imaging-detected findings.

Results: Eighty-four women were included for analysis. CEDM, in comparison to CEMRI, had a significantly higher specificity (66.7% vs 22.3%, P = 0.021), similar sensitivity (94.6% [78/84] vs 93.5% [81/84], PPF = 0.93 vs 86.0%) and a fewer false positive results (66.7% [19/29] vs 93.3% [14/15]) in detecting index cancer. For detection of secondary cancers on ipsilateral breast and occult cancer in contralateral breast, no significant differences were found between CEDM and CEMRI (all P > 0.05). Regarding changes in surgical management, CEDM made less change (36.9% [31/84] vs 41.7% [38/84] than CEMRI, owing to fewer findings (48.4% [20/35] vs 54.3% [19/35]).

Conclusions: CEDM showed comparable diagnostic performance with CEMRI in depicting index, secondary cancers, and occult cancer in contralateral breast. The CEDM, owing to fewer false positive results, made less change in surgical management compared to CEMRI.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

253P

Relationship between androgen receptor and tumor-infiltrating lymphocytes in triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) is considered a poor prognostic subtype and a heterogeneous entity. Its only treatment is chemotherapy. Immunotherapy and antiandrogen therapies are being tested. Androgen receptor (AR) is expressed in up to 53% of TNBC. It is associated with a better disease-free survival and overall survival. The relation between tumor infiltrating lymphocytes (TIL) and AR in uterine cervical cancers has been assessed, unlike in TNBC.

Methods: 50 stage III TNBC patients diagnosed between 2008 and 2013 were analyzed. Minimum follow-up was 57 months or until death. On these samples fixed in 10% formalin and included in paraffin, the evaluation of the expression of AR, CD20, CD3 and CD8 was performed by immunohistochemistry. AR+ was defined by more than 1% expression. Lymphocytes were evaluated as per the recommendations of the International Expert Consensus. We also analyzed total lymphocytes as high/low if they were over/under 80%. Data was analyzed by SPSS version 23.

Results: Clinical characteristics are as follows: mean age of 61 years old, and postmenopausal 68%. 74% of the patients did not relapse and progression-free survival (PFS) was 95.6 months. Main tumor characteristics were Ki67>20%, 67.3%; T1-T2 88%; high grade 67.4%; lymph node (N) positive 51%. Early stage (stage I-II) was the 80%. High level of lymphocytes (HIL) was present in 70% of them. AR+ was associated with younger patients (p = 0.009), lower Ki67 (p = 0.014) and N+ (p = 0.025). No relation was obtained between AR and TIL, tumor size, grade, stage or survival. CD8+ were more present in AR+ (p = 0.002) and so the proportion CD4/CD8 (CD4+/CD8+) in AR+; CD4+ in AR–, p = 0.026. HIL was related with higher Ki67 (p = 0.021) and grade 3 (p = 0.029). However, lower relapse and also lower deaths were observed in those with HIL, 15.8% vs 84.6%; 21.4% vs 78.6%; in HIL, percentage of CD8+ was inversely proportional (p = 0.021 mean 27.9%).

Conclusions: High grade tumors and higher Ki67 unleash a higher immune response, protecting from a worse prognosis. CD8+ lymphocytes are associated with AR expression. More studies are needed to understand the relationship between AR and TIL and also the role of AR blockade in TNBC and its role in immune-mediated lysis.

Legal entity responsible for the study: Complejo Asistencial Universitario de León.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

254P

Use of redvelver in premenopausal breast cancer patients receiving hormonal adjuvant treatment: Biological and clinical implications from a randomized clinical trial

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Background: Premenopausal women with breast cancer (BC) experience early onset of treatment-induced menopausal syndrome with adjuvant hormone therapy (HT). Isoflavones in the red velvet (RC) are biologically active agents providing a source of rapidly available phytoestrogens acting as natural selective estrogen receptor modulators. Aims of the study are: to improve quality of life reducing menopausal symptoms from HT in BC premenopausal women and preventing weight gain and metabolic syndrome with personal lifestyle intervention; to evaluate in vitro safety profile of BC used in combination with the Oestrogen antagonist. Methods: Eighty-eight premenopausal BC women (DCIS, T1-T2N0M0) receiving adjuvant HT were randomly assigned to have 80 mg/die of RC dry extract (MCE-11) (verum group) or a tablet without active principle (placebo group) for 2 years. The Menopausal Rating Score (MRS) questionnaire was given every three months during the first year then biannually. Diet program was personalized with the WCRF/AICR recommendations and Mediterranean diet. Body Mass Index (BMI), hip and waist circumference, body fat, bone mass, calcium and other parameters (HOMA, IGF-I, Insulin, HbA1C, LDL, HDL cholesterol, triglycerides) were recorded. Pool serum of women from the two groups was run for in vitro evaluation of the safety profile using specific cell lines selected to be representative of hormone-sensitive BC with high expression of estrogen receptor a (MCF7, T47D) and b (BT20).

Results: Menopausal symptoms significantly decreased in both groups over time (p < 0.0001). In the verum group BMI, hip and waist circumference were more reduced than in placebo group (P < 0.0011). HDL cholesterol significantly improved over time (p < 0.01). There was no significant difference in endometrial rhyme, while mammary density significantly decreased in both arms (p < 0.0001). In vitro, no significantly different differences were observed in cell growth and induction of estrogen regulated/related genes in the cell lines treated with serum from women of the two arms.

Conclusions: Isoflavones can be safely used in premenopausal BC women under HT to contrast symptoms related to treatment.


Legal entity responsible for the study: Cristina Ferrandis.

Funding: Named S.p.A.

Disclosure: All authors have declared no conflicts of interest.
RT to lower values than at baseline and were then considered satisfactory (MD 15.6, 19.7, 4.1 and p < 0.001, <0.001, 0.005, respectively). AO scored by the patient and with the BCCT.core associated well with each other and with the body image measures. There was no association between AO and global cancer-related QOL in the present cohort.

Conclusions: Small quality of life impairments present during RT with good recovery up to one year after RT. Body image is disturbed during RT and improves up to two years after RT. Around one third of patients score their long-term AO as unfavourable and these PBOs correlate well with body image.

Legal entity responsible for the study: Caroline Welten.

Funding: KOM OP Tegen Kanker.

Disclosure: All authors have declared no conflicts of interest.

Oncological outcome of fat grafting for breast reconstruction after cancer

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Background: Fat grafting (FG) has become widely used in breast reconstruction after breast cancer (BC). FG might express postoperative factors or after radiological aspect of the breast, raising some concerns on its oncological safety. The aim of the study was to describe clinical outcome of patients (pts) undergoing FG.

Methods: Records of 424 pts who underwent FG between 2010 and 2017 at the Plastic Surgery Dept. of Padova University were reviewed. Pts without invasive BC or not followed at Istituto Oncologico Veneto were excluded, leaving 206 pts for analysis.

Cumulative incidence of relapse was calculated from first FG. Association between clinico-pathological factors and relapse was explored.

Results: Patients were mostly post-menopausal (n = 115, 56%) and the majority had HR+/HER2+. BC (n = 134, 65%). Eight pts (4%) were BRCA-mut carriers. Disease stage at diagnosis was: I (42%), II (34%), III (24%). Median interval from surgery to first FG was 23 months (range 0-257). 336 FG interventions were performed (median per patient: 1, range 1-9). At median follow-up of 58.9 months, 35 pts relapsed (10 locoregional, 25 distant relapses). Cumulative Incidence of relapse according to clinical-pathological factors is reported in the table. Semannal hazard rates of relapse in the three years after FG were: 0.010, 0.035, 0.034, 0.007, 0.009, and 0.038, respectively. 59 pts (29%) underwent additional breast imaging over standard recommendation (range 1-6 per patient), and 40 (20%) pts underwent breast biopsies (range 1-4, 10 confirmed a local recurrence).

Conclusions: This study describes a not negligible rate of recurrence in BC pts receiving FG, especially in stage III and conservative surgery pts. High risk of relapse in the first years after FG might suggest a potential relation between the procedure and events. Moreover, a significant proportion of pts underwent additional breast imaging and biopsies, which can adversely affect quality of life. A careful discussion in multidisciplinary setting is crucial for proper pts selection.

Legal entity responsible for the study: Valentina Guarnieri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Changes in body weight over 18-months follow-up among Chinese patients after breast cancer diagnosis

W. Ye1, Y.Y. Le1, A.C. Cheng2, C.C. Kwak2, K.L. Cheung2, I.C. Lee2, R. Lee2, S. Ho2
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Background: Weight gain has commonly been reported among patients after breast cancer diagnosis in western countries. Based on limited data in the literature, weight gain in Asian counterparts appears to be less. In this prospective study, we investigate the weight changes among Chinese breast cancer patients during 18-month follow-up from diagnosis.

Methods: This is part of the ongoing Hong Kong NTEC-KWC Breast Cancer Survival Study (HKNKBCSS). Chinese patients with newly diagnosed early-stage breast cancer were consented. Studied patients had their weights recorded at breast cancer diagnosis (T0), at study entry (T1; within 12 months from T0) and at 18-month follow-up (T2). Potential associating factors including socio-demographic, lifestyle and clinical factors were assessed.

Results: A total of 1265 patients had detailed weight at the 3 time-points of assessment. The mean age at diagnosis was 51.8 years. The proportion of patients who received chemotherapy, radiotherapy and endocrine therapy were 77%, 70% and 72% respectively. Compared to T0, the median weight change was -0.5 kg (range: -11.4, 18.3) at T1 and 0 kg (range: -18.6, 19.5) at T2. At T1 and T2, 2.4% and 16% of women respectively gained weight between 2-5kg, 0.5% and 4.7% respectively gained >5kg, while 6.1% and 24.2% of women respectively had weight loss >2kg. On univariate analysis, patients who received radiotherapy had more weight loss at T1; no significant difference in weight change was noted with other factors including socio-demographic, lifestyle and clinical factors were assessed.

Conclusions: A total of 1265 patients had detailed weight at the 3 time-points of assessment. The mean age at diagnosis was 51.8 years. The proportion of patients who received chemotherapy, radiotherapy and endocrine therapy were 77%, 70% and 72% respectively. Compared to T0, the median weight change was -0.5 kg (range: -11.4, 18.3) at T1 and 0 kg (range: -18.6, 19.5) at T2. At T1 and T2, 2.4% and 16% of women respectively gained weight between 2-5kg, 0.5% and 4.7% respectively gained >5kg, while 6.1% and 24.2% of women respectively had weight loss >2kg. On univariate analysis, patients who received radiotherapy had more weight loss at T1; no significant difference in weight change was noted with other factors including socio-demographic, lifestyle and clinical factors were assessed.

Legal entity responsible for the study: Valentina Guarnieri.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 256P

<table>
<thead>
<tr>
<th>Clinicopathological factors</th>
<th>Number of patients (%)</th>
<th>3-years cumulative incidence of relapse</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>HR status</td>
<td>HR negative</td>
<td>26 (13%)</td>
<td>1.13 ref</td>
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<tr>
<td>HER2 status</td>
<td>HER2 positive</td>
<td>170 (87%)</td>
<td>1.57 (0.47-5.18)</td>
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<tr>
<td>Stage at diagnosis</td>
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<td></td>
<td>Stage II</td>
<td>67 (34%)</td>
<td>2.84 (1.06-7.62)</td>
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<td>Stage III</td>
<td>47 (24%)</td>
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<td>Interval from surgery</td>
<td>&gt;2 years</td>
<td>99 (48%)</td>
<td>1.07 (0.55-2.08)</td>
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<td></td>
<td>Conservative</td>
<td>26 (13%)</td>
<td>1.00 (0.00-1.00)</td>
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Overall Population 206 (100%) 17% -
Abstract:

Breast cancer diagnosis. Funding: World Cancer Research Fund International (Grant Number WCRF 2010/249 and WCRF 2014/1197).

Legal entity responsible for the study: Joint CIUHK-NTCE Clinical Research Ethics Committee and the KWC Research Ethics Committee.

Funding: World Cancer Research Fund International (Grant Number WCRF 2010/249 and WCRF 2014/1197).

Disclosure: All authors have declared no conflicts of interest.

258P **Incidence of clinically significant toxicities in patients with high endoxifen concentrations**


Background: Tamoxifen is essential in the treatment of estrogen receptor positive breast cancer. Concentrations of its active metabolite endoxifen > 3.97 ng/mL have been associated with a 26% lower recurrence rate in the adjuvant setting (Madlensky 2011). Providing a rationale for therapeutic drug monitoring. However, the risk of high endoxifen concentrations has not been established. Therefore, we investigated whether extremely high endoxifen levels are correlated with a higher incidence of clinically significant toxicities.

Methods: Patients receiving adjuvant tamoxifen treatment (20 mg) with a steady state endoxifen level above 25 ng/mL were retrospectively identified in databases of the CYPTAM study (n = 667, NTR 1509) and of samples collected in routine care (n = 1768). The percentage of patients with clinically significant toxicities, defined as toxicities leading to either dose reduction or treatment discontinuation, was compared to the overall tamoxifen population. As historical comparison, studies described in the EBCOG overview (2011) in which patients received adjuvant tamoxifen (20 mg) and which reported clinically significant toxicities were selected.

Results: 26 patients (1.5%) had an endoxifen level > 25 ng/mL of which 4 patients (15%) had clinically significant toxicities, compared to 10.2% in the overall tamoxifen population (p < 0.001, weighted average of 10 clinical trials, n = 9688, Baum 2002; Margolese 2016; Chirgwin 2016; Berutti 2004; Colleoni 2016; Chirgwin 2016; Leeuwenhoek Hospital, Amsterdam, Netherlands; 5. Department of Medical Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 9. Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; 6. Department of Pharmacy & Pharmacology, The Netherlands Cancer Institute and MC Stichting, Amsterdam, Netherlands; 7. Department of Medical Oncology & Clinical Pharmacology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.

Results: 26 patients (1.5%) had an endoxifen level > 25 ng/mL of which 4 patients (15%) had clinically significant toxicities, compared to 10.2% in the overall tamoxifen population (p < 0.001, weighted average of 10 clinical trials, n = 9688, Baum 2002; Margolese 2016; Chirgwin 2016; Berutti 2004; Colleoni 2016; Chirgwin 2016; Leeuwenhoek Hospital, Amsterdam, Netherlands; 5. Department of Medical Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; 9. Department of Medical Oncology & Clinical Pharmacology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.

Clinical trial identification: CYPTAM study: NTR 1509 (release date 27 October 2008).

Legal entity responsible for the study: The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital.

Funding: Has received no funding.

Disclosure: N. van Leeuwen, J. van Leeuwen: Research funding (all to the institution): Novartis, GSK, Boehringer-Ingelheim, Gilead, Roche, Pfizer, Sanofi. R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Fampgene, Pfizer, Roche and Sanofi; Consultation fees: Novartis, Servier; Travel Support: Astellas, Pfizer, N. Steeghs: Research funding (all to the institution): AstraZeneca, Bayer, BMS, Novartis, GSK, Pfizer, Roche, Boehringer Ingelheim, Blueprint. All other authors have declared no conflicts of interest.

260P **The aesthetic results after oncoplastic surgery in early breast cancer**

A. Zikryahmedian, A. Sulikhorzko, A. Tulmakov

1. Oncology and Plastic Surgery, P.A. Gerzen Moscow Oncology Research Institute, Ministry of Health of Russia, Moscow, Russian Federation; 2. Oncology and Plastic Surgery, Herzen Cancer Research Institute, Moscow, Russian Federation.

Background: To create of the new concept of surgical treatment as a component of multi-therapy treatment of patients with breast cancer on postoperative quality of life (Qol). According to Clough K. B. (2010), the advantage of the oncoplastic approach is the expansion of indications for operations in achieving the best aesthetic results.

"Oncoplastic surgery is the ‘third way’ between standard organ preservation surgery and mastectomy."

Methods: We assessed 370 women who underwent breast conserving surgery (BCS) or total mastectomy (TM) with immediate reconstruction in P.A. Gerzen Moscow Research Institute from 2013 to 2017. Of the 437 patients, 300 (66.4%) had oncoplastic breast surgery. OBS included glandular reshaping (rotation flap, round-block technique, batting mastopexy, wise pattern-inverted T, vertical pattern). The distribution of patients according to the stage of disease was as following: stage I-II – 348 (79.6%), IIIA – 91,4% (p < 0.05). A median follow-up period was 58 months. 94 (21.5%) patients received adjuvant polychemotherapy, combinations adjuvant polychemotherapy and radiation therapy – 27 (6.1%) or endocrine therapy – 376 (5.9%).

Results: During a median follow-up period local recurrent were detected at 5 (1,8%), distant metastasis – 15 (2,6%) patients. Overall disease-free survival in patients with BCS stage I was 96.2%, IIA– 90%, IIB– 86.7%, IIIA– 86.2% (p<0.05). Overall disease-free survival in patients with NNM stage I was 92.9%, IIA– 91.2%, IIB– 84.4%, IIIA – 91.4% (p>0.05). The postoperative cosmetic result after BCS was assessed in 79.3% patients.

Conclusions: In breast reconstructive the most effective method is using breast tissue after BCS. Oncoplastic surgery contributes is the better phyletic local adaptation of patients. Variety of modifications and options of reconstructive surgery causes problem of choice, which should be solved with patient taking into account the clinical data. The extent of surgical intervention does not affect the performance of the 5-year overall and recurrent survival and depends on the distribution process.

Legal entity responsible for the study: P.A. Gerzen’s Cancer Research Institute – The National Medical Research Radiologic Center of the Ministry of Health of the Russian Federation.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Approximately 40% of patients with node positive in axilla (N1) will have axillary pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC). The application of sentinel lymph nodes (SLNs) biopsy (SLNB) following NAC for initially node negative breast cancer is unclear because of high false-negative rates in previous studies (SENTINA, ACOSOG Z1071). These trials, using blue dye (BD) and/or radioisotope (RI) agent, showed the diagnostic accuracy of SLNB was closely related to the number of SLNs. We presented the efficacy of indocyanine green (ICG) fluorescence navigation method for SLNB in clinically node-negative (cNO) patients (ACCO2008). The fluorescent ICG method can provide higher number of SLNs. Moreover, some reported that fluorescence SLNs with metastases could not be identified by radioactivity. To determine the detection rate, the false-negative rate of SLNs using the fluorescent ICG method after NAC for biopsy-proved N1 breast cancer retrospectively.

Methods: Of 2301 patients (January 2010 - March 2018), 135 women with N1 (fine needle aspiration or core needle biopsy proven) received NAC. Node status after NAC was evaluated by ultrasound findings in Group 1 (n = 105) and Group 2 (N1 remained ycN1, n = 30). All patients underwent SLNB using both ICG and BD method and axillary lymph node dissection.

Results: The average number of SLNs removed were Group 1 (ICG: 3.65, BD: 1.37), Group 2 (ICG: 2.99, BD: 0.93). Detection rate of SLNs: Group 1 ICG 97.1% (95% CI 91.9-99.0, 102 of 105), BD 77.3% (95% CI 68.2-84.1, 81 of 105), Group 2 ICG 86.7% (95% CI 70.3-94.7, 7 of 26), BD 33.3% (95% CI 26.1-69.8, 16 of 30). Resulting of a false-negative rate: Group 1 ICG 2.9% (95% CI 2.6-3.3, 3 of 39), BD 62.5% (95% CI 3.7-95.5, 9 of 39), Group 2 ICG 11.5% (95% CI 4.00-29.0, 3 of 26), BD 68.8% (95% CI 6.39-43.0, 3 of 16). Axillary pCR was 46.7% (6/13).

Conclusions: In patients whose axillary nodal status converted from N1 to ycN0, the fluorescent ICG method with higher number detection of SLNs showed a remarkable high detection rate and a low false-negative rate of SLNs, compared with those of Blue dye which is one of conventional method.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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**Table: 264P**

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<tr>
<th>Phenotype</th>
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<th>RCB1 type I</th>
<th>RCB2 type II</th>
<th>RCB3 type II</th>
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<tr>
<td>Overall</td>
<td>Median DFS:167 HR:1</td>
<td>Median DFS:156 HR:2.6</td>
<td>Median DFS:130 HR:4.5</td>
<td>Median DFS:85 HR:9.6</td>
</tr>
<tr>
<td>HER 2 positive</td>
<td>Median DFS: 90 HR:1.6</td>
<td>Median DFS: 90 HR:1.6</td>
<td>Median DFS: 100 HR:2.5</td>
<td>Median DFS: 90 HR:4.4</td>
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<tr>
<td>Luminal</td>
<td>Median DFS: 167 HR:2.8</td>
<td>Median DFS: 167 HR:2.8</td>
<td>Median DFS: 115 HR:4.8</td>
<td>Median DFS: NA HR: NA</td>
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<tr>
<td>Triple negative</td>
<td>Median DFS: 141 HR:8.8</td>
<td>Median DFS: 117 HR:16.7</td>
<td>Median DFS: 117 HR:16.7</td>
<td>Median DFS: 122 HR:28.4</td>
</tr>
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</table>

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263P  The application of indocyanine green fluorescence navigation method to a sentinel lymph node biopsy after neoadjuvant chemotherapy in node-negative breast cancer

K. Yamagami1, H. Matsumoto1, T. Hashimoto2, S. Yana1, S. Ueno1, Y. Yata1, Y. Ichinose1, T. Deai3, M. Toi1

1Department of Breast Surgery and Oncology, Shinko Hospital, Kobe, Japan, 2Breast Surgery, Hashimoto Clinic, Kobe, Japan, 3Breast Surgery Dea Clinic, Kobe, Japan, 4Department of Breast Surgery, Kyoto University, Japan

Background: The median age at the time of surgery was 44.4 years. The median number of retrieved SLNs was 5.6. The SLN detection rate was 98.3% (234/238 patients), and the false-negative rate (FNR) of SLNB after NAC was 7.9% (9/106 patients). There was no significant difference in disease-free survival (DFS, p = 0.578) or overall survival (OS, p = 0.149) among Groups A, B, and C.

Conclusions: These results suggest that SLNB can be feasible and oncologically safe after NAC for node-negative breast cancer and could help reduce arm morbidity by avoiding standard ALND in negative SLN patients.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

263P  Omission of axillary lymph node dissection after positive sentinel lymph node biopsy: Validity and safety among early breast cancer patients treated with mastectomy

A. Matsumoto, Y. Umemoto, H. Iino

Department of Surgery, Tokyu University School of Medicine, Tokyo, Japan

Background: ACOSOG Z0011 trial showed that axillary lymph node dissection (ALND) had no impact on recurrence and survival in patients with positive sentinel lymph node (SLN) after breast-conserving surgery. However, it is still unknown if omission of ALND can be acceptable to patients treated with mastectomy. The aim of this study was to evaluate whether ALND could be safely omitted for patients with SLN-positive breast cancer after mastectomy.

Methods: From a prospective database of 296 patients with clinically node-negative breast cancer who underwent mastectomy and sentinel lymph node biopsy (SLNB) from March 2006 to December 2016, 81 patients who had positive SLNs were analyzed. Patients treated with neoadjuvant chemotherapy were excluded from the analysis. Lymphatic mapping was performed with a combined method of blue dye and radiotracers.

Results: The median age was 57.9 years (range: 32-85) years and the median tumor size was 2.3 cm (range: 0.6-7.9 cm). Of 81 patients, 23 (28.4%) patients omitted ALND. Patients with SLNB alone were more likely to have smaller SLN involvements (p = 0.001): micrometastasis was identified in 13 (56.5%) patients in SLNB-alone group and 9 (15.5%) patients in ALND group. The number of positive SLN was comparable between SLNB-alone (median: 1.0, range: 1-6) and ALND groups (median: 1.3, range: 1-5) (p = 0.063). There was no significant difference in characteristics including age, tumor size and tumor subtypes between the two groups. Post-mastectomy radiotherapy was performed in 5 (21.7%) patients with SLNB alone and 16 (27.6%) patients with ALND (p = 0.358). The majority of patients with micrometastatic SLN received adjuvant chemotherapy in both groups (83.3% vs. 75.5%, p = 0.562). After a median follow-up of 54.7 months, no axillary recurrence was observed in both groups and 3-year disease-free survival was not significantly different between the two groups (75.0% vs. 88.8%, p = 0.489). Lymphedema was observed significantly more often after ALND than after SLNB (22.4% vs. 4.3%, p = 0.045).

Conclusions: These data suggested that ALND could be safely omitted in SLN-positive breast cancer patients treated with mastectomy and appropriate systemic therapy.

Legal entity responsible for the study: Akiko Matsumoto.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

264P  Pathologic response as a strong predictor of survival irrespective of phenotype in early breast cancer

A. Guard Caroluzo1, S. Moraes Munilla2, J. Vera Rodriguez2, F. Vladoseli Vileias2, D.R. Sanchez Guzman1, E. Iglesias Martinez1

1Breast Cancer Unit, Hospital Arnau de Vilanova, Lleida, Spain, 2Oncology, Hospital Arnau de Vilanova, Lleida, Spain

Background: Pathologic complete response after neoadjuvant chemotherapy is considered as a surrogate of survival by most authors, although there are special phenotypes, such HER2 positive, where their potential as a predictor of survival is stronger.

Methods: Overall survival was analyzed according to pathologic response in a cohort of early breast cancer patients (all subtypes) treated with standard neoadjuvant chemotherapy. Between March 2000 to October 2016, 459 breast cancer patients were treated with neoadjuvant chemotherapy with anthracycline and taxane regimens.

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**Table:**

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<td>Median DFS: 117 HR:16.7</td>
<td>Median DFS: 122 HR:28.4</td>
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</table>
Results: Median age was 52 (range 28-87), 173 tumors (38%) were classified as HER2 positive, 148 (32%) triple negative and 138 (30%) as luminal breast cancer. Median initial size was 34 mm (10-100) and 237 patients (51%) had initial node involvement. We achieved a total of 152/159 complete pathologic response with a 43% rate in HER2 positive, 44% in triple negative and 9% in luminal breast cancer patients. Ten years disease free survival in the whole serie was 83%, with a 72% for patients without complete pathologic response versus 90% for complete pathologic response (log rank <0.00001). A strong correlation between pathologic response and survival was found in all subtypes (log rank p<0.033; 0.028 and 0.027 in HER2 positive, luminal and triple negative respectively). A table with survival results according the RCB response by Symmans method in the whole serie and different phenotypes is attached.

Conclusions: Pathologic response is a strong predictor of overall survival in all breast cancer phenotypes although in the triple negative has the highest magnitude with a HR of 28.4 in patients with worse pathologic response (RCB type III). Neoadjuvant chemo-therapy should be considered in the majority of patients who are candidates to chemotheraphy, specially in triple negative and HER2 positive; however, in luminal phenotype a better selection for neoadjuvant chemotherapy is needed.

Legal entity responsible for the study: University Hospital Aracau de Vilanova.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

265P Nomogram to predict non-sentinel lymph node status of breast cancer using total tumor load determined by one-step nucleic acid amplification (OSNA)

P. O-choarenrat, D. Sa-ruanmuak, A. Kulprom

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Background: Axillary dissection might be omitted in selected breast cancer patients with positive sentinel node (SLN). Total tumor load (TTL) in SLN expressed by cytotokin 19 (CK19) mRNA, detected by automated molecular technique-one-step nucleic acid amplification (OSNA), can quantitatively determine tumor burden in SLN. This study aimed to create nomogram to predict non-sentinel lymph node (NSLN) status.

Methods: Breast cancer patients were recruited at Division of Head Neck and Breast Surgery, Department of Surgery, Siriraj Hospital, Mahidol University, Thailand from November 2015 to January 2018. The patients with invasive breast cancer T1-T3, clinically negative axillary lymph node and able to give informed consent underwent SLN biopsy assessed by OSNA. The patients with positive SLN underwent axillary lymph node dissection. Correlations between TTL, clinicopathological parameters and NSLN status were analyzed by chi-square statistic and logistic regression model discrimination was evaluated using receiver-operating characteristic (ROC) analysis.

Results: Total number of the patients who underwent SLN biopsy was 262. There were 85 patients with positive SLN. Mean age at diagnosis of the patients in this group was 54.52±11.66 years. NSLN were positive in 37 patients. Larger tumor size (23.5±9.20 mm vs 37.78±16.88 mm) and presence of lymphovascular invasion (24.5% vs 67.6%) were the independent factor that predict positive NSLN. TTL (expressed by CK19 mRNA copy number can discriminate NSLN status with the area under ROC curve of 0.784 (95%CI 0.683-0.885). At the cut off level at 6550 copies/ML, sensitivity, specificity, and negative predictive value were 86.49%, 57.14%, and 84.85%, respectively. Nomogram containing tumor size and TTL status can predict NSLN involvement with area under ROC curve of 0.827 (95%CI 0.737-0.918).

Conclusions: Nomogram using the results by OSNA technique can predict NSLN status and help in decision for axillary lymph node dissection.

Legal entity responsible for the study: Porochai O-choarenrat.

Funding: Symesx.

Disclosure: All authors have declared no conflicts of interest.

266P Detecting bone density in early breast cancer survivors: The arm-DXA method

Y. Al-Fahat

Department of Oncology, Tolna County Teaching Hospital, Szekszárd, Hungary

Background: Breast cancer survivors who are on adjunct therapy with Aromatase Inhibitors (AIs) or pretreatment menopause due to chemotherapy are known to have an increased risk of osteoporosis and bone fracture. Being at high risk for osteoporosis, these patients should be screened using with dual energy X-ray absorptiometry (DXA) to measure bone mineral density (BMD) according to national guidelines. This study screened the population of patients with early breast cancer utilizing the Arm-DXA method as a user friendly and efficient method.

Methods: All Breast breast cancer patients at the Tolna County Cancer Center, Szekszárd who are diagnosis of early invasive breast cancer were scanned using Arm-DXA during their regular visit to the center. Cancer patients under hormone therapy were scanned annually. Patients who have metastatic disease or known to have osteoporosis were excluded from the study. A total of 431 patients were subject of an arm-DXA scan for BMD during the period February 2015 to September 2017.

Results: Out of 431 patients, normal T score -1.5 detected in 223 patients (51.7%), clinically significant osteopenia (CSO) T score -2.5 detected in 129 patients (29.9%), and osteoporosis T score <-2.5 detected in 79 patients (18.3%). For the 224 patients who were under hormone therapy or/and chemotherapy about 29.9% (n: 67) had a CSI, and 20.9% (n:46) had osteoporosis.

Conclusions: This study highlights the fact that osteoporosis is under-detected in early breast cancer survivors who are on or after hormone and chemotherapy. About 48% of early breast cancer survivors found to have osteoporosis or clinically significant osteopenia in our study. Our BMD test results shows that half the 224 patients who were under hormone therapy need to take treatment (zoledronic -acid or denosumab) to prevent bone fracture.

Legal entity responsible for the study: Al-Fahat Yousaf.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.
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<tr>
<td>Role physical</td>
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<td>36.0-37.5</td>
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<tr>
<td>Bodily pain</td>
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<td>44.4-45.7</td>
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<td>Role emotional</td>
<td>44.6</td>
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<tr>
<td>Mental health</td>
<td>46.7</td>
<td>46.1-47.4</td>
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Legal entity responsible for the study: GEICAM Spanish Breast Cancer Group.

Disclosure: All authors have declared no conflicts of interest.

**Background:** Breast cancer (BC) diagnosis may have a high emotional impact in patients. Health-related quality of life (HRQL) can be impaired by the psychological impact of the diagnosis, by choices having to be made about treatment and by treatments themselves.

**Methods:** Cross-sectional analysis of HRQL in BC women from the Epi-GEICAM case-control study carried out in 23 Spanish hospitals. Women fulfilled a questionnaire about sociodemographic and lifestyle factors, HRQL (SF-36), mental health (GHQ-28) and social support (F Scale). Spanish population norm-based scores were calculated for the SF-36 scales. Physical (PSS) and mental (MSS) summary scores ≥5 points under the norm were considered suboptimal. Psychological distress (PD) was defined as GHQ-28 ≥5 points.

**Results:** Among 1017 cases, 896 had complete SF-36 and GHQ-28. Median time since diagnosis was 77 days, 82% had been operated on, and 41% were on radiation/chemotherapy. Prevalence of PD was 54.4% (95% CI: 51.1-57.6). PD increased with TNM stage (p = 0.03). Other factors associated with PD were chemotherapy (OR = 1.7; 95% CI: 1.2-2.6), low social support (OR = 2.0; 95% CI: 1.2-3.5) and low education (OR = 2.1; 95% CI: 1.2-3.8). SF-36 scores are described in the table. Factors related to suboptimal PSS were surgery (PR = 3.2; 95% CI: 2.0-5.1), low education (OR = 1.9; 95% CI: 1.1-3.6) and number of comorbidities (OR = 1.3; 95% CI: 1.0-1.5). No differences in PD or PSS were observed according to BC subtype.

**Conclusions:** PD is very frequent during the initial stages of BC diagnosis and treatment. Advanced disease stage, lack of social support and low education are strong determinants of PD. The highest impact in HRQL was observed in the role-physical domain. PD and low PSS are interrelated and both are more frequent in patients with low education.
Ablation with radiofrequency waves is performed. The Cool-tip™ RF Ablation Single Electrode Kit (Medtronic, Boulder, CO, USA) is recommended to standardize the evaluation of the effect of ablation. All pts receive RT and systemic therapy according to the ER, HER2, tumor grade and lymph node status of the breast tumor. Residual lesions after RFA will be assessed in all patients approximately 3 months after RT using imaging studies and pathological examination. VAB will be performed in all patients regardless of imaging results. If biopsy specimens reveal suspicious of viable tumor, additional excision will be performed. Follow-up evaluation for residual tumors every 12 months after RFA included clinical breast examination, diagnostic imaging (ultrasound, magnetic resonance, and mammography). The primary endpoint is 5-year local recurrence-free survival, and the secondary endpoints are residual lesion rate after treatment, overall survival, distant recurrence-free survival and adverse events of RFA. The pts accrual was started in August 2013. From 9 participating institutions, enrollment of 372 pts is planned over a 5-year accrual period.

Background: Treatment of triple negative breast cancer (TNBC) is hampered by lack of established therapeutic targets like hormone receptors or HER-2. Surgery, chemotherapy and radiotherapy are the standard of care yet cure rates in patients with TNBC remain inferior compared to other BC subtypes. Approaches tailored to the patient’s individual tumor signature may lead to improvement. The “Mutanome Engineered RNA Immuno-Therapy (MERICAN)” consortium is developing an innovative individualized mRNA-based vaccine for TNBC treatment. MERICAN is a collaboration of 5 European partners (academia and industry) dedicated to realize a personalized approach for TNBC treatment. The consortium set up a clinical workflow covering drug development from target discovery and validation to GMP manufacturing and drug release for each individual patient (MUTANOME). Moreover, the consortium established an on-demand manufactured MUTANOME vaccine encoding the most frequently shared tumor-associated antigens (TAA) in TNBC for drug supply (WAREHOUSE).

Trial design: A phase 1 trial in 2 European countries assesses the feasibility, safety and biological efficacy of this personalized immunotherapy: TNBC patients (≥18years) with TNBC after surgery and (neo-)adjuvant chemotherapy will be allocated to one of two study arms. Patients in ARM1 receive 8 WAREHOUSE vaccinations with personalized TAA combinations corresponding to the patient tumor’s antigen-expression profile. Patients in ARM2 are first treated with the WAREHOUSE approach followed by 8 vaccination cycles of an on-demand manufactured MUTANOME vaccine encoding the unique mutation signature of the individual patient identified by NGS. The mRNA is administered intravenously as a RNA-lipoplex formulation which protects RNA from degradation, activates innate immunity, transmits APCs and consequently induces highly potent antigen-specific T-cell responses. Three clinical sites are open for recruitment; > 12 patients were screened and vaccinations with WAREHOUSE or MUTANOME RNAs have started. We give insights into features of the established therapeutic approach and the setting.

Legal entity responsible for the study: BioNTech AG.

Funding: European Commission’s FP7; BioNTech AG. Clinical Trial identification: EudraCT, 2014-00274-37.

Legal entity responsible for the study: BioNTech AG.

Funding: European Commission’s FP7; BioNTech AG.

BREAST CANCER, LOCALLY ADVANCED

274P
CD8+ , CD4+ and FOXP3+ cell profiles and their change after neoadjuvant chemotherapy in patients with triple negative breast cancer

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Background: Neoadjuvant therapy for breast cancer has been increasingly used in recent years as first-line treatments for breast cancer. A high lymphocytic infiltration is known to correlate with response to neoadjuvant chemotherapy and prognosis, however little attention has been paid to changes in CD8+, CD4+ , FOXP3+ immune cell profiles during perioperative chemotherapy.

Methods: Treatment results of 41 patients with TNBC stages III–IIB homogeneously treated with neoadjuvant chemotherapy were analyzed. We studied the baseline and post-treatment FOXP3+, CD4+, CD8+ tumor infiltrating immune cells by immunohistochemistry. Therapeutic pathomorphism was evaluated in terms of the residual tumor burden identification (RCB) (using Miller–Payne classification). Variables distribution was scored using ANOVA test. Survival probabilities were estimated by the Cox proportional hazards model.

Results: Pathological complete response (pCR) to neoadjuvant chemotherapy was identified in 12% of patients. In group without pCR high baseline levels of the stromal CD4+ cells were identified in 39.4% of patients, peritumoral CD4+ cells – in 44.7%; high levels of stromal CD8+ cells were identified in 28% and peritumoral CD8+ – in 52% of patients; and high levels of FOXP3+ were identified 47.3% of patients. The levels of CD8+ and FOXP3+ cells decreased during treatment in 13% of patients. The levels of peritumoral CD4+ cells decreased during treatment in 34%, 9% of patient, whereas levels of stromal CD4+ increased during treatment in 10.6% of patients. We found that in the population with residual disease after neoadjuvant chemotherapy the high baseline levels of peritumoral CD4+ immune cells were strongly associated with adverse outcome (HR 3.55, CI 1.29–8.58; p = 0.013).

Conclusions: The high baseline levels of peritumoral CD4+ lymphocytes in triple negative breast cancer tumor failing to achieve pCR were associated with adverse outcome. Further studies are required for identifying patients who are likely to benefit from immunotherapeutic adjuvants to conventional treatment approaches.

Legal entity responsible for the study: National Cancer Institute, Ukraine, Kiev.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

275P
Multiplex immunoassays analysis of plasma biomarker levels and response to neoadjuvant chemotherapy for locally advanced breast cancer


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Background: Neoadjuvant chemotherapy (NAC) has become as the preferred initial therapy for locally advanced breast cancer (LABC) patients. A pathologic complete response (pCR) following NAC correlates strongly with both prolonged disease-free survival and overall survival especially for patients with HER2+ or triple negative breast cancer (TNBC). A lot of modalities and molecular markers for assessing chemotherapy response have been evaluated; however, they have demonstrated only limited predictive value.

Methods: Plasma samples have been collected from 167 patients diagnosed with LABC and received NAC from month, year to month, year prospectively. Samples were collected three times from each patient, prior to NAC (pre-treatment), prior to second cycle of NAC (on-treatment), and after breast surgery (post-treatment). Samples were assayed by multiplex immunoassays for 45 biomarkers. Plasma biomarker levels using Cytokine/Chemokine/Growth Factor 45-Plex Human ProcartaPlexTM Panel were compared with pathologic treatment responses. pCR was defined as the absence of residual tumor both in breast and axillary lymph nodes. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2014-11-015-017).

Results: A median age at diagnosis of the 167 patients was 42 (range, 23–68 years). Most of the patients were treated with anthracycline and taxane-based regimen including adriamycin with cyclophosphamide plus docetaxel (AC-T), or AC-T plus trastuzumab. The patients were divided into the following four groups: HR+/HER2+ (n = 46–28%), HR+/HER2− (n = 26–16%), HR−/HER2+ (n = 32–19%), and TNBC (n = 63–38%). Thirty four patients (20%) achieving a pCR were compared with 133 patients (80%) demonstrating no pCR. Several groups of biomarker expression, BDNF, BNGF, HGF, IFN-γ, IL-6, IL-10, MCP-1, RANTES, and SDF-1 were significantly different among pre-treatment, on-treatment and post-treatment. Multivariate analysis on pCR showed that analysis using the multiplex panel has predictive power.

Conclusions: Plasma biomarkers including immune–cytokine may have a role to predict treatment response in the neoadjuvant setting.

Legal entity responsible for the study: Samsung Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

276P
Prognostic role of changes in neutrophil-to-lymphocyte ratio, tumor-infiltrating lymphocyte with programmed death ligand-1 in triple-negative breast cancer

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Background: Neutrophil-to-lymphocyte ratio (NLR), tumor-infiltrating lymphocyte (TIL) and programmed death-ligand 1 (PD-L1) expression has been known to correlate with response to neoadjuvant chemotherapy and prognosis, how¬ever little attention has been paid to changes in CD8+ lymphocytes in triple negative breast cancer. We analyzed baseline NLR and its clinical association in triple-negative breast cancer (TNBC). The changes of NLR, TIL and PD-L1 during neoadjuvant chemotherapy (NAC) and their association to recurrence was analyzed.

Methods: Between Jan 2008 to Dec 2015, 358 TNBC patients were analyzed. NLR was based on initial complete blood count (CBC). Fifty paired NLR (initial diagnosis, after completion of NAC) and 34 paired tissues (initial diagnosis, surgical specimen) were collected. The changes of TIL, CD4, CD8, forkhead box P3 (FOXP3) and PD-L1 expression were assessed with immunohistochemical stain. The relationship of prior markers and tumor recurrence was analyzed.

Results: Low NLR (NLR<3.16) was associated to superior survival (overall survival; 41.83 vs. 36.5 months, P = 0.002; disease-free survival (DFS) 37.85 vs. 32.14 months, P = 0.032). After NAC, patients with radical NLR changes (NLR change < -30% or >100%) showed inferior DFS (38.37 vs. 22.37 months, P = 0.015). Same or increased TIL after NAC showed trends for superior DFS (80.0 vs. 46.0 months, P = 0.366). Positive PD-L1 (≥1%) in tumor cells at baseline was associated to superior DFS (97.45 vs. 33.02 months, P = 0.031), and positive tumor PD-L1 at post-NAC tissues showed trends for superior DFS (86.43 vs. 38.96 months, P = 0.056).

Conclusions: In TNBC patients, low NLR might be associated with superior survival. Modest changes of NLR or increased TIL after NAC may reflect good prognosis. Positive tumor PD-L1 was associated with superior DFS in our study.

Legal entity responsible for the study: Seoul St. Mary’s Hospital, Incheon St. Mary’s Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

277P
Expression of Sp17 and its association with clinicopathological parameters of breast cancer

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Background: Sperm protein 17 (Sp17) was found to be only expressed in breast cancer and not the normal breast tissue. Although Sp17 antibody can effectively inhibit the growth of human cancer cells, suggesting a potential therapeutic target, the role of Sp17 in tumor remains unclear. Hence, we examined the expression status of Sp17 in breast cancer and analyzed the correlation between Sp17 expression and clinicopathological parameters of breast cancer. We then proceeded to assess whether the expression of Sp17 has any effect on patient prognosis.

Methods: Quantitative real-time PCR and immunohistochemistry were conducted to test expression rate of Sp17 mRNA and protein in breast cancer samples, respectively.
Table: 278P Relation between biological factors and pathological response

<table>
<thead>
<tr>
<th>Grade</th>
<th>Non-pCR</th>
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<td>10</td>
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<tr>
<td>3</td>
<td>20</td>
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<td>Ki-67</td>
<td>&lt; 20%</td>
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<td>&gt; 20%</td>
<td>22</td>
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<td>ER</td>
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<td>negative</td>
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<td></td>
<td>HER2</td>
<td>0.06</td>
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<td></td>
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<td>DnDPET, intratumoral distribution</td>
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<td></td>
<td>Heterogeneity</td>
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<td>Homogeneity</td>
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</table>

Conclusions: The SUVmax of DnDPET associates with intratumoral heterogeneous distribution. In addition, intratumoral heterogeneity on DnDPET provides predictive value for achieving pCR on ER positive-breast cancer and might inform therapeutic decisions.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

279P Results from NRG oncology/NSABP protocol DMP-1: Physician counseling

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Background: Although selective estrogen receptor modulators (SERMs) reduce the risk of developing breast cancer (BC) in women at increased risk of the disease, there are also risks to consider. Guidelines suggest that such women should be counseled on risk-reducing options including SERMs. However, overall uptake is low. Previous results of DIMP-1 showed that the health care provider’s (HCP) recommendation plays an important role in a woman’s decision to use a SERM. In this secondary analysis we aimed to better understand the counseling process of HCPs in the clinical care setting.

Methods: Women (N = 1,022) and their HCPs discussed SERM use for BC risk reduction and were asked about the counseling, including risks and benefits presented and whether the HCP recommended SERM use. HCPs were also asked to report on the reasons for their recommendation and if the patient was likely to take a SERM or not. We describe the counseling and evaluate the agreement between the HCP’s and women’s responses.

Results: HCPs reported on 1,022 counseling sessions. Benefits of SERMs in BC risk reduction were discussed in 96% of consultations; the risk of thromboembolism, endometrial cancer, and menopausal symptoms was discussed in > 86%; the risk of cataracts and decrease in libido in < 58%. Five HCPs reported no SERM discussion and were excluded. 66% of HCPs based their recommendation of SERM use on the Gail model risk score. Data for 895 participants were available to evaluate agreement. There was a modest agreement between the women’s and the HCP’s statements on SERM recommendation (kappa = 0.30), with fair agreement on the strength of the recommendation (weighted kappa = 0.22) and substantial agreement between a woman’s decision and the HCP’s assumption of what his/her patient would do (kappa = 0.65).

Conclusions: Most severe medical risks associated with SERM use were discussed during the counseling. The fairly low percentage of discussions about potential sexual consequences was comparable to that of other studies. Overall, there was a fair to moderate agreement between HCPs and women’s perceptions of the counseling. Of note, HCPs had a good sense of what treatment the counseled women would choose. Support: U10CA180868, -180822; UGI-CA189867.

Clinical trial identification: NRG Oncology/NSABP DMP-1; NCT0199359; Opened to accrual: 8-1-11.

Legal entity responsible for the study: NRG Oncology.

Funding: NRG Oncology via NIH Grants: U10CA180868, -180822; UGI-CA189867.

Disclosure: All authors have declared no conflicts of interest.

280P Neoadjuvant eribulin plus carboplatin vs. paclitaxel plus carboplatin in patients with triple-negative breast cancer (TNBC)

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Background: Eribulin is a novel microtubule poison, which has certain advantages as compared to taxanes in some laboratory experiments and shows clinical efficacy in breast cancer patients after failure of taxane and anthracycline treatment. Promising activity of neoadjuvant eribulin plus carboplatin combination was shown in TNBC studies [Kaklamani et al. Breast Cancer Res Treat, 2015]. This investigation aimed to directly compare the efficacy of neoadjuvant eribulin/carboplatin vs. paclitaxel/carboplatin doublets in TNBC patients.

Methods: 61 TNBC patients (median age 45, range 31-76) were randomized to receive carboplatin AUC6 with either eribulin (1.1 mg/m2 on days 1 and 8, every three weeks) or paclitaxel (80 mg/m2 on days 1 and 8, every three weeks). Each patient was treated with four cycles of neoadjuvant therapy followed by surgery and four cycles of adjuvant FAC (5-fluorouracil 500 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2). After adjuvant chemotherapy, patients with breast-conserving surgery or with positive lymph nodes also received radiation treatment.

Results: The rates of clinical complete responses were similar in both cohorts (eribulin/carboplatin: 12/24 (50%); paclitaxel/carboplatin: 19/35 (54%). Pathologic complete responses (pCR) were numerically less frequent in patients receiving eribulin [9/24 (38%) vs. 20/35 (54%), although the difference was below statistical significance (p = 0.2)]. Five patients were carriers of deleterious BRCA1 alleles; pCRs were observed...
in 2/3 (67%) and 2/2 (100%) women in eribulin and paclitaxel arms, respectively, 56 patients had a follow-up above 12 months at the time of data analysis. 4/24 (17%) distant recurrences were documented in the eribulin arm, while only 1/32 (3%) TNBC recurrences were documented in the paclitaxel arm (p = 0.15).

Conclusions: Eribulin plus carboplatin combination does not outperform, in terms of pathomorphological response to treatment, paclitaxel plus carboplatin doublet while given as a neoadjuvant treatment for triple-negative breast cancer.

Legal entity responsible for the study: Petros S’s National Medical Research Center for Oncology.

Funding: Russian Science Foundation [grant number 14-25-00111].

Disclosure: All authors have declared no conflicts of interest.
2840  Primary results of the first nationwide molecular screening program in Spain for patients with advanced breast cancer (AGATA SOLTI-1301 study)


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2900 Patient-reported outcomes (PROs) in advanced breast cancer (ABC) treated with ribociclib + fulvestrant: Results from MONALEESA-3

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291O Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal patients (pts) with hormone receptor-positive (HR+) HER2-negative (HER2-) advanced breast cancer (ABC): MONALEESA-7 patient-reported outcomes (PROs)

N. Harbeck1, R. Villanueva2, F. Franke3, G. Babu4, P. Wheatley-Price5, Y-H. Im6, K. Altundag7, B. Lanoue8, J. Alam8, D. Chandiwana8, M. Colleoni9
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292O Patient-reported outcomes (PRO) in patients (pts) with advanced breast cancer and a germline BRCA1/2 mutation (gBRCAm) receiving talazoparib (TALA) vs physician’s choice chemotherapy treatment (PCT): A focus on the EMBRACA triple negative (TNBC) subpopulation

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285PD Balixafortide (a novel CXCR4 inhibitor) and eribulin in HER2-neg metastatic breast cancer (MBC) patients (pts): A phase I trial

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286PD Post-treatment biopsies show evidence of cell cycle arrest and immune cell infiltration into tumors of ladiratuzumab vedotin-treated advanced breast cancer patients


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287PD Oral paclitaxel and HM30181A demonstrate clinical activity in metastatic breast cancer (MBC) patients

M-S. Dai1, T-Y. Chao2, T-C. Chao3, C-F. Chiu4, Y-S. Lu5, H-S. Shiah6, Y-Y. Wu1, G. Gerald Fetterly7, N. Hung8, D.L. Cutter9, R. Kwan1, D. Douglas Kramer7, W-K. Chan7, T. Hung9

1Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, 2Division of Hematology-Oncology, Taipei Medical University - Shuang Ho Hospital, New Taipei, Taiwan, 3Medical Oncology, Taipei Veterans General Hospital, Taipei, Taiwan, 4Hematology/Oncology, China Medical University Hospital, Taichung, Taiwan, 5Hematology/Oncology, National Taiwan University Hospital, Taipei, Taiwan, 6Hematology/Oncology, Taipei Medical University Hospital, Taipei, Taiwan, 7Athenex, New York, NY, USA, 8University of Otago, Dunedin, New Zealand, 9Zenith Technology Corporation Limited, Dunedin, New Zealand
PERNETTA: A non-comparative randomized open label phase II trial of pertuzumab (P) + trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer (MBC): (SAKK 22/10 / UNICANCER UC-0140/1207)


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Lucitanib for the treatment of HR+ HER2- metastatic breast cancer (MBC) patients (pts): Results from the multicohort phase II FINESSE trial


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295P
Exploratory biomarker analysis in patients treated with vinorelbine plus everolimus or vinorelbine monotherapy as second-line treatment for HER2-negative advanced breast cancer: Final results from the randomized phase II trial VICTORIA

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Background: The purpose of the VICTORIA trial was to evaluate efficacy and safety of the combined treatment of everolimus (EVER) and vinorelbine (VINO) compared to VINO monotherapy as second-line treatment to HER2-negative advanced breast cancer. The study was accompanied by an exploratory analysis of phosphoinositide 3 kinase subunit (PIK3CA) as potential predictive marker for response.

Methods: Patients were randomized 1:1 to receive i. V. VINO at a dose of 25 mg/m² on days 1, 8 and 15 q 3w 5 mg EVINO once daily or i. V. VINO at a dose of 25 mg/m² on days 1, 8 and 15. The primary objective was progression-free survival (PFS). Safety and tolerability, overall survival (OS) and overall response rates were secondary objectives. The mutational status of PIK3CA was determined at baseline from plasma samples. The study was initially planned to enroll 166 patients.

Results: Between December 2013 and February 2016 138 patients were enrolled from 32 sites across Germany. Of 69 patients randomized to receive VINO plus EVINO, 68 received treatment and 65 of 69 patients randomized to VINO monotherapy received treatment. Baseline characteristics were balanced. Median age was 63 and 62 years, ECOG 0-1 98.9% and 90.7%, postmenopausal status 79% and 80.0%, and visceral metastases 89.7% and 87.7%, respectively. Median PFS was 4.01 months (95% CI, 2.40-6.09) for the combination vs. 4.08 months (95% CI, 2.80-5.33) for VINO monotherapy (HR = 1.05 [0.730-1.512], log rank p = 0.7988). The median OS was not statistically different between treatment arms (VINO + EVINO: 16.25 months [95% CI, 11.38-19.95] vs. VINO: 15.78 months [95% CI, 10.23-19.95]), log rank p = 0.9361. PIK3CA mutational status was neither associated with PFS nor with OS in the total patient cohort, in patients treated with VINO + EVINO and in patients treated with VINO monotherapy, respectively.

Conclusions: The addition of EVER to VINO was not associated with a benefit in PFS. Overall survival also did not significantly differ between treatment arms. No correlation between PIK3CA mutation status and outcome was detected.


Legal entity responsible for the study: AIO-Studien-gGmbH

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296P
Applicability of the lung immune prognostic index (LIPI) to metastatic triple negative breast cancer (mTNBC) patients treated with immune checkpoint targeted monoclonal antibodies (ICT mAbs)

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Background: The role of immune checkpoint PD-1/PD-L1 inhibitor (ICi) in breast cancer (BC) is being investigated in clinical trials. Predominant evidence strongly supports the synergistic effects of CDK4/6 inhibitor and ICi. A phase II trial is testing the safety and efficacy of the combination of letrozole, palbociclib and pembrolizumab in patients with hormone receptor positive (HR+) BC (NCT02778685). Currently, there is no well-defined circulating biomarker to predict response to ICi.

Methods: Peripheral blood mononuclear cells (PBMC) were collected at day 1 of cycles 1 (pre-treatment), 2, 4, 6 and 8. The comprehensive characterization of 14 innate cell types, 7 adaptive T-cells, and 16 exhaustion-related T-cells was performed using 15-color flow cytometry. Core biopsies were taken at baseline and optionally on-study to assess immune cell subsets.

Results: Preliminary analysis included nine patients with the following responses by RECIST 1.1: complete response, 3 partial responses, 2 stable disease, and 2 progression of disease. Analysis showed correlation of clinical response to high baseline levels of 8 T-cells (r = 0.74, p = 0.09) and exhausted T-cells: CD4+ PD-1+ KLRG1+ (r = 0.74, p = 0.02), CD4+ PD-1+ CD160+ (r = 0.71, p = 0.03). Most patients showed a decrease in the number of CD38+ myeloid-derived suppressor cells (p = 0.04) and CD4+ PD-1+ TIM3+ exhausted T-cells (p = 0.04) in peripheral blood at C2D1. Strong indicators of clinical response included increased CD38+ myeloid-derived suppressor cells (r = 0.70, p = 0.04) and decreased type-I CD8+ T-cells (r = 0.81, p = 0.009) at C4D1.

Conclusions: High pre-treatment peripheral blood exhausted CD4+ T-cells is associated with clinical response to ICi in HR+ BC. Further analysis including tumor tissue immune profiling is currently ongoing to verify these findings.

Clinical trial identification: NCT02778685.

Legal entity responsible for the study: City of Hope.

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Annals of Oncology
300P Differential molecular signature in patients from African origin with triple-negative breast cancer

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Background: Breast cancer (BC) is more aggressive in pre-menopausal women of Black race (BW). These women usually have worse prognosis and higher mortality rate when compared with patients of other races, even when socioeconomic factors are accounted for. Triple-negative BC (TNBC), the most aggressive and less treatable BC, due to the lack of therapeutic targets, such as oestrogen and progesterone receptor or HER2, is more frequently diagnosed in these young BW.

Methods: To identify the driving biological factors of this racial disparity we performed a comprehensive differential gene expression (DGE) analysis using the R package edgeR and RNA-sequencing BC data from The Cancer Genome Atlas, which has specifically USA data. In a total of 1097 BC patients, 183 are BW, 32 with TNBC (17.5% of all BW), 737 are White, 69 with TNBC (9.1%); and 61 are Asian, 8 with TNBC (13.1%).

Results: DGE between BW with TNBC and TNBC patients of other races revealed 251 up- and 269 downregulated genes (adjusted p-value < 0.05, log2(FoldChange) ≥ 1, applied in all the analysis). To remove genes associated with race alone and not with TNBC in BW per se, we performed a DGE analysis between all non-TNBC cases in BW and all non-TNBC patients in the other races, resulting in 315 up- and 139 downregulated genes in non-TNBCs of BW.

Conclusions: Our work will unveil the molecular signature(s) that characterise and define molecularly TNBC in BW and, ultimately, will guide the development of new therapeutics for this unmet medical problem.

Legal entity responsible for the study: CEDOC, Nova Medical School, Lisbon, Portugal.

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Disclosure: All authors have declared no conflicts of interest.

309P The prevalence of PIK3CA mutations in HR+/HER2– metastatic breast cancer (BELLEZ, BELLE2 and BELLE3) and circulat-

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Background: Breast cancer (BC) is the most common form of malignant tumor in women worldwide. 60-70% of BC are hormone receptor-positive (HR+), HER2-negative (HER2−) (HR+/HER2−). The purpose of this analysis was to enhance understanding on the epidemiology for women with PIK3CA-mutant HR+/HER2– metastatic breast cancer (mBC).

Methods: PIK3CA mutations were tested from tumor biopsy (N = 1617) and circulating tumor DNA (ctDNA) (N = 1466) from patients enrolled into BELLEZ, BELLE2 and BELLE3, which are three randomized Phase III studies in HR+/HER2− mBC. Various PIK3CA mutation testing methods were applied, including Next-Generation Sequencing (NGS) and Polymerase Chain Reaction (PCR) for tumor biopsies, as well as BEAMing and droplet digital PCR for ctDNA samples.

Results: Prevalence of the PIK3CA mutations among tissue biopsies ranged from 34.1% to 41.1% while prevalence of the PIK3CA mutations among liquid biopsies ranged from 27.3% to 43.3%. Besides gene-level analysis, the PIK3CA prevalence by hot spots and by exons was examined as well. Further, subgroup analysis of PIK3CA prevalence had been conducted based on patient cohort (2L vs 3L), mutation testing methods, ethnicity, biopsy source (primary tissue vs metastatic) and previous treatment.

Conclusions: PIK3CA mutations (specifically hotspots H1047R, E545K and E542K) frequently occur in HR+/HER2– mBC. The prevalence of PIK3CA mutations are in a relatively narrow range across the three randomized Phase III studies in HR+/HER2– mBC, regardless of tissue types and testing methods.

Legal entity responsible for the study: Novartis Pharma.

Funding: Novartis Pharma.

EMBRACA: Comparison of efficacy and safety of talazoparib (TALA) and physician’s choice of therapy (PCT) in patients (pts) with advanced breast cancer (aBC) and a germline BRCA1 mutation (gBRCA1); BRCA1/BRCA2 subgroup analysis


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Background: TALA is a dual-mechanism PARP inhibitor that prevents DNA damage repair by trapping PARP on DNA, resulting in cell death in BRCA1/2-mutated cells. EMBRACA is an open-label, randomized, 2-arm phase 3 trial comparing the efficacy and safety of talazoparib (TALA) (1 mg/day) with standard single-agent PCT (cabcitabine, eribulin, gemcitabine, or vinorelbine) in pts with aBC and a gBRCA1 mutation. The primary efficacy endpoint was median progression-free survival (PFS) in BRCA1 pts receiving TALA compared with PCT in both groups. In this analysis, clinical outcomes were assessed in BRCA1 and BRCA2 subgroups.

Methods: EMBRACA is an open-label, randomized, 2-arm phase 3 trial comparing the efficacy and safety of talazoparib (TALA) (1 mg/day) with standard single-agent PCT (cabcitabine, eribulin, gemcitabine, or vinorelbine) in pts with aBC and a gBRCA1 mutation. In this analysis clinical outcomes were assessed in 2 subgroups of pts who had either received prior platinum (PP) or had no prior platinum (NPP) treatment.

Results: Of 431 pts randomised, 196 were BRCA1 (133 TALA; 63 PCT), 235 were BRCA2 (154 TALA; 81 PCT). Mean (SD) age was 45.4 (11.66) years (BRCA1) and 50.4 (11.66) years (BRCA2). Pts in all groups had received a median of 1 prior cytotoxic regimen for aBC. TALA demonstrated a statistically significant improvement in both objective response rate (odds ratio [OR] [95% CI] BRCA1 7.01 [2.99-19.54]; BRCA2 0.59 [0.39-0.90]; BRCA1 0.47 [0.32-0.70]) in BRCA1 and BRCA2 subgroups compared with PCT. Mean (SD) duration of TALA therapy was 7.5 (7.58) mo (BRCA1) and 9.2 (6.88) mo (BRCA2), with 15% (BRCA1) and 22% (BRCA2) of pts receiving TALA for >12 mo. Median duration of response (DOR) to TALA was longest in BRCA1 pts (15.3 mo) and PCT (12.4 mo) compared with BRCA2 pts (10.2 mo). In BRCA1 pts receiving TALA had a DOR of approximately 5.0 mo. Pts on TALA achieved a clinical benefit rate at 24 weeks (BRCA1 62%; BRCA2 74%) with OR significantly favouring TALA over PCT in both groups. Pts receiving TALA, particularly those with the most common adverse event (AE) in BRCA1 pts (56%) and fatigue in BRCA2 pts (30%). Serious AEs occurred in both BRCA1 (39%) and NPP pts (32%) taking TALA. Clinical trial identification: NCT01945775.

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Exposure-efficacy progression-free survival (PFS) analyses of breast cancer patients with germline BRCA1/2 mutations receiving talazoparib in the phase III EMBRACA trial

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Background: Talazoparib is a potent, orally bioavailable, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor that is currently under development for the treatment of breast cancer. This exploratory study assessed the relationship between talazoparib exposure and progression-free survival (PFS) in pts with locally advanced and/or metastatic breast cancer with germline breast cancer susceptibility gene (BRCA) mutations based on the phase 3 EMBRACA trial.

Methods: 285 patients, who were treated with talazoparib and had available pharmacokinetic (PK) parameters from the phase 3 EMBRACA trial, were included in the analysis. There were 185 PFS events at the data cut of the analysis. The apparent talazoparib clearance (CL/F) for each patient was obtained from a population PK analysis. To account for dose modifications over time, individual time-varying concentrations from time 0 up to the time of each PFS event using the Cox proportional hazards model. Other potential prognostic factors were also tested as covariates for PFS. The significant covariates identified in univariate analyses were further examined in multi-variate analyses.

Results: The ER analysis for PFS showed that there was a significant correlation between PFS and talazoparib exposure. A longer PFS was associated with higher talazoparib exposure. In addition, longer PFS was also associated with lower baseline lactate dehydrogenase. PFS was longer in patients without visceral disease than patients with visceral disease. A disease-free interval of > 12 months was associated with a longer PFS than that of ≤ 12 months.

Conclusions: PFS was found to be associated with Cavg,t, and a longer PFS was associated with lower baseline hemoglobin. Higher risk of anemia and thrombocytopenia was associated with higher Cavg,t and neutropenia was observed although the relationship was not statistically significant (P = 0.0631). Higher risk of all tested safety endpoints was associated with lower baseline hemoglobin. Higher risk of neutropenia was associated with lower absolute neutrophil count and lower body weight.

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BRCA1m separately from BRCA2m (16 of 24 studies). In 3 studies of HR+/HER2- BC, BRCAm prevalence varied from 5% (USA) to 9.9% (South Korea). BRCAm prevalence ranged from 14.2% (USA) to 53.8% (Israel) in those of Ashkenazi Jewish ancestry.

**Conclusions:** Reported BRCAm prevalence in BC varies widely in clinical and demographic subgroups across countries; there are few studies on all BC and most lack germline BRCAm status specification. Further BC BRCAm epidemiologic studies are warranted to validate the prevalence of BRCAm with germline status.

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**308P** Genetic screening, counselling, and treatment of BRCA mutation (BRCAm) carriers: A systematic review (SR) of international breast cancer (BC) guidelines

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**Background:** Considering the availability of BRCAm targeted therapeutic drugs in BC and an evolving clinical guidelines landscape, an SR of international guidelines on screening and management of BRCAm BC patients was carried out.

**Methods:** The current SR adhered to Cochrane’s guidance. Major electronic databases (e.g. Medline & Embase; n = 7) and grey literature sources were searched (Jan 2007 to Dec 2017). Latest guideline reporting recommendations (and evidence grades) on genetic screening, counselling, and BC treatment of BRCAm carriers were summarised. Guidelines specific to germline (gBRCAm) (ie, hereditary) were captured where available.

**Results:** 3775 records were retrieved and 33 guidelines from Europe (n = 17), USA (n = 11), Canada (n = 3), Australia (n = 1), and Japan (n = 1) were included. Genetic counselling was recommended at multiple points in the care pathway, though the format (eg, frequency, decision tools) was not always clearly defined. US guidelines emphasised BRCAm testing should occur after specialised genetic counselling; other European guidelines were less prescriptive. BRCAm testing eligibility criteria differed with some guidelines being less restrictive; US NCCN BC guidelines specified that HER2- BC patients eligible for single-agent therapy should strongly consider gBRCAm testing, while also having separate more restrictive high-risk BRCAm testing criteria. Similar restrictive criteria were observed in some European guidelines. Fast-track BRCAm testing was recommended in the Netherlands if treatment choice affects BC survival, but only as part of a clinical trial in the UK. Other guidelines suggest testing only if it affects therapy decisions. ESMO ABC3 guidelines recommended platinum therapy for advanced BRCAm BC, more recent ESO-ESMO BCy3 and US NCCN guidelines recommended newly approved gBRCAm-targeted PARP inhibitor therapy.

**Conclusions:** Differences exist between regions and within organizations for guidelines regarding genetic counselling, consent, and treatment of BRCAm BC patients. Harmonisation of guidelines could optimise the identification and management of BRCAm BC patients.

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**309P** Efficacy and toxicity of endocrine therapy + cyclin-dependent kinase 4/6 inhibitors (iCDK4/6) in metastatic breast cancer patients according to gBRCA status


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**Background:** Endocrine therapy (ET) and iCDK4/6 have demonstrated efficacy in terms of progression free survival (PFS), and clinical benefit as first and second line treatment in hormone receptor positive (HR+) HER2 negative, metastatic breast cancer (MBC). Cost and toxicity has limited its worldwide indication. No predictive biomarkers of response or toxicity have been validated. The aim of this exploration is to use the utility of the gBRCA testing as a predictive factor of efficacy and toxicity in HR+, HER2 negative, MBC treated with the combination of ET + iCDK4/6.

**Methods:** Prospective cohort study of patients under ET + iCDK4/6 toxicity registry. Next Generation Sequencing (NGS) for gBRCA1 and 2 and genetic counseling was offered according to physician regular practice.

**Results:** 92 patients were available for analysis, 24 had been studied for gBRCA. Still 3/ 24 (12%) have pending results, but 21/3 (24%) were positive (2 gBRCA1- and 3 gBRCA2-), and 16/24 (67%) were negative (gBRCAneg). Median age of the global cohort was 46 years old (range 27-84), only 21% were stage IV at onset. The overall clinical benefit was 44%, significantly better for gBRCAneg (81% (13/16) versus 20% (1/5), p-value 0.011213. PFS was 46 weeks for the global cohort (C95% 43.7-57.4 months), with trend to better results among gBRCAneg 97 (C95% 42.2-80.5) versus 47 weeks (C95% 21.2-72.7) for gBRCA +. The overall toxicity grade 3-4 was 24% (33/ 96) without differences according to gBRCA status (gBRCA + 20% versus gBRCAneg 25%, p-value 0.818769).

**Conclusions:** We observed a significantly higher clinical benefit with a tendency to higher PFS in gBRCAneg HR+, HER2 negative MBC under ET + iCDK4/6 treatment and similar toxicity in both groups. This exploratory analysis suggests a potential role for gBRCA status as a biomarker of efficacy in this scenario. We believe that prospective, pre-stratified and adequately powered studies warrant further investigation and could help to design the proper sequence of treatments in light of the availability of upcoming target therapies such as PARP inhibitors.

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**310P** Clinical outcomes, treatment patterns and health resource utilization (HRU) among metastatic breast cancer (mBC) patients (pts) with germline BRCA mutation (gBRCAm)

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**Background:** With evolving gBRCA BC guideline landscape, we present latest gBRCA testing rates among mBC US pts with HR+/HER2- or triple negative BC (TNBC), including clinical outcomes, treatment patterns and HRU in gBRCAm pts.

**Methods:** The Flatiron Health database was used in a real world retrospective analysis of mBC pts with HR+/HER2- or TNBC, ≥18 yrs old, diagnosed between Jan 2011-Feb 2018. Rates of gBRCA testing were assessed. One- to 5-yr overall survival (OS) post-mBC diagnosis for gBRCAm HR+/HER2- and TNBC pts were estimated. Cox proportional hazards model was used to estimate OS of TNBC vs HR+/HER2-. Outcomes between TNBC vs HR+/HER2- pts were compared while adjusting for imbalances. Antineoplastic treatment was summarized and HRU patterns were analyzed using t-tests.

**Results:** The study included 12,021 mBC pts (10,291 HR+/HER2-; 1730 TNBC). Results for gBRCA testing were available for 16.7% of pts overall; (HR+/HER2-: 15.4%, TNBC: 24.2%). The most common 1st line treatments for gBRCAm TNBC were carboplatin (19%) and carboplatin/gemcitabine (15%) and 1st line treatments for gBRCAm HR+/HER2- included letrozole (10%) and fulvestrant (7%). Pts counts, OS estimates and HRU for gBRCAm carriers are shown in the table. Cox regression results showed lower OS for gBRCAm TNBC pts vs gBRCAm HR+/HER2- mBC pts, Hazard Ratio (HR) = 0.67 (0.54, 0.84) and 95% CI 0.39 (0.59, 0.70). Estimated median OS and 5-yr OS rates are (33.9 mths, 22.3 mths) and (12.8%, 26.4%) for gBRCAm HR+ /HER2- and TNBC pts respectively. Number of HRU visits per pts-per-year were significantly higher among TNBC pts.

**Conclusions:** gBRCA testing rates among mBC pts with HR+/HER2- or TNBC, were low. Among mBC pts with gBRCAm, 5-yr OS rates were < 29% for both HR+/HER2- and TNBC, poor prognosis and HRU burden demonstrates a significant unmet need for more targeted, less HRU-intensive treatment options among these pts.

**Table: 310P**

<table>
<thead>
<tr>
<th>Total Patients (N = 12,021) n (%)</th>
<th>HR+/HER2-</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with gBRCA test results (n = 2005) n (%)</td>
<td>10,291 (85.6)</td>
<td>1730 (14.4)</td>
</tr>
<tr>
<td>Patients with gBRCAm (n = 229) n (%)</td>
<td>165 (72.1)</td>
<td>64 (27.9)</td>
</tr>
<tr>
<td>gBRCAm patients with ≥ 1st Line antineoplastic treatment (n = 188) n (%)</td>
<td>142 (75.5)</td>
<td>46 (24.5)</td>
</tr>
</tbody>
</table>

**Continued**

<table>
<thead>
<tr>
<th>Year</th>
<th>Overall Survival Estimates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>93.4</td>
</tr>
<tr>
<td>2</td>
<td>58.6</td>
</tr>
<tr>
<td>3</td>
<td>45.8</td>
</tr>
<tr>
<td>4</td>
<td>30.7</td>
</tr>
<tr>
<td>5</td>
<td>28.9</td>
</tr>
</tbody>
</table>
311P Early results from an open-label phase Ib/II study of eribulin mesylate (EM) + pegvorhyaluronidase alfa (PEGPH20) combination for the treatment of patients with HER2-negative, high-hyaluronan (HA) metastatic breast cancer (MBC)

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Background: HA in the tumor microenvironment can inhibit the effectiveness of anti-breast cancer agents such as EM warrant further investigation in pts with HER-2 neg MBC. A complete dataset is expected in October 2018.

Methods: Overall, 14 enrolled pts were treated IV at 2 PEGPH20 dose levels (DL1 ¼ 3 mg/kg or DL0 ¼ 1.6 mg/kg on D1, D7) & EM 1.4 mg/m2 on D1, D8 of a 21 day cycle. 5 pts were treated at DL1, with 2 DLTs observed (G3 muscle cramp, G3 knee/leg pain); 6 pts were enrolled in DL0 with no further DLTs. An additional 3 pts were enrolled at DL0 (RP2D).

Results: All 14 pts were evaluable for safety and efficacy. Median age was 53 years (33–78 years); 14% (2/14) of pts had TNBC. Median number of treatment cycles was 6.0. Drug-related TEAEs occurred in 86% of pts during PEGPH20 + EM therapy. 79% of pts had G2/3 TEAEs. There were 3 SAEs (1 in DL1 and 2 in DL0). As of April 2018, the individual safety profile was as expected for PEGPH20 and EM; no new significant safety signals identified. Key pt characteristics and BORs are shown below. Out of the 5 pts with confirmed PR, 3 had 1 prior and 2 had no prior systemic anticancer therapy in the metastatic setting.

Table: 311P

<table>
<thead>
<tr>
<th>Category</th>
<th>PEGPH20 (3 µg/kg)</th>
<th>PEGPH20 (1 µg/kg)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 5)</td>
<td>(n = 9)</td>
<td></td>
</tr>
<tr>
<td>Enroll. Strata – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC</td>
<td>0 (0)</td>
<td>2 (22)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>ER and/or PRo-positive</td>
<td>5 (100)</td>
<td>7 (78)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>ECOG Status – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (80)</td>
<td>4 (44)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>1</td>
<td>1 (20)</td>
<td>5 (56)</td>
<td>6 (43)</td>
</tr>
<tr>
<td>No. Prior Systemic Anticancer Therapy in Metastatic Setting – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (20)</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>1</td>
<td>3 (60)</td>
<td>5 (56)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: Pfizer, Inc.
Funding: Pfizer, Inc.
Background: The EMBRACE trial demonstrated significantly improved survival with eribulin compared to physician's choice (13.1 vs 10.9 months (p = 0.041). Eribulin has been funded by the NHS in the UK for the management of locally advanced or metastatic breast cancer after at least two lines of treatment. We describe the UK experience of eribulin in this setting.

Methods: Data from 577 patients was analyzed on an individual patient basis from 14 different hospitals after institutional review board approval. Data was collected retrospectively using computerized records and chemotherapy records. Data was collated on: age, breast cancer characteristics, prior chemotherapy regimens, toxicity, PFS and OS. Statistical analysis was performed using SPSS.

Results: Data from 577 patients who received eribulin in specialist cancer centres, teaching hospitals and cancer units throughout the UK between 2011-2017 were included. The median age of patients was 56 (33-84), 447 were ER positive, 129 triple negative, 100 patients were Her2 positive. 1 unknown. The cohort was heavily pre-treated with eribulin being on average 4 (median 2-11). The median number of eribulin cycles received was 4 (range 1-29). The OS of the cohort was 288 days (95%CI 260-315), triple negative patients had a worse outcome than ER/Her2 expressing patients (198 vs 278 days (p = 0.021). Less heavily pre-treated patients (≤2 prior treatments) had significantly better survival (328 vs 264 days). Patients aged over 65 had better survival 325 of 285 days. 11% experienced grade 3-4 neuropathy, 14% experienced nausea, 19% experienced G3-4 neutropenia, there were no treatment related deaths.

Conclusions: This real world data demonstrates that even in a heavily pre-treated population, eribulin was associated an OS advantage in a year in patients over 65 is and associated with better survival if used earlier in metastatic patients.

Legal entity responsible for the study: The authors.

Funding: Eisa.


114P Eribulin as first- or second-line chemotherapy for advanced or metastatic HER2-negative breast cancer: A real-world prospective study


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Background: A global phase III study confirmed the effect of eribulin mesylate (ERI) as this drug is the front line treatment for breast cancer in Japan. However, limited reports can be found on time to treatment failure (TTF) and/or OS for ERI as first- or second-line therapy comparing to late-line therapy in clinical practice.

Methods: We conducted a prospective study in patients with inoperable or recurrent HER2-negative breast cancer starting in September, 2014. We enrolled a similar number of patients receiving ERI as first- or second-line therapy and those receiving ERI as third- or later-line therapy comparing to late-line therapy in clinical practice.

Results: We analyzed 634 patients. The mean age (± standard deviation) was 59.6 years (± 11.0), and 157 patients (24.8%) had triple-negative breast cancer. Of these patients, 319 received ERI as first- or second-line therapy and 315 as third- or later-line therapy. The median TTF (95% confidence interval [CI]) was 135 (121–164) and 119 (106–128) days, and the median OS (95% CI) was 555 (475–628) and 383 (342–459) days for first- or second-line, and third- or later-line therapy, respectively. A history of radiation therapy, complication of diabetes, liver metastasis,ECOG performance status, blood hemoglobin and aspartate aminotransferase levels at baseline, triple-negative breast cancer, and development of peripheral neuropathy after treatment were significant factors influencing both TTF and OS.

Conclusions: Our real-world study showed patients with first- or second-line therapy of ERI have longer OS and TTF than those in third- or later-line therapy. These results suggested that patients with first- or second-line therapy of ERI have the potential for similar or more favorable outcomes from the ERI treatment compared with patients with third- or later-line therapy of ERI.


Legal entity responsible for the study: Eisai Co., Ltd.

Funding: Eisai Co., Ltd.


115P Prospective cohort study of real world chemotherapy sequence for metastatic breast cancer (KBCRN A001: E-SPECS study)

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Background: The prognosis for triple negative (TN) and hormone-refractory metastatic breast cancer (MBC) remains poor and treatment options are limited to cytotoxic agents. Furthermore, the optimal sequence of chemotherapy (CT) is unclear. In this prospective cohort study (E-SPECS), we observed optimal sequences of CT for improving long-term survival. This trial was registered with ClinicalTrials.gov (no. NCT02551263).

Methods: The study was conducted under a multi-institutional prospective observational design and involved patients with HER2 negative hormone-refractory MBC. Eligibility criteria were age 20-75 years; refractory to hormone therapy defined as TN type or recurrence during or within 6 months after the end of adjuvant treatment or refractory to at least one previous hormone therapy for MBC, and scheduled for first- and second-line CT after registration. All treatments were performed according to physician’s choice.

Treatment regimens, efficiencies and quality of life (QoL) were prospectively surveyed. Baseline data analysis included patient characteristics, real-world CT sequence of first- and second-line CT regimen and the reason for cessation of first-line CT.

Results: Between June 2015 and July 2017, a total of 201 patients were enrolled, 194 of whom were analyzed. Mean age was 58.9 years, 142 patients (73.2%) had ER- and/or PgR-positive disease, 52 patients (26.8%) had TN. Most frequent regimen for first- or second-line CT was eribulin (ERI) (88.9%) among patients who received second-line CT. First-line CT sequences were oral fluorouracil (FU) followed by ERI (18.3%), bevaczumab/paclitaxel (BVe/P) followed by ERI (13.5%), and ERI followed by BVe/P (11.1%). Patients who received taxanes as a first-line CT had a significantly more adverse event discontinuation than those with oral FU or ERI (p < 0.01).

Conclusions: In this real-world setting, ERI was administered in almost first- or second-line regimens and taxane-based regimens were associated with more adverse event discontinuations. We intend to further investigate overall survival among CT sequences, as well as progression-free survival, new metastasis-free survival, type of progression and QoL.

Clinical trial identification: NCT02551263.

Legal entity responsible for the study: Masakazu Totsuka.

Funding: Eisai.

Disclosure: All authors have declared no conflicts of interest.
Comparative effectiveness of nab-paclitaxel vs. paclitaxel monotherapy as first-line (1L) treatment of metastatic triple-negative breast cancer (mTNBC) in US clinical practice

Methods: A total of 200 patients in the Flatiron Health EHR-derived database were included based on a confirmed diagnosis of mTNBC from 1 Jan 2011 and 31 October 2016 and receipt of nab-paclitaxel or paclitaxel monotherapy as 1L treatment. The primary outcome, OS, was estimated by Kaplan-Meier methods and compared by the log-rank test and by univariate and multivariate Cox regression models. Time to next treatment (TTNT) was assessed as a secondary outcome.

Results: Compared with pts who received paclitaxel (n=105), 201 patients received nab-paclitaxel (n=95), at baseline, those who received nab-paclitaxel were more likely to have been diagnosed at an earlier stage (I-III), have a treatment free interval of 12 months (in pts with recurrent disease), adjuvant treatment with a taxane, a prior diagnosis of neuropathy and coverage by commercial healthcare insurance. Other characteristics were balanced between groups. Over 90% of pts with evaluable dosing data (179 of 195) received weekly doses of either taxane, with 100 mg/m² as the most common dose for nab-paclitaxel and 80 mg/m² for paclitaxel. Median OS was 11.2 months in pts treated with nab-paclitaxel and 10.8 months in pts treated with paclitaxel (log-rank P = 0.82). The OS hazard ratio (HR) from the adjusted Cox model was 0.90 (95% CI: 0.61, 1.32), indicating a similar risk of death between the two groups. The robustness of this result was confirmed in several sensitivity analyses. TTNT for nab-paclitaxel and paclitaxel was 4.7 and 4.3 months (log-rank P = 0.44), respectively, and did not differ in adjusted analyses (HR = 0.95 [95% CI: 0.65, 1.38]).

Conclusions: Nab-paclitaxel and paclitaxel monotherapy demonstrated similar outcomes, suggesting that they may be considered interchangeable as 1L treatments for mTNBC.

Clinical utility of hepatic arterial infusion chemotherapy for heavily pretreated metastatic breast cancer patients: A review of a single institution

Methods: We reviewed our medical records of MBC to patients with resistance to standard systemic chemotherapies, including first-line liver metastasis, and who received HAIC with an EMEMA regimen (5-fluorouracil 333 mg/m² [weekly], epirubicin 30 mg/m² [every 4 weeks], and mitomycin-C 2.7 mg/m² [every 2 weeks]) in our institute.

Results: We identified 58 patients who received HAIC (median age at initiation, 58 [38-80] years) in our institute between 2002 and 2017. Their ECOG performance (PS) statuses were as follows: PS0, 44; PS1, 10; and PS 2, 4. Their receptor statuses were as follows: hormone receptor positive (HR+) 441 (95% CI: 30-80), HER2+, 441 (95% CI: 30-80); HER2-, 441 (95% CI: 30-80). The median number of liver metastases was 8 (1-20); the maximum median size of liver metastases was 5.2 cm (1.6-20.1). The median number of extrahepatic metastatic site was 2 (0-17). The median overall survival (OS) from paclitaxel, docetaxel, nab-paclitaxel, and vinorelbine. The primary endpoint was progression-free survival (PFS). Secondary endpoints included time to treatment failure (TTF), response rate (RR), duration of response, and safety. (UMIN000009886).

Results: From May 2013 to January 2017, 72 patients were enrolled. The full analysis set comprised data from 58 patients (median age, 58 years; range, 33–82 years); 38 (65.5%) received first-line treatment and 20 (34.5%) received second-line treatment. 43 patients (74.1%) were ER−, positive. The per protocol set comprised data from 57 patients. PFS, TTF, RR, and duration of response in both groups are shown in the table. The most common grade 3 or worse adverse events were neutropenia (9/27 [22.2%] in the eribulin group versus 5/31 [16.1%] in the TPC group). The incidence of sensory neuropathy was low in both groups.

Table: Clinical utility of hepatic arterial infusion chemotherapy for heavily pretreated metastatic breast cancer patients: A review of a single institution

<table>
<thead>
<tr>
<th>Eribulin (n = 26)</th>
<th>TPC (n = 31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Median(M)</td>
<td>6.5(0.8-11)</td>
</tr>
<tr>
<td>TTF</td>
<td>Median(M)</td>
<td>6.04(7-7.3)</td>
</tr>
<tr>
<td>Tumor response</td>
<td>CR</td>
<td>0.00%</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>5(19.2%)</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>16(61.5%)</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>5(19.2%)</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>5(19.2%)</td>
</tr>
<tr>
<td>Duration of response</td>
<td>Median(M)</td>
<td>3(0.2-1.3)</td>
</tr>
</tbody>
</table>

Conclusions: Eribulin was not shown to be superior to TPC in terms of efficacy. However, patients in the eribulin group had slightly longer PFS and TTF.

Legal clinical trial identification: UMIN000009886.
A randomized, open label, phase II study of prophylactic octreotide (OCT) to prevent/reduce the frequency and severity of diarrhea in patients (pts) receiving lapatinib (LAP) with capcitabine (CAP) for the treatment of metastatic breast cancer (mBC)

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Disclosure: All authors have declared no conflicts of interest.

Background: The combination of LAP+CAP is approved for the treatment of pts with HER2+ mBC who progressed on prior therapy, which must have included anthracyclines, taxanes and trastuzumab. Octreotide long acting release (OCT) is approved for the treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid and vasovagal potentiating-secretory tumors. Here we investigated the efficacy of the prophylactic use of OCT in the prevention or reduction of diarrhea associated with the treatment involving LAP+CAP.

Methods: Pts (N = 62) were randomized (1:1) to OCT (0.1mg/mL) + LAP (1250 mg/day) + CAP (2000 mg/m²/day) (n = 30) or LAP+CAP (n = 32), between 17-Dec-2014 and 13-Jan-2016. The primary objective was to determine the efficacy of prophylactic OCT in reducing the proportion of pts experiencing diarrhea with a severity of ≥ grade 2 based on NCI-CTCAEv4.0 version 4.03 during the first 3 cycles. The secondary objectives were ORR, CBR and other safety. Pearson chi-square test was used to compare the superiority of OCT+LAP+CAP arm with LAP+CAP arm.

Results: All pts enrolled in the study (database lock: 13-Feb-2018) were female with a median age of 56.5 years, and the majority was non-Hispanic or Latino (98%). Seven (23.3%) pts in the OCT+LAP+CAP arm and 8 (28.1%) pts in the LAP+CAP arm had at least one episode of ≥ grade 2 diarrhea during the first 3 cycles. The difference between the 2 arms was 4.8% with 95% CI (-29.2%, 20.0%) and was not statistically significant (P = 0.775). The ORR and CBR in OCT+LAP+CAP vs LAP+CAP arms was 20.0% vs 18.7%, and 23.3% vs 28.1%, respectively. Two (17%) pts from OCT+LAP+CAP arm and 9 (9%) pts from LAP+CAP arm, died due to the disease under study. The most common grade adverse events in OCT+LAP+CAP vs LAP+CAP (>15% in either arm), respectively, were-diarrhea (39% vs 43%), palmar-plantar erythrodysesthesia syndrome (43% vs 33%), rash (14% vs 21%), and anemia (7% vs 21%).

Conclusions: Prophylactic use of OCT did not result in a lower incidence of ≥grade 2 diarrhea in mBC pts receiving LAP+CAP. No new safety issues were identified.

Clinical trial identification: NCT02294786.

Editorial acknowledgement: Medical editorial assistance was provided by Sai Krishna Areppalli, PhD (Novartis Healthcare Pvt Ltd).

Legal entity responsible for the study: Novartis Healthcare Private Limited.

Funding: Novartis Healthcare Private Limited.

Disclosure: P. Krivokostka: Personal fees: Novartis, during the conduct of the study and outside the submitted work. J.P. Zarate, C. Babanova Pisal, L. Smith: Employee: Novartis. All other authors have declared no conflicts of interest.

321P Response evaluation of cancer therapeutics in metastatic breast cancer to the bone: A single arm phase II study of whole-body magnetic resonance imaging


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Background: Accurate and reliable evaluation of response to systemic anti-cancer therapy (SACT) is fundamental in the management of metastatic breast cancer (MBC). CT and bone scans (BS) have significant limitations in assessing SACT response in bone disease in MBC, whereas whole-body magnetic resonance imaging (WB-MRI) shows significant promise. Published retrospective data show that the addition of WB-MRI to body CT alters treatment decisions in MBC. The primary objective of this study was to evaluate whether WB-MRI identifies progressive disease (PD) earlier than CT scans in patients with bone-only MBC.

Methods: Participants were enrolled when starting first or subsequent SACT for bone-only MBC, as established initially by BS and CT thorax, abdomen and pelvis. Baseline WB-MRI was performed within 2 weeks of trial entry. CT and WB-MRI were performed every 12 weeks until definitive PD was evident in one or both modalities. At PD, BS was assessed for bone disease progression. Radiologists independently reported CT, WB-MRI or BS and were blinded to the other modalities. Participant questionnairenaires were undertaken at weeks 12 and 36 to evaluate tolerability and satisfaction with WB-MRI and CT.

Results: Forty-five participants were enrolled, with a median time on-study of 24 weeks (range 1-84 weeks). Two patients were excluded due to unequivocal liver metastases on
baseline WB-MRI, two had clinical progression before imaging (PD); one was lost to follow-up. Twenty-nine had PD on imaging, eleven continue on study. In 65.3%, PD was evident on WB-MRI only; 34.3% had PD on CT and WB-MRI concurrently; none had PD on CT only (McNemar's test p < 0.0001). PD on BS was reported in 35.6% of cases of bone CT/MRI progression. Overall questionnaire responder rate was 68.8%. No differences were found between CT and WB-MRI in levels of concern, comfort or pain at week 12 or 36. All participants reported satisfaction levels as 'good' or 'very good' for both modalities.

Conclusions: WB-MRI identifies PD before CT in most patients with bone-only MBC. Further studies will evaluate whether earlier identification of PD with WB-MRI and earlier SACT changes can lead to improved patient outcomes.

Clinical trial identification: NCT03266744.

Legal entity responsible for the study: East and North Hertfordshire NHS Trust.

Funding: Paul Strickland Scanner Centre.

Disclosure: M.-L. Ah-See: Consulting or advisory role: AstraZeneca, Novartis, Pierre Fabre, Merck Sharp and Dohme; Honoraria: Roche. A. Marshall: Educational research grants: Bayer AG outside of this submitted work that was used in part to pay for salary for research undertaken. All other authors have declared no conflicts of interest.

**322P** Anti-tumor cell activity and in vitro profile of the next generation CXCR4 antagonist Balixafortide

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**Background:** Balixafortide is a very potent, well tolerated and highly selective next generation CXCR4 antagonist derived over the past decade through multiple rounds of optimization starting from the natural product polyphemusin. Clinical proof-of-concept was achieved in a Ph 1/2 study in combination with Erbitux in metastatic HER2-negative breast cancer. The anti-cancer effects and pluripotent action of Balixafortide may include sensitization of tumor cells to chemotherapy, suppression of metastatic spread, inhibition of angiogenesis, and activation of the immune system.

**Methods:** Balixafortide was tested in a HTSE-based CXCR4 ligand binding assay, in functional assays (Calcium flux and beta arrestin), and further profiled in a large panel of other receptors including CXCR7. Effects on tumor cell sensitization were followed with an intracellular pERK / pAKT signaling assay. Tumor cell migration was assessed by chemotaxis assays, and inhibition of angiogenesis was determined by HUVEC sprouting. Evidence for immune cell activation came from evaluation of corresponding marker such as interferon gamma. Balixafortide was also detailed in profiled in an extensive in vitro ADME panel.

**Results:** Balixafortide binds CXCR4 with high affinity (IC50 < 10nM). It blocks beta arrestin recruitment and Calcium flux with IC50 < 10nM. A high 1000-fold selectivity window was demonstrated in a large panel of receptors including CXCR7. Balixafortide potently inhibits pERK / pAKT signaling in the lymphoma lines Namalwa (IC50 < 200 nM) and Jurkat (IC50 < 400 nM). Balixafortide efficiently blocks SDF-1 dependent chemotaxis of MDA MB 231 breast cancer cells (IC50 < 20 nM). Namalwa and Jurkat cells (IC50 < 10 nM). Receptor occupancy wash-out studies with competitive antibody 12G5 revealed prolonged binding of Balixafortide to CXCR4. In addition, Balixafortide was optimized for favorable mouse and human ADME properties with balanced plasma protein binding, greater plasma and microsomal stability.

**Conclusions:** Balixafortide is a product of an extensive optimization process which started from polyphemusin and now represents a favorable balance between ADMET properties, potency and tolerability which allows high and frequent dosing of a CXCR4 antagonist in cancer patients.

Legal entity responsible for the study: Polyphor Ltd.

Funding: Has not received any funding.


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**322P**

**Subcutaneous trastuzumab (SC) with intravenous pertuzumab (P IV) and docetaxel (D IV) in HER2-positive advanced breast cancer (BC): MetaPhER second interim analysis**

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**Background:** SC HER2 (Herceptin® SC) was approved based on the HANNAH study (Ismael Lancet Oncol 2012). The single arm, open-label MetaPhER study (NCT02402712) is the first large Phase IIb study to evaluate the safety and tolerability of SC + P IV (PERTEIRA) + D IV as first-line treatment in patients (pts) with HER2-positive metastatically advanced BC. Here, we report interim safety and preliminary efficacy.

**Methods:** Pts are ≥18-year-old females whose disease was not previously treated with systemic non-hormonal anticancer therapy. Pts receive 600 mg fixed-dose SC Herceptin + 840 mg loading/420 mg maintenance P IV q3w + 6 cycles D IV q3w (>6 at investigator discretion; 75 mg/m² initial dose) until disease progression (PD), unacceptable toxicity, withdrawal of consent, death or predefined study end. The primary endpoint is overall and cardiac safety and tolerability. Adverse events (AEs) are graded per NCI-CTCAE v4.0.

**Results:** Of 418 enrolled pts, 412 started study treatment; 330 (196 on treatment, 134 in post-perfusion [FU]) were on study by data cutoff (5 Jan 18). Median FU duration was 16.3 months. In the safety population 406/412 pts (98.5%) experienced ≥1 any-grade AE; 213 (21.1%) grade 3 AEs; 101 (24.5%) serious AEs (SAEs); and 86 (20.9%) AEs leading to P IV, P IV or D IV discontinuation. 47 pts (11.4%) died: 38 (9.2%) due to PD; 9 (2.2%) due to AEs; none from cardiac death. AEs of interest included grade ≥3 cardiac AEs (3 pts, 0.7%); electrophysiological changes; and premature drug discontinuation. AEs: 239 (58%) AEs; 13 (3.2%) AEs leading to P IV, P IV or D IV discontinuation. 47 pts (11.4%) died: 38 (9.2%) due to PD; 9 (2.2%) due to AEs; none from cardiac death. AEs of interest included grade ≥3 cardiac AEs (3 pts, 0.7%); electrophysiological changes; and premature drug discontinuation.

**Conclusions:** Safety and efficacy profiles of H SC + D IV as first-line treatment for pts with HER2-positive advanced BC were consistent with the known profiles for the H IV + D IV combination, and no new safety signals identified. The final analysis is planned for 2019.

Clinical trial identification: NCT02402712.

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

Funding: F. Hoffmann-La Roche Ltd.

Methods: MEDLINE and conference abstracts were identified using the search terms "biosimilar" AND "trastuzumab" from 1 January 2013 to 14 March 2018. Abstracts and manuscripts were manually reviewed to assess availability of efficacy data comparing the proposed biosimilar with reference trastuzumab.

Results: A total of 84 results were obtained. After selection for studies with comparative clinical efficacy results, 8 phase 3 clinical trials for 6 proposed biosimilars were included in the final analysis: 4 in EBC (primary efficacy outcome, pathologic complete response [pCR]) and 4 in MBC (primary efficacy outcome, overall response rate (ORR)). In all trials, the proposed biosimilar was equivalent to reference trastuzumab in terms of efficacy. Two biosimilars (CT-P6 and CT-P14) demonstrated equivalent clinical efficacy based on regulatory guidelines and clinical results. Together, these data support extrapolation between settings.

Conclusions: All biosimilars assessed demonstrated equivalent efficacy to reference trastuzumab, regardless of clinical setting. Two biosimilars demonstrated equivalent efficacy in both the EBC and MBC settings. Although the FDA and European Medicines Agency determine biosimilarity based on totality of evidence, both the EBC and MBC settings appear to have similar sensitivity and be appropriate for determination of equivalent efficacy based on regulatory guidelines and clinical results. Together, these data support extrapolation between settings.

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Table: 325P Demographic characteristics and treatment details

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<td>Median age (year, range)</td>
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<td>Prior trastuzumab</td>
<td>De novo metastatic patients</td>
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<tr>
<td>Histopathology</td>
<td>N = 309</td>
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<td>IDC</td>
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<td>Mixt</td>
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<td>ER/PR negative</td>
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<td>Prior trastuzumab</td>
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Background: In patients with HER2-positive ABC who were previously treated with taxane and trastuzumab without pertuzumab, TDM1 showed a progression-free survival (PFS) of 9.6 months and an overall survival (OS) of 29.9 months. Paucity of data for the present analysis was performed on patients who received second-line TDM1 after the Gruppo Italiano Mammella (GIM) 14/BIOMETA is a retrospective/prospective multicenter study on treatment patterns and outcomes of patients with ABC. This real-life practice population differs from the CLEOPATRA study in clinical effectiveness and therefore warrants consideration in the treatment algorithm of HER2-positive ABC patients. To our knowledge this study represents one of the first reports assessing clinical and demographic factors on PFS and OS were assessed using Cox's proportional hazards regression model.

Results: Of 1858 patients included in the GIM14/BIOMETA study, 70 were eligible for the present analysis. Median age was 54 years; 36 patients (51%) had hormone receptor-positive/HER2-positive disease, and 27 (39%) had visceral involvement. All patients received TPH in the first-line setting, and 35 (50%) received taxane and trastuzumab in the adjuvant setting. At the time of data cutoff (April 30, 2018), median duration of follow-up 17.8 months), 30 patients (43%) were still receiving TDM1. Disease progression was the reason for treatment discontinuation in the remaining cases. Median PFS was 8.5 months (95% confidence intervals [CI] 5.3-12 months), and CR rate was 73%. One-year survival rate was 91%.

Conclusions: Our findings suggest that TDM1 is effective in patients progressing after TPH. A better performance was observed as compared to data previously published on TDM1 effectiveness after first-line TPH. Clinical trial identification: NCT02284581.

Legal entity responsible for the study: Consorzio Oncotech.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.

Table: 325P continued

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<th>Treatment</th>
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<th>1 year OS (95% CI)</th>
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<td>Pertuzumab-trastuzumab</td>
<td>10</td>
<td>1 (7-5)</td>
<td>100</td>
<td>68%</td>
<td>88%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>6</td>
<td>1 (2-3)</td>
<td>100</td>
<td>93%</td>
<td>100%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>3</td>
<td>1 (2-6)</td>
<td>67</td>
<td>78%</td>
<td>91%</td>
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<tr>
<td>TDM1</td>
<td>50</td>
<td>1 (2-6)</td>
<td>73</td>
<td>81%</td>
<td>96%</td>
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</tbody>
</table>

Conclusions: This real-life practice population differs from the CLEOPATRA study in terms of visceral only metastatic disease, and inclusion of brain metastatic patients. Regardless of these negative prognostic characteristics, results are concordant with the pivotal study. Elderly patients had overall lower PFS, which necessitates further investigation of pertuzumab-trastuzumab combination with cytotoxic/antihormonal therapies. To our knowledge, this is the largest scale real-life clinical practice study of PTT to date.

Legal entity responsible for the study: Ece Eskin, on behalf of Turkish Oncology Group.

Disclosure: All authors have declared no conflicts of interest.
and the majority of pts (99.3%) had an Eastern Cooperative Oncology Group performance status ≤1. 40.0% had stage IV disease at diagnosis. Bone (73.9%), lung (31.4%), and liver (30.7%) were the most common metastatic sites. The most frequent adverse events (AEs) were neutropenia (35.8%), fatigue (31.0%), constipation (29.9%), asthenia (27.1%), nausea (24.5%), and vomiting (21.9%); 99.3% had an Eastern Cooperative Oncology Group performance status ≤1. QT prolongation was infrequent (2.0%). Dose adjustment/treatment interruption due to AEs was required for 48.4% of pts. Four patients (2.6%) discontinued treatment due to AEs.

**Conclusions:** Initial safety results from CompLEEment-1 demonstrate the tolerability of ribociclib (RIB) + LET + ovarian functional suppression in premenopausal women, consistent with previous reports. NCT02949126.

**Clinical trial identification:** NCT02949126.

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329P Abemaciclib with fulvestrant in patients with HR+, HER2- advanced breast cancer (ABC) that exhibited primary or secondary resistance to prior endocrine therapy (ET)

329P Abemaciclib with fulvestrant in patients with HR+, HER2- advanced breast cancer (ABC) that exhibited primary or secondary resistance to prior endocrine therapy (ET)

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**Background:** Abemaciclib, a selective inhibitor of CDK4 & 6, dosed on a continuous schedule is approved for the treatment of HR+, HER2- ABC. In the intent-to-treat population, abemaciclib with fulvestrant (F) demonstrated improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P) (F: 16.4 vs 9.3 mos, HR: 0.553; P < 0.0001; ORR in measurable disease 48.1 vs 21.3%; P < 0.001). ET resistance (ETR) were classified into primary ETR, which includes pts whose disease relapsed within the first 2 years of (non)adjunctive ET or progressed while receiving the first 6 mos of ET for ABC, and secondary ETR. Here, we compare the efficacy and safety of abemaciclib + F vs P + F in the primary and secondary ETR subgroups.

**Methods:** MONARCH 2 was a phase 3 randomized, double-blind, placebo-controlled study of abemaciclib + F vs P + F in pts with HR+, HER2- ABC that progressed on ET. Key eligibility criteria were previously discussed. Pts received orally administered abemaciclib 150 mg Q12H + 500 mg F (per label) or P + F. Pts were stratified by sensitivity to ET. Primary outcome was investigator-assessed PFS. Secondary outcomes included efficacy, safety, and tolerability.

**Results:** 169 pts (25.3%) had primary ETR and 489 pts (73.1%) had secondary ETR. Key efficacy endpoints are summarized (Table). The most frequent adverse events in primary and secondary ETR population are similar. For primary ETR, abemaciclib + F vs P + F were diarrhea (87.3 vs 22.4%), neutropenia (43.6 vs 5.2%), nausea (41.8 vs 25.9%), abdominal pain (36.4 vs 13.8%), and anemia (31.8 vs 5.2%), respectively.

**Conclusions:** Abemaciclib + F improved PFS and ORR in pts with primary and secondary ETR, and had a generally tolerable safety profile. Although pts with primary ETR typically have poor prognosis the benefit for abemaciclib + F was maintained in pts HR+, HER2- ABC.

**Clinical trial identification:** NCT02107703.

**Legal entity responsible for the study:** Eli Lilly and Company.

**Funding:** Eli Lilly and Company.

**Disclosure:** Y. Lin: Employee and stakeholder: Eli Lilly and Company. All other authors have declared no conflicts of interest.

330P Tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) with ribociclib (RIB) in premenopausal patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): MONALEESA-7 subgroup analysis

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**Background:** In the MONALEESA-7 study (NCT02772182), RIB + TAM/NSAI + goserelin significantly prolonged progression-free survival (PFS) and had a manageable safety profile vs placebo (PBO) + TAM/NSAI in premenopausal pts with HR+, HER2- ABC. Here we present data for the TAM and NSAI subgroups.

**Methods:** Premenopausal pts (N = 672) with HR+, HER2- ABC (<1 line of chemotherapy; no prior endocrine therapy [ET] for ABC) were randomized 1:1 to RIB (600 mg/day, 3 weeks on/1 week off) or PBO + either TAM (20 mg/day) or NSAI (letrozole [2.5 mg/day] or anastrozole [1 mg/day]) + goserelin (3.6 mg every 28 days). Primary endpoint: locally assessed PFS. A predefined subgroup analysis evaluated PFS by ET partner (TAM or NSAI).

**Results:** 177 (26%) pts received TAM (RIB vs PBO: 87 vs 90) and 495 (74%) received an NSAI (248 vs 247). As of August 20, 2017, treatment was ongoing in 49% vs 31% of pts in the TAM subgroup and 53% vs 38% in the NSAI subgroup; the most common reason for discontinuation was disease progression (TAM 39% vs 54%; NSAI 39% vs 51%). PFS was prolonged for RIB vs PBO in the TAM (median 22.1 months [mos] vs 11.0 mos; hazard ratio 0.585; 95% CI 0.387–0.884) and NSAI (median 27.5 mos vs 13.8 mos; hazard ratio 0.569; 95% CI 0.436–0.743) subgroups. The most common Grade (3) adverse events (AEs; regardless of causality; 29% of pts; RIB vs PBO): neutropenia (TAM 39% vs 2%; NSAI 55% vs 3%); leukopenia (TAM 8% vs 1%; NSAI 15% vs 1%); elevated GGT (TAM 6% vs 3%; NSAI <1% vs 4%); elevated ALT (TAM 7% vs 2%; NSAI 5% vs 1%); and hypertension (TAM 6% vs 2%; NSAI 2% vs 3%); the only G4 AE in 2% of pts was neutropenia (TAM 9% vs 1%; NSAI 10% vs <1%). Increases >60 ms from baseline in the QTcF interval (RIB vs PBO; TAM 16% vs 7%; NSAI 7% vs 0%) and new QTcF >480 ms (TAM 11% vs 1%; NSAI 5% vs 1%) were more common with TAM; there were no associated clinical symptoms or arrhythmias.
Conclusions: RIB demonstrated consistent treatment benefit vs PBO in premenopausal pts with HR+, HER2- ABC—RECAL: ABC irrespective of ER status—vs ABC. The safety profiles of RIB + ET were manageable and consistent, with the exception of QTc findings, which were more prevalent with TAM.

Clinical trial identification: NCT02229120 and October 29, 2014.

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Table: 331P

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<th>2L setting</th>
<th>Early relapse setting</th>
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<tr>
<td>RIB + FUL</td>
<td>RELAPSE &gt; 12 months from (neo)adjuvant endocrine therapy and subsequent progression on endocrine therapy for ABC</td>
</tr>
<tr>
<td>PBO + FUL</td>
<td>RELAPSE on or &lt; 12 months after (neo)adjuvant endocrine therapy with no treatment for ABC</td>
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<table>
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<tr>
<th>Pts, n</th>
<th>Median PFS, months</th>
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<th>PBO + FUL</th>
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<tr>
<td>99</td>
<td>18.8</td>
<td>0.539 (0.333–0.873)</td>
<td>137</td>
<td>71</td>
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</table>

332P Clinical outcomes in patients (pts) with estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) with objective response (OR) without objective response (non-OR) in PALOMA-2

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Background: In the phase 3 PALOMA-2 trial, palbociclib (PAL) + letrozole (LET) significantly improved progression-free survival (PFS) vs placebo (PBO) + LET in pts with ER+ /HER2- ABC. We investigated clinical outcomes of pts who achieved a confirmed OR compared with those who did not (data cutoff date: 31 May 2017).

Table: 332P

<table>
<thead>
<tr>
<th>Pts, n</th>
<th>Median PFS, months</th>
<th>Hazard ratio (95% CI)</th>
<th>RELAPSE on or &lt; 12 months after (neo)adjuvant endocrine therapy with no treatment for ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>137</td>
<td>13.1</td>
<td>0.591 (0.422–0.830)</td>
<td></td>
</tr>
</tbody>
</table>
Results: The PAL-LET and BPO-LET groups comprised 444 and 222 pts, respectively: 338 and 171 pts had measurable disease (MD) at baseline. Baseline characteristics were similar in OR and non-OR pts. OR was achieved by 194 (overall, 44%; MD, 57%); and 77 (35%; 45%) pts in the PAL and PBO arms, respectively. Of the pts who achieved OR in the PAL arm, 49% occurred within the first 3 months, 75% within 6 months, and 90% within 1 year. In the PAL arm, more than 90% had no OR pts had visceral disease (62% vs 38%), a disease site (50% vs 28%), and no prior hormonal therapy (55% vs 35%); fewer than OR pts had a disease-free interval of ≤ 12 months (14% vs 28%). mPFS was significantly prolonged with PAL-LET vs BPO-LET in both OR and non-OR pts (overall and with MD). Table shows in OR pts, mDOR was longer with PAL-LET vs BPO-LET. Safety profiles were similar and independent of response; neuropathy was the same most common grade AE in the PAL arm (OR, 86%; non-OR, 78%) and rates of PAL dose reduction due to AEs were similar (41%, 38%).

Conclusions: PAL-LET provided significant clinical benefit vs BPO-LET in both OR and non-OR pts; the safety profile was similar to previously reported results in the overall population. PAL is an effective treatment regardless of OR. Pfizer (NCT01740427).

Table: 332P Clinical benefit in patients with or without confirmed OR in PALOMA-2

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Non-OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts, n</td>
<td>194</td>
<td>77</td>
</tr>
<tr>
<td>mPFS (95% CI), mo</td>
<td>37.2 27.4</td>
<td>16.5 8.2</td>
</tr>
<tr>
<td>(28.1–11.1)</td>
<td>(12.8–22.2)</td>
<td>(5.6–11.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.46–0.92)</td>
<td>0.55 (0.43–0.70)</td>
</tr>
<tr>
<td>(mDOR)</td>
<td>27.7</td>
<td>20.9</td>
</tr>
<tr>
<td>(24.7–36.1)</td>
<td>(16.5–27.6)</td>
<td></td>
</tr>
<tr>
<td>Pts with MD, n</td>
<td>194</td>
<td>76</td>
</tr>
<tr>
<td>mPFS (95% CI), mo</td>
<td>37.2 27.4</td>
<td>10.9 5.6</td>
</tr>
<tr>
<td>(28.1–11.1)</td>
<td>(8.2–11.2)</td>
<td>(5.3–8.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.66 (0.47–0.94)</td>
<td>0.72 (0.54–0.97)</td>
</tr>
</tbody>
</table>

HR=hazard ratio; NE=not estimable.
Health related quality of life in women with HR+/HER2- advanced or metastatic breast cancer treated in real world settings in Italy and Germany

M. De Laurentiis1, A. Kärgel1, KL. Davis2, D. Mitra3, C.M.A. Nuzzo4, M. Ajmera5, S. de Pasquale6, S. Brucker7, N. Yarbrough8

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Background: Real-world data on health-related quality of life (HRQoL) in women with HR+/HER2- advanced/metastatic breast cancer (ABC/mBC) are limited. This study aims to address this gap.

Methods: MARIA is a non-interventional, prospective, multi-center study that includes women in Italy and Germany initiating their first or second therapy in the HR+/HER2- ABC/mBC setting. Breast cancer-specific HRQoL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B). We report baseline clinical characteristics and HRQoL assessments at enrollment (baseline) and at 3 and 6 months for the first 262 patients enrolled. Change from baseline was calculated for patients with both baseline and follow-up measurement and tested for statistical significance using t-tests for the overall cohort and within subgroups stratified by visceral and bone metastases status.

Results: Median age was 61 years and 46% had visceral disease. At enrollment, 32% were receiving endocrine monotherapy, 34% endocrine/targeted therapy combinations, and 7% other regimens. A statistically significant (p < 0.05) deterioration was observed in the overall cohort at Month 3 for both FACT-B (−18.9 [14.9] and FACT-G (−4.1 [13.2]) and at Month 6 for the total FACT-G score (−21.7 [12.7]). In the subgroup with visceral and bone metastases, a statistically significant (p < 0.05) deterioration was observed in FACT-G scores at 3 months (−6.6 [16.1]) and at 6 months (−3.6 [12.3]) while no significant change was observed in FACT-B scores. Statistically significant (p < 0.05) deterioration from baseline was observed in the subgroups with visceral disease and without bone metastases in FACT-B score at 3 months (mean [SD]: −6.7 [13.9]) and at 6 months (−3.9 [16.6]), respectively while no significant change was observed in FACT-G scores.

Conclusions: A statistically significant deterioration was observed in HRQoL scores at some time points after initiating a new line of therapy in the overall cohort and some subgroups of HR+/HER2- ABC/mBC patients in a prospective study in Italy and Germany. Further follow-up is ongoing to examine the longer-term impact of therapy on HRQoL.

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: M. De Laurentiis: Honoraria; Pfizer, Novartis, Roche, Celgene, AstraZeneca, Eisai, Eli Lilly. KL. Davis, M. Ajmera: Employee: RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this abstract. D. Mitra, C.M.A. Nuzzo: Employment and stock ownership. Pfizer. N. Yarbrough: Honoraria Lilly, Novartis, Pfizer. All other authors have declared no conflicts of interest.

Breast cancer (BC) treatment (tx) with everolimus (EVE) and exemestane (EXE) in hormone receptor positive (HR+) / HER-2 negative (HER2-) postmenopausal women: Final analysis of the French observational TANGO study

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Background: TANGO is a French observational prospective study of women with advanced BC treated with EVE/EXE. The main objective was to describe the management of stomatitis and noninfectious pneumonitis (NIP) in clinical practice. Overall safety, duration of EVE/EXE tx and progression-free survival (PFS) were also assessed.

Methods: Eligible patients (pts) were postmenopausal women ≥18 years with advanced HR+/HER2- BC, for whom EVE/EXE was initiated. Statistical analyses were mainly descriptive. Tx duration and PFS were estimated with Kaplan-Meier methods.

Results: From Nov 2014 to Mar 2016, 596 pts had received EVE/EXE (Pts characteristics: see table).

Conclusions: Results from this real-life observational study reinforce the known safety profile of EVE and better characterize stomatitis and NIP, as well as their management in EVE-treated pts.

Clinical trial identification: EU-PAS: EUPAS7325.

Editorial acknowledgement: Florence Arts and Jérôme Leemans; Keyrus Biopharma, Belgium.

Legal entity responsible for the study: Novartis Pharma S.A.S. (France).

Funding: Novartis Pharma S.A.S (France).


Table: 335P Pts baseline characteristics at EVE/EXE initiation

<table>
<thead>
<tr>
<th>Pts who received EVE/EXE (N = 596)</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Mean (standard deviation) age, years</td>
</tr>
<tr>
<td>Pts aged ≥75 years – n (%)</td>
</tr>
<tr>
<td>Median (range) time since initial BC diagnosis to inclusion, years</td>
</tr>
<tr>
<td>Pts with de novo metastatic BC at diagnosis – n (%)</td>
</tr>
<tr>
<td>Pts with ECOG ≤1 – n (%)</td>
</tr>
<tr>
<td>Metastases</td>
</tr>
<tr>
<td>Pts with bone-only metastases – n (%)</td>
</tr>
<tr>
<td>Pts with visceral metastases – n (%)</td>
</tr>
<tr>
<td>Previous lines of tx for metastatic disease</td>
</tr>
<tr>
<td>Pts without previous line – n (%)</td>
</tr>
<tr>
<td>Pts with 1 previous line – n (%)</td>
</tr>
<tr>
<td>Pts with 2 previous lines – n (%)</td>
</tr>
<tr>
<td>Pts with ≥3 previous lines – n (%)</td>
</tr>
<tr>
<td>BC relapses related to adjuvant hormonal tx</td>
</tr>
</tbody>
</table>

350 pts (51%) experienced stomatitis and 80 (13%) experienced NIP (median time to 1st event [range]: 21 [1 – 335] and 104 days [1 – 396], respectively). Most stomatitis (87%) and NIP (91%) were grade 1-2. Stomatitis was mainly treated with mouthwashes (77%), topical analgesics (19%) and antibiotics (15%), and NIP with corticosteroids (40%) and antibiotics (10%). 509 pts (85%) had EVE-related adverse events (AE), the most common (excluding stomatitis/NIP) being asthenia (19%), diarrhea (11%) and rash (10%). 90 pts (15%) had EVE-related serious AE, the most common (excluding stomatitis/NIP) being asthenia (2%). 5 pts (1%) had EVE-related fatal AE, health deterioration, multiple organ failure, epistaxis, intrastitial lung disease, pleural metastases and disorientation. With 562 analysed pts, the median PFS was 6.9 months (95% confidence interval [CI]: 6.2 – 7.8) and median duration of EVE/EXE tx was 3.3 months (95% CI: 4.8 – 6.0). After EVE discontinuation, most pts continued EXE alone (55%) or had chemotherapy (8%).

Conclusions: Results from this real-life observational study reinforce the known safety profile of EVE and better characterize stomatitis and NIP, as well as their management in EVE-treated pts.

Everalobin in advanced breast cancer: A systematic review and meta-analysis

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1Oncology, Western University, London Regional Cancer Program, London, ON, Canada, 2Oncology and Anatomy and Cell Biology, Western University - London Regional Cancer Program, London, ON, Canada.

Background: Everalobin (E) plus exemestane are approved for advanced hormone receptor (+) breast cancer (BC) after progression on non-steroidal aromatase inhibitors. The role of E is less well defined in other BC phenotypes and with other drugs. We conducted a systematic review and meta-analysis to assess the efficacy and safety of adding E to standard of care (SoC) in advanced BC regardless of tumor phenotype and treatment type.
Methods: The electronic databases PubMed and EMBASE were searched for eligible randomized trials. Pooled hazard ratios (HR) for progression-free survival (PFS) and overall survival (OS) and pooled odds ratios (OR) and odds ratios (OR) for objective response rates (ORR), clinical benefit rates (CBR) and grade 3 or higher toxicity were meta-analyzed using the generic inverse variance, the Mantel-Haenszel and Peto method. To account for between-studies heterogeneity, random-effect models were used. Subgroup analyses compared survival outcomes by tumor phenotype.

Results: Data of 2,685 patients from 7 trials were analyzed. The addition of E to the SoC reduced the risk of disease progression by 33% (7 trials, HR 0.67, 95%CI 0.52-0.86). This did not translate into an OS benefit (4 trials, HR 0.91, 95%CI 0.62-1.35). In addition, E improved the ORR (6 trials, RR 0.81, 95%CI 0.85-0.97) and CBR (7 trials, RR 0.79; 95%CI 0.63-0.97) while it increased the risk of developing grade 3 toxicity including stomatitis (OR 5.00, 95%CI 3.63-6.89) and pneumonitis (OR 3.13, 95%CI 1.83-5.36). The PFS benefit was more prominent for patients with hormone receptor (+) /HER2 (-) HR 0.51, 95%CI 0.34-0.79) than HER2 (+) disease (HR 0.83, 95%CI 0.73-0.96; p for subgroup differences <0.001). For the HER2 (+) subgroup, the PFS benefit was restricted to hormone receptor (+) patients (HR 0.65, 95%CI 0.53-0.81 and HR 0.96, 95%CI 0.83-1.19 for hormone receptor (+) patients; p for subgroup differences =0.004).

Conclusions: E reduces the risk of disease progression in hormone receptor (+) advanced BC independent of endocrine therapy type. In HER2 (+) patients, the benefit is limited for hormone receptor (-) patients. Given the use of newer drugs in the first line, real-world data are needed to confirm whether the benefit persists for patients who develop resistance to CDK4/6 inhibitors.

Legal entity responsible for the study: Jacques Raphael.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**337P** First-line treatment for endocrine sensitive bone-only metastatic breast cancer: Is more always better?

A. Toss1, M. Venturinelli1, I. Spenderdi2, C. Isca1, E. Barbieri3, F. Pacentini1, C. Omari1, L. Cortesi4, S. Cascini1, L. Moscetti1

1Department of Oncology and Haematology, Azienda Ospedaliero - Universitaria Policlinico di Modena, Modena, Italy, 2Bio-Statistics Unit, IRCCS Regina Elena National Cancer Institute, IRCCS Regina Elena National Cancer Institute, Rome, Italy

Background: The standard first-line for endocrine sensitive metastatic breast cancer (BC) is represented by endocrine therapy. Several phase III clinical trials searched for more effective strategies. The SWOG, FACT and FALCON trials analyzed the role of Fulvestrant (Fv), producing contradictory results. The Monaleesa2, Monaleesa2, Monarch3 and Palomar2 trials showed that the addition of a CDK4/6 inhibitor to an aromatase inhibitor (AI) increases the PFS. The use of the combination for the first-line treatment of bone-only disease (BoD) is widely discussed. Our meta-analysis aims to explore the role of the new endocrine strategies in BoD.

Methods: The Prisma statement was used. A systematic review of electronic databases identified the phase III clinical trials comparing the standard AI to a novel experimental strategy. The hazard ratios (HR) for PFS for the subgroup of BoD were used in a meta-analysis. The heterogeneity of the data was evaluated by Chi-square Q test and I2 statistic.

Results: 7 studies were included in the analyses, 4 trials explored the role of CDK4/6 inhibitors (Monaleesa2 and 7, Monarch3 and Palomar2), 2 trials analyzed Fv + AI (SWOG and FACT), while one trial studied Fv monotherapy (FALCON). 5 studies reported data regarding the BoD, while 2 trials included the BoD in the non-visceral disease. Overall, the meta-analyses showed a PFS advantage for the experimental arms [HR 0.67 (p=0.01), with a significant moderate/high heterogeneity [I2 69.88; p=0.003]. Only the FALCON and Palomar2 showed a significant improvement in PFS, respectively for Fv and Palbociclib + Letrozole. Considering only trials reporting data for BoD, the experimental arms significantly improved the PFS [HR 0.60 (p=0.01), with a low/moderate non-significant heterogeneity [I2 37.73; p=0.17].

Conclusions: The meta-analyses of trials reporting data for BoD, showed that the novel strategies are able to improve the PFS. Nonetheless, only Palbociclib + Letrozole provided statistically significant data of advantage in this setting. In clinical trials, BoD is often included in the non-visceral disease subgroup. Future clinical trials should take into account the differences in natural history and better prognosis of BoD, in order to define the best approach to these patients.

Legal entity responsible for the study: Angela Toss.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**339P** Management of abemaciclib associated adverse events in patients with hormone receptor positive (HR+) breast cancer: Analysis of the MONARCH trials

H.S. Rugo1, S.M. Tolianay2, J. Huo2,3, M. Taf3, V. André4, S. Barriga5, T. Forrester6, G.W. Sledge7, M.P. Goetz8

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Background: Abemaciclib is a CDK4 & 6 inhibitor dosed continuously with demonstrably efficacious and an acceptable safety profile in pts with HR +, HER2-negative advanced breast cancer as monotherapy (MONARCH 1) and in combination with endocrine therapy; with fulvestrant (MONARCH 2) or with non-steroidal aromatase inhibitors (MONARCH 3). The most frequent adverse event (AE) is low-grade diarrhoea; neutropenia is the most frequent grade 3/4 AE. We describe the timing and management of common AEs in the MONARCH trials.

Methods: Enrollment criteria, study designs and key eligibility criteria of MONARCH 1, 2 and 3 have been reported (Dicker et al. 2017; Sledge et al. 2017; Goetz et al. 2017). Pts were advised to initiate antidiarrheal therapy at first sign of diarrhoea and notify the investigator, drink fluids. If not improved within 24 hours to < grade 1, treatment was suspended until diarrhoea resolved. Dose reductions required for grade ≥ 3 or persistent grade 2 diarrhoea. For grade 3 neutropenia, abemaciclib was held until < grade 2. The dose was reduced for recurrent grade 3 or grade 4 neutropenia.

Results: Across MONARCH, the median time to onset of diarrhoea was between day 6-8. First dose reductions for diarrhoea occurred at a median of 28-41 days. Dose holds for diarrhoea were brief, constituting 1.7-3.8% of total treatment time. The median time to onset of grade 3/4 neutropenia was 29-36.5 days, and resolved at a median of 11-15 days. AEs were managed by dose adjustments and/or supportive medication (Table).
Conclusions: The dose adjustment strategy used in the MONARCH studies was effective in managing AEs by dose adjustment and/or supportive medication. Understanding the safety profile of abemaciclib can inform AE management and can extend time on treatment.

Clinical trial identification: NCT02102490 (MONARCH 1), NCT02107703 (MONARCH 2), NCT02246621 (MONARCH 3).

Legal entity responsible for the study: Eli Lilly and Company.

Funding: Eli Lilly and Company.

Disclosure: H.S. Rugo: Grants/research support: GSK, Genentech/Roche, Novartis, Pfizer, Merck, Eisai, Pfizer, Mavion, Lilly, OBI (all funding to UC Regents only); V. Andre, S. Barriga, T. Forrester: Employee and stakeholder: Eli Lilly and Company. M.P. Goetz: Consultant: Eli Lilly and Company, bioTheranostics, Novartis, Eli Lilly, Pfizer, Amgen, Biogen, Lilly, Pﬁzer, Merck. V. Andre, S. Barriga, T. Forrester: Employee and stakeholder: Eli Lilly and Company. All other authors have declared no conﬂicts of interest.

Table: 339P

Summary of Dose Adjustments in Pts Experiencing Diarrhea or Neutropenia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MONARCH 1</th>
<th>MONARCH 2</th>
<th>MONARCH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abemaciclib</td>
<td>Abemaciclib</td>
<td>Abemaciclib</td>
</tr>
<tr>
<td></td>
<td>+ F</td>
<td>+ F</td>
<td>+ NAI</td>
</tr>
<tr>
<td>N = 132</td>
<td>N = 441</td>
<td>N = 327</td>
<td></td>
</tr>
</tbody>
</table>

Diarrhea (any grade), n (%) 119 (90.2) 381 (86.4) 269 (82.3)

Grade 3 26 (19.7) 59 (13.4) 31 (9.5)

Incidence per patient, n (%) 1 60 (50.4) 185 (48.6) 124 (46.1)
2 29 (24.4) 90 (23.6) 52 (19.3)
≥3 30 (25.2) 106 (27.8) 93 (34.6)

Outcome, number (% of events) 263 995 802

Not recovered/resolved 15 (5.7) 106 (10.7) 70 (8.7)

Treatment change, n (%) 119 381 269

Dose reduction of study drug 27 (22.7) 83 (21.8) 45 (16.7)

Dose omission 32 (24.2) 83 (21.8) 51 (19.0)

Treatment discontinuation 1 (0.8) 13 (3.4) 6 (2.2)

Antidotal medication, n (%) 80 (60.6) 333 (75.3) 226 (69.1)

Neutropenia (any grade), N (%) 49 (37.1) 203 (46.0) 143 (43.7)

Grade 3 15 (12) 117 (26.5) 78 (23.9)

Treatment change, n (%) 14 (10.6) 44 (10.0) 42 (12.8)

Dose omission 21 (15.9) 72 (16.3) 57 (17.4)

Treatment discontinuation 0 7 (1.6) 9 (2.8)

Progression free survival (PFS) benefit from first line endocrine based therapies in postmenopausal women with HR+/HER2- metastatic breast cancer (MBC) according to different prognostic subgroups: A combined analysis of data from PALOMA 2, MONALEESA 2, MONARCH 3, FALCON, SWOG and FACT trials

340P

V. Andre, S. Barriga, T. Forrester: Employee and stakeholder: Eli Lilly and Company. M.P. Goetz: Consultant: Eli Lilly and Company, bioTheranostics, Novartis, Genomic Health, Eisai, Biovica, and Sermonis; Grant/Research support from Eli Lilly and Pfizer. All other authors have declared no conflicts of interest.

Background: This analysis combines data from six phase III trials investigating the role of endocrine-based therapies in the first-line setting of MBC to identify which factors may guide the clinical choice among available drugs.

Methods: For PFS, Hazard Ratio (HR) and 95% CI were reported. Subgroup meta-analysis was conducted stratifying by age (ECOG, ethnicity, prior chemotherapy or endocrine therapy exposure, measurable disease at the time of metastasis occurrence, visceral or bone only disease, time from the initial diagnosis of breast cancer to the metastasis onset. Random-effect model was used and heterogeneity was quantified by I² statistics. Test of interaction was performed to compare treatment effect in subgroups. Data analysis was performed using R Statistical Software version 3.4.3.

Results: In absence of indirect comparison between cyclin dependent kinase (CDK) 4/6 inhibitors (Palbociclib, Ribociclib, Abemaciclib) combined to nonsteroidal aromatase inhibitors (AI) and Fulvestrant endocrine-based therapies, all these therapeutic options resulted in significant PFS benefit compared to AIs endocrine-monotherapy (HR: 0.74; 95% CI 0.67-0.80). Test of interaction showed similar treatment effects among sub-groups with the exception of Ethnicity and ECOG. Specifically, a longer PFS from CDK 4/6 inhibitors plus AIs strategies was observed in Asian (Asian HR: 0.38; 95% CI 0.20-0.72 versus non-Asian population HR: 0.61; 95% CI 0.50-0.75, p < 0.001) and ECOG≥1 patients (ECOG≥1 HR: 0.53; 95% CI 0.51-0.56 versus ECOG<0 HR: 0.60; 95% CI 0.49-0.74, p < 0.02).

Conclusions: CDK 4/6 inhibitors or Fulvestrant endocrine-based therapies as first-line treatment for postmenopausal women with HR+/HER2- MBC showed significant PFS improvement in comparison with AIs endocrine-monotherapy. Further indirect comparison by a network meta-analysis is needed to explore which patients may derive the greatest benefit from the different therapeutics options.

Legal entity responsible for the study: Valentina Rossi.

Funding: Disclosure: All authors have declared no conflicts of interest.

341P

Palbociclib in combination with letrozole as first or later line therapy for patients with locally advanced, inoperable or metastatic HR+/HER2- breast cancer in Germany: Interim results of the INGE-B phase II study


Background: Based on the pivotal PALOMA trials investigating the combination of the CDK4/6 inhibitor palbociclib with letrozole or with fulvestrant after prior endocrine therapy, extended European approval was granted for this patient population to receive palbociclib in combination with any aromatase inhibitor or with fulvestrant after prior endocrine therapy. The prospective multi-centre phase 2 study INGE-B was designed to a) investigate the combination of palbociclib with letrozole or with fulvestrant in accordance with the PALOMA trials in Germany and b) to obtain so far lacking data on the combination of palbociclib with the aromatase inhibitors exemestane or anastrozole.

Methods: In total, 360 patients with locally advanced, inoperable or metastatic HR+/HER2- breast cancer were recruited at 82 sites across Germany. Eligible patients were treated with palbociclib either in combination with letrozole, anastrozole, exemestane or fulvestrant as first-line therapy or in combination with letrozole or fulvestrant as later-line therapy. Primary objective is the clinical benefit rate (CBR), defined as the percentage of patients with response or stable disease at week 24. Key secondary endpoints include progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and safety. Quality of life, fatigue, anxiety and depression are assessed with validated questionnaires. Data were analysed for each treatment group separately with descriptive statistics.

Results: The first interim analysis of the INGE-B study was scheduled to analyse data of patients receiving palbociclib and letrozole in first or later line. Between 09/2016 and 01/2018, 63 first- and 59 later-line patients were enrolled at 38 sites and observed for at least 6 months of treatment, unless discontinued earlier for disease progression or any other reason. Baseline patient and tumour characteristics will be presented. Efficacy in terms of CBR and best response and treatment-emergent adverse events will be described.

Conclusions: The results of the first interim analysis of the INGE-B study will be discussed with respect to data from the PALOMA 1/2 trials.

Clinical trial identification: NCT02894398.

Legal entity responsible for the study: iOMEDICO AG.

Funding: Pfizer.

Disclosure: D. Lüfter: Membership on an advisory board or board of directors, remunerations: Amgen, Pfizer, Eli Lilly, Celgene, Lofelot, A. Welt: Membership on an advisory board or board of directors: Roche, Pfizer, Novartis. All other authors have declared no conflicts of interest.
Response to primary treatment for first recurrence independently influences survival of patients with hormone receptor-positive, HER2-negative breast cancer: A multicenter study of 236 recurrent metastatic patients

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Background: There is little current evidence for the optimal primary treatment (PT) for patients with recurrent metastatic hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer. These patients may be resistant to metastatic treatment due to continuous adjuvant endocrine therapy (ET). Here, we identify the significant factors correlating to prognosis in a retrospective study. Recognizing the prognostic factors for recurrent HR+/HER2- breast cancer may improve the delivery of healthcare to at-risk groups and play an important role in the treatment and care for these patients.

Methods: We performed a retrospective review of records from 236 patients with recurrent metastatic HR+/HER2- breast cancer who were diagnosed between January 2000 and December 2013 at Saitama City Medical Center and Kanazawa University Hospital, Japan. We assessed the clinicopathologic features, treatment patterns, and overall survival (OS) following diagnosis of first distant recurrence.

Results: Median OS after first recurrence was 3.73 years. Patients with longer disease-free survival (DFS) (>2 years), a longer interval after the end of adjuvant ET (>1 year), or first recurrence without liver metastasis had a significantly better prognosis (p < 0.001, p = 0.007, and p < 0.001, respectively). Patients with a good response to PT for first recurrence also had significantly better prognosis, regardless of ET or chemotherapy (p < 0.001). Longer DFS, no liver metastasis, and good response to PT were found to be independent prognostic factors for better OS in multivariate analysis (HR=0.467; 95% CI=0.291-0.736, p=0.002, HR=0.443; 95% CI=0.285-0.688, p<0.001, and HR=0.312; 95% CI=0.201-0.484, p<0.001, respectively). Good responders to PT were also shown to have a significantly longer response to subsequent lines (p < 0.007).

Conclusions: Good response to PT for first recurrence may be the key to favorable OS for recurrent metastatic HR+/HER2- patients, regardless of visceral metastasis. In addition to a novel targeted agent, more optimal treatment to first recurrence could improve drug resistance and eventually lead to better prognosis.

Legal entity responsible for the study: Saitama City Hospital Organization.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Application of CDK4/6 inhibitors in practice: Effect of online education on clinician competence and confidence

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2Global Education, Medscape, New Jersey, NJ, USA

Background: This study determined whether online continuing professional development (CPD) activity could improve oncologists’ (Oncs) and obstetrician/gynaecologists (Ob/Gyns) competence and confidence in the use of CDK4/6i in practice.

Methods: An interactive text-based activity that included discussion of 2 detailed patient cases was launched for countries outside the United States in March 2017, with responses overall, and for each question, were determined with Cramer’s V (effect size: <0.30 small, 0.30–0.40 medium, >0.40 large).

Results: 204 Oncs and 51 Ob/Gyns completed both pre- and post-assessments. A large education effect was observed for both Oncs (V = 0.311) and Ob/Gyns (V = 0.459). At baseline, 46% of Oncs and 16% of Ob/Gyns answered all 3 questions correctly, increasing to 51% and 76%, respectively, post-assessment. An average of 79% of Oncs selected the best response on pre-assessment (range, 66% to 80%), improving to 96% post-assessment (range, 96% to 97%). Statistically significant change for all 3 questions and a medium to large education effect was observed for the questions covering appropriate treatment selection, patient monitoring and management of neutropenia. Baseline understanding was lower for Ob/gyns with a large education effect seen for all 3 questions. 38% of Oncs and 45% of Ob/Gyns reported increased confidence managing neutropenia due to CDK4/6i.

Conclusions: This on-demand, text-based activity with 2 interactive cases resulted in a significant, positive education effect. Baseline findings indicate that both specialties, would benefit from education to facilitate application of CDK4/6i in practice. Online medical education is important in supporting the practical application of new treatment regimens in practice.

Legal entity responsible for the study: Medscape.

Funding: Pfizer.

Disclosure: All authors have declared no conflicts of interest.

First report of real-world patient characteristics and treatment patterns from POLARIS: Palbociclib in hormone receptor-positive (HR+) advanced breast cancer: A prospective, multicenter, noninterventional study

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2Hematology/Oncology, Northwest Georgia Oncology Centers, Marietta, GA, USA
3Hematology/Oncology, West Virginia University Cancer Institute, Morgantown, WV, USA
4Hematology, Oncology and Transplantation, Health Partners Institute, St Paul, MN, USA
5Hematology/Oncology, OSF St. Joseph Medical Center, Bloomington, IL, USA
6Hematology/Oncology, Saint Vincent’s Birmingham, Birmingham, AL, USA
7Medical Oncology and Hematology, CARTI Cancer Center, Little Rock, AR, USA
8Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA
9Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL, USA
10Biostatistics, Cytel Inc, Waltham, MA, USA
11Biostatistics, Pfizer Inc, Groton, CT, USA
12Breast Cancer, Oncology, Pfizer Inc, Santa Rosa, CA, USA
13Oncology Clinical Development and Medical Affairs, Pfizer Inc, New York, NY, USA
14Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: This study describes real-world use and population characteristics in HR+/HER2- advanced breast cancer (ABC) patients receiving palbociclib (PAL) in routine practice.

Methods: This prospective, noninterventional study has a targeted enrollment of 1500 men and women from ~110 sites. Site and patient data, monitored remotely for clarity/completeness, are collected from medical charts, physician surveys, and patient-reported outcomes; optional blood samples are collected during standard-of-care lab draws.

Results: This is an interim report of the first 312 patients with completed baseline case report forms as of 9Mar18 from 66 US sites (data snapshot: 3Apr18). Most sites were community sites (79%) with 1-10 treating physicians (61%). Of 33 sites that use clinical pathways, 49% were based on NCCN and 42% on US Oncology guidelines. Selected patient characteristics are shown (Table). Before starting PAL at enrollment, 18% of patients received chemotherapy, 21% hormonal therapy, 11% radiotherapy, 4% surgical resection, and 66% had no prior ABC therapy. Overall, 72% of patients received PAL combination first-line, of whom 56% received PAL + letrozole or anastrozole, 41% PAL + fulvestrant, and 4% PAL + exemestane. Of patients receiving >second line PAL, 46% received prior hormonal monotherapy, 43% prior chemotherapy alone, and 6% both.

Table: 344P Selected patient demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Age at study enrollment, y</th>
<th>Distribution, n (%)</th>
<th>Race, n (%)</th>
<th>Hispanic/Latino ethnicity, n (%)</th>
<th>Insurance provider, n (%)</th>
<th>Men</th>
<th>Women</th>
<th>Uninsured</th>
<th>Pre/perimenopausal, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>12 (3.8)</td>
<td>256 (82.1)</td>
<td>46 (14.7)</td>
<td>7 (2.2)</td>
<td>3 (1.0)</td>
<td>152 (48.7)</td>
<td>133 (42.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>40-50</td>
<td>40 (12.8)</td>
<td>156 (50.0)</td>
<td>1 (0.3)</td>
<td>7 (2.2)</td>
<td>3 (1.0)</td>
<td>152 (48.7)</td>
<td>133 (42.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>51-69</td>
<td>41 (13.1)</td>
<td>51 (16.3)</td>
<td>31 (9.9)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>152 (48.7)</td>
<td>133 (42.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>70-84</td>
<td>12 (3.8)</td>
<td>308 (98.7)</td>
<td>4 (1.3)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>152 (48.7)</td>
<td>133 (42.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>≥85</td>
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</table>

Continued
**Table: 344P Continued**

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (N = 312)</th>
</tr>
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<tbody>
<tr>
<td>Cardiac disorders, n (%)</td>
<td>49 (15.7)</td>
</tr>
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</table>

*Distribution of disease-free interval, mo, n (%)*  

<table>
<thead>
<tr>
<th>Interval</th>
<th>All Patients (N = 312)</th>
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<tr>
<td>&lt;12</td>
<td>97 (31.6)</td>
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<tr>
<td>12-24</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>24-36</td>
<td>25 (8.1)</td>
</tr>
<tr>
<td>≥36</td>
<td>174 (56.7)</td>
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</table>

*Number of patients with metastatic disease sites*  

<table>
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<tr>
<th>Site</th>
<th>All Patients (N = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal</td>
<td>299 (95.8)</td>
</tr>
<tr>
<td>Bone</td>
<td>46 (14.8)</td>
</tr>
<tr>
<td>Brain</td>
<td>27 (8.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>24 (7.7)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>34 (10.9)</td>
</tr>
</tbody>
</table>

**Conclusions:** This is the first large, prospective multicenter study assessing real-world use of a CDK4/6 inhibitor. In the first 312 patient cohort, most were treated at community sites. A heterogeneous real-world population received PAL, including elderly, pemenopausal, African-American, Latino/Hispanic, and male patients not commonly represented in clinical trials. Hormone partners received with PAL included steroidal and nonsteroidal aromatase inhibitors or fulvestrant, predominantly first-line.

**Clinical trial identification:** NCT03280393.

**Editorial acknowledgement:** Editorial support was provided by Anny Wu, PharmD, of Complete Healthcare Communications, LLC (West Chester, PA), a CHC Group company, and funded by Pfizer Inc.

**Legal entity responsible for the study:** Pfizer Inc.

**Funding:** Pfizer Inc.

**Disclosure:** J. Blum: Steering committee; Pfizer Inc. M.A. Salkenti: Contracted research funding as study PI via author’s institution: West Virginia University. J.I. Migas, J. Wang: Contracted research: Pfizer Inc. A. Bardia: Advisory board: Novartis, Pfizer Inc. Spectrum Pharma. G. Rocque: Steering committee; Pfizer Inc. Contracted research: Genentech, Carevive, Pack Health, Medscape. J.C. Cappellero, G. Comstock, Y. Wang: Employee and stockholder: Pfizer Inc. D. Tripathy: Steering committee; Novartis, Pfizer Inc. Contracted research: Novartis, Pfizer Inc. All other authors have declared no conflicts of interest.

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**345P**

**Everolimus-based therapy versus conventional therapy for refractory breast cancer patients with PIK3/AKT/mTOR mutations**

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Department of Medicine, 3D Medicines Inc., Shanghai, China  
Department of Oncology, Jiangsu Province Hospital, Nanjing, China

**Background:** Molecular screening using next generation sequencing (NGS) with the aim of guiding therapy for patients with refractory cancer, is becoming increasingly more common in clinical practice. Given that tumors with alterations in PIK3/AKT/mTOR (PI3K) pathway exhibit sensitivity to mTORC1 inhibitor everolimus, everolimus is often off-label used to target PI3K pathway. However, efficacy of off-label-use of everolimus in refractory breast cancer is unknown. We conducted this retrospective study to assess the efficacy of molecular matched off-label use of everolimus for refractory breast cancer patients with mutations in PI3K pathway, compared with conventional therapy.

**Methods:** Patients with refractory metastatic breast cancer who received NGS with the aim of guiding therapy between 2015 and 2017, were screened for eligibility at two sites in China. Patients with mutations in PI3K pathway and treated with everolimus-based or conventional therapy were included. Everolimus was used outside its indications. The primary outcome was progression-free survival (PFS). Secondary outcomes were overall response rate (ORR), disease control rate (DCR) and safety profile.

**Results:** 33 patients with mutations in PI3K pathway were included in this analysis. 18 (54.3%) patients were hormone receptor positive and 14 (42.4%) patients were HER2 positive. 20 patients received everolimus-based therapy and 13 patients received conventional therapy. The PFS was shorter in everolimus group than conventional group (median, 2.05 vs 6.1 months; HR, 4.45; 95% CI, 1.64-12.10; P = 0.0016). ORR was 14.3% (2/14) in everolimus group and 23.1% (3/13) in conventional group (P = 0.648). DCR was 55.7% (5/9) in everolimus group and 100% (13/13) in conventional group (P = 0.001). The incidence of grade 3 or worse treatment-related adverse event was similar between groups (5 (38.5%) of 13 in everolimus group, 5 (25.0%) of 20 in conventional group, P = 0.393).

**Conclusions:** The off-label use of everolimus to target the PI3K/AKT/mTOR pathway is associated with poorer outcome in patients with refractory breast cancer. These data suggests that off-label use of everolimus to target PIK3/AKT/mTOR should not be encouraged.

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**Disclosure:** All authors have declared no conflicts of interest.
Abstracts

346P
Potential survival gains from first-line (1L) systemic therapy advances in metastatic triple-negative breast cancer (mTNBC)

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Background: Approximately 15% of the 67,000 women diagnosed with metastatic breast cancer (mBC) annually in the U.S. have mTNBC. Few effective treatment options for mTNBC patients have been identified in the past decade & outcomes are poor vs. other mBC subtypes. The objectives of this study were to quantify overall survival gains from new therapies approved by 2020.

Methods: We created a simulation model to estimate OS in mTNBC cohorts diagnosed from 2010-2020. OS data were derived from mTNBC clinical trials & were extrapolated from 2010-2015 & projected the potential magnitude of OS gains from new therapies approved by 2020.

Results:
- Over a lifetime horizon, mean per-patient OS could improve by 10.2 months (8,543 population LYs) in mTNBC.
- mTNBC OS could triple from 5.2% in 2010 to 15.6% in 2020.
- Over a lifetime horizon, 5-year OS increased by 2.2% & mean OS increased 1.6 months from 2010-2015 & projected the potential magnitude of OS gains from new therapies approved by 2020.

Conclusion: We report modest mTNBC survival gains from 2010 to 2015, but show that clinically meaningful gains could be achieved if new treatments in development achieve realistic levels of effectiveness & are widely adopted. There is high unmet need in mTNBC & these new treatments offer hope for improved future outcomes.

Legal entity responsible for the study: Genentech, Inc.

Funding: Genentech, Inc.

346P
Partial survival gains from first-line (1L) systemic therapy advances in metastatic triple-negative breast cancer (mTNBC)

347P
Potential survival gains from first-line (1L) systemic therapy advances in metastatic triple-negative breast cancer (mTNBC)

348P
Economic evaluation of eribulin in the treatment of triple negative breast cancer in the United Kingdom

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1HEMA, Amaris, London, UK, 2Global Value and Access, Eisai Europe, Hatfield, UK, 3Market Access, Eisai, Hatfield, UK, 4Health Economics, Eisai, Hatfield, UK

Background: Eribulin is indicated in the European Union for patients with locally advanced or metastatic breast cancer after ≥1 prior chemotherapy for advanced disease, including an anthracycline and a taxane. The license is based on clinical trials which included patients with triple negative breast cancer (TNBC). We sought to evaluate clinical and cost-effectiveness of eribulin in this population using decision analytic modelling.

Methods: Data on OS, PFS and TTD from TNBC patients from two randomized open label studies of eribulin, 305 (NCT00388726) and 301 (NCT00337103), were pooled (N = 352). The comparators were TPC (any single-agent chemotherapy, hormonal or biological treatment; radiotherapy; or symptomatic treatment alone) (305) and capecitabine (301). A partitioned survival model developed for the National Institute for Health and Clinical Excellence submission based on pooled Kaplan-Meier data, accounting for tumour objective response and adverse events with health-state specific utilities mapped from QLQC30 data from study 301 was used. Lifetime horizon with discount rate of 3.5% for costs and quality-adjusted life years (QALYs) was applied. Threshold analysis was based on 2017 UK costs and reimbursement decision criteria.

Results: Use of eribulin versus the pooled comparator of capecitabine or TPC was associated with greater mean overall survival (16.0 vs 12.38 months) and progression-free survival (4.4 vs 3.6 months) with 0.3 life years (LYs) gained and 0.2 incremental QALYs. 77% of LYs and 75% of QALYs were gained in progressive disease. Using UK end of life criteria and considering the patient access scheme price, eribulin falls well within the cost-effectiveness threshold of £50,000/QALY and would be considered cost-effective in the UK setting. The results were sensitive to price of eribulin, utility in the progressive disease state, discount rates and drug administration costs.

Conclusions: Eribulin is cost-effective in the treatment of patients with TNBC after ≥1 prior chemotherapy for advanced disease, including an anthracycline and a taxane in the UK.

Legal entity responsible for the study: Amaris.

Funding: Has not received any funding.


Table: 346P

<table>
<thead>
<tr>
<th>Diagnosis Year</th>
<th>Events, n/n</th>
<th>5-Year OS (%)</th>
<th>Mean OS (Months)</th>
<th>Population LYs</th>
</tr>
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<tbody>
<tr>
<td>2010</td>
<td>52</td>
<td>22.9</td>
<td>19,179</td>
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</tr>
<tr>
<td>2015</td>
<td>74</td>
<td>24.5</td>
<td>20,519</td>
<td></td>
</tr>
<tr>
<td>2020 (Projected)</td>
<td>15.6</td>
<td>33.1</td>
<td>27,721</td>
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</table>

Table: 347P

<table>
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<tr>
<th>Ki67</th>
<th>Median PFS, months</th>
<th>Hazard ratio (95% confidence interval)</th>
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<tr>
<td>Low</td>
<td>55/118</td>
<td>19.4</td>
</tr>
<tr>
<td>High</td>
<td>95/208</td>
<td>19.1</td>
</tr>
<tr>
<td>Total</td>
<td>8/32</td>
<td>Not reached</td>
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Table: 348P

<table>
<thead>
<tr>
<th>5-Year OS (%)</th>
<th>Mean OS (Months)</th>
<th>Population LYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5.2</td>
<td>22.9</td>
</tr>
<tr>
<td>2015</td>
<td>7.4</td>
<td>24.5</td>
</tr>
<tr>
<td>2020 (Projected)</td>
<td>15.6</td>
<td>33.1</td>
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</tbody>
</table>
349P Use of bone-modifying agents (BMA) and osteonecrosis of the jaw (ONJ) among older patients with metastatic breast cancer (BC)

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Background: BC patients who have evidence of bone metastases should be treated with BMAs in order to reduce skeletal related events. ONJ is a serious complication associated with the use of BMAs. In this large population-based study we evaluate the patterns of use of BMAs and ONJ rates in a cohort of older BC patients.

Methods: Patients diagnosed with de novo metastatic BC between 2007-2013 were identified in the SEER-Medicare database. We identified the presence of bone metastases using specific PEDSF variables and claims. All patients were required to receive systemic anticancer therapy within one year of diagnosis. HCPCS codes were used to identify the use of BMAs within 1 year of cancer diagnosis, ONJ was identified using an established ICD-9 codes. Descriptive statistics and regression models were used.

Results: A total of 1,528 patients were included. The median age of the cohort was 74 yo. Within one year of diagnosis of bone metastases 71.1% of the patients received BMAs (68% bisphosphonates, 23% denosumab, 5% both). Older patients (OR = 0.64; 95%CI 0.46-0.89), those with more comorbidities (OR = 0.61; 95%CI 0.43-0.85) or with full/part-time Medicare coverage (OR = 0.65; 95%CI 0.49-0.87) -surrogate for poverty- were less likely to receive BMAs. Nineteen cases of ONJ were identified, all of them occurred among BMAs-treated patients (1.7%), the 2-year and 4-year cumulative rates were 1.4% and 4.0%, respectively. Similar rates of ONJ were observed between patients treated with bisphosphonates and denosumab. Median duration of BMA therapy among patients who developed ONJ was 20 months (IQR 10-43). No clinical predictors of ONJ were identified.

Conclusions: In this large, nationally representative cohort, the majority of the BC patients with evidence of bone metastases received treatment with BMA according to current guidelines. Similar rates of ONJ were observed among bisphosphonates and denosumab users. ONJ occurred in approximately 2% of this SEER-Medicare population of patients with BC and bone metastases treated with BMA. Our findings are of significant value since they reflect the patterns of care and complications associated with these commonly used agents in the general population.

Legal entity responsible for the study: Mariana C q vez Mac Gregor

Funding: CERCT, Sudun G. Kome

Disclosure: All authors have declared no conflicts of interest.

350P Liver surgery of breast cancer liver metastases: Rapid surgical decision after diagnosis does not negatively impact long-term results

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Background: Surgery could be indicated in selected patients with breast cancer liver metastases (BCLM) but accurate identification of the candidates for surgery remains a challenge. We investigated if an observational period of time after the diagnosis of BCLM could improve the selection for surgery.

Methods: We performed a retrospective analysis of 72 consecutive patients operated for BCLM between 2000 and 2015. Clinicopathologic and outcome data were compared between 2 groups: Early surgery (ES), including patients operated for BCLM ≤ 12 months after liver metastases (LM) diagnosis, and late surgery (LS), including patients operated > 12 months after diagnosis.

Results: Mean age was 48 years (28-74) at time of liver surgery. Median time between primary and LM diagnosis was 35 months (0-211) and median time between LM diagnosis and surgery was 12 months (0-134). Clinicopathologic characteristics were similar in ES (n=37) and LS (n=35) patients. In the whole population, 1, 3, and 5-years progression-free (PFS) and overall (OS) survivals were respectively of 79%, 43%, 30% and 99%, 66%, 43%. In multivariable analysis, neither PFS nor OS differences were observed between ES and LS groups (PFS - HR = 1.13 p = 0.72 and OS - HR = 1.06, p = 0.85 for ES), only primary tumor estrogen receptor positivity had a positive impact for OS (HR = 6.48 p = 0.03).

Conclusions: No difference in survival was observed between patients operated rapidly for BCLM as compared with patients operated after observational period, suggesting that it is not necessary to postpone the surgery in patients with resectable LM.

Legal entity responsible for the study: Hôpital Erasme ULB

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

351P Impact of breast cancer molecular subtypes on the occurrence, kinetics and prognosis of central nervous system metastases in a large multicenter cohort

W. Jacob1, G. Louvel2, A. Darlu1, J. Fraisse1, E. Brain1, M. Debled1, M.A. Mourret Reyniers3, A. Gonzalves1, F. Dalenc1, P. Augereau2, J-M. Ferrero10, C. Levy1, J.O. Fumetti6, C. Jaunauria1, C. Veyret1, V. Diers2, M. Robam2, C. Courtaudard5, D. Pasquier6, T. Bachet13 1Medical Oncology, KIM Regional Cancer Institute of Montpellier, Montpellier, France, 2Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France; 3Biomarks Unit, KIM Regional Cancer Institute of Montpellier, Montpellier, France, 4Department of Medical Oncology, Institut Curie, Paris & Saint-Cloud, France, 5Department of Medical Oncology, Institut Bergonie, Bordeaux, France, 6Department of Medical Oncology, Centre Jean Perrin, Clermont-Ferrand, France, 7Department of Medical Oncology, Institut Paoli Calmettes, Marseille, France, 8Department of Medical Oncology, Centre Claudius-Regaud - IACT Oncopole, Toulouse, France, 9Department of Medical Oncology, Institut Jean-Germaine, Caen, France, 10Department of Medical Oncology, Centre Georges-François Leclerc, Dijon, France, 11Department of Medical Oncology, Institut Jean Gadrat, Reims, France, 12Department of Medical Oncology, Centre Henri Bequeret, Rouen, France, 13Medical Oncology Department, Centre Eugène Marquis, Rennes, France, 14Department of Research and Development, UNICANCER, Paris, France

Background: Metastatic breast cancer (MBC) behavior differs depending on the molecular subtype based on hormone receptors (HR) and HER2 statuses. We aimed at evaluating the kinetics of central nervous system metastases (CNSM) occurrence, and the prognosis after CNSM, according to the molecular subtype.

Methods: Retrospective analysis of 16703 MBC patients from the French Epidemiological Strategy and Medical Economics (ESME) database involving 18 specialized cancer centers (01/01/2015 to 31/12/2017). The time between stage IV and CNSM diagnosis (CNSM-free survival CNSMFS) and between CNSM diagnosis and death from any cause (overall survival OS) were estimated with the Kaplan-Meier method and compared with the log-rank test.

Results: Median follow-up was 42.8 months. Among the selected patients, 64.1% of patients had HR+/HER2-, 11.0% HR+/HER2+, 7.5% HER2+/HR- and 17.4% triple negative (TN, HR-/HER2-). MBC. Median age at MBC diagnosis was 61.2, 4118 patients (24.6%) were diagnosed with CNSM at initial diagnosis of primary tumor or during their MBC follow-up: 17.8%, 34.9%, 49.2% and 38.0% of patients with HR+/HER2-, HR+/HER2+, HER2+/HR+ and TN tumors, respectively. Median age at CNSM diagnosis was 58.1 overall, 54.1 for TN patients and 59.9 for HER2+ patients (p < 0.0001). 1290 patients (7.2%) had CNSM at the time of stage IV diagnosis, while 2918 developed CNSM during the course of MBC, with a median CNSMFS of 17.0 months (95% CI 16.5-17.9). The molecular subtype was independently associated with CNSMFS: HER2+/HR- (HR = 0.48), HER2- (HR = 0.61; 95%CI 0.51-0.74), HER2+/HR- (HR = 2.2; 95%CI 1.7-2.9) and CNSM diagnosis (CNSMFS) and between CNSM diagnosis and death from any cause (overall survival OS) were estimated with the Kaplan-Meier method and compared with the log-rank test.

Conclusions: We found that the breast cancer molecular subtype strongly impacts the occurrence, kinetics and prognosis of CNSM in MBC patients.

Legal entity responsible for the study: UNICANCER

Funding: Pierre Fabre, Pfizer, AstraZeneca and MSD

Disclosure: All authors have declared no conflicts of interest.

352P Features associated with long-term survival in metastatic breast cancer

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Background: 5-10% of women with metastatic breast cancer (MBC) survive > 5 years. Predictors of long-term survival are not clearly elucidated. We used data from 122 long-term MBC survivors (>5-year survival from date of MBC diagnosis) and 191 short-term MBC survivors (<2-year survival from date of MBC diagnosis) to identify clinicopathologic and socioeconomic features associated with MBC survival.

Methods: Women initially diagnosed with breast cancer (BC) in or after 1999, and diagnosed with MBC at Magee Women’s Cancer Program of UPMC were included (N = 315). Data abstracted from medical records included: stage at initial BC diagnosis, body mass index (BMI), Charlson Comorbidity Index (CCI), age, menopausal status at initial BC diagnosis, tumor receptor status at initial BC diagnosis, site of initial metastases, time between initial diagnosis and MBC, household income, race, employment status, and partner status. Differences between groups were assessed using t-tests and
Results: Long-term survivors were significantly (P < 0.05) younger, had more ER positive, PR positive, and HER2 positive disease, lower CCI, more often premenopausal at initial diagnosis, lower rates of visceral metastases, higher household income, and more often partnered than short-term survivors. Long-term term survivors were also significantly more often diagnosed with de novo MBC compared to short-term survivors. The association with long-term survival remained significant after adjustment for age, tumor receptor status, and CCI (OR: 3.0, 95% CI 1.6-5.4). Time interval between initial diagnosis and MBC, BMI, race, and employment status were not associated with survival.

Conclusions: Diagnosis of de novo MBC, ER-, PR- and/or HER2-positive primary tumor, higher household income, younger age, lower CCI, premenopausal status, and having a partner are associated with long-term survival after diagnosis of MBC. This is one of the first studies to show a survival benefit in MBC patients with de novo MBC, positive partner status and higher household income.

Legal entity responsible for the study: Maggi Women’s Breast Program.

Funding: Has not received any funding.

Disclosure: A.M. Breuklyn: Consulting fees: Roche. All other authors have declared no conflicts of interest.

Table: 355P

<table>
<thead>
<tr>
<th>M1 Subdivision</th>
<th>Training set</th>
<th>Validation set</th>
<th>Whole set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate (%)</td>
<td>95% CI</td>
<td>Incidence rate (%)</td>
</tr>
<tr>
<td>M1a</td>
<td>42.4</td>
<td>39.8 - 44.9</td>
<td>44.1</td>
</tr>
<tr>
<td>M1b</td>
<td>53.7</td>
<td>49.1 - 58.0</td>
<td>50.6</td>
</tr>
<tr>
<td>M1c</td>
<td>72.1</td>
<td>68.3 - 75.6</td>
<td>70.4</td>
</tr>
</tbody>
</table>

P < .001 < .001 < .001

Results: Multivariate analysis showed the involvement of brain or liver and the number of metastatic organs were independent prognostic factors for BCSD. Therefore, we subdivided the M1 stage into three categories: M1a, involvement of single organ but no brain or liver, M1b, liver metastasis only as involvement of multiple organs but no brain or liver, M1c, involvement of multiple organs including liver but no brain, or brain involvement with or without liver, irrespective of the number of metastatic organs (M1b vs M1a, subdistribution hazard ratio (SHR) 1.43, 95% CI 1.28 - 1.63; M1c vs M1a, SHR 2.47, 95% CI 2.22 - 2.75; M1c vs M1b, SHR 1.67, 95% CI 1.47 - 1.90). The dose-response risk estimation was also observed in the validation and whole sets. Primary tumor surgery decreased from 43.2% in 2010 to 29.8% in 2014, with similar patterns seen in all M1 subdivisions. And patients of M1a benefited most from primary tumor surgery (M1a: SHR 0.55, 95% CI 0.49 - 0.66; M1b: SHR 0.71, 95% CI 0.60 - 0.82; M1c: SHR 0.63, 95% CI 0.55 - 0.72) in the adjusted competing risks model. Three-year cancer-specific mortality cumulative rates.

Conclusions: The M1 subdivisions system can better guide the prognosis prediction and treatment planning in patients with de novo MBC.

Legal entity responsible for the study: Ethics Committee, Shanghai Ruijin Hospital, Shanghai Jiao Tong University, College of Medicine, Shanghai, CN.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 355P

A prospective observational study of mobile application-based patient-reported outcomes (PRO) in advanced breast cancer: Interim baseline data from the MADELINE study

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Background: MADELINE is a multicenter study enrolling women with advanced metastatic breast cancer (ABC/MBC) receiving palbociclib in combination with an aromatase inhibitor (AI) as initial endocrine therapy or fulvestrant after progression on prior endocrine therapy according to the FDA-approved indication for palbociclib (Group 1) or approved therapies for ABC/MBC other than palbociclib (Group 2). A novel mobile application was developed to collect real-time PRO data to assess patient (pt) functioning and quality of life through daily, weekly, and monthly questionnaires for 6 months. Patient demographic and clinical information was recorded in an electronic case report form at baseline and for the planned 6-month follow-up.

Methods: Patients were administered the 12-Item Short Form Health Survey (SF-12) and the Center for Epidemiologic Studies Depression Scale (CES-D-10) at baseline. An analysis of baseline data as of March 1, 2018, on Group 1 pts with baseline mobile app and electronic case report form data was performed.

Results: Thirteen sites contributed 50 pts for this baseline analysis. Mean (SD) age was 58.6 (11.48); 86% were white. The most common metastatic sites were bone (54%) and lymph nodes (52%). ECOG performance status was 0, 1, and 2 in 61%, 24%, and 2% of pts, respectively. At enrollment, 27 pts (54%) initiated palbociclib plus AI, and 23 (46%) initiated palbociclib plus fulvestrant. There were no substantial differences between these palbociclib subgroups on SF-12 domain scores or CES-D-10 score; overall cohort scores are shown in the table.

Conclusions: This initial analysis describes the current population of palbociclib-treated pts in the MADELINE study. Recruitment and data collection are ongoing with plans for 30 total sites and up to 250 patients, with final results expected August 2019.

Disclosure: All authors have declared no conflicts of interest.
Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: D. Odom, K. Hollis, D. Richardson, J.A. Kaye: Employee: RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this abstract. D. Mitra, L. McRoy: Employment and stock ownership: Pfizer.

Table: 356P

<table>
<thead>
<tr>
<th>Measure Mean (SD)</th>
<th>Group 1 (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12</td>
<td></td>
</tr>
<tr>
<td>General Health</td>
<td>46.7 (7.91)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>45.4 (11.07)</td>
</tr>
<tr>
<td>Role Physical</td>
<td>44.3 (11.46)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>45.1 (12.90)</td>
</tr>
<tr>
<td>Vitality</td>
<td>43.3 (10.06)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>47.2 (10.83)</td>
</tr>
<tr>
<td>Role Emotional</td>
<td>47.3 (9.76)</td>
</tr>
<tr>
<td>Mental Health</td>
<td>48.8 (10.73)</td>
</tr>
<tr>
<td>Physical Component Summary</td>
<td>44.4 (11.65)</td>
</tr>
<tr>
<td>Mental Component Summary</td>
<td>48.7 (10.53)</td>
</tr>
<tr>
<td>CES-D-10</td>
<td>7.5 (4.95)</td>
</tr>
</tbody>
</table>

Legal entity responsible for the study: Pfizer Inc.

Funding: Pfizer Inc.

Disclosure: D. Odom, K. Hollis, D. Richardson, J.A. Kaye: Employee: RTI Health Solutions, who were paid consultants to Pfizer in connection with the development of this abstract. D. Mitra, L. McRoy: Employment and stock ownership: Pfizer.

Steroelectronic radiosurgery (SRS) for brain metastases (BM) from breast cancer (BC): A single centre experience of factors influencing survival

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Background: BM occur in up to 30% of patients with BC. SRS can be considered as an alternative to surgery or whole brain radiotherapy for control of single or multiple metastases. Factors that could predict overall survival (OS) and guide treatment choice have not been clearly defined.

Methods: Data for consecutive patients with BC treated with SRS between November 2013 and August 2017 in a single tertiary referral centre were collected to assess factors that might predict survival. T-tests, Kaplan Meier and log-rank methods were used for statistical analysis.

Results: 93 patients (pts) received SRS, of whom 32 were alive when data was censored on 1/2/18. The median overall survival (OS) post SRS was 14.0 mths (95% CI 7.9-20.2 mths) with a significant correlation between age and OS (53 pts >60yr, OS = 18.1 mths; 40pts >60yr OS = 10.3 mths, r = 0.21, p = 0.04). There were 51 ER+/HER2- pts (OS 12.6 mths), 14 ER+/HER2+ pts (OS 15.2 mths). There was significantly better for pts with HER2+ disease (p = 0.0018) with the poorest survival in pts with TN cancer (p = 0.0001). 39pts had 1 lesion treated (OS 16.2 mths), 35pts had 2-5 lesions treated (OS 15.7 mths), 16 Triple negative (TN) pts (OS 8.5 mths). OS was significantly better for pts with HER2+ disease (p = 0.0018) with the poorest survival in pts with TN cancer (p = 0.0001). 39pts had 1 lesion treated (OS 16.2 mths), 35pts had 2-5 lesions treated (OS 15.7 mths), 16 Triple negative (TN) pts (OS 8.5 mths). Whilst the number of lesions treated did not correlate with OS (r = 0.37, p = 0.37) a larger volume of tumour treated (r = 0.23, p = 0.01). At the time of SRS 17pts had no other systemic disease (OS 13.7 mths). When present, control of systemic disease outside the brain was associated with improved OS (16 pts stable systemic disease OS = -20 mths, 32 pts progressive systemic disease (PSD) OS = 9.7 mths, p = 0.0013). 49 pts had known disease status at death, 17 had PSD, 16 had progressive CNS disease (PCD), 13 had PSD + PCD and 3 had no progression.

Conclusions: Age, receptor status, control of systemic disease, total tumour volume treated, but not the number of lesions appears to influence survival following SRS treatment of BM in BC. Our results are consistent with other series with worse outcomes seen in older patients and those with TN cancers. In addition to treating BM, control of systemic disease outside the brain remains important in prolonging survival.

Legal entity responsible for the study: Jeremy Braybrooke.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

358P

Prolonged overall survival for patients with bone-only metastases at presentation of metastatic breast cancer

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Background: More than 50% of metastatic breast cancer patients experience bone metastases over the course of disease and around 15% of cases have metastases confined to the skeleton at metastatic presentation. The aim of this study was to access the overall survival of breast cancer patients with bone-only metastases at presentation.

Methods: Among 907 patients, we identified from our prospective computerized database 123 patients with bone-only metastases at diagnosis of metastatic breast cancer. We retrospectively collected data from the patients’ files.

Results: The median overall survival was 8.3 years (CI 95%: 6.7-10.3) and 73% and 41% of patients were alive at 5 and 10 years, respectively. No multivariate model with factors identified at presentation was able to predict overall survival length. Sixty per cent of patients developed visceral metastases over the median and the median interval between the diagnosis of bone metastases and the occurrence of visceral metastases was 28 months (4 - 193). In multivariate analysis, negative progesterone receptor status was associated with the occurrence of visceral metastasis (HR = 2.4, p = 0.01). Eleven per cent of patients had a solitary bone metastasis; 67% of patients developed axial metastases and 41% long bone metastases.

Conclusions: Breast cancer patients with bone-only metastases at presentation of metastatic disease might form a distinct clinical entity among metastatic breast cancer patients with a favorable prognosis and a prolonged overall survival. No prognostic factors identified at the presentation of the disease were able to predict very long survivors. Further investigations on these tumors biology and clinical trials dedicated to this population are required.

Legal entity responsible for the study: CHRU Besançon.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

359P

Surgery of the primary tumor for de novo metastatic breast cancer: The controversy continues

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Background: De novo metastatic breast cancer (dnMBC) represents 6–10% of breast cancer. Due to its incurability, dnMBC is generally treated with systemic therapies to achieve disease control and reduce tumor-related symptoms. The need for radical locoregional treatment and its consequent benefit in this setting remains still controversial. Meta-analysis of retrospective studies and prospective randomized studies did not report a clear survival benefit. The aim of this study was to analyze the impact of surgery to primary tumor (PT) in patients (pts) presenting with dnMBC.

Methods: Between Feb 2006-Oct 2015 we performed a retrospective chart review of 129 consecutive pts who attended our hospital with dnMBC. Descriptive, Kaplan–Meier and Cox regression analyses were carried out using SPSS version 23.0.

Results: A total of 129 pts were analyzed. Median age was 68 years (range: 20-95), 59 pts (46%) had single organ metastasis, and their distribution according to the predominant site of disease was: skin/soft tissue 42 pts (35%), bone 87 pts (67%) and visceral 85 pts (66%). Surgery (% of the PT was done in 32 pts (29%), 24 was radical procedures, 8 palliative and besides, 27 pts underwent axillary dissection. Initial 5 treatment was the choice for 29 pts. In the S group single organ disease was present in 66% vs 59% non-S group. Metastatic sites were: 50% vs 71% visceral, 44% vs 21% with bone metastasis in the S vs non-S group respectively. With a median follow-up of 2 years (SD 2.20), the 5-yr overall survival (OS) was 11.64% in the entire de novo MBC population, with a median OS of 36 m in the S-group vs 21 m. in the non-S group (HR 1.46 p = 0.001). Subgroup analyses did not show a benefit of PT surgery in OS regardless of the number of metastasis and site of disease, and BC subtypes. The multi-adjusted HR for surgery was 0.14 (p = 0.188). The multivariate Cox regression analysis model included the site of disease (p = 0.971), the histopathologic grade (p = 0.876) and the hormone receptor status (p = 0.033).

Conclusions: In our series, surgical treatment of the primary tumor in patients with de novo metastatic breast cancer did not show a benefit in overall survival. Results of ongoing randomized trials are needed.

Legal entity responsible for the study: Medical Oncology Service, Basurto University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Systemic chemotherapy with anti-HER2 therapy is the standard of care for HER2-positive advanced breast cancer. Patient outcomes have improved remarkably with the use of novel anti-HER2 drugs, including trastuzumab (H), pertuzumab (P), and docetaxel (D) (HPD) as defined by the 1st-line treatment for HER2-positive advanced breast cancer. In contrast, for elderly patients over 65 years of age, this regimen seems to be intolerable medically and physically, and impairs their quality of life.

A new standard treatment with less toxicity and non-inferior efficacy for elderly patients is needed.

Trial design: We have planned a randomized, multicenter, open-label, phase III trial to confirm the non-inferiority of 1st-TM1 compared to HPD in terms of overall survival (OS) in elderly patients with HER2-positive advanced breast cancer. The eligibility criteria are as follows: 1) histologically proven HER2-positive breast cancer with metastatic disease 2) age 65-74 years with a performance status (PS) score 0-2, or 75-79 years with a PS score 0-1, and 3) no anti-HER2 therapy with chemotherapy for breast cancer, excluding peri-operative adjuvant therapy. Patients will be randomized to receive either H, P, and D (HPD) or H, P, and docetaxel (HPC) as the 1st-line treatment for patients with HER2-positive advanced breast cancer. In contrast, for elderly patients over 65 years of age, this regimen seems to be intolerable medically and physically, and impairs their quality of life.

A new standard treatment with less toxicity and non-inferior efficacy for elderly patients is needed.


Clinical trial identification: UMIN000030783.

Legal entity responsible for the study: Hiroji Iwata.

Funding: Japan Agency for Medical Research and Development.

Disclosure: N. Niikura: Research fund: Chugai Pharmaceutical Co., Ltd. S. Saji: Honoraria for lecture: Eisai, Chugai and Pfizer; Research grant: Taiba and Chugui. N. Masuda: Honoraria: Chugai, AstraZeneca, Pfizer and Takeda; Research funding: Chugai, AstaRia, Kyowa-kirin, MSD, Novartis, Pfizer Eh-Lilly and Daichi-Sankyo. F. Nagashima: Research funding: Taiba, Ono, Oncotherapy, Merck, Zeria, Lilly Japan, Takeda, Chugai, Yakult, Sumitomo Dainippon, Daichi Sankyo, Shinonou, Novartis, J-Pharma, Bristol-Myers Squibb, Kyowa Hakko Kirin, Mochida, Astellas, Bayer, MSD, Eisai, Jansen, H. Iwata: Honoraria: Chugai, Daiichi Sankyo, AstraZeneca, Pfizer; Consultant: Chugai, Daiichi Sankyo, Kyowa Hakko Kirin, Lilly, Novartis, AstraZeneca, Pfizer; Received research funding: Chugai, MSD, Kyowa Hakko Kirin, GSK, Daiichi Sankyo, Chugai, Lilly, Novartis, Bayer and Pfizer. All other authors have declared no conflicts of interest.
Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after first line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: A phase II trial (AMICA) GBG 97

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Background: Although longer duration of chemotherapy (CT) is associated with longer progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer (MBC), the duration of CT is usually dictated by toxicities and patient and physician preferences, resulting in treatment durations of less than 6 months. Therefore, well tolerated maintenance treatments with the potential to prolong PFS and OS are needed.

Trial design: AMICA is a multicentre, prospectively, randomized, open-label, controlled phase II study. Patients with hormone receptor (HR)+/HER2- MBC achieving stable disease or tumor response after at least 4 cycles of first-line CT at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracyclines) will be eligible to be randomized 2:1 to receive maintenance endocrine therapy (ET) per investigator’s choice either with or without the CDK4/6 inhibitor ribociclib. Patients might have received up to one prior line of ET. Maintenance ET could have already been started up to 6 weeks before randomisation, but after achievement of stable disease or tumor response. Life expectancy of > 6 months is required. In both study arms, treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent. Primary objective is to evaluate the impact of a maintenance ET after first-line CT with or without ribociclib on PFS. Secondary objectives are OS, clinical benefit rate, safety, compliance and patient reported outcomes. Biomarkers predicting response to CDK inhibition and ET in formalin-fixed paraffin-embedded metastatic tissue and blood as well as the role of mutations in cTNA will be analysed. Overall, 350 patients will be recruited. The study is conducted in 20–30 sites in Germany. One patient has been recruited so far.

Clinical trial identification: AMICA, GBG 97.

Legal entity responsible for the study: GBG Forschungs GmbH.

Disclosure: C. Denkert: Honoraria from Teva, Novartis, Pfizer, Roche, Amgen, MSD Oncology; Other: Sividon Diagnostics, outside the submitted work. K. Lübbe: Consulting or advisory role: Roche and Novartis. M. Schmidt: Honoraria: Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, Novartis, Roche, Teva; Consulting or advisory role: Hexal, Roche, Pfizer, Amgen, Daichi Sankyos, Nektar, ESIAT; Travel accommodation: Roche, Pfizer. M. Schmidt: Honoraria: Roche, Novartis, Pfizer; Consulting or advisory role: Roche, Novartis, Pfizer; Speakers’ bureau: Roche, Novartis, Pfizer; Travel accommodations: Roche, Pfizer. M. Thill: Travel reimbursement, Consulting, Honoraria: Amgen, AstraZeneca, Celgene, Eisai, Genomic Health, Lilly, Myriad, Neodinamica, Novartis, Pfizer, pfm Medical, Roche, RTI Surgical, Surgery, Teva; Writing assistance: Roche and Celgene; Research funding: Genomic Health. S. Loibl: Grants for Institution: AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Teva; Vifor during the conduct of the study as well as outside the submitted work. All other authors have declared no conflicts of interest.
**Background:** Navelbine is an antineoplastic agent that has shown efficacy in the treatment of a variety of solid tumors, including breast cancer. The drug can be given intravenously, but also as oral tablet treatment. Preclinical studies, as well as clinical observations, suggest that the administration of small, frequent doses of chemotherapy (metronomic dosing) has an effect, not only on cancer cells, but also on endothelial cells in the tumor vasculature. By giving smaller, but more frequent doses of the drug, higher dose intensity, without corresponding side effects, is obtained. Whether treatment under the metronomic principle is superior to conventional treatment, has not yet been validated in the clinic, so this study is hoped to clarify this.

**Trial design:** This is a investigator-initiated, prospective randomized phase II, non-blinded multinational, multicentre study running in Denmark and Norway. 200 women diagnosed with HER2 metastatic breast cancer will be enrolled. Patients are randomized to either: Arm A: Classical treatment: Navelbine Oral: 60 mg/m² day 1, day 8 (and day 15), every three weeks for the first cycle. Hereafter 80 mg/m² day 1 and day 8, every three weeks for the following cycles. Or Arm B: Metronomic treatment: Navelbine Oral: with 3 weeks of cyclic daily doses of 30 mg. (Patients with body surface < 1.54 m² or 65 years or more start on 20 mg daily.) Treatment is given first or second line (chemotherapy). The primary Objectives is to evaluate the Disease Control Rate (CR + PR + SD > 3 months) in the two arms. Secondary Objectives are to compare the duration of Disease Control, TTP, RR, DR and OS and side effects for the two regimens. Also Evaluation of the Global Health Status/QoL, on the basis of the EORTC QOL C30 questionnaire is made. Finally a comparison of all objective and subjective measures, such as global health status, QoL, performance status (ECOG), and OS and side effects for the two regimens. The study is an investigator-initiated, prospective randomized fase II, non-blinded multinational, multicentre study running in Denmark and Norway. The study will be conducted over three years. The first patient was included in March 2018. As of May 2018, 3 patients have been screened and 1 patient has been randomized.

**Clinical trial identification:** EudraCT: 2016-002165-63. Health Board no: 2017040059. Approved by Research Ethics Committee and Data Protection Agency June 2017.

**Legal entity responsible for the study:** Sven Tyge Langkjaer.

**Funding:** The study is an investigator-initiated study, but financially supported by the pharmaceutical company Pierre Fabre.

**Disclosure:** All authors have declared no conflicts of interest.

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**LUCY: A phase IIb, real-world study of olaparib in HER2-negative metastatic breast cancer patients with a BRCA mutation**

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**Background:** The Phase III OlympiAD trial (NCT02006622) showed a significant improvement in progression-free survival (PFS) in favour of olaparib vs physician’s choice chemotherapy in patients with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm). In January 2018, the US FDA expanded the approved use of olaparib to treat patients with HER2-negative mBC and a gBRCAm. LUCY (NCT03286842) has been initiated to evaluate the clinical effectiveness of olaparib in these patients in a real-world setting, and has been expanded to include a cohort of patients with somatic BRCA mutations (sBRCAm).

**Trial design:** LUCY is an open-label, single-arm, multicentre, International Phase IIb trial. Patients with HER2-negative mBC and a deleterious BRCAm (gBRCAm or sBRCAm), who have received treatment with taxane or anthracycline in either the adjuvant or metastatic setting, and ≤ 2 prior lines of chemotherapy for metastatic disease, will be enrolled. Patients will be treated with open-label olaparib tablets (300 mg twice daily) until disease progression, unacceptable toxicity, or other discontinuation criteria. For gBRCAm patients (Cohort 1), the primary objective is to evaluate the clinical effectiveness of olaparib via investigator-assessed PFS (radiological, symptomatic, or clear progression of non-measurable disease); secondary objectives include overall survival, time to second progression, and clinical response rate. For sBRCAm patients (Cohort 2), and for patients with somatic sBRCAm (Cohort 3), the primary objective is to evaluate the clinical effectiveness of olaparib via investigator-assessed PFS. Up to 36% of triple-negative breast cancer (TNBC) are androgen receptor (AR)-positive (> 10% by immuno-histochemistry, IHC). When these tumours metastasise, several clinical trials assessing antagonists of the AR or androgen synthesis inhibitor showed promising clinical benefit rates (CBR). Darolutamide is a novel, effective and well tolerated AR antagonist tested in prostate cancer clinical trials. Thus we aim to assess clinical activity and safety of darolutamide in AR-positive TNBC.

**Trial design:** This is an open-label, multicenter, randomized, two-arm non-comparative phase II trial (NCT03383679). Women with locally recurrent (unreatsectable) or metastatic and centrally confirmed AR-positive TNBC are eligible. Patients should be chemotherapy naive or have received a maximum of one line of chemotherapy for advanced disease. Eligible patients are randomized (2:1) between darolutamide experimental arm (400 mg twice daily) and capecitabine control arm (according to each center policy, minimum 1000 mg/m² twice daily, 2 weeks on and 1 week off). Randomization (minimization) is stratified by number of previous lines of chemotherapy (0 versus 1). In each arm, the primary endpoint is the clinical benefit rate (CBR) at 16 weeks, defined as complete response, partial response or stable disease as per RECIST 1.1 criteria. Tumour biopsies and sequential circulating tumour DNA are collected as part of a translational research program. A total of 90 patients will be randomized. The first patient was included in March 2018. As of May 2018, 3 patients have been screened and 1 patient has been randomized.

**Clinical trial identification:** NCT03383679.

**Legal entity responsible for the study:** UNICANCER.

**Funding:** Bayer.

**Disclosure:** All authors have declared no conflicts of interest.
369TIP

PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + Anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+) HER2-positive metastatic breast cancer (MBC)

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Background: Pre-clinical data showed the role of CDK4/6 inhibition in HER2+ disease. Results from phase 2 clinical trials point to synergistic antitumor activity and potential efficacy of palbociclib when given in combination with anti-HER2 therapy (tx), particularly in HR+ HER2+ breast cancer. The aim of PATINA is to evaluate the efficacy and safety of the addition of palbociclib to anti-HER2 and ET maintenance after induction tx in the 1st line setting for HR+ HER2+ MBC.

Trial design: The PATINA trial (AFT-38/NCT02947685) is a pivotal, open-label, international, phase III trial. The trial is open to patients (pts) with histologically confirmed HR+ HER2+ MBC provided they are without evidence of disease progression by local assessment after induction tx. Following 4-8 cycles of chemotherapy (taxane or vinorelbine) with anti-HER2 tx for MBC, pts will be randomized 1:1 to standard anti-HER2 tx (trastuzumab + pertuzumab) in combination with ET with or without palbociclib until disease progression. ET options are either an aromatase inhibitor or fulvestrant.

370TIP

A phase Ib, multicenter, open-label study of the antibody-drug conjugate trastuzumab deruxtecan (DS-8201a) combination with nivolumab for advanced HER2-expressing breast or urothelial cancer


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Background: DS-8201a is a novel antibody-drug conjugate comprised of a humanized HER2 antibody attached by a cleavable peptide-based linker to a topoisomerase I inhibitor, characterized by a high drug-to-antibody ratio of about 8. In an ongoing phase I trial, DS-8201a showed high and durable responses across multiple tumors, with a confirmed objective response rate (ORR) of 61.4% in previously T-DM1-treated HER2-positive (HER2+ or IHC2+ and ISH-) breast cancer (BC) and 31.6% in HER2 low-expressing (IHC 2+/1+ and ISH-) BC (Oct 2017 cutoff, Modi et al, SABCS 2017). Nivolumab, an anti-PD-1 antibody, is FDA-approved for metastatic urothelial carcinoma (UC) after platinum failure. A xenograft model of HER2-expressing cancer showed significantly increased survival with the combination of DS-8201a with an anti-PD-1 antibody vs either treatment alone (Iwata et al, ASCO 2017).

Trial design: This phase Ib, multicenter, open-label study will assess the combination of DS-8201a with nivolumab in previously chemotherapy-treated HER2-expressing advanced BC or UC. Previous treatment with anti-PD-1/PD-L1 therapy is an exclusion criterion. A dose escalation (part 1) will identify the recommended dose for expansion (RDE), and dose expansion (part 2) will evaluate efficacy and safety/tolerability of the DS-8201a RDE combination with nivolumab (360 mg IV; q3wk). Part 1 is a 3+3 design with 3 dose cohorts of DS-8201a (3, 2.5, and 4 mg/kg q3wk); enrollment will start at 3.2 mg/kg. Following RDE determination, enrollment in part 2 will open (Table); estimated total enrollment is 99–117. ORR is the primary efficacy endpoint; secondary endpoints include overall survival, disease control rate, duration of response, progression-free survival, time to response based on central review, and safety/tolerability. The study is open for enrollment as of May 2018.

Table: 370TIP

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<tr>
<td>2 BC</td>
<td>HER2 low-expressing (IHC 2+/1+ and ISH-)</td>
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<tr>
<td>3 UC</td>
<td>HER2 high-expressing (IHC 3+/2+)</td>
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<tr>
<td>4 UC</td>
<td>HER2 low-expressing (IHC 1+)</td>
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Clinical trial identification: NCT03523572

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Legal entity responsible for the study: Daiichi Sankyo, Inc.


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CNS TUMOURS

3710 Intra-CSF liposomal cytarabine plus systemic therapy as initial treatment of breast cancer leptomeningeal metastasis: A randomised, open-label trial
E. Le Rhun1, A. Mailley1, J. Wallet2, J. Rodrigues1, T. Boulanger1, I. Desmoulires1, J. Barriere1, M. Fabris3, S. Tailibert1, C. Andre3, M.C. Le Deley1, M. Weller4, J.M. Barnetiere1
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3720 Mutational and inflammatory microenvironment characteristics in primary and matched local recurrent non-small cell lung cancer brain metastases
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3730 Results of phase II trial of SL-701, a novel immunotherapy targeting IL-13Ra2, EphA2, and survivin, in adults with second-line recurrent glioblastoma (GBM)
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Mismatch repair deficiency (MMRd) in glioma patients (PTS): Frequency and correlation with clinical, histological and molecular characteristics

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Radiological phenotyping of IDH mutation status in gliomas using dynamic susceptibility contrast perfusion-weighted MRI

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Impact of a molecular prescreening program (MPP) in the management of patients with non-glioblastoma brain tumors


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377PD  Multiplex digital PCR for the diagnostic of pilocytic astrocytoma and glioneuronal tumors

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379PD  Hypothyroidism is associated with improved survival prognosis in patients with newly diagnosed brain metastases

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380PD  Understanding biological activity, tumor response and pseudoprogression in a phase-IIb study of MDNA55 in adults with recurrent or progressive glioblastoma (GB)

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Comprehensive geriatric assessment (CGA) for outcome prediction in elderly patients (PTS) with glioblastoma (GBM): A mono-institutional experience

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Second-line treatment of bevacizumab plus lomustine versus bevacizumab plus irinotecan in patients with recurrent glioblastoma

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Worldwide trends in survival from adult glioma 2000-2014 (CONCORD-3): Impact of morphology

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Background: The CONCORD programme initiated world-wide surveillance of trends in population-based cancer survival in 2015. The third cycle (CONCORD-3) covered 18 cancers, including brain tumours. Data for 656,699 adults (15-99 years) diagnosed with a brain tumour were provided by 286 registries in 59 countries. For adults diagnosed during 2010-2014, 5-year net survival from all brain tumours combined varied between 15% and 42%. We will present detailed comparison of survival trends for gliomas defined by anatomic location, morphology and WHO grade.

Methods: We will present the numbers of adults diagnosed with a glioma and the subtype distribution by continent. We will estimate net survival up to 5 years, using the unbiased Pohar Perme estimator. Net survival is the probability that patients survive their cancer until a given time since diagnosis, after controlling for competing risks of death (background mortality) by age, sex, country and calendar year.

Results: Data were obtained for 545,184 adults. Glioblastoma was the most common morphology (57%). Astrocytic, oligodendrogial and oligo-astrocytic tumours specified as WHO grade I-III made up 21% of all gliomas, while glioma not otherwise specified (NOS) and astrocytoma NOS made up 15%. Rarer tumours, such as oligodendroglioma, fibrillary astrocytoma, pilocytic astrocytoma, mixed glioma, anaplastic oligodendroglioma and anaplastic astrocytoma made up less than 10% of gliomas in all continents. The frequency of glioblastoma was 58% or higher in Europe, North America and Oceania, 53% in Africa and around 45% in Asia and Central and South America. The frequency of astrocytoma NOS was lowest in Europe, North America and Oceania (below 9%) and highest in Central and South America (22%).

Conclusions: The distribution of gliomas varies around the world. The differential was the frequency of unspecified morphologies, which may be partly attributable to diagnostic capacity. We will assess the extent to which disparities in morphology contribute to worldwide variation in survival from adult brain tumours. When comprehensive survival analyses are available, this project is expected to become the reference for international comparison of brain tumour survival, to help inform national cancer control plans.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Children with Cancer UK.

Disclosure: All authors have declared no conflicts of interest.
Background: GBM is the most common and aggressive primary brain tumor in adults. This study investigated RWD-based differences among 3,030 GBM patients stratified by three economic regions.

Methods: The analysis was based on IQVIA syndicated cross-sectional surveys, collecting anonymized patient-level data between January 2016 and September 2017 in different countries, grouped into three economically different regions. Region 1 (high): EU5 (France, Germany, Italy, UK, Spain), Canada, Australia, Region 2 (upper middle): Korea, China, Taiwan, Region 3 (lower middle): Brazil, Mexico.

Results: The percentage of patients aged >65 years was 23.9% for region 1, 6.3% for region 2 and 13.6% for region 3, confirming younger GBM population in region 2. The age difference among the regions was statistically significant (P < 0.0001). The incidence of male (65%) and female (35%) patients was homogeneous across all regions. Region 1 showed the highest testing rate (60%) for MGMT promoter methylation and region 3 the lowest (33%). EGFR mutation was not studied in more than 50% of patients across the regions. However, in overall tested population, the EGFR V826 mutation varied: 39%, 90%, and 73% for regions 1, 2 and 3, respectively. Concerning drug treatment options, temozolomide was the leading therapy (56.5%) followed by 25% and 22% in regions 1 and 3, respectively. We did not find any differences in Performance Status or comorbidities among the regions, with no reported comorbidities in >60% of patients.

Conclusions: This multi-variable analysis from RWD shows differences in clinical characteristics (i.e., age, biomarkers and MMSE), which may be taken into consideration in the design of GBM global studies. To our best knowledge, this study was based on the largest GBM database ever published.

Legal entity responsible for the study: IQVIA.

Funding: IQVIA.

Disclosure: All authors have declared no conflicts of interest.
Impaired survival in resected glioblastoma multiforme patients treated with early chemoradiation

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Background: The best time to initiate concurrent chemoradiation (ChRT) with temozolomide after surgery in glioblastoma multiforme (GBM) patients has not been clearly established. Our aim was to investigate whether survival is influenced by the time to ChRT in patients with different types of surgery.

Methods: We conducted a retrospective study of all the patients treated in our centre from January 2003 to December 2017, with a histological diagnosis of GBM, who underwent surgery and completed concurrent ChRT with temozolomide. The time to ChRT was grouped in 4 quartiles, and early ChRT was defined as happening during the first quartile. Surgery type was divided into resection (R) and biopsy (B). Survival at 12 months (OS12m), median progression-free survival (mPFS) and overall survival (mOS) were calculated. Other relevant clinical factors were also analyzed.

Results: From a total of 160 patients, 119 who completed ChRT were included. The median time to ChRT was 37 days. (Q1–28, Q3–57, Q4–95). 35 (30%) received early ChRT (<26 days). Patients who underwent R were 101 (85%) and 18 (15%) R. The mean age was 62y, 94 patients (79%) had PS 0–1, MGMT methylation was positive in 23 (19%). There were no significant differences between groups regarding age, PS and MGMT status; but more patients treated with R received early ChRT (31% vs 8%). The OS12m was shorter for patients who underwent R and received early vs no-early ChRT (35% vs 73%, p = 0.002). No differences in OS12m were found for B patients (0% vs 36%, p = 0.41) according to time to ChRT. For patients who received early ChRT, the mOS was similar despite surgery type (9.9, 95% CI 9.6 – 11 vs 12.9, 95% CI 6.5 – 19.3, p = 0.02). But for patients who did not receive early ChRT, longer survival was achieved in the R vs B subgroup (16.2, 95% CI 11.1 – 17.8 vs 11.1, 95% CI 4.5 – 17.7, p = 0.024, for R and B, respectively) and resection type remained significant in the multivariate analysis (HR = 1.2, p = 0.02).

Conclusions: We have found that patients with GBM who underwent resection had a worse prognosis if they received early ChRT (<26 days). No differences were found for biopsied patients. A no-early chemoradiation approach for patients who underwent resection may be safe. Prospective studies are encouraged.

Legal entity responsible for the study: Hospital de la Santa Creu i Sant Pau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Beverazumab-induced hypertension correlation with survival in recurrent glioblastoma multiforme

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Background: Patients with Glioblastoma multiforme (GBM) have a poor prognosis and therapeutic options are scarce after recurrence. Beverazumab (Bv) is approved for use in this setting with proven benefits in progression-free survival (PFS) but not in overall survival (OS). Arterial hypertension (HT), a well described side effect of Bv, has been proposed as a predictive marker of clinical response in GBM as well as in other neoplasms, though conflicting data is available. This study tried to evaluate the prognostic impact of HT and other factors in recurrent GBM.

Methods: Retrospective cohort of adult patients with recurrent GBM treated with a combination of Bv + Trastuzumab (BvL) or Lomustine (BvL) between 01/2009 and 31/12/2017. Clinical records were analysed. Bv-induced HT was defined as a single evaluation >140/90 mmHg during first 3 months of treatment or the need to initiate or increase dose of antihypertensive drugs. OS and PFS were estimated by Kaplan-Meier method and multivariate analysis according to Cox regression; a significant level of 0.05 was chosen to assess the statistical significance.

Results: 120 patients were included with male gender predominance (64.2%) and a median age at Bv onset of 58.7 (27.78 yo). All patients were treated in first line with surgery (complete resection 61.7%, partial resection: 38.3%) and Stupp protocol. BvL was used in 70.8% (n = 85) and BvL in 29.2% (n = 35) patients. Bv-induced HT was found in 29% of patients (n = 29) and proteinuria (PU) in 15% (n = 18). Median PFS was 4.4 months (mo) (CI 95% 3.5–5.4) and median OS was 7.8 mo (CI 95% 6.8–8.7). In multivariate analysis (Table), both HT and PU had an impact in PFS. OS was significantly prolonged in patients with HT and in those without corticosteroids (CCS) at Bv.

Table: 389P

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<th>Genotype</th>
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</tr>
</tbody>
</table>

Conclusions: Even though no significant difference in overall survival in GBM patients regardless of the examined polymorphism of VEGF gene was found, it was also shown that genotypy GG has one month longer overall survival in the examined patients group.

Table: 390P Descriptive statistics for overall survival in three genotypes of VEGF gene

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Mean OS</th>
<th>SD</th>
<th>SE</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No -</td>
<td>13.4</td>
<td>105.6</td>
<td>8.918</td>
<td>2.973</td>
<td>3.70</td>
</tr>
<tr>
<td>Yes</td>
<td>13.4</td>
<td>11.00</td>
<td>9.449</td>
<td>1.670</td>
<td>7.55</td>
</tr>
<tr>
<td>Total</td>
<td>26.8</td>
<td>11.31</td>
<td>8.910</td>
<td>1.132</td>
<td>9.04</td>
</tr>
</tbody>
</table>
is probable that random selection of patients regardless of applied treatment, or without treatment, and EOCOG 1-4 requires larger number of patients to be included in order to provide final proof whether this polymorphism has any effect on overall survival.

Legal entity responsible for the study: Milos Lucic.

Funding: Provincial Secretariat for High Education and Science of Vojvodina Province.

Disclosure: All authors have declared no conflicts of interest.

393P Expression and clinical prognostic role of ZWINT in glioma: Analysis based on data-mining and integration of gene databases

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Background: Human ZW10 interacting kinetochore protein (ZWINT) gene plays critical roles in mitotic cycle maintenance and is known to be linked with poor clinical prognosis in various tumors. However, the clinical significance of ZWINT in glioma has not yet been understood. The purpose of this study was to determine the expression profile and functions of ZWINT in glioma, to confirm its prognostic value.

Methods: The gene expression and clinical information profile were downloaded from The Cancer Genome Atlas (TCGA) database and a statistical analysis was made. We probed the edgeR and qplots packages in the R language to identify differentially expressed genes (DEGs). The Kaplan–Meier plotter online tool was used to study the association of ZWINT expression and overall survival (OS) of glioma patients. Immunohistochemistry (IHC) and quantitative RT-PCR were performed to evaluate protein and mRNA expression levels of ZWINT. ZWINT-siRNA was transfected into U251 and U87 glioma cells to inhibit the expression of ZWINT. Then, the effects of ZWINT silencing on glioma cell lines proliferation, invasion and apoptosis were determined by the Cld3 assay, MTT assay, transwell assay, Annexin V FACS assay and Caspase-3/7 assay in vitro. Functional and pathway enrichment analysis were performed for DEGs using the DAVID database. Protein–protein interaction (PPI) network analysis was established by STRING and visualized by Cytoscape.

Results: Integrated analysis revealed that ZWINT protein and mRNA expression were significantly upregulated in glioma versus normal tissues, its expression was positively correlated with the patient age, poor pathological grade, and conferred poor prognosis. Knockdown of ZWINT expression inhibited the proliferation and invasion of U251 and U87 cells, and apoptosis was distinctly increased following ZWINT-siRNA infection. 20 hub genes and a significant module showed that the DEGs were principally related to cell division, and mitotic cell cycle.

Conclusions: Our preliminary study highlighted that the expression of ZWINT is up-regulated in glioma, which is correlated with poor prognosis. ZWINT silencing can effectively inhibit proliferation, induce apoptosis and suppress migration and invasion during human glioma development, which may provide a new promising tumor-specific therapeutic combination hub genes target for anti-mitosis agents.

Legal entity responsible for the study: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Funding: China National Natural Fund Project (NO.81272870).

Disclosure: The author has declared no conflicts of interest.
Annals of Oncology

Conclusions: In summary, neriifolin obtained from extracts of C. manghas may serve as a drug lead compound for GBM therapies.

Editorial acknowledgement: Louise T. Chew

Legal entity responsible for the study: Department of Life Science, National Taiwan Normal University.

Funding: Ministry of Science and Technology, Taiwan, ROC.

Disclosure: All authors have declared no conflicts of interest.

Can diffusion tensor MRI imaging identify glioma IDH mutation status?

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Background: The isocitrate dehydrogenase (IDH) mutation status is a recognized molecular biomarker for glioma stratification. Additionally, glioma clinical management benefits from advanced MRI sequences including diffusion tensor imaging (DTI). For first time, we investigated the diagnostic power of DTI to characterize gliomas with respect to IDH mutation status.

Methods: This retrospective study examined the accuracy of DTI for staging of IDH mutant (98) and wild-type (67) gliomas in a treatment-naive setting. The tumour was manually segmented in the MRI and two DTI-derived parameters, namely fractional anisotropy (FA) and mean diffusivity (MD) values were calculated and plotted as histograms. Thresholds for the optimal diagnostic performance in terms of IDH mutation were sought in selected histogram parameters of FA and MD maps using parametric and non-parametric tests as well as receiver operating characteristic curve analysis.

Results: Significantly higher MD median values and significantly lower FA median values were observed in the IDH mutant compared with the wild-type group. As follows, the median MD value was defined as a robust predictor for IDH mutation status [area under the curve (AUC) = 0.82]. The developed logistic regression model included the top 5 correlating histogram parameters and the patient age. The assessment using the parameter combination reached better performance (AUC=0.85) compared with the prediction using parameter of the median MD value alone.

Conclusions: MR imaging DTI-derived metrics (MD and FA values) in combination with demographic information has the potential to non-invasively predict molecular stratification of gliomas.

Legal entity responsible for the study: University College London.

Funding: Has not received any funding.

Disclosure: D. Roettger: Head of Scientific and Medical Affairs IAG. All other authors have declared no conflicts of interest.

Radiologically evident treatment effects in patients with glioblastoma (GBM) and its clinical implications

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Background: GBM is the most common primary brain tumor. Survival is poor with standard surgery followed by radiotherapy (RT) and temozolomide (TMZ). Pseudo-progression on MRI is well described post RT, particularly within the first 3 months, and confounds response assessment. Whilst not previously described for drug treatment alone, anecdotal cases were described in a Phase 1 study of depatuxizumab mofetil (depatux-m). Depatux-m is an antibody-drug conjugate, comprised of a tumor-specific anti-EGFR antibody linked to a microtubule cytos toxin. Monomethyl auristatin F, that demonstrated promising antitumor activity in adult GBM pts with EGFR-amplified tumors. This exploratory study will determine if depatux-m exhibits radiologically evident treatment effects in pts with GBM, i.e. drug induced pseudo-progression.

Methods: This non-interventional study enrolls pts with GBM who underwent tumor debulking surgery after MRI evidence suggested treatment failure in Phase 1-3 depatux-m trials. Pts had received depatux-m alone or in combination with TMZ. Rejected tumor tissue is formalin-fixed, paraffin-embedded and centrally reviewed. Radiographic assessments were collected per original study protocol (typically q8 wks), or as clinically indicated, and centrally reviewed. Clinical response is evaluated by RANO criteria. This study will assess correlation between radiographic and histologic evidence of disease progression after depatux-m treatment. Exploratory endpoints are progression-free survival and overall survival.

Conclusions: MR imaging DTI-derived metrics (MD and FA values) in combination with demographic information has the potential to non-invasively predict molecular stratification of gliomas.

Legal entity responsible for the study: University College London.

Funding: Has not received any funding.

Disclosure: D. Roettger: Head of Scientific and Medical Affairs IAG. All other authors have declared no conflicts of interest.

Comparative assessment of orthoptic brain tumor growth using bioluminescence and magnetic resonance imaging

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Background: Small animal tumor models are essential for developing translational therapeutic strategies in oncology research. Intracranial brain tumor models are of high clinical relevance, since they closely resemble the tumorigenesis in humans. The use of such models, however, requires the application of imaging methods to quantitatively assess tumor growth and therapy efficacy. The objective of this study was to evaluate intracranial tumor growth and treatment response in mouse models using magnetic resonance imaging (MRI) and bioluminescence imaging (BLI). Further aim was to establish correlation between tumor volume and bioluminescence signal and compare the imaging modalities in terms of accuracy and efficiency.

Methods: Three groups (untreated, vehicle and Temozolomide-treated group) of ten mice each were implanted intracranially using stereotactic device with U87 glioma cells expressing firefly luciferase. Two cycles of temozolomide at 50 mg/kg 5days on/5days off were administered orally by gavage. The mice were imaged using bioluminescence and MR (proclinical 4.7 T MR scanner) once per week.

Results: The data showed that both imaging methods can efficiently measure tumor growth and therapy response but significantly differ in their throughput and type of information. MRI offers detailed tumor localization and 3D volumetric measurements, but has limited capacity to assess early tumor growth. BLI identifies tumors early but not tumor localization, precluding discrimination of intraventricular and extracranial tumor growth. Tumor volume determined with MRI and BLI signal intensity showed a strong linear correlation (r = 0.918).

Conclusions: BLI appears a reliable technique to evaluate intracranial tumor growth in mouse models. Adding MR scans to longitudinal BLI improves assessment of tumor properties such as volume, location, hemorrhage and necrosis. Other intracranial tumor xenografts, with varying characteristics, i.e. diffuse growth, are being analyzed to improve assessment of both imaging modalities.

Legal entity responsible for the study: Bayer AG.

Funding: Bayer AG.

Disclosure: All authors have declared no conflicts of interest.
Results: 7 pts with recurrent GBM were enrolled at 2 sites in Australia. All pts completed RT at a minimum of 11 months (range 11-26) prior to re-resection. 4 pts had histological confirmation of recurrence prior to treatment. Conclusions: Histology showed that 57% (4/7) of pts with disease progression by RANO criteria after deputus-m, with or without TMZ, had predominantly treatment effect per local pathologist assessment. Central review indicated that of these 4 pts, 2 pts were >75% necrotic and 2 showed complete absence of tumour. 2 pts had histological confirmation of recurrence prior to treatment. Cases and associated clinical impact are presented.

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Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

Disclosure: H.K. Gan: Consulting/advisory role: AbbVie; Speakers’ bureau: Ignyta; Bristol-Myers Squibb, Research funding: AbbVie; Travel, accommodations, expenses: Ignyta. E. Kennedy, D. Maag: Employee and stock: AbbVie. All other authors have declared no conflicts of interest.

MELANOMA WITH BRAIN METASTASES: EXPERIENCE OF IMMUNOTHERAPY IN A SINGLE CENTER

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Background: The effectiveness of conventional chemotheraphy (temozolomide, fotemustine, lomustine) alone and in combination with radiation therapy in patients with melanoma with cerebral metastases does not exceed 7-10%. There is no significant impact on overall survival, which is 2-4 months. Research of immunotheraphy (nivolumab, pembrolizumab) is relevant in melanoma patients with brain meta- stases in the absence of mutations of the BRAF, or in the case of the progression of the disease while therapy BRAF inhibitors in patients with mutations of the BRAF.

Methods: The effect of the various schemes immunotherapy was evaluated in 22 patients with melanoma with brain metastases in Russian N.N. Blokhin Cancer Research Center. Patients received the following treatment options: nivolumab (6 patients), ipilimumab (11 patients), nivolumab + ipilimumab (2 patients), pembrolizumab (3 patients). The immunotherapy was combined with whole brain irradiation in 1 patient (4.5%), in 11 patients (50.0%) – in combination with stereotactic radiotherapy/radiosurgery.

Results: Complete regression of brain metastases was achieved in 3 patients (13.6%), partial regression in 2 (9.1%), stabilization in 11 (50.0%). Thus, the tumor control in the brain was observed in 16 patients (72.7%). In 22 patients (100.0%) were also established metastases in other sites (extracranial lesions). Complete regression of metastases in extracranial lesions was achieved in 4 patients (18.2%), partial regression – in 2 (9.1%), stabilization in 13 (59.1%). The median time to disease progression was 5.0 months. The median survival of patients was 11.0 months.

Conclusions: The preliminary results of our study show that the application of immunotheraphy (nivolumab, pembrolizumab, ipilimumab) is relevant in melanoma patients with brain metastases provides control over the disease in the majority of patients and has a significant advantage with a group of historical control (chemotheraphy therapy z. 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.

SYSTEMIC MANAGEMENT OF MALIGNANT MENINGIOMA: A COMPARATIVE SURVIVAL AND MOLECULAR MARKER ANALYSIS BETWEEN OCTEREODIN WITH COMBINATION EVEN WITH TEMOZOLOMIDE COMPARED TO SUNITINIB

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Background: Anaplastic and atypical recurring meningioma constitute a rare pathology with very few available effective systemic treatments.

Methods: A comprehensive analysis of 31 patients with atypical (WHO II) or anaplastic meningioma (WHO III) that were recurrent and refractory to radiotherapy was conducted in two reference centers of Colombia. Only patients who had received some systemic treatment (sunitinib, everolimus, octreotide and bevazucizumab) and had a complete response were included. Overall survival (OS), progression free survival and toxicities were evaluated. Additionally, tissue samples were examined for PDGFRα and VEGFR2 and its expression was correlated with outcomes.

Results: Twenty-two patients (72%) were females with a median age of 55 years (SD ± 15.3). The most prevalent histology was anaplastic meningioma in 20 patients (63%) with 48% of patients suffering from three previous relapses before the start of systemic treatment. A total of 14 patients received combination therapy with octero- ide/everolimus, 11 received sunitinib and the remaining 6 other second line agents. Median OS was 37.3 months (95% CI 28.5-42.1) and the PFS during the treatment with everolimus/octreotide (EO) and sunitinib (Su) was 12.1 months (95% CI 9.2-21.1) and 9.1 months (95% CI 6.8-16.6); p = 0.43, respectively. The OS of the group treated with the EO–Su–Bev sequence (1728/238/341yn) was 6.5 months longer than the Su–EO–Bev sequence, a finding that was not significant (36.0 vs. 29.5 months; p = 0.349). When analyzing molecular markers, the positive PDGFRα and negative VEGFR2 expression were associated with longer survival both in OS and PFS.

Conclusions: Sunitinib and octereodine/everolimus have similar efficacy and safety in the systemic management of refractory meningioma. VEGFR2 and PDGFRα expression are strongly associated with major survival endpoints.

Legal entity responsible for the study: Foundation for Clinical and Applied Cancer Research – FICMAC.

Funding: Supported by the Foundation for Clinical and Applied Cancer Research – FICMAC (Bogotá Colombia) research grant 011-2017SD.

Disclosure: All authors have declared no conflicts of interest.

IMPACT OF POSTOPERATIVE RESIDUAL TUMOR AND MENINGEAL DISSEMINATION IN ADULT MEDULLOBLASTOMA: A RETROSPECTIVE ANALYSIS

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Background: Medulloblastoma (MB) is the most common central nervous system (CNS) malignant tumor in children and reaches its peak in the first decade of life. In adults, MB is very rare, comprising less than 1% of total CNS tumors. Although molecular subtypes are well defined, the impact of other prognostic variables, such as postoperative residual tumor (PRT) and the presence of neuroaxis dissemination (NAD) are controversial.

Methods: We performed a retrospective analysis in consecutive adult patients with MB treated at Instituto do Câncer do Estado de São Paulo from 2008 to 2016. Patients data on tumor histology, ECOG-PS at diagnosis, low/high-risk clinical-classification (according to tumor size, metastasis, NAD and PRT) and adjuvant radiotherapy (RT) or chemotherapy (CT) were reviewed through medical records.

Results: Thirty-eight patients were included. Median age was 28.8 years-old (18.3 to 40.8) and patients were followed-up for a median of 3.28 years. Five patients died during follow-up, all cancer related, and 8 had progression events. All patients were submitted to surgical resection; 15 were considered high-risk patients; 34 were submitted to RT and 23 to CT in addition to RT. The most common RT regimen was 36 Gy on neuroaxis and 16 Gy boost on the posterior fossa (67%) and the most common CT protocol was a combination of lomustine, vincristine and cisplatin (39%). The two most common histological subtypes were classical (19), followed by desmoplasic (14). Fifteen patients were considered high-risk. On univariate analysis, the presence of PRT (p = 0.0001) and NAD (p = 0.008) had a negative impact on survival. Cox proportional-hazards regression for multivariate analysis confirmed the detrimental impact of PRT, while NAD had a marginal effect.

Conclusions: Medulloblastoma seems to bear a general favorable prognosis among adults. The presence of postoperative residual tumor, and perhaps neuroaxis dissemination, seem to impact negatively survival.

Legal entity responsible for the study: Olavo Fehér.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

ADULT MEDULLOBLASTOMA: AN ONCOLOGY RADIATION THERAPY DEPARTMENT EXPERIENCE WITH 22 CASES

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Background: Medulloblastoma is the most common central nervous system tumor in children. However, the occurrence in adults is rare and accounts for about 1%–2%. The objective of this study is to define the clinical characteristic of this entity and thera- peutic results.

Methods: We retrospectively evaluated the treatment data of 22 adult patients (≥18 years) treated for medulloblastoma from 1993 to 2013 in our department. Median follow-up was 161.5 months (58, 296 months).

Disclosure: All authors have declared no conflicts of interest.
**Results:** Male female ratio was 2.14:1. Median age was 25 years [18 ; 57]. Eight patients (36%) had cerebellar hemispheric tumors, nine cases (41%) occur in the vermis and five patients (23%) had an hemispheric-vermicinal localisation. Twenty one patients (95%) underwent macroscopically total excision. Surgery outcomes (75%) had classic form; five patients had desmoplastic (23%) type and one patient had extensive nodularity type. Patients were stratified into standard and high risk in 4 and 5 cases respectively. The risk couldn’t be identified for 3 patients. Among patients in the high-risk group, four received a cisplatin/etoposide chemotherapy before radiation. All patients had craniospinal radiotherapy. The mean interval between surgery and the beginning of radiation therapy was 107 days. Craniospinal dose range between 30Gy and 36Gy. The dose in the posterior fossa was respectively 54Gy and 64Gy in 18 (82%) and 4 (18%) cases. The 5 year overall survival was 63%.

**Conclusions:** There are differences between pediatric and adult patients with medulloblastoma in terms of clinical and pathological characteristics. Ultimately, prospective trials including adult patient with medulloblastoma are needed to optimize the management of this rare and complex disease.

**Legal entity responsible for the study:** Kallel Mouna.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Pineal parenchymal tumors: Patterns of care from a tertiary cancer centre in India**

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**Background:** The aim of this study is to report clinical features and treatment outcome of pineal parenchymal tumors (PPTs).

**Methods:** Between 2006-2017, medical records of 34 patients of PPTs were analyzed to study patterns of care of patients who received adjuvant radiotherapy (RT) with or without chemotherapy (CT) following surgery. Overall survival (OS) and progression-free survival (PFS) were analyzed by Kaplan–Meier method.

**Results:** According to WHO classification, the study comprises of 19 pineoblastomas (PB), 11 pineal parenchymal tumors of intermediate differentiation (PPTID) and 4 pineocytomas (PC). Median age at presentation was 10, 26 and 30 years, respectively. Headache was commonest symptom (77%) followed by visual disturbance. 59% underwent surgical resection and 41% had biopsy only. Median MIB labelling index of PPTID was 6%, whereas it was 35% in PB and 2% in PC. Spinal drop metastasis was present in 8 patients with PB and 3 patients with PPTIDs. All PBs and PPTIDs with spinal drop metastasis (2) received craniospinal irradiation (CSI) and adjuvant CT. The rest of the PPTIDs and PC received focal RT to the brain. The commonest regimen was a combination of carboplatin and etoposide (CE), used in 6 (32 %) PB. CE with vincristine and IT-MTX was given in patients who developed drop metastasis subsequently. At a median follow-up of 16 months, 9 (47%) patients of PB and 3 (27%) of PPTID developed recurrence in cranio-spinal axis. 5 year progression-free survival was 41%, 62% and 70%, respectively. Median overall survival (OS) was 27, 50, 18 months, and 5 year OS was 38%, 47% and 75%, respectively.

**Conclusions:** PPTs reflect a broad spectrum of malignant potential and prognosis. PB is an aggressive tumor and requires adjuvant CSI and CT following surgery. PPTIDs are relatively rare and require meticulous pretreatment evaluation of neuraxis and knowledge of pathological factors for management. Multi-institutional cooperation in the form of prospective studies is recommended in view of rarity of tumor.

**Legal entity responsible for the study:** AIIMS, New Delhi.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Advantages of next-generation sequencing in revealing low-level somatic mosaic in blood samples of retinoblastoma patients**

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**Background:** Retinoblastoma (RB) is an embryonic malignant tumor of retina caused by inactivation of both alleles of the RB1 tumor suppressor gene. Identifying low-level mosaic mutations in RB1 gene in blood samples is challenging. Mosaic mutations arise in early embryogenesis and require high-resolution techniques for detection. In approximately 10% of families, the initial RB1 mutation is mosaic. The ability to identify RB1 mosaicism is important for genetic counseling because mosaicism increases the risk for developing RB in the other eye, second cancers and transmitting the mutation to progeny.

**Methods:** Using NGS we have evaluated the spectrum and frequency of RB1 mutations mosaic in peripheral blood of 120 patients with sporadic RB (82 unilateral and 38 bilateral).

**Results:** In 5,8% (71/120) of patients a low-level mosaic mutation was found. The spectrum of identified mosaic RB1 mutations, the degree of mosaicism and clinical characteristics are shown in the table. Additionally, we analyzed the Sanger sequencing data from 72 blood samples from patients with sporadic RB (48 unilateral and 24 bilateral), performed earlier in our laboratory, and have not identified mosaic cases.

**Conclusions:** NGS is an efficient method for detecting low-level mosaic mutations in blood samples from RB patients. Clinically, RB1 mosaicism is variable, it can manifest as a bilateral or a unilateral form with early or late onset, or without disease, which make the diagnosis even more difficult.

**Legal entity responsible for the study:** FASO Russia.

**Funding:** The research was carried out within the State assignment of FASO Russia.

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 404P The spectrum of identified mosaic RB1 mutations**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Form (uni/bi lateral)</th>
<th>Age of onset</th>
<th>Mosaic mutation</th>
<th>Degree of mosaicism</th>
<th>Mutation in relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Uni-</td>
<td>6 mo</td>
<td>c.C1336T (14ex)</td>
<td>C:80, T:20</td>
<td>Negative</td>
</tr>
<tr>
<td>R2</td>
<td>Uni-</td>
<td>1yr 8 mo</td>
<td>c.C1336T (14ex)</td>
<td>C:74, T:20</td>
<td>Negative</td>
</tr>
<tr>
<td>R3</td>
<td>Bi-</td>
<td>3 weeks</td>
<td>c.3252delC (23ex)</td>
<td>wt:80, del:20</td>
<td>Negative</td>
</tr>
<tr>
<td>R4</td>
<td>Uni-</td>
<td>3 yr</td>
<td>c.C598T (10ex)</td>
<td>C:80, T:20</td>
<td>Negative</td>
</tr>
<tr>
<td>R5</td>
<td>Uni-</td>
<td>3 mo</td>
<td>c.C751T (8ex)</td>
<td>C:84, T:16</td>
<td>Negative</td>
</tr>
<tr>
<td>R6</td>
<td>Uni-</td>
<td>1yr 8 mo</td>
<td>c.1215 + 1G-A</td>
<td>G:87, A:13</td>
<td>Negative</td>
</tr>
<tr>
<td>R7</td>
<td>Uni-</td>
<td>8 mo</td>
<td>c.C1735T (18ex)</td>
<td>C:79, T:21</td>
<td>Negative</td>
</tr>
<tr>
<td>R8</td>
<td>No symptoms</td>
<td></td>
<td>c.887delG (9ex)</td>
<td>wt:85, del:15</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**405TiP Avelumab in newly diagnosed glioblastoma multiforme: The SEJ study**

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**Background:** Patients with Glioblastoma Multiforme (GBM) despite standard therapy have a dismal prognosis and thus represent a significant unmet medical need. GBM has well documented systemic and local immunosuppressive mechanisms to escape immune surveillance and grow. GBM tumor cells as well as the microglia within it have a high incidence of PD-L1 surface expression which makes it more susceptible to anti-PD-L1 antagonism and ADCC through avelumab therapy. Combination of avelumab with other anticancer therapies have been shown safe and perhaps synergistic. A clinical trial looking at adding avelumab to standard therapy in patients with GBM is therefore indicated.

**Trial design:** This is a single center, phase 2, open label, open-ended add-on, single dose study of 52 weeks duration in patients receiving standard therapy for newly diagnosed GBM. In total 30 patients who meet the entry criteria will be entered into the study within 3 weeks of finishing their last day of combined radiotherapy/temozolomide. Avelumab will be initiated concurrently with the initiation of the first 5-day, monthly cycle of temozolomide and continued for a total of 52 weeks. The study will consist of 3 different phases: Combination Phase a Monotherapy Phase and an Extended Safety Follow-up Phase.

**Clinical trial identification:** NCT03847473.

**Legal entity responsible for the study:** Clinique Neuro-Outaouais.

**Funding:** Study is funded by an unrestricted grant from Merck Serono.

**Disclosure:** All authors have declared no conflicts of interest.
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**Background:** The Stupp protocol is the standard treatment of glioblastoma multiforme (GBM). The non-dividing nature of normal brain cells is an opportunity to enhance the therapeutic ratio by combining radiation with inhibitors of replication-specific DNA repair pathways such as PARP inhibitors as olaparib. PARP inhibition also increases cellular sensitivity to radiation and may be higher in tumor than in normal tissue. Progress in technical imaging and intensity-modulated-radiotherapy (IMRT) techniques provide new possibilities for sparing healthy tissues. We propose a phase 1/2a trial to assess the safety and efficacy of Olaparib combined with TMZ plus fractionated IMRT as a first-line treatment in unresectable GBM patients (pts).

**Trial design:** Based on the Stupp phase 2 design, 2 treatment periods are considered. The radiotherapy (RT) period occurs after the last surgery: the pt receives IMRT, daily TMZ during IMRT, and olaparib, given at the same dose until 4 weeks after the end of IMRT. For the maintenance (MT) period, the pt receives TMZ (days 1-5 every 28 days, for 6 cycles) plus olaparib (at the MT dose level up to disease progression or unacceptable toxicity). The phase 1 includes 2 consecutive dose escalations to separate both periods for DLT (Dose Limiting Toxicities) assessment. Next 15 pts will receive olaparib only during the RT period to determine the MTD1 (Maximum Tolerated Dose) among 7 dose levels, by assessing DLT on this period. Next 15 pts will all receive MTD1 during the RT period, and a new dose-escalation will determine MTD2 (≤ MTD1) during the MT period, assessing DLT from the first 2 cycles. For phase 2a, IMRT and TMZ are given according to the Stupp protocol. Olaparib is given at the MTD1 during the RT period and at the MTD2 during the MT period. Brain disease is assessed using RANO criteria. The trial includes ancillary studies on tumor biopsies, spectro-MRI and neurocognitive and quality of life assessment. Up to 79 pts will be enrolled: 30 in the phase I and 49 pts in the phase 2a (CasMorgan two-stage design). This trial (NCT03212742) is granted by the French Cancer Institute and Health Ministry and at the MTD2 during the MT period. Brain disease is assessed using RANO criteria. The trial includes ancillary studies on tumor biopsies, spectro-MRI and neurocognitive and quality of life assessment. Up to 79 pts will be enrolled: 30 in the phase I and 49 pts in the phase 2a (CasMorgan two-stage design). This trial (NCT03212742) is granted by the French Cancer Institute and Health Ministry.

**Legal entity responsible for the study:** Comprehensive Cancer Centre Francois Baclesse.

**Funding:** AstraZeneca.

**Disclosure:** All authors have declared no conflicts of interest.

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**Phase II/II trial study of concomitant radiotherapy with olaparib and temozolomide in unresectable high-grade gliomas patients: OLA-TMZ-RTE-01**

**406TiP**

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**Background:** Treatment of brain tumors, including tumors of the central nervous system (CNS), is a major challenge in cancer research. The Stupp protocol, consisting of radiotherapy and concurrent temozolomide followed by adjuvant temozolomide, is currently the standard of care for glioblastoma multiforme (GBM). Despite its proven efficacy, the Stupp protocol is associated with a high incidence of toxicities, particularly neurocognitive impairment. The combination of temozolomide and olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has shown promise in preclinical and early clinical studies for the treatment of GBM. The objective of this study is to evaluate the safety and efficacy of concomitant radiotherapy with temozolomide and olaparib in patients with unresectable high-grade gliomas.

**Trial design:** This trial is a phase II/II randomized, open-label study designed to evaluate the safety and efficacy of concomitant radiotherapy with temozolomide and olaparib in patients with unresectable high-grade gliomas. The study will recruit patients with newly diagnosed GBM who are not eligible for surgical resection, including patients with performance status (PS) 0-2 and no prior systemic therapy. Patients will be randomly assigned to receive radiotherapy and concurrent temozolomide plus olaparib or radiotherapy and concurrent temozolomide alone. The primary endpoint of this study is overall response rate (ORR), defined as the proportion of patients achieving a complete or partial response according to the Response Assessment in Neuro-Oncology (RANO) criteria. Secondary endpoints include progression-free survival (PFS), overall survival (OS), and safety/tolerability. The study will enroll up to 80 patients per treatment arm and will be conducted at multiple centers in Europe and the United States.

**Disclosures:** All authors have declared no conflicts of interest.

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**Phase II open-label, global study evaluating dabrafenib in combination with trametinib in pediatric patients with BRAF V600–mutant high-grade glioma (HGG) or low-grade glioma (LGG)**

**407TiP**

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**Background:** Activation of the MAPK pathway via the BRAF V600 mutation has been demonstrated in several tumors, including HGG and LGG for which limited therapeutic options are currently available. In a phase I/I clinical trial of pediatric patients (pts) with recurrent or refractory BRAF V600–mutant relapsed tumors, the BRAF inhibitor dabrafenib demonstrated its efficacy, including complete responses, in pediatric pts with HGG and LGG. As the combination of dabrafenib plus the MEK inhibitor trametinib has resulted in improved efficacy in multiple adult BRAF V600–mutant tumors, including melanoma and non-small cell lung cancer, this combination warrants further investigation in pediatric pts with gliomas bearing the same mutation.

**Trial design:** This global, open-label, phase II study (NCT02684058) will evaluate the anti-tumor activity of the combination of dabrafenib plus trametinib in 2 pediatric CNS cohorts recruiting from up to 70 sites across 17 countries. The single-arm BRAF V600–mutated HGG cohort of approximately 40 pts (aged ≥ 6 and < 18 y) with relapsed or refractory disease will be treated with dabrafenib twice daily (BID) plus trametinib once daily (QD) based on age and weight. The primary endpoint for this cohort is overall response rate (ORR) per investigator’s assessment according to Response Assessment in Neuro-Oncology (RANO) criteria. The BRAF V600–mutated LGG cohort of approximately 102 chemotherapy-naïve pts (aged ≥ 6 and < 18 y) with unresectable disease will be randomized 2:1 to receive either dabrafenib (BID) plus trametinib (QD) or carmustin plus vincristine. The primary endpoint for the LGG cohort is ORR per independent assessment according to RANO criteria. Pt crossover from the chemotherapy arm to the experimental arm will be allowed after independent confirmation of radiologic disease progression. Key secondary endpoints for both cohorts include duration of response, progression-free survival, time to response, clinical benefit rate, overall survival, and safety/tolerability.

**Clinical trial identification:** NCT02684058.

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**Funding:** Novartis Pharmaceuticals Corporation.

Sitravatinib demonstrates activity in patients with novel genetic alterations that inactivate CBL

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Larotrectinib efficacy and safety in TRK fusion cancer: An expanded clinical dataset showing consistency in an age and tumor agnostic approach

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First-in-human, first-in-class study of the CD44v6 inhibitor AMC303 as monotherapy in patients with advanced epithelial tumors


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Initial results from a phase I/lla trial evaluating BMS-986158, an inhibitor of the bromodomain and extra-terminal (BET) proteins, in patients (pts) with advanced cancer


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Clinical activity, safety, and PK/PD from a phase I study of RO6874281, a fibroblast activation protein (FAP) targeted interleukin-2 variant (IL-2v)


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413PD Phase I clinical and translational evaluation of AZD6738 in combination with durvalumab in patients (pts) with lung or head and neck carcinoma


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414PD Phase I study of the CTLA-4 inhibitor MK-1308 in combination with pembrolizumab in patients with advanced solid tumors


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415PD Clinical response and pharmacodynamic assessment of INVAC-1, a DNA plasmid encoding an inactive form of human telomerase reverse transcriptase (hTERT), on immune responses, immune tolerability, tumor burden and circulating tumor DNA (ctDNA) in patients with advanced solid tumors


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416PD Final results from a phase I clinical trial evaluating the safety, immunogenicity, and anti-tumor activity of SNS-301 in men with biochemically relapsed prostate cancer

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417PD Combination therapy optimization in gastrointestinal cancers using multi-omic molecular profiling

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In this era of personalized medicine there is an outburst of information and evidence intensive, evidence based treatment decisions. These findings are encouraging for the use of this technology. Additional investigations are needed to understand information intensive, evidence based treatment decisions. These findings are encouraging for the use of this technology. Additional investigations are needed to understand new treatment options and challenges.

**Methods:** Watson for oncology (WFO) & multidisciplinary tumor board (MDT) recommendations between artificial intelligence advisory programme and oncology advisors. Results are presented as the proportion of concordant cases.

**Results:** Artificial intelligence treatment recommendations with Watson for oncology showed high levels of concordance with a multidisciplinary tumor board. This cognitive computing technology holds much promise in helping oncologists make information intensive, evidence based treatment decisions. These findings are encouraging for the use of this technology. Additional investigations are needed to understand new treatment options and challenges.

**Conclusion:** Artificial intelligence treatment recommendations with Watson for oncology showed high levels of concordance with a multidisciplinary tumor board. This cognitive computing technology holds much promise in helping oncologists make information intensive, evidence based treatment decisions. These findings are encouraging for the use of this technology. Additional investigations are needed to understand new treatment options and challenges.

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Preliminary results of pamiparib (BGB-290), a PARP1/2 inhibitor, in combination with temozolomide (TMZ) in patients (pts) with locally advanced or metastatic solid tumors

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Background: DNA damage caused by TMZ can sensitize tumors to the effects of PARP inhibitors. Pamiparib is a selective PARP1/2 inhibitor with potent PARP trapping that can cross the blood-brain barrier and has shown synergetic cytotoxicity with TMZ in nonclinical experiments. In Phase 1 studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed preliminary antitumor activity; single-agent RP2D was defined as 60 mg PO BID. Methods: This dose-escalation/expansion study (NCT03150810) is enrolling pts using a modified 3 + 3 design to establish the safety and MTD of pamiparib plus TMZ. During dose escalation, pts receive pamiparib 60 mg PO BID plus escalating doses of TMZ QD on Days 1–7 (Arm A) or continuously (Arm B) for each 28-day cycle. The primary endpoint is safety/tolerability, including estimation of MTD and RP2D. Key secondary endpoints are PK profiles of TMZ and pamiparib and antitumor activity (RECIST v1.1) of combination treatment; biomarker (eg, gBRCA) assessment is exploratory.

Results: As of 16 Feb 2018, 16 pts (Arm A, n = 4, 60 mg TMZ; n = 8, 40 mg TMZ; n = 3, 120 mg TMZ; Arm B, n = 4, 20 mg TMZ; n = 10, 40 mg TMZ) with a median age of 69.5 yr (range 30–85) have enrolled. It remains on treatment. Prostate and small cell lung cancers (n = 4 each) were the most common tumors; most pts (n = 14) had received ≥3 prior treatments. Most common pamiparib-related AEs were nausea (n = 6), and nausea and thrombocytopenia (n = 5 each) for TMZ. In Arm A, 2 pts at 120 mg TMZ reported a DLT of grade 4 neutropenia >7 days. Neutropenia and thrombocytopenia (n = 4 each) were the only ≥3 grade AEs occurring in ≥2 pts. No AEs led to treatment discontinuation or death. Plasma exposure for pamiparib and TMZ were consistent with single-agent trials. One pt with peritoneal cancer in Arm A had a 99% decrease in INR in 5 wk by wk 12. In the 7 pts with ≥1 post-baseline tumor assessment, 2 pts in Arm A (kidney, n = 1; SCLC, n = 1) achieved unconfirmed PRs.

Conclusions: In pts with solid tumors, pamiparib 60 mg PO BID combined with pulsatile or continuous flat dose TMZ showed preliminary antitumor activity and was generally well tolerated with the expected toxicity of bone marrow suppression.

Clinical trial identification: NCT03150810

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Background: Navoximod is a small molecule inhibitor of indoleamine-2,3-dioxygenase 1 (IDO1) which catalyzes the oxidation of L-tryptophan (Trp) into kynurenic (Kyn). This study aimed to investigate maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and pharmacodynamics of navoximod as monotherapy and in combination with atezolizumab, an anti-PD-L1 antibody, in Japanese patients (pts) with advanced solid tumors.

Methods: Phase 1, open-label, 3 + 3 dose-escalation study. Primary endpoints were safety, tolerability, and PK. Pts received navoximod (400, 600 or 1000 mg orally twice daily [BID], for 21 days/cycle) monotherapy (Stage 1) or navoximod (200, 400, 600 or 1000 mg orally BID, for 21 days/cycle) in combination with atezolizumab (1200 mg IV, every 21 days) (Stage 2).

Results: Twenty pts were enrolled in the 400 mg (n = 3), 600 mg (n = 4) and 1000 mg (n = 5) cohorts of Stage 1, and in the 200 mg (n = 3), 400 mg (n = 5), 600 mg (n = 3) and 1000 mg (n = 1) cohorts of Stage 2. Across all cohorts, no DLT was observed and MTD was not reached in either stages. In Stage 1, treatment related adverse events (TRAEs) of any grade occurring in ≥ 20% of pts were chromatia (30%) and
maculopapular rash (20%). Grade ≥3 TRAEs were reported in 2 pts (20%), including maculopapular rash and lipase increased. In Stage 2, TRAEs ≥20% were fatigue (20%), chromaturia (60%), decreased appetite (40%), hypotenraemia (20%), AST increased (20%), ALT increased (20%) and lymphopenia (20%). Grade ≥3 TRAEs were reported in 3 pts (30%), including hypotension, AST increased, ALT increased, lymphopenia and neutropenia. Cmax and AUC of navoximod as monotherapy were dose-proportional from 400 to 1000 mg and PK profile was similar in combination with atezolizu-

Results: Cisplatin resistance derives, in part, via tumour suppressor gene promo-

Conclusions: SD was observed in 4 pts (7) more tracer was present in the blood pool, while tumor lesions were not visualized, possibly reflecting target saturation.

Conclusions: In this first-in-human study high specific uptake of 89Zr-AMG 211 in immune cells by counting Ficoll separated whole blood fractions.

Results: Before AMG 211 treatment, the optimal imaging dose was 200 μg 89Zr-AMG 211 + 1,800 μg cold AMG 211. At 3 h the highest blood pool SUVmax was 4.0, and tracer serum half-life was 3.3 h. Uptake in CD3-rich lympic tissues such as the spleen and bone marrow was SUVmax 3.2 and 1.8, respectively. Uptake in these tissues decreased slower than in other normal tissues. 89Zr-AMG 211 remained intact in plasma and was excreted predominantly via the kidneys in degraded forms. Of all visible tumor lesions, 37 were PET quantifiable, with a SUVmax of 4.0 (interquartile range 2.7 - 4.4) at 3 h using the optimal imaging dose. The maximum tracer uptake differed between tumor lesions 5-fold within and 9-fold between patients. During AMG 211 treatment (n = 2) more tracer was present in the blood pool, while tumor lesions were not visualized, possibly reflecting target saturation.

Conclusions: In this first-in-human study high specific 89Zr-AMG 211 accumulation was observed in CD3-rich lymphoid tissues. In addition, a clear, inter- and intra-indi-

INDO1.

Disclosure: A. Jorritsma-Smit 4, M.N. Lub-De Hooge 4, R.S.N. Fehrmann 1, D.J. de Groot 1, E.G.E. de Vries 1, Elisabeth de Vries.

Funding: A. Jorritsma-Smit 4, M.N. Lub-De Hooge 4, R.S.N. Fehrmann 1, D.J. de Groot 1, E.G.E. de Vries.

Methods: Blood was drawn at baseline, 3, 6, and 24 h post-AMG 211 injection. Serum samples were processed for 5'-nucleotidase (5'-NT) activity, lactate dehydrogenase (LDH) activity and kidney function (urea, creatinine).

Conclusions: 5'-NT and LDH activity were elevated in all patients. Post-dose increase in activity were not observed, indicating that AMG 211 does not exert a direct toxicity to hepatocytes and renal cells. LDH activity correlated with the dose, indicating that the increased activity was dose-related.

Abstracts

**428P** Interim results from a phase I trial of SL-801: A novel XPO-1 inhibitor, in patients with advanced solid tumors

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**Background:** SL-801 is a novel, oral, small molecule reversible inhibitor of Exportin-1 (XPO-1), a critical nuclear export protein overexpressed in many cancers. SL-801 has demonstrated potent in vitro and in vivo anti-tumor activity against a broad range of hematologic and solid cancers. SL-801’s reversible inhibition of XPO-1 may translate to selective activity and potential safety benefits. Interim results from the dose-escalation study are reported.

**Methods:** STML-801-0115 is a first-in-human, multicenter Phase 1 3x3 dose escalation study in patients with localized unresectable, or metastatic solid tumors resistant to or relapsed following standard therapy. Objectives are to evaluate safety, tolerability, identify maximum tolerated dose (MTD) or optimal dose/regimen, and assess pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity. SL-801 is orally administered on days 1-4 and 8-11 of 21-day cycle. Starting dose is 3 mg. Currently enrolling 60 mg (escalation ongoing).

**Results:** As of 4/27/18, 35 patients received SL-801 (median age 64 years: range 39-76, 18 females, range 1-13 prior therapies, 69% ≥3rd line). No dose limiting toxicity (DLT) has been identified, and a MTD has not been reached. Median follow-up was 1.4 months (range: 0.2-10.8). Dose-dependent increases in Cmax and AUC have been observed. The most frequent treatment-related grade 1-2 adverse events (TRAEs) were nausea (46%), vomiting (34%), fatigue (29%), decreased appetite (20%), and diarrhea (17%). Grade 3 TRAEs included nausea (n=3; 45, 45, 45 mg), vomiting (n=1; 45 mg), diarrhea (n=2; 10, 10 mg), acute renal injury (n=1; 30 mg), and neutropenia (n=1; 10 mg). No grade 4 or 5 TRAEs reported. Eight patients (23%) had stable disease (SD) and remained on study for 3-15+ cycles. Six patients, with mucinous adenocarcinoma, GE junction, colon, neuroendocrine, basal cell, and breast cancer, had SD for ≥2.5 months; notably, the basal cell carcinoma patient had a SD response >9 months. Radiographic tumor shrinkage >10% noted in 3 patients.

**Conclusions:** SL-801 appears to be well tolerated in advanced solid tumor patients, and to date 23% of heavily pre-treated patients have achieved SD or a best response. Enrollment and dose escalation continues.

**Clinical trial identification:** NCT02866783.

**Legal entity responsible for the study:** Stemline Therapeutics.

**Funding:** Stemline Therapeutics.

**Disclosure:** D Qi: Consultant: Stemline Therapeutics. A Olguin, J Bullington, M Sardone, V Dunn, S Shemesh, J Chen, C Brooks: Employment and stock ownership: Stemline Therapeutics. All other authors have declared no conflicts of interest.

**Table: 428P**

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<td>SK-BR-3</td>
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<tr>
<td>SDL1-1</td>
<td>Colon</td>
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<td>SW1116</td>
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</tbody>
</table>

**T24** NEO2734: A novel potent oral dual BET and P300/CBP inhibitor

**F Giles** 1, M Witcher 1, B Brown 3

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**Background:** The Bromodomain (BRD) and Extra-Terminal domain (RET) family of proteins are key regulators of epigenetic control. Modulation of the BET family is a developmental therapeutics priority. Cyclic AMP response element binding protein (CREB) binding protein (CBP) and E1A interacting protein of 300 kDa (EP300 or P300) are highly homologous BRD-containing transcriptional co-activators and are validated oncology targets. We have developed a series of potent dual inhibitors of BET-CBP/P300 with NEO2734 and NEO1132 as lead clinical candidates.

**Methods:** NEO2734 was profiled against the BET inhibitor ibet762 in cellular assays and multiple human cancer xenograft models including castrate resistant prostate cancer (CRPC) (Vcap) and colon cancer (MC38).

**Results:** NEO2734 antiproiferative activity against a variety of solid tumor cell lines (Table). In a MDA-MB-231 Triple negative breast cancer cell line NEO2734 was more efficient at killing the cancer cells (85%) than a range of non-dual BET inhibitors which killed up to 50% of the cancer cells. NEO2734 has major activity at 10mg/kg (p.o.) in both CRPC and a colon cancer xenograft model whereas ibet762 has minimal activity at 80mg/kg (p.o.) both dosed once daily for 18 days. In the CRPC (Vcap) xenograft, mice were treated by oral gavage with NEO2734 (10mg/kg, and 15mg/kg) and the reference compound ibet762 (30mg/kg) for 18 days. In this model, NEO2734 led to potent tumor regression in a dose dependent manner. Much weaker activity was observed for ibet762 at either 30 mg/kg. The antitumor activity correlated well with the reduction of PSA. The colon cancer xenograft was carried out in Syngeneic mice and the activity was compared with ibet762, anti-CTLA4 and anti-PDL1. NEO2734 was active at 10mg/kg (p.o.), as seen with the anti-PDL1 and superior to the anti-CTLA4 and ibet762.
Conclusions: NCT02734, a novel oral potent dual inhibitor of RET and CRI1/RET3 P300, has significant pre-clinical activity in a spectrum of human solid tumours. Clinical studies are in preparation.

Legal entity responsible for the study: Neomed Therapeutics 1 Ltd.

Funding: Neomed Therapeutics 1 Ltd.

Disclosure: F. Giles: Consultant: Neomed Therapeutics 1. B. Brown: Employee: Neomed Institute. All other authors have declared no conflicts of interest.

Phase I study: Safety and tolerability of varlitinib (VAR) in combination with oxaliplatin and capcitabine (COX) or oxaliplatin and 5-FU (FOL) in advanced solid tumours


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Background: Varlitinib (VAR, ASLAN001) is a potent pan-HER oral tyrosine kinase inhibitor, with efficacy in EGFR mutant and HER2 overexpressing tumours. We evaluated the safety, tolerability and maximum tolerated dose (MTD) of VAR with CAPOX (COX) and mFolfox6 (FOL), in pts with advanced solid tumours.

Methods: Eligible pts had advanced solid tumours, ECOG performance status (PS) 0-1 and adequate organ function. Colorectal cancer (CRC) with RAS/RAF mutations were excluded. COX (Capcitabine 850mg/m² BID D1-D14 with oxaliplatin (OX) 130mg/m² IV D1, Q21 days) or mFolfox6 (3-FU 400mg/m² IV bolus D1 and 2400mg/m² over 46 hrs with 5-FU 400mg/m² IV D1, Leucovorin 400mg/m² IV D1, Q14 days) was given with VAR 200-400mg BID. Maximum 6 cycles COX or 9 cycles FOL, followed by VAR alone. Dose-limiting toxicity (DLT) period was 2 cycles.

Results: 30 pts were enrolled, 9 COX and 21 FOL arms. 15 (52%) CRC (all prior OX), 6 (21%) cholangiocarcinoma (CC), 3 (10%) gallbladder cancer and 6 (20%) others. Sex M/F 13/17, median age (range), PS, lines of prior chemo was 62yrs (36-71), 1 (0-1) and median 6 cycles (range 4-9) respectively. 28 pts were evaluable for MTD. MTD of VAR was 300mg/BID when given with FOL or COX.

Table: 430P

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pt enrolled/evaluable</th>
<th>DLT</th>
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<tbody>
<tr>
<td>COX + VAR 400mg/BID</td>
<td>3/2</td>
<td>6/G3 Fatigue x2</td>
</tr>
<tr>
<td>COX + VAR 300mg/BID</td>
<td>6/6</td>
<td>G3 Fatigue</td>
</tr>
<tr>
<td>FOL + VAR 400mg/BID</td>
<td>4/4</td>
<td>G4 Transaminitis, G3 Raised Bilirubin</td>
</tr>
<tr>
<td>FOL + VAR 300mg/BID</td>
<td>11/9</td>
<td>G4 Encephalopathy, G3 Rash</td>
</tr>
<tr>
<td>FOL + VAR 200mg/BID</td>
<td>6/6</td>
<td>G3 Encephalopathy</td>
</tr>
</tbody>
</table>

Grade 3/4 AEs (occurring ≥ 5%): neutropenia (5 17%), fatigue (3 10%), transaminitis (2%), diarrhoea (2%), febrile neutropenia (2%), transient metabolic encephalopathy (2%). 28 pts evaluable for response, 3 (11%) had PR and 16 (57%) SD. Disease control rate (PR + SD) for 12wks was 13 (46%). 5 (18%) had long PFS (223-645 days), comprising a gallbladder and CRC (both HER2-overexpressing, prior platinum), CC, bladder and CRC (prior OX and cetuximab). PK analysis did not show VAR accumulation. Plasma free cell DNA and HER2 pathway inhibition results will be presented later.

Conclusions: MTD for VAR with COX and FOL was 300mg/BID. Durable efficacy was seen in biliary cancers and CRC. ASLAN pharmacokinetics and the Singapore National Medical Research Council supported this study.

Clinical trial identification: NCT02435927.

Legal entity responsible for the study: National Cancer Centre, Singapore.

Funding: Asian Pharmaceuticals.

Disclosure: M. Ng. Member: Asian Pharmaceuticals advisory board; Speaker and research funding. Industry associated funding. All other authors have declared no conflicts of interest.

Population pharmacokinetic analyses for talazoparib (TALA) in cancer patients

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Background: This analysis described the population pharmacokinetics (popPK) of TALA in cancer patients to identify significant covariates, evaluate the PK comparability of 4 x 0.25 mg capsules and 1 x 1 mg capsule as a 1 mg dose, and provide individual PK predictions for PK/pharmacodynamic analysis.

Methods: The data used for the analysis included 6207 PK observations from 490 patients treated with TALA in 4 studies (PRP-001, PRP-002, ABRAZO, and EMBRACA); the detailed PK data will be disclosed in the poster. TALA concentration-time data were analyzed by using a nonlinear mixed-effects modeling approach with NONMEM. Inclusion of covariates was conducted by visual inspection of ETAs vs covariates of interest followed by statistical test (stepwise covariate modeling).

Results: A 2-compartment model with 1st-order absorption best described the PK of TALA. The estimated population-typical value for CL/F was 6.37 L/h, apparent volume of central compartment (Vc/F) 162 L, and absorption rate constant (ka) 0.121 h⁻¹. While fixed and formulation were significant covariates on ka, they had no impact on bioavailability (F). Coadministration with strong P-gp inhibitors increased the relative bioavailability by 44.7%. Baseline creatinine clearance was significant for CL/F with a 14.4% and 37.1% decrease in CL/F for patients with mild and moderate renal impairment, respectively. Asian (23.7% higher CL/F), age (on CL/F), and baseline body weight (BWt) (on Vc/F) are significant covariates but not considered clinically relevant. Other covariates tested (sex, liver enzymes, acid-reducing agents) were not significant on relevant PK parameters.

Conclusions: The population PK model adequately described the observed PK data of TALA. Results suggest that no dose adjustment is necessary based on a patient’s age, BWt, race, or sex for patients with mild renal or hepatic impairment or for patients taking acid-reducing agents. TALA can be taken without regard of food. The PK of 1 x 1 mg capsule and 4 x 0.25 mg capsules as 1 mg dose was comparable. The dose of TALA should be reduced to 0.875 mg for patients taking strong P-gp inhibitors or for patients with moderate renal impairment.

Clinical trial identification: NCT01945775, NCT02034816, NCT01286987, NCT01399840.

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Table 43P

<table>
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<tr>
<th>Positive cohorts</th>
<th>Pts analyzed</th>
<th>CR/PR at 2 mo</th>
<th>ORR % (95% CI)</th>
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<td>ALCL ALK tlc</td>
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<td>12</td>
<td>54 (34-75)</td>
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<tr>
<td>NSCLC MET amp</td>
<td>25 37 26*</td>
<td>7 20 5**</td>
<td>28 (10 - 46) 54 (38 - 70)</td>
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<tr>
<td>Esogastric MET amp</td>
<td>9 3</td>
<td>3</td>
<td>38 (2-76)</td>
</tr>
<tr>
<td>IMT ALK tlc / ROS1 tlc</td>
<td>8 3</td>
<td>3</td>
<td>38 (2-76)</td>
</tr>
</tbody>
</table>

*including 4 pts wIth MET mut on other exon than exon 14

**pts with MET mut exon 14 19S ge≥23 adverse events (AEs) or SAEs were reported in 83/237 pts. Grade 3 ≥3 AEs were: ALT increased (6%), neutropenia (5%) and lymphopenia (5%)

Conclusions: Cab displayed a wide antitumor activity in several MET, ALK and ROS1 + malign. Equal and safe access across France to molecular testing and targeted therapies outside their approved indication is feasible.

Clinical trial identification: NCT02349811

Legal entity responsible for the study: UNICANCER

Funding: ARC Foundation Inca Pfizer.

Disclosure: G. Vassal: Travel, accommodations, expenses. BMS. J-Y. Blay: Advisory Board: Roche, Lilly, Ignyta, Decipheira, Novartis, Bayer. BMS. Corporate-sponsored research: Roche, Lilly, Ignyta, Decipheira, Novartis, Bayer, Novartis, GSK, AstraZeneca. MSD. Other substantive relationships: Surveillance committee of Innate Pharma. M. Perol: Advisory board: Pfizer. P. Brice: Advisory board. Takeda France. Corporate-sponsored research: Takeda Millenium, BMS, MSD, D. Moro-Sibilot: Speaker or advisory board: Eli Lilly, MSD, Roche, Novartis, BMS, Astra Zeneca. Takeda, Boehinger Ingelheim. All other authors have declared no conflicts of interest.

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Biomarker-driven access to crizotinib in ALK, MET or ROS1 positive (+) malignancies in adults and children: The French National Acé program


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Background: Crizotinib (cab) was registered for ALK + NSCLC in 2013 and recently for ROS1 + stage IV NSCLC. Cbz targets (ALK, MET, ROS1) are also altered (translocation [tcl], amplification [amp], mutation [mut]) in a wide range of malignancies (malg.) in adults and children. To generate high evidence-based knowledge and to prevent off-label use, the French National Cancer Institute (INCa) launched the Acé Program: equal access to tumor molecular diagnosis including an exploratory phase II trial.

Methods: Biomarker testing was proposed to patients (pts) ≥ 1 year old (yo) with an advanced disease among more than 15 malg. known to harbor a cbz target alteration. If not eligible for any other trial, pts may enter one of the 22 cohorts defined by the type of tumor and target. Tumor response was evaluated every 2 months (mo) using RECIST v1.1. The primary endpoint is the objective response rate (ORR) at 2 mo (complete + partial response). A two-stage Simon design is applied to each cohort.

Results: From 08/2013 to 03/2018, 13179 pts from 186 centers have entered the bio-marketer program. Tumor alterations found in pts were: ALK tlc, mut, amp in 14/2070, 8.313/10, 18/1586; MET amp: (26 copies/diploid genome) in 39/7952 [251/4171 NSCLC, 60/1232 glioblastomas, 26/939 colon, 35/770 esogastric, 7/640 ovarian cancers], MET mut in 102/2836; ROS1 tlc in 82/4755 [NSCLC, cholangiocarcinoma, inflammatory myofibroblastic tumor (IMT)]. Overall, 237 pts (median age, 57 [1–92]) received cbz (adult 250 mg bid, child 280 mg/m² bid).

Conclusions: Cab displayed a wide antitumor activity in several MET, ALK and ROS1 + malign. Equal and safe access across France to molecular testing and targeted therapies outside their approved indication is feasible.

Clinical trial identification: NCT02349811

Legal entity responsible for the study: UNICANCER

Funding: ARC Foundation Inca Pfizer.

Disclosure: G. Vassal: Travel, accommodations, expenses. BMS. J-Y. Blay: Advisory Board: Roche, Lilly, Ignyta, Decipheira, Novartis, Bayer. BMS. Corporate-sponsored research: Roche, Lilly, Ignyta, Decipheira, Novartis, Bayer, Novartis, GSK, AstraZeneca. MSD. Other substantive relationships: Surveillance committee of Innate Pharma. M. Perol: Advisory board: Pfizer. P. Brice: Advisory board. Takeda France. Corporate-sponsored research: Takeda Millenium, BMS, MSD, D. Moro-Sibilot: Speaker or advisory board: Eli Lilly, MSD, Roche, Novartis, BMS, Astra Zeneca, Takeda, Boehinger Ingelheim. All other authors have declared no conflicts of interest.

433P

Preliminary results of PROCLAIM-CX-072: The first-in-human, dose-finding trial of PD-L1 probody therapeutic CX-072 as monotherapy in patients (pts) with advanced solid tumors


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Background: Antibodies (AbS) against programmed cell death ligand-1 (PD-L1) have improved survival in many types of cancer when used as monotherapy. However, anti-PD-L1 agents can be associated with high-grade immune-related adverse events (irAEs), particularly when used in combination with other anticancer agents. CX-072 is an anti-PD-L1 ProbodyTM (Pb-Tx) designed to be preferentially activated by proteases in the tumor microenvironment and not in healthy tissue. Preclinically, Pb-Tx exhibited anticancer activity of the parent Ab with reduced toxicities in models of autoimmunity.

Methods: In parts A and A2 of the ongoing phase 1/2a Probody Clinical Assessment In Man (PROCLAIM)-CX-072 study (NCT03813493), CX-072 monotherapy is evaluated in a dose-escalation cohort of pts with advanced, heavily pretreated solid tumors. Part A2 required PD-L1-positive tumors and paired biopsies. Eligible pts were PD-1, PD-L1, and CTLA-4 inhibitor naive, with immunotherapy (IUT) unavailable as a standard of care. CX-072 is given every 14 days in cohorts of intravenous doses ranging from 0.03-50 mg/kg.

Legal entity responsible for the study: Pfizer, Inc.

Disclosure: Pfizer, Inc.

Funding: Pfizer, Inc.

Results: As of April 20, 2018, part A/A2 had enrolled 37 pts. Pts had a median (range) of 3 (1-15) prior anticancer treatments. 14 (37.8%) pts are still on treatment at time of data cut. Median (range) treatment on time was 2.1 months (1-10). One DLT was observed (grade 3 febrile neutropenia, 3 mg/kg), MTX was not reached. Grade 3-4 treatment-related events were observed in 10 (40.0%) pts. irAEs with reversible 3 grade events occurred in 3 patients: thrombocytopenia, amonitrasferase increases, and dyspnea. Two subjects discontinued CX-072 due to AEs. Across all dose levels, best response based on investigators’ assessment was 23 evaluable pts included 2 partial responses (thyromegaly, 3 mg/kg, TNBC, 10 mg/kg), 10 stable disease, and 11 progressive disease.

Conclusions: Preliminary data suggest that CX-072 demonstrates the characteristics of an antibody prodrug with antitumor activity and an acceptable safety profile in heavily pretreated pts with IMT-naïve solid tumors. These data warrant further exploration of CX-072 as monotherapy and in combination with other anti-cancer agents.

Clinical trial identification: NCT03013491.

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

Funding: CytomX Therapeutics, Inc.

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Preliminary results of the first-in-human, dose-finding PROCLAIM-CX-072 trial evaluating the PD-L1 probody therapeutic CX-072 in combination with ipilimumab (ipii) in patients (pts) with advanced solid tumors


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Background: Combination treatment with PD-1 + CTLA-4 checkpoint inhibitors shows improvement in breadth, depth, and durability of response, coupled with a disproportionate increase in immune-related adverse events (irAEs). CX-072, a Probody™ therapeutic (Pb-Tx) directed against PD-L1, is designed to be preferentially activated by tumor-associated proteases and not in healthy tissue. Preclinically, anti-PD-1 Pb-Tx + anti-CTLA-4 Pb-Tx showed comparable efficacy with improved safety compared to the non-Pb-Tx combination. This dose-escalation cohort examines safety and tolerability of CX-072 (anti-PD-L1 Pb-Tx) + the CTLA-4 inhibitor ipii in pts with advanced solid tumors.

Methods: In this ongoing phase 1/2 study (NCT03013491), PD-1, PD-L1, and CTLA-4 inhibitor-naïve pts receive combination CX-072 + ipii (part B1). Planned doses of CX-072 (0.3, 1, 3, or 10 mg/kg) are administered in combination with ipii (3, 6, or 10 mg/kg) every 21 days for 4 cycles, followed by CX-072 monotherapy every 14 days.

Results: As of April 20, 2018, part B1 enrolled 16 pts. None of 16 pts reached the MTD. 2 pts were still on treatment at time of data cut. Median number (range) of CX-072 (0.3, 1, 3, or 10 mg/kg) and ipii (3 mg/kg) doses were 3 (1-20) and 3 (1-4), respectively. All cohorts through 10 mg/kg CX-072 (dose selected for monotherapy cohort expansion) are now enrolled without reaching the MTD. 1 DLT (grade 3 dyspnea, 0.3 mg/kg CX-072 + ipii) occurred. Grade 3 treatment-related-related (TR) irAEs occurred in 2 pts (12.5%); colitis and dyspnea/pneumonitis). No subject discontinued due to TR irAEs. Best response in 10 evaluable pts included 1 complete response (anal SCC, 0.3 mg/kg CX-072 + ipii), 2 partial responses (non-seminal testis tumor, 1 mg/kg CX-072 + ipii; small bowel, 3 mg/kg CX-072 + ipii), 1 stable disease, and 6 progressive disease.

Conclusions: Despite small pt numbers and limited follow up, early data suggest manageable safety profiles at all doses and antitumor activity with CX-072 + ipii in tumor types not approved for checkpoint inhibitors. The study is ongoing and escalation of ipii to 10 mg/kg is pending.

Clinical trial identification: NCT03013491.

Editorial acknowledgement: Editorial support was provided by Andrew Occiano (CytomX Therapeutics, Inc).

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

Funding: CytomX Therapeutics, Inc.

Disclosure: R.E. Sanborn: Research funding/grant: Merck; Investigator initiated Study: BMS, MedImmune; Institutional research support, honoraria: AstraZeneca; Advisory board: AstraZeneca, Seattle Genetics, Takeda, Genentech, Abbvie, Celldex; Travel, accommodations, investigator meeting: Janssen. E.G.E. de Vries: Research grant: Amgen, Genentech, Roche, Chugai, Synthex, CytomX, Nordic Nanovector, Regeneron, G1 Therapeutics, AstraZeneca, Radius Health; Consulting (institution): Pfizer. Sanofi; all other authors have declared no conflicts of interest.

437P

PT-112: A novel well-tolerated novel immunogenic cell death (ICD) inducer with activity in advanced solid tumors


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Background: PT-112, a novel platinum pyrophosphatase agent under development in solid tumors and hematologic malignancies, is a potent inducer of damage associated molecular patterns (DAMPs) characteristic of ICD. It also affects G1/S cell cycle transition independent of DNA damage or repair pathways. Here we present a clinical update and analysis of single-agent activity in heavily pre-treated pts.

Methods: We treated 62 pts in an all-comer phase 1 dose escalation study. PT-112 was given IV for 1hr on days 1,8,15 (28 cycles) at dose levels 12-420 mg/m².

Results: All dose levels completed were deemed safe, with dose-linear pharmacokinetics, and MTD was not reached. Fatigue was the most common side effect. No significant acute neurotoxicity was reported in 533 infusions. Grade 1-2 peripheral neuropathy was seen in 8/62 pts (13%), and Grade 3 in 2 pts (3%) with cumulative doses of 3.1 and 4.3 g/m². Neutropenia (6 pts) and thrombocytopenia (8 pts) were limited. No infections or bleeding. Median prior line of therapy = 5. Tumor control, metabolic and biomarker responses were observed at doses at/ above 125 mg/m², with PSA reduction in 4/ 8 pts, and a non small cell lung cancer pt previously unsensitive to anti-PD-1 immunotherapy achieved a 6+ month RECIST PR at 250 mg/m² and complete PET response in liver / bone sites. A small cell lung pt who rapidly progressed on CTLA-4 + PD-1 immunotherapy achieved PR at 360 mg/m², progression free at 7.5 months. Marked tumor reduction at 360 mg/m² is ongoing after 6 mos. in a malignant thymoma pt with bulky thoracic disease. Time to response was 5-8 wks in all 3 pts. PFS at 6 mos. was reached in 8/ 46 evaluable pts at/ above 125 mg/m² (17.4%). The ORR in 28 evaluable pts at/ above 250 mg/m² was 10.7%. At the provisional RP2D, now under confirmation (360 mg/m², 2 of 3 pts experienced durable tumor shrinkage.

Conclusions: PT-112 is a novel ICD inducing agent that is safe and well tolerated. Single-agent activity occurred in heavily pre-treated pts. Neither acute neurotoxicity nor kidney damage occurred. Fatigue was the most common side effect. Beneficial activity was observed at a range of doses, indicative of a broad therapeutic index, lack of cross-resistance with standard agents and feasibility for combinations.


Legal entity responsible for the study: Phosphatase Therapeutics LLC.

Funding: Phosphatase Therapeutics LLC.

Disclosure: D.D. Kang: Member of the scientific advisory board: Phosphatase Therapeutics. T.D. Armes, J.M. Jimeno: Employee and part owner: Phosphatase Therapeutics. All other authors have declared no conflicts of interest.
Background: ABBV-181 is a humanized, recombinant, IgG1 monoclonal antibody targeting programmed cell death 1 (PD-1), incorporating an Fc mutation to limit FcgR-mediated effector function. Here we present preliminary ABBV-181 monotherapy data received ABBV-181 to progression at 1, 3, or 10 mg/kg IV Q2W (3 + 3 dose finding phase). Following dose finding, multi-histology, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC) cohorts opened. Dose limiting toxicities (DLTs) were assessed on days 1-28 of dose finding focused on immune mediated (DM) events, hemolysis, and cytopenia. Response was assessed Q2W per response evaluation criteria in solid tumors (RECIST v1.1) and immune related RECIST. Results: As of January 15, 2018, 53 pts were treated with ABBV-181: 25 in dose finding, 17, 6, and 5 in multi-histology, HNSCC and NSCLC cohorts, respectively. Median age was 61 (range 17-86) years, 41% male, most frequent diagnoses in dose finding and multi-histology cohorts were lung, breast, and cervical carcinoma. Median days on study were 34 (range 1-379), 42 (79%) pts had ≥ 1 adverse event (AE), 22 pts (42%) had ≥ 3 AEs and 8 (15%) pts had IM AEs. The most frequent AEs of any grade were: fatigue (18 pts), constipation and vomiting (9 pts each). No DLTs were reported. ABBV-181 was discontinued in 33 (62%) pts, 27 for progression and 1 each for AEs of diabetic ketoacidosis, pneumonia, and hemolysis. Kaplan-Meier estimates of PFS and OS were 20% and 40%, respectively. The most frequent AEs of any grade were: fatigue (18 pts), constipation and vomiting (9 pts each). No DLTs were reported. ABBV-181 was discontinued in 33 (62%) pts, 27 for progression and 1 each for AEs of diabetic ketoacidosis, pneumonia, and hemolysis. Kaplan-Meier estimates of PFS and OS were 20% and 40%, respectively.

Conclusions: ABBV-181 monotherapy demonstrates target engagement and encouraging efficacy without unexpected safety signals. PK and pharmacodynamic data from dose finding support flat doses of 250 mg/week, 375 mg/mq/week or 500 mg/Q2W for expansion. Enrollment in the expansion cohorts continues.

Clinical trial identification: NCT03000257.

Legal entity responsible for the study: AbbVie Inc.

Disclosure: P.A. Cassier: Honoraria: Novartis, Roche-Genentech, Blueprint Medicines, Avena, Institution research funding: Novartis, Roche/Genentech, Lilly, Blueprint Medicines, Genentech, AstraZeneca; C. Forloni: Consultant or institutional research support: AbbVie; M.M.E. Tanner: Employment: AbbVie; A. Parikh: A. Reddy: G. Vosganian: Employee and may own stock: AbbVie; W.A. Tolcher: Consultant: AbbVie. All other authors have declared no conflicts of interest.

ABBV-181 is a humanized, recombinant, IgG1 monoclonal antibody targeting programmed cell death 1 (PD-1), incorporating an Fc mutation to limit FcgR-mediated effector function. Here we present preliminary ABBV-181 monotherapy data received ABBV-181 to progression at 1, 3, or 10 mg/kg IV Q2W (3 + 3 dose finding phase). Following dose finding, multi-histology, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC) cohorts opened. Dose limiting toxicities (DLTs) were assessed on days 1-28 of dose finding focused on immune mediated (DM) events, hemolysis, and cytopenia. Response was assessed Q2W per response evaluation criteria in solid tumors (RECIST v1.1) and immune related RECIST. Results: As of January 15, 2018, 53 pts were treated with ABBV-181: 25 in dose finding, 17, 6, and 5 in multi-histology, HNSCC and NSCLC cohorts, respectively. Median age was 61 (range 17-86) years, 41% male, most frequent diagnoses in dose finding and multi-histology cohorts were lung, breast, and cervical carcinoma. Median days on study were 34 (range 1-379), 42 (79%) pts had ≥ 1 adverse event (AE), 22 pts (42%) had ≥ 3 AEs and 8 (15%) pts had IM AEs. The most frequent AEs of any grade were: fatigue (18 pts), constipation and vomiting (9 pts each). No DLTs were reported. ABBV-181 was discontinued in 33 (62%) pts, 27 for progression and 1 each for AEs of diabetic ketoacidosis, pneumonia, and hemolysis. Kaplan-Meier estimates of PFS and OS were 20% and 40%, respectively. The most frequent AEs of any grade were: fatigue (18 pts), constipation and vomiting (9 pts each). No DLTs were reported. ABBV-181 was discontinued in 33 (62%) pts, 27 for progression and 1 each for AEs of diabetic ketoacidosis, pneumonia, and hemolysis. Kaplan-Meier estimates of PFS and OS were 20% and 40%, respectively.

Conclusions: ABBV-181 monotherapy demonstrates target engagement and encouraging efficacy without unexpected safety signals. PK and pharmacodynamic data from dose finding support flat doses of 250 mg/week, 375 mg/mq/week or 500 mg/Q2W for expansion. Enrollment in the expansion cohorts continues.

Clinical trial identification: NCT03000257.

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Disclosure: P.A. Cassier: Honoraria: Novartis, Roche-Genentech, Blueprint Medicines, Avena, Institution research funding: Novartis, Roche/Genentech, Lilly, Blueprint Medicines, Genentech, AstraZeneca; C. Forloni: Consultant or institutional research support: AbbVie; M.M.E. Tanner: Employment: AbbVie; A. Parikh: A. Reddy: G. Vosganian: Employee and may own stock: AbbVie; W.A. Tolcher: Consultant: AbbVie. All other authors have declared no conflicts of interest.
OT-1096: A first-in-class immunoactivating small molecule that targets the thioredoxin reductase/thioredoxin axis causes strong tumor growth inhibition by downregulating intratumoral Tregs in a humanized TNBC-PDX model


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Background: Triple-negative breast cancer is an aggressive subtype associated with poor prognosis and limited treatment options, and new effective medicines are needed. We have developed a novel class of SecTrAP and shown in several models that leads to a decrease in tumor growth through the thioredoxin reductase/thioredoxin axis. Recent data from a combination study with pembrolizumab showed that OT-1096 can increase the efficacy of pembrolizumab and delay tumor growth in preclinical models of TNBC.

Methods: NSG mice, humanized with CD34+ stem cells from 3 different human donors were engrafted with TNBC-derived d4 tumors. The mice were treated with OT-1096 at 10mg/kg (IV) or 30mg/kg (IV) and compared to treatment with pembrolizumab alone and combination of pembrolizumab and OT-1096. Tumor volume was measured using calipers for 28 days and xenografts were analyzed for PKC to determine immune cell infiltration at day 41.

Results: OT-1096 showed statistically significant tumor growth inhibition (TGI: 63%) when compared to treatments arms with all three donors. OT-1096 also presented improved tumor growth control compared to pembrolizumab. EAGs analysis of xenografts showed OT-1096-treated tumors to have a lower fraction of Tregs within the TIL population as compared to controls. OT-1096 treatment was both safe and well tolerated.

Conclusions: OT-1096 shows promising results in a humanized mouse TNBC PDX model with improved tumor growth control compared to pembrolizumab. The results suggest that OT-1096 possesses both redox system modulation and beneficial immunomodulatory potential, and warrants further investigations of OT-1096 in TNBC and other malignancies.

Legal entity responsible for the study: Oblique Therapeutics AB

Funding: Oblique Therapeutics AB


443TP

First-in-human trial design for W0101: A first-in-class antibody-drug conjugate targeting IGF-1R and identification of the target patient population

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Background: IGF-1R is over-expressed by neoplastic cells in many human cancers, associated with tumorigenesis, metastasis and treatment resistance. W0101 is a First-in-Class Antibody Drug Conjugate (ADC), designed for treatment of patients with tumors overexpressing membrane IGF-1R. Preclinically, internalization and anti-tumor activity of W0101 was shown in models expressing membrane IGF-1R (AACR 2018). To select potential responders to W0101 we developed a prototype immuno-histochemistry assay using a proprietary monoclonal antibody detecting a specific epitope on human IGF-1R, different from that of W0101. Using this test, we evaluated the membrane expression of IGF-1R in samples of squamous non-small-cell lung cancer (squNSCLC), head-and-neck cancer and ER+ HER2- invasive breast cancer. This assay is currently used for retrospective assessment of patients included in the current trial and other studies with another of Nucana’s compounds. Here, we present the design of a phase I/II international, multicentre, open label dose escalation and dose expansion study of intravenous infusion of W0101 in patients with advanced or metastatic solid tumors.

Trial design: This phase I/Ii consists of 2 parts: an initial dose escalation phase (I) followed by an expansion cohort (phase II). In the dose escalation phase, 2 schedules of administration in 2 successive cohorts of patients will be assessed: Q2W schedule (A1) and a Q4W or Q6W schedule (A2). The initial dose and the schedule of administration in cohort A2 will be determined using all safety and pharmacokinetics data generated in cohort A1 and using a PR/PD model. The phase I will allow to determine the Maximum Tolerated Dose and Schedule (MTDS) and to characterize dose-limiting toxicities (DLTs). The dose-toxicity relationships established via a Bayesian Logistic Regression Model will support the dose escalation process and will be used to assess the MTDS and recommended doses for expansion. Following completion of the dose escalation phase, the expansion phase will enroll up to 4 cohorts of patients prospectively tested for overexpression of IGF-1R to assess preliminary efficacy. A Simon design will be used for futility analysis.

Clinical trial identification: NCT03316638

Legal entity responsible for the study: Pierre Fabre Medicament Represented by Institut de Recherche Pierre Fabre

Funding: Has not received any funding.


In conclusion, OT-1096 was found to be safe and effective in preclinical models of TNBC, showing promising results in terms of tumor growth inhibition.

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Phase III study investigating safety, tolerability, pharmacokinetics, and preliminary antitumor activity of anti-PD-L1 monoclonal antibody BGB-A333 alone and in combination with anti-PD-1 monoclonal antibody tislelizumab in patients with advanced solid tumors

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Background: PD-1 and its ligand, PD-L1, play critical roles in immune modulation of tumor progression. Tislelizumab is a humanized IgG4 monoclonal antibody against PD-1. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors at the recommended phase 2 dose (RP2D) of 200 mg administered every 3 weeks (QW). BGB-A333 is a humanized IgG1 monoclonal antibody against PD-L1 that increased functional activities of human T cells in in vitro studies, and showed antitumor activity in various cancer xenograft models. BGB-A333 blocks the interaction between PD-L1 and CD80 (B7-1), which in turn releases inhibitory signals to T cells, enhances T-cell expansion, and prevents T-cell anergy induction. Therefore, the combination of anti-PD-1 and anti-PD-L1 can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments.

Trial design: This open-label study (NCT03379259) consists of two phases, each phase consisting of two parts. Phase 1 will investigate the safety and tolerability of the BGB-A333-alone and in combination with tislelizumab. Phase 1A (BGB-A333 dose escalation) will follow a 3+3 design to establish the RP2D of BGB-A333. Phase 1B (combination dose confirmation) explores the safety and tolerability of IV BGB-A333 (dose determined from dose escalation) in combination with IV tislelizumab (200 mg QW). Phase 2 will evaluate the antitumor activity of BGB-A333-alone and in combination with tislelizumab. Phase 2A (BGB-A333 dose expansion) has two cohorts: non-small cell lung cancer and urothelial carcinoma. Phase 2B (combination dose expansion) will enroll patients with specific tumor types, which will be chosen from phase 2A and other studies. The primary endpoint of the phase 2 study is overall response rate. A total of 156 patients are estimated to be enrolled, as of 11 August 2018, 9 patients have been enrolled.

Clinical trial identification: NCT03379259.

Editorial acknowledgement: Medical writing and editorial assistance provided by Aarati Rai, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeGenne, Ltd.

Funding: BeGenne, Ltd.

Disclosure: J. Desai: Honoraria, consulting/advisory role, or research funding: Amgen, GlaxoSmithKline, Novartis, Bioinnos, Lilly, Plexpodix, or Roche. B. Markman: Consulting fees and travel/accommodations expenses: Novartis and BeGenne. J. Hou, D. Zeng: Employee: BeGenne. T. Mienawiy: Honoraria, travel/accommodations expenses, consulting fees: AstraZeneca, Roche/Genentech and MedImmune; Research funding: Bristol-Myers Squibb, Incyte, BeGenne, AstraZeneca/MedImmune, Regeneron, Bayer, Merck Serono, Roche/Genentech. All other authors have declared no conflicts of interest.

Comprehensive profiling and molecularly guided therapy (MGT) for carcinomas of unknown primary (CUP): CUPISCO: A phase II, randomised, multicentre study comparing targeted therapy or immunotherapy with standard platinum-based chemotherapy


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Background: CUPs are heterogeneous tumours of diverse origins that often have poor prognosis and high treatment needs. The heterogeneity makes the conduct of classical trials difficult. The CUPISCO study aims to compare the overall efficacy and safety of MGT with standard platinum-based chemotherapy for patients (pts) with CUP.

Trial design: Eligible pts have a histological diagnosis of adenocarcinoma of unknown primary tumour according to ESMO diagnostic guidelines. The CUPISCO study aims to compare the overall efficacy and safety of IV BGB-A333 (200 mg QW) with or without IV tislelizumab (200 mg QW) with or without BeGenne's monoclonal antibody 6SD2, in the treatment of patients with advanced solid tumors.
The cancer molecular screening and therapeutics program (MoST): A multiple-molecular screening platform with multiple, parallel, signal-seeking therapeutic substudies


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Background: Innovative approaches are needed to translate molecular opportunities into clinical care. MoST tests a novel paradigm for evaluating of biomarker-driven treatments (tx) for patients (pts) with advanced cancer, with a particular focus on rare or neglected cancers.

Trial design: Tx-refractory pts (N = 1000) undergo molecular screening using archival tumour tissue. Results are reviewed by the Molecular Tumor Board (MTB) to identify actionable variants and eligibility for substudies. A master protocol allows expedited addition of ≥12 open-label, phase Ib/IIa, single-arm substudies, with 16 pts per modality deemed reasonable for signal-seeking purposes. The primary objectives are to identify potential clinical activity for biomarker-driven tx, biomarkers that predict for antitumour immune response. Inhibition of vascular endothelial growth factor (VEGF) has been reported to enhance PARP inhibitor activity. Combinations of immune checkpoint inhibitors and bevacizumab have shown promising results in other tumour types. Here, the efficacy and safety of bevacizumab (anti-VEGF-A antibody) is investigated in combination with olaparib + durvalumab in platinum-sensitive relapsed (PBR) non-gBRCAm ovarian cancer (OC) pts (NCT02734894).

Trial design: Initially, 148 pts were enrolled across several tumour types (small-cell lung cancer, gastric cancer, germline BRCA-mutated [gBRCAm] breast cancer, or PBR gBRCAm OC). Pts received olaparib 300 mg po bid for 4-wk run-in, followed by olaparib 300 mg po bid and durvalumab 15 mg IV q4w. Primary endpoints were disease control rate (DCR) at 12 wks, safety and tolerability. Secondary endpoints: pharmacokinetics (PK), DCR at 28 wks, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Tumours were assessed at baseline, 4 wks and every 8 wks thereafter. Enrolment was completed for these initial cohorts, and new PSC OC cohorts (Table) have been added, based on the preliminary results. These cohorts have no olaparib run-in, tumour assessments are performed at baseline and every 8 wks thereafter, bevacizumab 10 mg/kg is given q2 weeks, and pts with 1–2 prior chemotherapeutic lines are allowed.

Other endpoints: Safety and tolerability, PK, DCR at 56 wks, ORR, PFS, and OS. Biomarker endpoints: Analysis of tumour-infiltrating lymphocytes and PD-L1 expression.

Clinical trial identification: NCT02734894

Legal entity responsible for the study: AstraZeneca.

Funding: AstraZeneca.


Table: 447TP New MEDIOLI cohorts

<table>
<thead>
<tr>
<th>OC cohort name</th>
<th>Drugs</th>
<th>Population</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansion (N = 80)</td>
<td>Olaparib+Durvalumab</td>
<td>gBRCAm</td>
<td>ORR</td>
</tr>
<tr>
<td>Doublet (N = 30)</td>
<td>Olaparib+Durvalumab</td>
<td>non-gBRCAm</td>
<td>DCR 24 wks</td>
</tr>
<tr>
<td>Triplet (N = 30)</td>
<td>Olaparib+Durvalumab+ Bevacizumab</td>
<td>non-gBRCAm</td>
<td>DCR 24 wks</td>
</tr>
</tbody>
</table>

**References**


2. Massachusetts General Hospital, Boston, MA, USA; Northen Institute for Cancer Care, Newcastle Upon Tyne, UK; Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands; Seoul St Mary's Hospital, Catholic University of Korea, Seoul, Republic of Korea; Samsung Medical Center, Seoul, Republic of Korea; Caucasian University Hospital, Lausanne, Switzerland; Boston West of Scotland Cancer Centre, Glasgow, UK; NKI Tayside, Dundee, UK; The Royal Marsden Hospital NHS Foundation Trust, London, UK; Cancer Treatment Centers of America, Augusta University, Augusta, GA, USA; Sheba Medical Center, Ramat Gan, Israel; AstraZeneca, Cambridge, UK; AstraZeneca, Gothenburg, MD, USA; Hospital of the University of Pennsylvania, Philadelphia, PA, USA.
Background: Rare cancers have had a challenge in establishing standard therapies for patients compared to major cancers, due to the lack of basis for clinical studies and investigations. We started a biomarker driven basket/umbrella trial using a “master protocol”, called the MASTER KEY Project, which aims to find more efficient ways to evaluate treatments for rare cancers and to build a treatment development infrastructure by collaborating with industries. Similar studies including NCI-MATCH trial are ongoing; however, MASTER KEY Project is the first to be reported for such large scale trials that focuses only on rare cancers.

Trial design: The project consists of two main parts: the prospective registry study part and the multiple clinical trials (sub-study) part. Patients with advanced rare cancers (annual incidence less than 6 cases per 100,000 population)/cancers of unknown primary/rare pathological subtypes of major cancers, who have priorly been evaluated by a molecular diagnostic testing, such as a validated next generation sequencing assay, are enrolled into the registry study. The primary objective of the registry study is to collect consecutive data on biomarker, patient background, and prognosis to build a large-scale database highly reliable for use as historical control data in future clinical trials. In the sub-studies, drugs are provided by various industries, who are collaborators. Sub-studies are placed under a “master protocol”, allowing new sub-studies to be added at any time. Each sub-study is ordinarily a single arm study and will enroll 5-20 patients with the appropriate biomarker of interest, regardless of histopathologic tumor type. A biomarker-negative sub-study will also be available so that all patients have a chance to be enrolled in a sub-study. The project opened in May 2017. As of April 2018, more than 200 of a planned 100 patients/year have been enrolled in the project. There are three ongoing sub-studies. Two of them are biomarker related studies, which enroll patients harboring BRAF mutation and mismatch repair deficiency, respectively. In addition, three sub-studies are under planning and they will open by fall of 2018.

Clinical trial identification: UMIN000027552.

Legal entity responsible for the study: National Cancer Center Hospital.


Disclosure: All authors have declared no conflicts of interest.
ENDOCRINE TUMOURS

**450PD** Potential therapeutic targets in recurrent and metastatic parathyroid carcinomas revealed by next-generation sequencing

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**451P** Pharmacokinetic drug-drug interaction between mitotane and etoposide in the treatment of adrenocortical carcinoma

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**Background:** Association between mitotane and platinum-etoposide chemotherapy is the front-line treatment in metastatic adrenocortical carcinoma (ACC), although this regimen shows limited efficacy. Drug-drug interaction between mitotane—which is a strong pharmacokinetic inductor of CYP3A4 and BRCP—and etoposide—which is a substrate of CYP3A4 and BRCP—may contribute to chemoresistance in ACC. The aim of this study was to evaluate the pharmacokinetic interaction between mitotane and etoposide.

**Methods:** From December 2016 to October 2017, this observational study included 5 consecutive ACC patients treated with platinum-etoposide (120 to 150 mg/m² J1-J2-J3 at cycle 1) chemotherapy in referral center for rare adrenal diseases and oncology department of Cochin hospital, Paris. Plasma etoposide concentrations were measured using liquid chromatography at 0, 4 and 24h after each etoposide infusion. In the absence of dose-limiting toxicity, a dose escalation of etoposide was proposed from cycle 2.

**Results:** Patients received a median of 3 [2 to 6] chemotherapy cycles, in association with mitotane (4 patients, median mitotane plasma concentration of 14.2 mg/L) or after mitotane discontinuation (1 patient, plasma concentration 1 mg/L). Etoposide clearance was higher in association with mitotane (4.95 L/h [2.67 to 6.20]) than after discontinuation (2.53 L/h [2.02 to 2.79], Wilcoxon *p* = 0.014) or in a reference population not treated with mitotane (1.81 L/h).1 Etoposide dose escalation was performed in 4 patients treated with mitotane, resulting in 2 minor tumor response at 300mg/m² and 1 febrile neutropenia.

**Conclusions:** Drug-drug interaction between mitotane and etoposide may partly explain the low efficacy of platinum-etoposide chemotherapy in ACC. Given the elimination half-life of mitotane is extremely long (18-159 days), this observation suggests further a potential benefit of increasing etoposide dosage in patients receiving mitotane than stopping mitotane before chemotherapy initiation in ACC patients.

**Legal entity responsible for the study:** Blanchet Benoit and Jouinot Anne.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
GASTROINTESTINAL TUMOURS, COLORECTAL

4520 DPYD genotype-guided dose individualization of fluoropyrimidine therapy: A prospective safety and cost-analysis on DPYD variants DPYD*2A, c.2846A>T, c.1679T>G and c.1236G>A

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453PD 1st-line mFOLFOXIRI + panitumumab vs FOLFOXIRI treatment of RAS wt mCRC: A randomized phase II VOLFI trial of the AIO (KRK-0109)

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454PD Influence of treatment with prior bevacizumab: A combined analysis of individual patient data from ASPECTT and WJOG6510G trial which compared panitumumab versus cetuximab in patients with wild-type KRAS exon 2 metastatic colorectal cancer

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455PD NORDIC9: A randomized phase II trial comparing first-line palliative full-dose monotherapy (S-1) with reduced dose-combination therapy (SOx) in older and frail patients with metastatic colorectal cancer (mCRC)

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456PD Serial circulating tumor DNA analysis for detection of residual disease, assessment of adjuvant therapy efficacy and for early recurrence detection in colorectal cancer

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Kinase fusions in colorectal cancers: A unique biologic subset

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Causal modeling of CALGB/SWOG 80405 (Alliance) identifies primary (1') side-related angiogenic drivers of metastatic colorectal cancer (mCRC)

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**459PD** Long-term results of postoperative chemoradiation therapy with capecitabine and oxaliplatin versus capecitabine alone for locally advanced rectal cancer: A randomized, multicenter, phase III trial

N. Li 1, J. Jin 2, Y. Li 1, Y. Zhu 1, W. Wang 1, J. Wang 1, Y. Feng 1, L. Liu 1, S. Wang 1, Y. Song 1, T. Chu 1, Y. Tang 1, W. Liu 1, H. Ren 1, H. Fang 1

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**460PD** The value of chemotherapy in stage II colon cancer: Much less than we thought

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**461PD** Folfox and intra-arterial DEBIRI as front-line treatment in patients with non resectable colorectal cancer liver metastases (FFCD 1201 phase II trial)


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**Abstract**

**462PD Postoperative carcinoembryonic antigen (CEA) association with survival and oxaliplatin benefit in stage II colon cancer (CC): Post hoc analysis of the MOSAIC trial**


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**463P Real-world dosing of regorafenib (REG) in metastatic colorectal cancer (mCRC): Final results from the prospective, observational CORRELATE study**


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**Background:** REG 160 mg/day for 3 weeks on/1 week off is approved for the treatment of patients with treatment-refractory mCRC. This final analysis of the prospective, observational CORRELATE study describes REG real-world dosing in mCRC.

**Methods:** CORRELATE (NCT02042144) was conducted in 13 countries across Europe, Latin America, and Asia and enrolled patients with mCRC for whom the decision to treat with REG was made by the treating physician. The primary aim was to assess safety.

**Results:** Of 1037 patients, 57% started treatment at 160 mg, 30% at 120 mg, and 13% at < 80 mg. The mean and median percent of the approved dose was 79%. At baseline, median age was 65 years, most patients were ECOG performance status (PS) 0–1 (87%), and 56% had KRAS mutations; age and ECOG PS was similar between dose groups (160 vs 120 mg, Table). Dose reductions were more frequent in the 160 versus 120 mg group, while the proportion of patients having an interruption/delay or treatment modification was similar. Treatment modifications were most commonly due to treatment-emergent adverse events (TEAEs) (66%). Overall, most discontinuations (49%) were due to radiologic disease progression, whereas 19% were due to REG-related TEAEs. Overall, TEAEs of any grade occurred in 95% of patients, and were attributed to REG in 36%. The most common REG-related grade > 3 TEAEs were fatigue (9%), hand–foot skin reaction (7%), and hypertension (6%). Grade 5 TEAEs occurred in 17% of patients and were considered REG related in 16%. Median overall survival (OS) was 7.6 months (95% CI 7.1–8.2) and the estimated 1-year OS was 34%.

**Table: 463P**

<table>
<thead>
<tr>
<th>% Starting dose</th>
<th>% Starting dose</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>160 mg (N = 91)</td>
<td>120 mg (N = 315)</td>
<td>Total (N = 1037)</td>
</tr>
<tr>
<td>Median age*</td>
<td>64 (24–85)</td>
<td>65 (33–89)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>58/42</td>
<td>66/34</td>
</tr>
<tr>
<td>ECOG PS 0–1/2–4</td>
<td>89/4</td>
<td>85/9</td>
</tr>
<tr>
<td>Metastatic site at study entry, liver/lung</td>
<td>73/57</td>
<td>69/57</td>
</tr>
<tr>
<td>Median treatment duration†</td>
<td>2.6 (0.03–29.5)</td>
<td>2.4 (0.03–20.6)</td>
</tr>
<tr>
<td>Treatment modification</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>Treatment interruption/delay</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Treatment modification due to AEs</td>
<td>76</td>
<td>58</td>
</tr>
</tbody>
</table>

*years (range); †months (range)

**Conclusions:** In this real-world, observational study, the starting dose of REG for nearly half of patients was less than 160 mg/day. Common TEAEs were generally consistent with the known safety profile of REG in mCRC.

**Clinical trial identification:** NCT02042144.

**Editorial acknowledgement:** Editorial assistance in the preparation of this abstract was provided by Katrin Gudmundsdottir of SuccinctChoice Medical Communications (London, UK), with financial support from Bayer.

**Legal entity responsible for the study:** Bayer.

**Funding:** Bayer.

**Disclosure:** J.M. O’Connor: Advisory board attendance: Merck Serono, Bayer, Servier; Speaker’s bureau: Merck Serono, Bayer, Servier. M. Ducreux: Grants/research support:
Safety and efficacy of trifluridine/tipiracil (FTD/TPI) in metastatic colorectal cancer (mCRC) patients according to previous treatment with regorafenib in the international phase IIIb PRECONNECT study

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Background: The oral chemotherapy trifluridine/tipiracil (FTD/TPI) or TS-102 is approved for treatment of previously treated mCRC patients (pts) beyond the second line of therapy (L2). However, the safety and efficacy of FTD/TPI in mCRC pts according to previous treatment with regorafenib in a preliminary analysis of the phase IIIb PRECONNECT study (NCT0306394).

Methods: PRECONNECT is enrolling pts with histologically confirmed mCRC previously treated with regorafenib (n = 296) with regorafenib. Optimal treatment sequencing between the two at this stage is not established. Here, a descriptive post hoc sub-group analysis assessed safety and efficacy of FTD/TPI in mCRC pts according to previous treatment with regorafenib in a preliminary analysis of the phase 3b PRECONNECT study (NCT0306394).

Results: Patient subgroups pretreated with regorafenib were broadly similar, with a slight imbalance for RAS mutant status (61% vs 56%). The median OS and TTF were 8.1 months (95% CI 7.2-8.9) and 2.4 months (95% CI 2.1-2.8), respectively, the DCR was 21.6%. Both efficacy and safety of FTD/TPI in the clinical practice were comparable with clinical trials. The continuous use of FTD/TPI after PD by RECIST could contribute to longer survival; however, further investigation is warranted.

Conclusions: Both efficacy and safety of FTD/TPI in the clinical practice were comparable with clinical trials. The continuous use of FTD/TPI after PD by RECIST could contribute to longer survival; however, further investigation is warranted.

Editorial acknowledgement: The authors would like to thank Enago for the English language review.

Legal entity responsible for the study: Japanese Foundation for Multidisciplinary Treatment of Cancer.

Funding: Taiho Pharmaceutical Co., Ltd.

**Background:** Regorafenib (REG) significantly increases overall survival (OS) in previously treated mCRC patients. However, no prospective trial specific to elderly populations including geriatric parameter evaluation has evaluated the safety and efficacy of REG in its registered indication.

**Methods:** Multicenter one-arm phase II that enrolled pts > 70 years, ECOG performance status ≤ 2, with mCRC. REG was administered at 160 mg/day, and in patients with at least 6 months of OS, dose escalation to 160 mg was allowed. The primary endpoint was tumor control rate (tcr) at 2 months in the 35 evaluable pts. Tumor control rate at 2 months in the 35 evaluable pts was 45.0% (95% CI, 32.4-60.1). The median duration of REG treatment was 45.0 days (5 to 440). 8 patients were not evaluable for the primary endpoint. Tumor control rate at 2 months in the 35 evaluable pts was 31.4% (18.8-44.8). Among the 27 pts treated with REG ≥ 160 mg (91.8%) were < 80 yrs. In the 42 treated pts, median progression free survival (PFS) and OS were 2.2 (1.9-3.3) and 7.5 (5.5-14.6) months, respectively. Modification of the initial dose was performed in 54.3% of the 116 cycles delivered. A grade 3-4 adverse reaction was observed in 37 (88.1%) pts: nausea (45.2%), hand foot syndrome (21.4%), arterial hypertension (21.4%), and diarrhoea (7.1%). Treatment was stopped for toxicity without protocol adherence in 20 (55.3%) pts. Among them, 19 (95%) pts who received REG ≥ 160 mg (ELOC G1, 6 (50%) were over 80 years and 6 (50%) had abnormal baseline ADL. No toxic death was observed.

**Conclusions:** Treatment with REG in heavily pretreated elderly pts gives a tumor control rate of 45.0% (95% CI, 32.4-60.1). The median duration of REG treatment was 45.0 days (5 to 440). 8 patients were not evaluable for the primary endpoint. Tumor control rate at 2 months in the 35 evaluable pts was 31.4% (18.8-44.8). Among the 27 pts treated with REG ≥ 160 mg (91.8%) were < 80 yrs. In the 42 treated pts, median progression free survival (PFS) and OS were 2.2 (1.9-3.3) and 7.5 (5.5-14.6) months, respectively. Modification of the initial dose was performed in 54.3% of the 116 cycles delivered. A grade 3-4 adverse reaction was observed in 37 (88.1%) pts: nausea (45.2%), hand foot syndrome (21.4%), arterial hypertension (21.4%), and diarrhoea (7.1%). Treatment was stopped for toxicity without protocol adherence in 20 (55.3%) pts. Among them, 19 (95%) pts who received REG ≥ 160 mg (ELOC G1, 6 (50%) were over 80 years and 6 (50%) had abnormal baseline ADL. No toxic death was observed.

**Clinical trial identification:** EudraCT: 2015-002086-29.
tumours) anti-EGFR therapy. The aim of the present study was to analyse the outcomes of treatment with regorafenib in real-world clinical practice based on data from a national registry.

**Methods:** The CORECT registry (http://corect-registry.eu) is a non-interventional database of patients with colorectal cancer treated with targeted agents. The analysis included 451 evaluable patients treated with regorafenib for mCRC.

**Results:** The median age at diagnosis was 61.1 years. The primary tumor was in the left colon or rectum in 343 patients (76.1%), right colon in 81 patients (18.0%), and data on location were not available for 27 patients (6.0%). KRAS mutation was detected in 202 patients (44.8%) and NRAS mutation in 40 patients (8.9%). The median duration of treatment was 2.7 months (range 0.0-23.4 months). Partial response was seen in 12 patients (3.2%). Progression of the disease was reported in 170 patients (44.7%) and disease stabilisation for at least 6 weeks in 110 patients (28.9%). Progression-free and overall survival data are shown in the table. Improved outcomes were observed in patients with longer interval from diagnosis of mCRC and in those without liver metastases. Age, tumour sidedness, and RAS status were not associated with outcome of regorafenib therapy. The main cause of treatment discontinuation was disease progression (71.3%) followed by general deterioration in the absence of radiological progression in 93 patients (24.5%), and adverse events related to regorafenib in (4.2%).

**Conclusions:** Overall survival of patients treated with regorafenib in real-world clinical practice exceeded that achieved in randomised trials.

**Legal entity responsible for the study:** Katerina Kopeckova and Tomas Buchler.

**Funding:** The Institute of Biostatistics and Analysis, Faculty of Medicine, Masaryk University, Brno provided financial support for the CORECT registry from Bayer, Amgen, Merck and Roche. Supported by Grant AZV 15-26355A from the Czech Health Research Council.

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**Table: 468P Progression-free survival and overall survival of patients treated with regorafenib**

<table>
<thead>
<tr>
<th>Median (95% CI)</th>
<th>3-month survival (95% CI)</th>
<th>6-month survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td>3.5 months (3.2–3.7)</td>
<td>57.6% (52.5–62.4)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>9.3 months (7.9–10.7)</td>
<td>88.8% (85.2–91.5)</td>
</tr>
</tbody>
</table>

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**469P** The combination of TAS-102 and bevacizumab as the third line chemotherapy for metastatic colorectal cancer (TAS-CC3 Study)

**H. Kaniymaniyi**1, Y. Yoshida1, H. Yoshida2, C. Kosugi3, K. Ishibashi4, K. Ikuta5, T. Tajima6, A. Maruyama7, H. Kurokawa8, H. Sone9, K. Yoshimotod, A. Matsui1, S. Yamaguchi2, H. Ishida2, S. Hasegawa2, Y. Yamada3, K. Sakamoto1, K. Koda4

**Background:** TAS-102 improved overall survival of refractory colorectal cancer patients with median progression free survival (PFS) of 2.0 months (RECOURSE trial). Subsequently, the combination of TAS-102 and Bevacizumab has been shown to extend median PFS with 3.7 months (TAS-CC2 trial). However, this study included patients with 2nd line and 3rd line chemotherapy. Our study was planned exclusively for patients with median progression free survival of 3.7 months (C-TASK FORCE). However, this study included patients with median progression free survival of 2.0 months (RECOURSE trial).

**Methods:** This phase II study was conducted in investigator-initiated, open-label, single-arm, multicenter manner in Japan. Eligible patients were 20-80 years old, and had to have an Eastern Cooperative Oncology Group performance status of 0-1; had confirmed unresectable metastatic colorectal cancer (mCRC) with histologically diagnosed adenocarcinoma; were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin in the 1st and the 2nd line chemotherapy; and had no previous treatment with regorafenib. TAS-102 (35 mg/m²) was given orally twice daily on days 1–5 and 8–12 in a 4-weeks cycle, and bevacizumab (5 mg/kg) was administered by intravenous infusion for 30 minutes in every 2 weeks. The primary endpoint was progression free survival (PFS), and the secondary endpoints were time to treatment failure (TTF), response rate (RR), overall survival (OS), and safety.

**Results:** Between June 1, 2016, and August 31, 2017, 32 patients with mCRC were enrolled in this study. The median PFS was 4.5 months. Partial response was observed in 2 patients. The most common adverse events above grade 3 were neutropenia (15 patients) followed by thrombocytopenia (4 patients). Treatment-related serious adverse events were reported in one patient. There were no non-hematologic adverse events above grade 3. No treatment-related deaths occurred.

**Conclusions:** This is the first study which involves the combination of TAS-102 and Bevacizumab as the 3rd line chemotherapy in the setting beyond cytotoxic doublet, and showed to improve PFS for the patients with mCRC. This combination has a potential to be one of therapeutic options of the 3rd line chemotherapy for mCRC.

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**Legal entity responsible for the study:** TAS-CC3 Study Group.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**470P** Safety run-in evaluation of the phase I trial of trifuridine/tipiracil (FTD/TPI) in combination with oxaliplatin and a monoclonal antibody (bevacizumab or nivolumab) in patients (pts) with metastatic colorectal cancer (mCRC)


**Background:** The addition of the monoclonal antibody bevacizumab to chemotherapy has shown survival benefits in pts with mCRC. Another potential strategy is to combine chemotherapy with immunotherapies to enhance antitumor effect of the immune system. In vivo studies have shown an increase in anti-tumor activity when combining FTD/TPI with oxaliplatin or bevacizumab, and an increase in tumor immunogenicity after treatment with FTD/TPI and oxaliplatin, leading to a better tumor response to anti-PD-1 exposure.

**Methods:** Further to the dose-escalation part (24 pts), the recommended dose (RD) was defined as FTD/TPI 35 mg/m² bid, days 1–5, and oxaliplatin 85 mg/ m² (day 1). Safety data were collected during expansion part from 24 evaluable pts treated with the doublet at the RD with either nivolumab 3 mg/kg (n=6) or bevacizumab 5 mg/kg (n=6) administered at day 1. Pts were monitored for safety for the first 2 months of treatment before allowing further enrollment. Eligibility criteria included measurable disease, performance status (PS) 0–1, normal organ function, and progression after 1 prior anti-tumor therapy (excluding oxaliplatin).

**Results:** Baseline characteristics were median age of 67 years (range 52 to 75 years); PS 0/1 (3/9 pts), male/female (8/4 pts); and colon/rectum (5/7 pts). Drug-related adverse events (AEs) reported in ≥2 pts were neutropenia, diarrhoea, asthma, and anaemia; mainly (93%) grade 1-2. The most common grade 3 or 4 drug-related event was neutropenia. Grade 1 neurotoxicity attributed to oxaliplatin was observed in 2 pts. No immune-related AE due to nivolumab were reported. Best overall response included 2 partial responses after 2 months of treatment (1 pt in bevacizumab cohort, 1 MSI-H pt in nivolumab cohort). Pharmacokinetics parameters for FTD/TPI were aligned with historical data.

**Conclusions:** The safety data showed that the two triplets were well tolerated. Expansion enrollment is continuing in both cohorts to confirm preliminary activity in a larger number of patients.

**Clinical trial identification:** NCT02848443.

**Legal entity responsible for the study:** Instituto de Investigaciones Biomédicas de la Universidad de Granada (IIB-UGR).

**Funding:** In the framework of the Project: Instituto de Investigaciones Biomédicas de la Universidad de Granada (IIB-UGR).

471P A phase I study to determine the maximum tolerated dose of trifluridine/tipiracil and oxaliplatin in patients with refractory metastatic colorectal cancer: LUPIN study

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Background: The effectiveness of reintroduction of oxaliplatin for metastatic colorectal cancer (mCRC) refractory to both oxaliplatin and irinotecan was previously reported in a single arm, open-label phase II study (RE-OPEN, Suegara, 2015). We conducted a phase I study to determine the maximum tolerated dose (MTD) and the safety of oxaliplatin plus trifluridine/tipiracil (FTD/TTP) also known as TAS-102 in patients with refractory mCRC (UMIN000015764).

Methods: Three dosages of intravenous oxaliplatin (50, 65 and 85 mg/m²) on days 1 and 15 and a fixed dose of FTD/TPI 35 mg/m² bid on days 1–5, 15–19 every 4 weeks were investigated in patients with refractory mCRC by using a + 3 design. Eligible patients had received prior oxaliplatin-based treatment that achieved a response or stable disease followed by confirmed disease progression at least 6 months before entering the study.

Results: 12 patients were enrolled in the study. Characteristics of patients were as follows: median age, 62 (range, 47–68) years; male/female, 6/6; ECOG PS 0, 75%; number of prior regimens ≥5, 33.3%; and median oxaliplatin-free interval, 24.3 (range, 6.2–71.4) months. 3 of 6 patients of the oxaliplatin 85mg/m² cohort had dose-limiting toxicity (DLTs): treatment delay on 2nd cycle (1 patient), grade 2 neutropenia or grade 2 AST/ALT increased (2 patients). No DLTs were observed in the other cohorts. The median of treatment cycles was 3 (range, 1–9), 9 patients continued the treatment until disease progression; and 3 patients discontinued due to toxicity or patient’s refusal. In safety, grade ≥3 adverse events were neutropenia (n = 3), thrombocytopenia (n = 1), anorexia (n = 1) and nausea (n = 1). There was no evidence of allergic reaction to oxaliplatin and severe peripheral sensory neuropathy.

Conclusions: According to the results of this phase I study, a combination of trifluridine/tipiracil 35 mg/m² bid on days 1–5, 15–19 and oxaliplatin 85 mg/m² on days 1 and 15 every 4 weeks could be a candidate for recommended dose of the trifluridine/tipiracil + oxaliplatin regimen in patients with refractory mCRC.

472P Sideliness of the primary tumor on the effect of TAS-102 for refractory metastatic colorectal cancer

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Background: TAS-102 study was shown to have clinical activity in a large population of Japanese and Western patients with heavily pretreated metastatic colorectal cancer, including those whose disease was refractory to fluorouracil. But we know few data of TAS-102 in daily medical practice. So we assessed efficacy and safety of TAS-102 for refractory metastatic colorectal cancer.

Methods: We retrospectively reviewed the data of 86 patients who received TAS-102 treatment in our institution between June 2014 and October 2017. TAS-102 (with each dose consisting of 35 mg per square meter) was administered twice daily, 5 days on and 2 days off for 2 weeks, followed by 2 weekrest. The regimen was repeated every 4 weeks.

Results: The median age was 69 years (range, 27–87). Performance status of 1 and 2 were 39 and 47 patients. RAS wild and mutant were 39 and 47 patients. Primary tumor site of right and left were 25 and 61 patients. All patients had received prior chemother­apy regimens containing a fluoropyrimidine, oxaliplatin, and irinotecan. 43 patients received 4 or more prior chemotherapy. Response rate and disease control rate of all were 1% and 24%. Right and left-sided of response rate were 4% and 9%. Right and left-sided of disease control rate were 32% and 19%. Median PFS was 62 days, right and left-sided were 55 and 64 days. Median OS was 216 days, right and left-sided were 262 and 208 days. OS was longer than previously reported. 40 patients received subsequent chemotherapy. Adverse events were mild with 18% of Grade 4 neutropenia and 4% of Grade 3 febrile neutropenia.

Conclusions: TAS-102 was active and tolerable for heavily treated refractory metastatic colorectal cancer. There were no significant difference of PFS and OS in primary tumor site.

Legal entity responsible for the study: The authors.
Funding: No has received any funding.
Disclosure: All authors have declared no conflicts of interest.

473P Influence of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib

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Background: The multitarget kinase inhibitor regorafenib (REG) is currently registered for the treatment of colorectal cancer (CRC), gastrointestinal stromal tumors (GIST), and hepatocellular carcinoma. REG exhibits a pH-dependent solubility, and therefore acid reducing drugs such as proton pump inhibitors (PPIs, e.g. esomeprazole) might reduce REG absorption by increasing the stomach pH as was shown for many other kinase inhibitors (van Leeuwen, Lancet Oncol, 2014). We performed a randomized, 3-phase, cross-over trial to compare the exposure of REG alone to REG with esomeprazole (concomitantly or 3 hours prior to REG intake) in CRC and GIST patients.

Methods: Patients were randomized into 2 sequence groups consisting of 3 phases: REG intake alone, REG with concomitant esomeprazole (for 3 days), and REG 3 hours preceded by esomeprazole (for 3 days). Pharmacokinetic (PK) blood sampling was performed at the 21st, 49th and 77th day of the trial. All patients were treated with REG 120 mg at steady-state. Primary endpoint was the relative difference (RD) in geometric mean for REG AUC0–24h. A linear mixed model was used to analyze log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied.

Results: A total of 14 patients were evaluable for the primary endpoint. Exposure (AUC0–24h) to REG alone was: 55.9 µg*h/mL (CV: 40.3%). For REG with concomitant esomeprazole or with esomeprazole 3 hours prior to REG intake was: 33.5 µg*h/mL (CV: 42.6%) respectively. No significant differences were identified when REG alone was compared to REG with concomitant esomeprazole (RD: -3.9%, 95% CI: -20.5-16.1%, p = 1.0) or REG with esomeprazole 3 hours prior to REG intake (RD: -4.1%, 95% CI: -22.8-19.2%, p = 1.0). Furthermore, no significant differences were observed in other PK parameters of REG and its active metabolite M-2 and M-5 (i.e. Cmax,Tmax). Most common adverse events grade 2 were hypertension (71%), fatigue (43%) and hand foot skin reaction (36%).

Conclusions: The use of esomeprazole concomitantly or 3 hours prior to REG intake did not alter REG pharmacokinetics. Our results indicate that PPIs like esomeprazole can be combined with REG without the appearance of a significant drug interaction.

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Legal entity responsible for the study: Erasmus University Medical Center.
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Disclosure: R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Pamgene, Pfizer, Roche Sanofi, Consultation fees: Novartis, Servier, Travel support: Astellas, Pfizer. All other authors have declared no conflicts of interest.
Background: Antiangiogenic agents are frequently used in the systemic treatment of metastatic colorectal cancer (mCRC). Since these strategies target not the tumor but the tumor associated endothelium establishing positive or negative predictive biomarkers is challenging. Recent research indicated a potentially predictive value of cytokines and angiogenic factors (CAF) for early detection of progression during treatment with chemotherapy and bevacizumab. The PERMAD trial is a two-phase trial with the primary objective to evaluate of the impact of a personalized, marker-driven treatment approach with early detection of progression and modifications of treatment. The aim of the first phase is to establish a combination of CAFs that allows early detection/ prediction of disease progression (PD) under a treatment with FOLFOX plus bevacizumab (Bev). The second phase is a randomized part with marker-driven switched of anti-angiogenic agent and maintenance of the chemotherapy backbone until definite radiological PD compared to a conventional treatment approach of changing chemotherapy and antiangiogenic agent at time of radiologic PD. Here we report the results from the first phase examining samples of 50 patients.

Methods: During the run-in phase 102 CAFs were established in blood samples taken prior to treatment and q2w thereafter until PD. Using machine learning we aimed at establishing a combination of 5 out of the 102 CAFs that fulfilled these criteria: cytokines should be affected by PD, but not by treatment itself and should indicate PD at least 2 months prior to the time of PD as determined by MD-CT which was performed every 2-3 months.

Results: Using our machine learning approach we could establish a combination of markers from 30 patients that is associated with > 80% accuracy with PD 2 months prior to radiological PD under a treatment with FOLFOX plus Bev. This combination will be corroborated in another 20 patients (data presented at the meeting) and used for the second, randomized part of the trial.

Conclusions: Using advanced bioinformatics we have identified a biomarker combination that is associated with subsequent PD with a high accuracy under a treatment with FOLFOX plus Bev.

*Clinical trial identification: NCT02331927*

*Legal entity responsible for the study: Ulm University Hospital.*

*Funding: Sanofi-Aventis.*
Affibebraf in combination with ritonvucir, fluorouracil and leucovorin (FOLFRIRI) as first-line chemotherapy in metastatic colorectal cancer (mCRC) patients: A phase II multicentric study

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Background: FOLFRIRI (5FU/leucovorin/irinotecan) + afibebraf significantly improves median overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) in patients (pts) with previously treated metastatic colorectal cancer (mCRC). The aim of this study was to investigate efficacy and tolerability of adding afibebraf to FOLFRIRI in the first-line setting.

Methods: Pts with untreated documented mCRC received afibebraf plus FOLFRIRI every 14 days until progression or unacceptable toxicity in an open, phase II single arm, multicenter trial. The primary endpoint was the 6-months PFS rate. Secondary endpoints were overall PFS, OS and tolerability. A two-steps bimodal design was used with H2L: 53% and 47% respectively (one-sided 95% CI: 5% vs 10%). Data were analyzed in intention to treat population. The study was stopped at the first stage.

Results: 41 patients were included and 40 analyzed (1 consent withdrawal) in 9 French centers between 10/2014 and 02/2017. Median age was 65 y (48-81). 42% were men, 53% two or more metastatic sites. Eighteen patients (34.5%, IC [38.9-40.6]) were alive and non-progressive at 6 months. Treatment with FOLFRIRI plus afibebraf was therefore considered ineffective, inclusions were stopped. Median follow-up was 20.5 months (95% CI 15.11; 27.66). OTR was 54% and disease control rate was 80%. Median duration of treatment was 5.2 months, median PFS and OS were 8.5 and 21.9 months respectively. Grade 3-4 adverse events were mainly gastrointestinal (18 pts, 53%, respectively (one-sided 95% CI: 35% vs 55%). Disease-related lethality occurred in 3/pts (12%). Median OS was 6.0 (95% CI 3.0-8.0) months. ORR was 54% and disease control rate was 80%.

Conclusions: First line FOLFRIRI + afibebraf for mCRC pts is feasible but with significant toxicities leading to dose reduction in the majority of patients. Median PFS and OS were close to those reported with classical doublet and targeted agents in this setting.


Legal entity responsible for the study: Federation Francaise de Cancérologie Digestive.

Funding: Sanofi.

Disclosure: S. Pernet: Honoraria: Amgen, Sanofi, Travel, accommodations, expenses: Amgen, Merck, Servier, Bayer T. Aparicio: Conference: Pfizer, Roche, Sanofi, Léo Pharma, Amgen, Servier, Pfizer, Pierre Fabre Ipsen, Halioxic, Abcixom, FLIX: Travels: Ipsen, Novartis, Roche, Hospice: Research: Novartis, L. Dahan: Honoraria: Sanofi, Amgen. T. Lecomte: Consultant, expert: Sanofi; Courses, trainings: Lilly, Merck, Amgen; Invitations to national or international congresses: Amgen C. Laptev: Clinical research: Ipsen, Novartis Oncology; Courses: Advanced Accelerator Applications; Invitations to national or international congresses: Amgen, Ipsen, Novartis Oncology, Bayer. J. Taieb: Consultancy: Roche, Merck KGA, Amgen, Celgene, Lilly, Baxalta, Servier, Sirtex Medical; Speaker’s bureau: Servier, Amgen, Baxalta, Roche; Genentech, Sanofi, Merck, Lilly. All other authors have declared no conflicts of interest.

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Folinic acid, oxaliplatin, bevacizumab (FOLFOXIRI) vs folinic acid, oxaliplatin, bevacizumab (FOLFOXIRI/BV) in colorectal cancer (mCRC) patients: results of a phase IIIb study

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Background: To date the treatment of mCRC patients (pts) relies on the administration of oxaliplatin-based chemotherapy and bevacizumab (BV) as first line. Intensive debate is open about second-line treatments.

Methods: This is a real practice study; consecutive and umtreated mCRC were treated at the oncologist discretion at presentation to FOLFOXIRI/BV (fluorouracil, 5-fluorouracil, oxaliplatin, bevacizumab) and FOLFOXIRI (fluorouracil, folinic acid, irinotecan, bevacizumab) (arm A) or FOLFOXIRI/BV (FOLFOXIRI, afibebraf) (arm B).

Results: Seventy-four patients were treated from January 2014 to January 2018: 31 treated with arm A, 43 with arm B. Among clinical factors there was a predominance of more extended disease (>2 metastatic sites) in arm B (25/31 [81.2%] vs 40/43 [93.0 %]; p < 0.001). Nineteen-nine pts were evaluable for response through RECIST: arm A, 5 PR, 15 SD, 8 PD; arm B, 5 PR, 16 SD, 10 PD. Second-line chemotherapy doses were reduced in 32.3% of pts in arm A and 38.1% in arm B. There were no grade 4 toxic events (NCI-CTC v4.0). The mean distance from first-line discontinuation to second-line start was 0.8 months in arm A and 2.4 months in arm B. Duration of first-line chemotherapy was significantly shorter in pts in treated in arm B (12 pts < 6 months arm B vs 1 pt in arm A; p = 0.0278). Analysis of overall survival (OS) was done excluding these 13 pts to avoid prognostic interferences. Median OS was 22.7 in arm A vs 25.3 months in arm B (t = 2.8 months; P = 0.0685; HR: 1.12, 95% CI: 0.62 to 2.03). No maintenance therapy was done in arm B while in arm A BEVA with or without fluorouracil and folinic acid was done; censoring the analysis of OS at the end of the induction phase of both arms favored arm B (P = 0.0425; HR: 0.42; 95% CI: 0.15 to 1.15).

Conclusions: In our real practice, oncologists tend to administer FOLFOXIRI/BV in more extended RAS-M mCRC and to delay to start therapy of FOLFOXIRI/BV and FOLFOXIRI/AFLI are equally effective in RE, during the induction phase (6 months), is associated with a lower risk of death.

Legal entity responsible for the study: Istituto Nazionale Tumori di Napoli, IRCCS “G. Pascale”.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
479P A phase II study of bevacizumab and irinotecan plus alternate-day S-1 as a second-line therapy for colorectal cancer: The AIRS study


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Background: The aim of this single-arm phase II clinical trial was to evaluate whether the alternate-day administration of S-1 plus irinotecan would reduce the incidence of severe diarrhea in comparison to consecutive-day S-1 administration (standard IRIS regimen) in second-line treatment in patients with metastatic colorectal cancer.

Methods: Patients with metastatic colorectal cancer after failure with first-line treatment of oxaplatinum and fluoropyrimidine were enrolled. Irinotecan (180 mg/m2) and bevacizumab (5mg/kg) were given intravenously on day 1. Oral S-1 was administered on alternate-days at a dose of 40-60mg twice a day. Cycles were repeated every two weeks. The primary endpoint was the incidence of grade ≥3 diarrhea. Our hypothesis set the 23% as a threshold incidence and 10% as an expected incidence from previous studies with one-sided alpha = 0.05. The secondary endpoints included the relative dose intensity, progression free survival, overall survival and other adverse events.

Results: A total of 51 patients were enrolled. The incidence of grade ≥3 diarrhea was 15.7% (8/51). Other common grade ≥3 adverse events were neutropenia, anemia, thrombocytopenia and fatigue were 13.7% (7/51), 5.9% (3/51), 20.0% (10/51) and 5.9% (3/51), respectively. The relative dose intensities of irinotecan, bevacizumab, and S-1 were 80.6%, 87.7%, and 87.7%, respectively. The median progression free survival and overall survival were 8.4 months (5.8 - 9.8) and 17.1 months (11.8 - 22.3).

Conclusions: The alternate day S-1 administration doesn’t have significant effectiveness to reduce diarrhea in patients who received second line treatment for metastatic colorectal cancer.

Clinical trial identification: UMIN000008947.

Legal entity responsible for the study: Epidemiological and Clinical Research Information Network (ECRIN).

Funding: Taiho Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

480P The efficacy of FOLFIRI plus molecular target therapy as a first-line treatment for metastatic colorectal cancer: A multicentre retrospective study

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Background: The TRIBE study showed that FOLFIRI plus bevacizumab therapy is an effective treatment for metastatic colorectal cancer (mCRC). This study aimed to determine the safety and effectiveness of FOLFIRI therapy as a first-line treatment.

Methods: We retrospectively collected data of patients with mCRC treated with FOLFIRI from March 2014 to December 2017 in two centres.

Results: Fifty-five patients were enrolled in this study (median age, 60 years; males 25, females 30). The tumour location was classified as right and left in 15 and 40 patients, respectively. Twenty-nine and twenty-six patients had mCRC wild-type disease and mutation-type disease, respectively. Anti-VEGF and anti-EGFR antibodies were used in 38 and 17 patients, respectively. The most common grade 3 or 4 adverse event was neutropenia (51%). Skin toxicities and hypomagnesaemia showed a statistically higher frequency among patients with anti-EGFR antibodies (P < 0.001). The overall response rate (ORR) was 67% (complete response [CR], 7 patients; partial response [PR], 30 patients; not evaluated [NE], 1 patient), and the disease control rate was 91% (CR, PR, NE patients). The median progression free survival (mPFS) was 11.0 (0.43 – 45.3) months and the median overall survival (mOS) was 41.9 (1.00 – 45.3) months. In FOLFIRI plus anti-VEGF antibodies, the ORR was 55% (CR, 5 patients; PR, 16 patients), and in FOLFIRI plus anti-EGFR antibodies, the ORR was 94% (CR, 2 patients; PR, 14 patients; NE, 1 patient) (P = 0.271). With a median follow-up of 18.4 months, mPFS and mOS were not significantly different in patients with anti-EGFR antibodies or anti-VEGF antibodies (hazard ratio [HR], 3.12 (0.883 – 11.0)); P = 0.143 and P = 0.063, respectively). Twelve patients had progressive disease (PD) during the induction phase. In these patients, mOS was significantly poorer (13.2 months versus 41.9 months; HR, 23.3 [6.77 – 80.1]; P < 0.001).

Conclusions: FOLFIRI plus molecular target therapy showed impressive results for patients with mCRC. The response rate was significantly higher in patients with anti-EGFR antibodies, although skin toxicities and hypomagnesaemia tend to occur in these patients.

Legal entity responsible for the study: Kobe City Medical Center General Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

481P Phase II study of cetuximab rechallenge in patients with ras wild-type metastatic colorectal cancer: E-rechallenge trial


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Background: Several previous reports indicated that cetuximab (Cmb) rechallenge may be efficacious in patients for whom Cmb was previously effective. On the other hand, some reports did not support this. Considering the plasticity of sensitive clone, we assumed that an anti-EGFR antibody-free interval (aEFI) and efficacy may be correlated. This current study investigates the efficacy and safety of Cmb rechallenge as a salvage chemotherapy.

Methods: The E-Rechallenge trial is a multicenter phase II study in mCRC patients who have become refractory to fluoropyrimidines, L-OHP, CPT-11, Cmb and bevacizumab, and in whom previous treatment with Cmb was effective in any earlier line (achieving CR, PR, or SD that persisted for ≥6 months). The other main eligibility criteria are: RAS wild-type, measurable disease, aEFI ≥6 weeks between the last dose of Cmb during previous treatment and the start of Cmb rechallenge. Protocol treatment is the combination of weekly Cmb with biweekly CPT-11. The primary endpoint is response rate (RR). Secondary endpoints are progression free survival (PFS), overall survival (OS), association between the aEFI and efficacy, and safety. Using a single-stage binomial design, 45 patients were required; a RR of ≥20% was considered promising, and a RR of ≤5% unacceptable (one-sided α = 0.05, β = 0.10). Additional research of ctDNA was conducted optionally.

Results: Between Dec 2014 and Oct 2017, 33 patients were enrolled. Patients' characteristics were as follows: mean age 64.4, male/female 84.8%/15.2%, primary location (right/left) 12.1%/87.9% and the efficacy in previous Cmb, CR/PR/SD ≥6 months 3%/78.8%/18.2%, respectively. The primary endpoint; the rates of PR/SD/PD (95%CI) were PR 16.5% (5.3-32.7%/SD 40.6% (23.5-67.6%)/PD 43.8% (26.4-62.3%). Secondary endpoint; median PFS and OS (95%CI) were 88 days (62-113days) and 262 days (195-307days). There were no statistical significant difference of PFS stratified by median aEFI. New signals of adverse events were not identified.

Conclusions: Cmb rechallenge showed some activity in the salvage setting, in patients for whom Cmb was previously effective. The additional research of ctDNA may contribute to identify patients with benefit from Cmb rechallenge.

Clinical trial identification: UMIN000006439.

Legal entity responsible for the study: Comprehensive Support Project for Oncological Research.

Funding: Merck Serono.

Disclosure: E. Shinohara, H. Satake: Honoraria: Merck Serono. All other authors have declared no conflicts of interest.
**Background:** RET rearrangements (RETr) are uncommon yet emerging oncogenic targets found in RAS/BRAF wild-type colorectal cancers (CRCs), particularly right-sided, MSI-high tumors. We describe the molecular landscape of metastatic CRCs harboring a somatic RET detected by next generation sequencing (NGS) of cell-free DNA (cfDNA). cfDNA data complement previous descriptions of RET in tissue, which are mostly described in MSI-high tumors. We describe the molecular landscape of metastatic CRCs harboring RET with 68-73 genes evaluated by the Guardant360® (Guardant Health, Redwood City, CA). This validated NGS assay evaluates single nucleotide variants, and select indels, fusions, and copy number gains with high sensitivity and analytic specificity. Relevant clinicopathologic correlates were obtained from clinician charts.

**Results:** Seventeen RET were detected in 16 pts (0.4%). Functionally significant alts in other cancer genes were found in 88% of samples with a RET (median 9.5 additional alts, max 23). There was a high co-occurrence of canonical KRAS alts (14 alts in 7/16 pts), 5 of which also had a KRAS in cfDNA only. Two also had KRAS, NRAS, and EGFR ECD alts, one had an EGFR activating alt, and the fourth had a EGFR3 fusion, all detected only in cfDNA. Prior to cfDNA collection, all had progressed on anti-EGFR therapy after a median of 12ms (range 8-16ms) of treatment. Four additional RET/RAS = pts had either a KRAS alt that was not detected in tissue (n = 2) or co-occurred with an ALK fusion and/or BRAF V600E in pts who had prior anti-EGFR therapy (n = 2).

**Conclusions:** RET commonly co-occur with RAS/RAF alts in cfDNA, a novel observation. The alt pattern and clinicopathologic history suggest RET contribution to acquired resistance to anti-EGFR therapy in metastatic CRC. Our data also raise the question of whether driver RET may be associated with primary resistance to anti-EGFR therapy.

**Legal entity responsible for the study:** Guardant Health.

**Funding:** Has not received any funding.

Clinical trial identification: to irinotecan in this study. Benefits appear clinically relevantly higher than for pts with post-study cetuximab, potentially masking any OS benefit of the addition of cetuximab to irinotecan significantly improved PFS and ORR in this suitable as a standard, second-line treatment for pts with RAS wt mCRC. Specifically, authors have declared no conflicts of interest.

BioMed Valley Discoveries, Pfizer, PTC Therapeutics, TG Therapeutics, Loxo, Vertex, Macrogenics, Novartis, Boehringer Ingelheim, Lilly, Seattle Genetics, Abbvie, Bayer, Merck (US). All other authors have declared no conflicts of interest. Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA.

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Retrospective RAS analysis of the EPIC trial: Cetuximab plus irinotecan vs irinotecan in patients (pts) with second-line metastatic colorectal cancer (mCRC)

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Background: The multicenter, open-label, randomized, phase 3 EPIC study (EMR 062202-025) investigated the addition of cetuximab to irinotecan vs irinotecan in pts with EGFR-expressing mCRC who had previously progressed on first-line fluoropyrimidine- and oxaliplatin-based chemotherapy. The primary endpoint was overall survival (OS). We present the extended RAS analysis (KRAS/NEFRS exons 2, 3, and 4) for the EPIC study population.

Methods: 1298 RAS-unselected pts were enrolled from May 2003 to February 2006. Existing DNA samples were reanalyzed using BEAMing (beads, emulsion, amplification, magnets) technology. RAS wild-type (wt) status was defined as having all alleles be analyzable and a sum of RAS mutations of ≤ 5%. Baseline characteristics, efficacy, safety, and post-study therapy were assessed. 10.3% had no RAS data available.

Results: Among the 452 (231 in the cetuximab + irinotecan arm and 221 in the irinotecan arm) pts with RAS wt mCRC, baseline characteristics were comparable to those of the unselected population. 67.5% had 1 prior line of therapy. In the cetuximab + irinotecan vs irinotecan arms, median progression-free survival (PFS) was 5.4 vs 2.6 months (HR, 0.57 [95% CI, 0.46-0.69]; P < 0.001), median OS was 12.3 vs 12.0 months (HR, 0.91 [95% CI, 0.71-1.17]; P = 0.465), and overall response rate (ORR) was 29.4% vs 5.0% (OR, 8.12 [95% CI, 4.04-17.40]; P = 0.001), respectively. 76.4% and 61.8% of pts in the cetuximab + irinotecan vs irinotecan arms, respectively, experienced a grade ≥ 3 adverse event. 47.1% of pts in the irinotecan arm received cetuximab in a subsequent line of therapy vs 11.3% in the cetuximab + irinotecan arm.

Conclusions: This retrospective analysis confirms that cetuximab-based therapy is suitable as a standard, second-line treatment for pts with RAS wt mCRC. Specifically, the addition of cetuximab to irinotecan significantly improved PFS and ORR in this population. A large proportion of pts in the irinotecan arm crossed over to receive post-study cetuximab, potentially masking any OS benefit of the addition of cetuximab to irinotecan in this study. Benefits appear clinically relevantly higher than for pts with RAS-unselected or KRAS wt mCRC.

Clinical trial identification: EMR 062202-025

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Legal entity responsible for the study: Merck KGaA.

Annals of Oncology
Results: This retrospective exploratory analysis suggest that patients with left sided KRAS wt mCRC and high expression of v616f showed the most benefit for median OS of 23.6 months versus 10.2 months (HR 0.36 [95% CI 0.17; 0.75]; median PFS of 8.6 months versus 4.2 months (HR 0.61 [95% CI 0.31; 1.12]). Median OS of 20 (95% CI 16; 22.5) versus 5/22 (32.7%), when treated with abituzumab 1000 mg + irinotecan + cetuximab versus irinotecan + cetuximab alone. No treatment benefit was observed in right sided mCRC with high expression of v616f and in all mCRC with low expression of v616f.

Conclusions: Although the sample size is small, patients with left sided KRAS wt mCRC and high expression of v616f in their tumor seem to benefit most from the addition of abituzumab to irinotecan + cetuximab compared to irinotecan + cetuximab alone. A prospective study in left sided mCRC with high expression of v616f is planned with the addition of abituzumab 100mg to SOC.

Clinical trial identification: Explorative, retrospective data analysis of study NCT01008475; first release October 19, 2019.

Legal entity responsible for the study: Merck KGaA and SFJ Pharmaceuticals.

Funding: Merck KGaA and SFJ Pharmaceuticals.


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Histopathologic evaluation of patients with liver-limited metastatic colorectal cancer receiving mFOLFOX6 plus bevacizumab or mFOLFOX6 plus cetuximab: The ATM trial

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Background: We previously reported the results of a randomized phase II controlled trial comparing mFOLFOX6 plus bevacizumab (Bmab) with mFOLFOX6 plus cetuximab (Cmab) for KRAS wild-type (wt) colorectal cancer (CRC) with liver limited metastases that were not optimally resectable. The current study is the first to examine the role of histopathologic response based on the study data of anti-VEGF versus anti-EGFR antibody.

Methods: In the ATM trial, KRAS wild-type CRC patients with liver-limited metastases were eligible if the number of lesions was more than 5 and/or the size of lesions was more than 5cm in the maximum diameter. The primary endpoint was progression-free survival (PFS). Of 116 eligible patients, patients who underwent liver metastasectomy were evaluated for histopathologic response in this study. Resected liver specimens were assessed by the independent pathological review committee. Preplanned pathological assessments included tumor regression grade (TRG), dangerous halo, and sinusoidal obstruction of resected liver specimens. Patients were categorized into major histopathologic response (MjHR) if they had TRG of 1 (viable tumor cells 0%) or 2 (<25%), partial histopathologic response (PRH) if they had TRG of 3 (<50%), or no histopathologic response (NHR) if they had TRG of 4 (<75%) or 5 (<75%).

Results: A total of 39 patients had TRG evaluation based on resected specimens by liver metastasectomy. Of those, 55 (28 in Bmab arm, 27 in Cmab arm) were eligible for analysis. In the Bmab arm, the number of patients with MjHR/PRH/NHR was 12/11/13 (43/41/56) and in the Cmab arm, 15/10/4 (45/30/25). Further results regarding other assessments will be presented.

Conclusions: In the TRG assessment, the proportion of MjHR was similar between the two arms. The impact of MjHR on PFS as compared to PRH/NHR was observed in both arms. Further results regarding other assessments will be presented.

Clinical trial identification: NCT01836653.

Legal entity responsible for the study: ATM study group.

Funding: Chugai Pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.
Impact of delayed addition of anti-EGFR monoclonal antibodies on the outcome of first-line therapy in metastatic colorectal cancer patients: A retrospective registry-based analysis

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Background: The addition of monoclonal antibodies against epidermal growth factor receptor (anti-EGFR Abs) to chemotherapy is commonly delayed in the real-world clinical practice, usually because of delays in obtaining RAS testing results. The aim of this retrospective registry-based analysis was to determine whether the delayed addition of anti-EGFR mAbs up to the fourth cycle of backbone chemotherapy adversely affects outcomes of mCRC patients treated with first-line regimens.

Methods: Clinical data of patients with RAS wild-type mCRC treated with first-line systemic therapy regimens containing anti-EGFR mAbs from a national database were analysed retrospectively. Patients were divided into three groups according to the timing of anti-EGFR mAbs addition to the chemotherapy backbone: Cohort A (n = 401) included patients with anti-EGFR mAbs added to chemotherapy from the first cycle, cohort B (n = 71) patients with anti-EGFR mAbs added to chemotherapy from the second cycle, and cohort C (n = 101) patients who had anti-EGFR mAbs added to chemotherapy from the third or fourth cycle. The chemotherapy backbone regimens consisted of FOLFOX or FOLFIRI regimens.

Results: 336 (58.6%) patients received panitumumab and 237 (41.4%) patients received cetuximab. The median progression-free survival (PFS) of the whole cohort was 12.2 months (95% confidence interval [CI]: 10.9–13.5), and the median overall survival (OS) was 33.5 months (95% CI 27.6–39.4). Survival results for the cohorts defined by the time of addition of anti-EGFR mAbs to chemotherapy are shown in the table. In a multivariate test, ECOG performance status and chemotherapy regimen were associated with PFS, whereas the site of primary tumour and chemotherapy regimen were associated with OS.

Table: 491P

<table>
<thead>
<tr>
<th>Cohort</th>
<th>PFS (95% CI), months</th>
<th>Log-rank p-value</th>
<th>OS (95% CI), months</th>
<th>Log-rank p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 401)</td>
<td>12.9 (11.5–14.3)</td>
<td>not reached</td>
<td>30.6 months (25.2–36.1)</td>
<td>not reached</td>
</tr>
<tr>
<td>B (n = 71)</td>
<td>9.7 (9.1–10.3)</td>
<td>0.185</td>
<td>not reached</td>
<td>0.645</td>
</tr>
<tr>
<td>C (n = 101)</td>
<td>11.5 (9.8–13.2)</td>
<td>0.052</td>
<td>37.9 months (28.6–47.3)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

Conclusions: Delayed addition of anti-EGFR mAbs up to the fourth cycle of first-line chemotherapy was not associated with inferior survival or response rates.

Legal entity responsible for the study: Tomas Buchler

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A multi-institutional randomized phase II study on the timing of oxaliplatin plus 5-fluorouracil (FOX) for patients (pts) with operable stage III rectal cancer: The KRIR study

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Background: Recent randomized studies have shown low compliance to adjuvant chemotherapy in stage III rectal cancer pts who received preoperative combined chemotherapy and external beam radiation (CT/EBRT) and surgery (instead of chemotherapy after RT and surgery, which is the current standard of care) for pts with node positive operable rectal cancer, would result in higher pt compliance to chemotherapy.

Methods: Between 2010-2017, 180 eligible pts were randomly assigned (2:1) to two arms, 6 cycles of FOX in adjuvant (Arm A (AA)), or 12 cycles of FOX in adjuvant (Arm B (AB)). The primary end point was compliance to chemotherapy (pts receiving at least 85% of full-dose CT prescribed at each cycle (x 12 cycles), 1 yr post-diagnosis); secondary end points were disease free survival rate (DFS), pT0N0, local recurrence rate and overall survival (US), 5 yrs post-surgery.

Results: All pts were randomly assigned to either AA (n = 120; 84 pts were male (M), median age (MA) was 65 years) or AB (n = 60, 35 pts were M, MA was 65.3 years).
Compliance on AA was 78% and 51.9% on AB. Levels of G3/G4 toxicity were 30.8% in AA and 28.3% in AB respectively. 17% of 178 pts completed HDBRT as planned (97.6%). In AA, 3 pts progressed locally under CT(1 yr) and 1 pt refused HDBRT after randomization in AB. pT0N0 for AA and AB were 35% (30.1%) and 15 pts (25%). The 3-year DFS was 80% with AA and 76% with AB (p = 0.6511). The 3-year OS for AA and AB were 86% and 85%, respectively (p = 0.8219).

Conclusions: The safety and improved compliance to neoadjuvant CT is confirmed in this study using HDBRT as a neoadjuvant modality for rectal cancer. There is no statistical difference in pT0N0 rate, local recurrence, and DFS between the two arms in the early result analysis, but favorable oncological outcomes are observed. At the time of this reporting, pelvic nodal recurrence is seldom isolated, asymptomatic and preceded by systemic failure.

Clinical trial identification: NCT02174962.

Legal entity responsible for the study: Jewish General Hospital-McGill.

Funding: Sanofi.

Disclosure: All authors have declared no conflicts of interest.

Tumor regression grading after preoperative hyperfractionated radiotherapy/chemoradiotherapy for locally advanced rectal cancers: A phase III clinical study

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Background: We investigated tumor regression grading (TRG) as a prognostic marker for disease-free survival (DFS) in patients with advanced rectal cancer treated within phase III randomized study. The study was prospective trial of preoperative hyperfractionated radiotherapy (HART) compared with concomitant hyperfractionated radiotherapy with co-administration of chemotherapy based on SFU (HART-CT) in patients with T2/N+ or T3/any N resectable mid-low primary rectal cancer.

Methods: The 136 patients were randomly assigned to HART (n = 69) and HART-CT (n = 67). The pelvis was irradiated twice a day (28 fractions of 1.5 Gy), with a minimal interfraction interval of 6 hrs to total dose 42 Gy over 18 days (HART) or mentioned scheme with concurrent chemotherapy: SFU-325mg/m2 (bolus) on days 1-3 and days 16-18 (HART-CT). Surgery was performed 5-6 weeks after HART/HART-CT. The TRG was recorded using 4-point scale: TRG0 (pCR) denoted no cancer cells; TRG1 - cancer cells less than 10% of a tumor mass; TRG2 cancer cells in 10-50% or TRG3 - cancer cells in more than 50% of tumor mass. Multivariable analysis was performed using Cox regression models adjusted for treatment arm, resection status and pathologic stage.

Results: The crude rate of patients with any serious adverse events during the follow-up was 12% vs. 17% for HART and HART-CT (p = 0.06). Of the 136 patients evaluable for pathologic response there were 34.8% vs. 91.6%, 16.23% vs. 24.76%, 40.4% vs. 30.45%, and 10.15% vs. 6.60% in HART and HART-CT, respectively (p = 0.502). The actuarial 2-year cumulative loco-regional relapse free survival control rates (LRC) for HART vs. HART-CT were 72% vs. 80.1% (p = 0.11), 58.6% vs. 71% (p = 0.18) and 58.6% vs. 69.3% (p = 0.18), respectively.

Conclusions: TRG is a significant predictor of survival in patients with advanced rectal cancer treated within phase III randomized study. The study was prospective trial of preoperative hyperfractionated radiotherapy compared with concomitant hyperfractionated radiotherapy with co-administration of chemotherapy based on SFU (HART-CT). TRG3 was associated with better DFS for HART compared with HART-CT.
HART-CT were 86% vs. 91% and actuarial DFS control rates were 70% vs. 76%, respectively.

**Conclusions:** Significant differences in the tumor regression grading (TRG) were found. Both LRC and DFS of rectal cancer patients treated with HART vs. HART-CT had favorable outcomes in those allocated to HART-CT. Also the sphincter preservation rate tended to favor HART-CT.

**Clinical trial identification:** NCT01814969.

**Legal entity responsible for the study:** Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, 44-100 Gliwice, Poland.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
A classifier of 53BP1, immune score and texture analysis of MRI images can predict pathological response to chemoradiotherapy in locally advanced rectal cancer.

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Background: Preoperative chemoradiotherapy is the standard care for advanced rectal cancer. Yet, predicting the response remains a challenge. Our previous studies found that 53BP1 protein deletion leaded to chemoradiotherapy resistance. 53BP1 deficiency played pivotal role in inducing lymphocyte mature. As the development of functional imaging, texture analysis can predict response to chemoradiotherapy. Our study aims to explore the relationship among 53BP1 protein, immune score, texture analysis and radiation sensitivity, then set a new classifier to predict response in advanced rectal cancer.

Methods: We enrolled 57 advanced rectal cancer patients who received neoadjuvant chemoradiotherapy in Wuhan Union hospital from January 2015 to January 2018. The expression of 53BP1, CD3, CD8, CD45RO was detected by immunohistochemistry. Immune score was calculated which are based on the combination of two lymphocyte populations (CD3/CD45RO, CD3/CD8 or CD8/CD45RO) both in the center (CT) and the invasive margin (IM) of tumors. T2W MRI images studies obtained in 34 patients before treatments, texture analysis by manually delineating a region of interest. The response rate, anus preservation rate were collected. The relationship among 53BP1 protein, immune score, texture analysis parameters and radiation sensitivity were explored by t-test. A new classifier was set to predict pathological response.

Results: The results indicated that the response rate in 53BP1 deletion group was significantly lower than that in 53BP1 high expression group (25.00% vs 84.44%, P < 0.005). “CD3 + CD8” is the most reasonable immune score, the patients of 33BP1 deletion had lower immune score. The response rate in lower immune score group was lower than higher immune score group (54.34% vs 88.57%, P < 0.005). Texture analysis parameters were related with response rate. We set a new classifier to predict response in advanced rectal cancer, we randomly selected 10 patients as training group, others were selected as predict group, the accuracy is 83.33%.

Conclusions: A classifier of 53BP1, immune score and texture analysis of MRI can predict response in advanced rectal cancer.

Legal entity responsible for the study: Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Funding: 2015CFB659.

Disclosure: All authors have declared no conflicts of interest.

500P Mismatch repair deficient rectal cancer is resistant to induction combination chemotherapy

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Background: Although most rectal cancers are responsive to combination induction chemotherapy, the sensitivity of mismatch repair deficient (MMR-D) rectal cancers to chemotherapy remains uncertain.

Methods: MMR-D rectal tumor cases were retrospectively reviewed with tabulation of baseline characteristics, treatment modalities and clinical outcomes. Prevalence of germline mutations in the MMR genes, diagnostic of Lynch syndrome (LS), was compared to LS-associated colon cancer patients. We also assessed somatic mutational status for a subset of these patients.

Results: Twenty of the 49 patients received induction chemotherapy with 5FU and oxaliplatin, 15 received standard neoadjuvant chemoradiation, and 14 proceeded directly to surgery. Of the 15 patients treated with induction chemoradiation, 93% (n = 14) experienced radiographic response and tumor downsizing; and none of these patients showed evidence of disease progression. In contrast, of the 18 patients treated with induction (n = 13) alone, only 61% (n = 15) experienced tumor response and 28% (n = 5) of patients demonstrated progressive disease while on therapy. The majority of these cases, 82% (41/50) harbored germline mutations in the MMR genes and the observed prevalence of germline MSH2 and MSH6 mutations was significantly higher in the rectal (n = 41) versus colon (n = 244) cancer patients (rectal vs colon: MSH2: 57% vs 37%; MSH6: 20% vs 11%; p-value < 0.0005).

Conclusions: Patients with MMR-D rectal tumors appear to have a high chance of disease progression on induction chemotherapy. As opposed to LS-associated colon cancers, LS-associated rectal cancers are more likely to harbor MSH2 or MSH6 germline mutations. Upfront testing for MMR status and initial treatment with chemoradiation in MMR-D rectal tumors should be undertaken until better therapies are available.

Legal entity responsible for the study: Andrea Cercek.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

501P Outcomes of chemoradiotherapy plus local excision in patients with clinical T1 or T2, N0 rectal cancer

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Background: NCNC guidelines recommend local excision (LE) as a standard treatment for selected patients with cT1/T2,N0,M0 rectal cancer. However, the rates of local recurrence after LE alone were 12.5% in cT1 disease and 22.1% in cT2 disease and those after total mesorectal excision (TME) were 6.9% and 15.1%, respectively. In pathologi-cal T1 disease, adding (chemo)radiotherapy (CRT) to LE decreased the rate of local recurrence to 5%, which was comparable to the rate after TME (4%). In pT2 disease who underwent LE, the local recurrence rate decreased slightly but remained high (14%) even after CRT.

Methods: In our institution, patients with cT1, N0 disease with a tumor diameter of less than 30 mm underwent transanal full thickness LE and additionally receive CRT (40/45Gy plus UFT or S-1). Patients with poorly differentiated adenocarcinoma or mucinous carcinoma should additionally undergo TME. Patients with cT2, N0 disease transanal LE after CRT. Patients whose tumors include poorly differentiated adenocarcinoma or mucinous carcinoma should receive TME.

Results: In accordance with these treatment policy, LE was performed in 63 patients with cT1, N0 disease, 50 of whom additionally received CRT. The median follow-up was 71 months. Local recurrence occurred in 1 patient (2%), and distant metastasis occurred in 3 patients (6%). The 5-year disease-free survival rate (5y DFS) was 86%, and the 5-year overall survival rate (5y OS) was 92%. Patients with pT1 disease who had nodal recurrence underwent abdominalperineal resection and are still alive with no recurrence. In 53 patients with cT2, N0 disease, LE was performed after CRT. Four patients had pT3 disease and additionally underwent TME. In the other 49 patients, six patients (12%) had local recurrence at the anastomotic site, and 7 (14%) had distant metastasis. The 5 y DFS was 70%, and the 5 y OS was 87%.

Conclusions: These results suggested that multidisciplinary treatment combining chemoradiotherapy with local excision is a treatment option in some patients with a pre-operative diagnosis of clinical T1; N0 or T2, N0 rectal cancer. However, further studies are needed to determine the optimal treatment for patients with clinical T2, N0 rectal cancer.

Legal entity responsible for the study: Sotaro Sadahiro.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

502P Comparison of immune microenvironment between different neoadjuvant radiotherapy regimens for rectal cancer

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Background: Conventional neoadjuvant radiotherapy regimens for rectal cancer are long-course radiotherapy in combination with chemotherapy (LCRT) and short-course radiotherapy (SCRT). We aimed to compare the different immune microenviron-ment in patients between the two different radiotherapy regimens. Methods: The expression of LAG-3, CD8 and CD3 was detected by immunohisto-chemistry on specimen of 76 rectal cancer patients following neoadjuvant treatment. The expression of proteins was assessed as the percentage of positive cells (PP). The variation of proteins expression was compared by Mann-Whitney U test analysis. Results: LCRT was given in 40 (52.6%) patients and the rest 36 (47.4%) patients were SCRT. The median PP of immune cells (LAG-3) expression was 15% (range: 0% - 80%) in all patients. The expression of CD8 and CD3 was 10% (range, 0 - 80%) and 30% (range, 0 - 90%), respectively. The LAG-3 expression was high in patients with SCRT.
Conclusion: Tumor microenvironment might be modified by different fractions and dose. Immune cells Lag-3 expression pattern was high with respect to SCRT. The diverse expression pattern of Lag-3 between SCRT and CRT supported different combination strategies of immune checkpoint blockade and neoadjuvant radiotherapy.

Legal entity responsible for the study: Junxin Wu.


Disclosure: All authors have declared no conflicts of interest.

503P

Prognostic factors of chemo-radiotherapy efficacy in patients with locally-advanced rectal cancer

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Background: We decided to evaluate prooperative clinical factors associated with progression free survival, overall survival and tumor regression in patients with locally-advanced rectal cancer after chemo-radiotherapy.

Methods: We analyzed retrospective database of patients with locally-advanced rectal cancer (cT3N0-2M0) who received prooperative chemo-radiotherapy followed by surgery in our center from 2004 to 2013. Multivariate regression analyses was performed to evaluate effects of absent morphological response (Dowswor tumor regression rate system 0-2) and hazards of progression and deaths. Statistical analyses was performed with SPSS v.20.

Results: Chemo-radiotherapy followed by surgery was performed in 457 patients with locally-advanced rectal cancer. The median f-up was 46 months (2-141), 3-year progression free survival and overall survival were 79% and 91%, respectively. Multivariate regression analyses revealed factors associated with tumor regression rate 0-2 as high level (above normal range) CEA (carcinoembryonic antigen) before chemo-radiotherapy (OR 1.49 95%CI 1.11-2.02, p = 0.008), neutrophil/lymphocyte count > 7000/μL (OR 2.29, 95%CI 1.05-5.2, p = 0.05) and CT4 (OR 3.75, 95%CI 2.03-6.86, p = 0.001). Independent negative prognostic factors for progression free survival were perineural invasion (HR 3.1, 95%CI 1.43-6.89, p<0.001), neutrophil/lymphocyte ratio before surgery > 3 (HR 1.8, 95%CI 1.37-2.42, p = 0.01) and ypT4 or/and N+ (HR 1.82, 95%CI 0.45-0.92, p = 0.001). For overall survival: ypT3-4 or/and N+ (HR 1.9, 95%CI 1.52-6.25, p<0.01), lymphatic vessel invasion (HR 2.4, 95%CI 1.27-4.59, p<0.001) and ki67 counts before surgery > 110 (HR 3.1, 95%CI 1.33-7.35, p<0.01). Conclusion: ypTNM after prooperative chemo-radiotherapy more effective than cTNM predicts progression free and overall survival in patients with locally-advanced rectal cancer.

Legal entity responsible for the study: Mikhail Fedyanin.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

504P

Association of systemic and local inflammation with prognosis in rectal cancer treated with neoadjuvant radiotherapy

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Background: To explore the characteristics of cancer-associated systemic and local inflammation and its impact on overall survival (OS) in locally advanced rectal cancer (LARC) treated with neoadjuvant radiotherapy (RT).

Methods: A consecutive cohort of 76 LARC patients underwent neoadjuvant RT were retrospectively analyzed from February 2012 to September 2015. Peripheral neutrophil to lymphocyte ratio (NLR) was calculated at diagnosis, and tumor-infiltrating lymphocyte was examined in postoperative tumor tissue by immunohistochemistry. The association between clinicopathological features and inflammation was explored through chi-square test. The prognostic factors in terms of OS were investigated through uni- and multivariate Cox regression. SPSS 22.0 was used for statistical analyses.

Results: The median follow-up time was 29.0 months (range, 2-59). The 1-, 3- and 5-year OS rates were 93.4% (95%CI 97.91-98.89), 80.0% (95%CI 68.91-90.39) and 68.6% (95%CI 46.06-91.14), respectively. High NLR (≥2.0) and low CD8+ T-cells (<9%) were more common in 76 patients (53.8% and 59.2%, respectively). For patients with high NLR and low CD8+ T-cells, 5-year OS was significantly worse than those with low NLR and high CD8+ T-cells (P = 0.014). Also, NLR > 2.0 was associated with poor tumor regression after neoadjuvant RT (P = 0.039), while no significant association was found between CD8+ T-cells and tumor regression. In addition, NLR was related to lymphovascular invasion (P = 0.031). CD8+ T-cells was related to neural invasion (P = 0.048) and mucinous adenocarcinoma (P = 0.045). Furthermore, NLR (HR 7.71, 95%CI 1.30-45.71, P = 0.025), CD8+ T-cells (HR 0.9, 95%CI 0.01-16.67, P = 0.018), age (HR 1.61, 95%CI 1.56-167.15, P = 0.020), lymphovascular invasion (HR 7.17, 95%CI 1.12-46.05, P = 0.038) and T stage (HR 0.35, 95%CI 0.00-0.45, P = 0.011) were independent risk factors for prognosis according to multivariate Cox regression.

Conclusions: High NLR and low CD8+ T-cells were significantly associated with dismal survival. Systemic combined with local inflammation might help to predict prognosis of LARC with neoadjuvant RT.

Legal entity responsible for the study: Jun-xin Wu.

Funding: National Clinical Key Specialty Construction Program.

Disclosure: All authors have declared no conflicts of interest.

505P

Early prediction of histopathological response by PET/CT after two weeks of neoadjuvant chemoradiotherapy for rectal cancer: Wishful thinking or reality?

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Background: Neoadjuvant chemoradiotherapy (CRT) is standard in locally advanced rectal cancer (LARC). Current data on the predictive value of early PET/CT, i.e. the correlation between the tumor’s early metabolic response, manifested by the reduction of its 18F-FDG uptake after two weeks of CRT compared with baseline, and histopathological response, are conflicting.

Methods: Patients (pts) with histologically confirmed LARC who were planned to receive standard CRT regimen of 50.4 Gray radiotherapy with concurrent fluorropyridine-based chemotherapy followed by radical surgery were eligible for the study. Baseline PET/CT was done within 4 weeks prior to CRT and the investigational scan was done two weeks +/- two days after its initiation. Maximum standardized uptake value (SUV-MAX) and the changes in FDG uptake between the two scans (ASUV-MAX) were compared with the histopathological response at surgery. Response was classified as tumor regression grade (TRG) and presence of pathological complete response (pCR).

Results: Twenty pts were included in the study, 65% with clinical stage II and 35% with stage III. Ninety percent of tumors were located at least 5 cm from the anal verge. Pts underwent surgery within a median of 8.6 weeks (4.5-12.8) after the completion of CRT. Six pts (30%) achieved pCR and 7 (35%) had TRG II. Absolute SUV-MAX values at both time points did not correlate with pCR (p = 0.099) nor with TRG (p = 0.670). Histopathological response did not correlate with ASUV-MAX. Pts who achieved pCR had median ASUV-MAX of -45%, while those who did not had median ASUV-MAX of -41% (p = 0.617). Similarly, pts with TRG II-I and those with TRG III-IV had the same median ASUV-MAX of -42% (p = 0.882). In addition, using ROC analysis we did not find any cutoff of any the PET-CT parameters that will predict pCR or TRG I-II.

Conclusions: In the current study, early PET/CT done after two weeks of neoadjuvant CRT for LARC, failed to predict histopathological complete response. Legal entity responsible for the study: Rabin Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Biopsy specimens were available were enrolled. Radiation consisted of 45.0–58.4 Gy Chemotherapy was given during radiation: 1000mg/m^2^ daily fluorouracil on day 1–4 and 29–32, and a single dose of mitomycin C 10mg/m^2^ administered on day 1 and 29. Distant failure and death were obtained until March 2017. Of 14 patients, 3 patients were positive as p16 was stained on tumor nuclei. PD-L1 positive was also defined as PD-L1 was overexpressed on tumor membrane with more than 2+ score and the area was more than 5%.

**Results:** Of 28 patients, the median age was 59 (range 35–82) years. Male to female sex ratio was 16:6 (4:2). Clinically staged at cT1 (4.4%) as II, II (17.9%) as IIIA, and 13 (46.4%) as IIIIB. SCCA remained or recurring with 1cStage II (11 cStage III (11) and with cStage III (7) with cStage IIIB. 3-year disease-free survival (DFS) was 68.8% (95%CI, 4.3–86.6%), and 3-year overall survival (OS) was 78.2% (95%CI, 53.4–91.7%). Of 28 cases, 27 (96.4%) were positive for p16, and 6 (21.4%) were positive for PD-L1. In univariate analysis for DFS and OS, lymph node metastasis was significantly related to poor outcomes (DFS, p = 0.0289; OS, p = 0.0001). The factor (p = 0.0005) significantly influencing OS. No significant difference was found in terms of PD-L1 expression (DFS, p = 0.595; OS, p = 0.544).

**Conclusions:** High expression rate of p16 was observed in Japanese patients with locoregional SCCA. Lymph node metastasis, advanced T factor and tumor stage were negative prognostic factors for CRT, but no prognostic impact of PD-L1 was found.

Legal entity responsible for the study: Ryo Takahashi.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

**SOPP**

**Factor influencing conversion to resectability and survival after resection of metastases in RAS WT metastatic colorectal cancer (mCRC): A FIRE-3 analysis**

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**Background:** Paired tumor evaluations before randomization and at best response (nadir) of 270 patients with RAS WT tumors treated with first-line therapy with cetuximab (cet) vs. bevacizumab (bev) in combination with FOLFIRI were reviewed for resectability of metastases. We assessed parameters influencing resectability, conversion to resectability and survival after nadir.

**Methods:** Baseline information and resectability were correlated with Fischer’s exact tests. Conversion to resectability was defined as unresectable disease before randomization and resectable disease at nadir. Univariate and multivariate logistic models were fitted with resectability at nadir as response variable. A Cox model comparing the survival from nadir used to measure the influence of treatment, resectability at nadir and resectable disease (time dependent variable).

**Results:** Of 28 patients, the median age was 59 (range 35–82) years. Male to female sex ratio was 16:6 (4:2). Clinically staged at cT1 (4.4%) as II, II (17.9%) as IIIA, and 13 (46.4%) as IIIIB. SCCA remained or recurring with 1cStage II (11 cStage III (11) and with cStage III (7) with cStage IIIB. 3-year disease-free survival (DFS) was 68.8% (95%CI, 4.3–86.6%), and 3-year overall survival (OS) was 78.2% (95%CI, 53.4–91.7%). Of 28 cases, 27 (96.4%) were positive for p16, and 6 (21.4%) were positive for PD-L1.

**Conclusion:** High expression rate of p16 was observed in Japanese patients with locoregional SCCA. Lymph node metastasis, advanced T factor and tumor stage were negative prognostic factors for CRT, but no prognostic impact of PD-L1 was found.

Legal entity responsible for the study: Ryo Takahashi.

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510P Targeted therapies in conversion therapy in mCRC: A systematic review and meta-analysis

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Background: Chemotherapy (CT) plays a vital role as conversion therapy for initially unresectable or borderline resectable colorectal cancer (CRC). Targeted therapies are recommended with CT for conversion therapy; however, their role in conversion of initially unresectable tumours has not been elucidated. This meta-analysis evaluated the outcomes and safety were presented as relative risk (RR) and 95% confidence interval (CI).

Methods: We conducted a literature search for randomized controlled trials (RCTs) in PubMed, Embase and Cochrane library evaluating the role of anti EGFR and anti VEGF as conversion therapies. A comparison was performed for anti-EGFR + CT vs. anti-VEGF + CT (Gp. A) and anti-EGFR + CT vs. CT (Gp. B). R0 resection rate and objective response rate (ORR) were the primary outcomes; with overall survival (OS), progression free survival (PFS) and safety evaluated as the secondary outcomes. Primary outcomes and safety were presented as relative risk (RR) and 95% confidence interval (CI), whereas survival was presented as hazard ratio (HR) and 95%CI.

Results: We identified 8 RCTs from the potential 81 studies. In Gp. A, a fixed effects model was used for analysis; and showed that although non-significant, anti-EGFR + CT had better R0 resection rate (RR 1.44, 95% CI 0.91,2.27; p = 0.1136, I2 = 0%) and ORR (RR 1.85, 95% CI 0.88, 1.24; p = 0.0609, I2 = 0%) compared with anti VEGF + CT. In Gp. B, ORR with anti EGFR + CT resulted in significantly higher R0 resection rate (RR 1.85, 95% CI 1.15,2.98; p = 0.0107; I2 = 57.16%) and ORR (RR 1.19, 95% CI 1.11, 1.28; p = 0.0011; I2 = 0%). In Gp. B, only PFS was significantly longer with anti EGFR + CT vs. CT (HR: 0.85, 95% CI 0.74, 0.98; p = 0.0015; I2 = 45.60%), and not OS. Safety evaluation showed anti EGFR + CT with significantly greater adverse events than CT alone (RR: 1.26; 95% CI 1.18, 1.35; p < 0.0001).

Conclusions: In conclusion, anti-EGFR + CT was an effective converting therapy compared with anti VEGF + CT and CT in patients with initially unresectable mCRC, however, frequency of AEs was more with targeted therapy.

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Disclosure: All authors have declared no conflicts of interest.

511P Morphologic response to chemotherapy containing bevacizumab in patients with colorectal liver metastases (CLM): A post hoc analysis of the WJO44407G phase III study

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Background: The phase III WJO44407G study showed non-inferiority of FOLFIRI plus bevacizumab to mFOLFOX6 plus bevacizumab in progression-free survival, as the first-line chemotherapy for patients with metastatic colorectal cancer. The aim of this study was to evaluate the predictive and prognostic value of morphologic response to first-line chemotherapy containing bevacizumab in patients with CLM.

Methods: This study is a post hoc analysis of patients from the WJO44407G study. Morphologic response was assessed with the comparison of baseline and week 8 contrast-enhanced CT images. Three blinded radiologists evaluated CT images and classified as optimal, incomplete or no response according to the morphologic criteria. RECIST response, early tumor shrinkage (ETS) and depth of response (DpR) were also evaluated. The Cox proportional hazards model was used to investigate the association between radiological variables and progression-free survival (PFS) and overall survival (OS).

Results: Of 995 patients who were eligible for efficacy analysis in the WJO44407G study, 70 patients had liver-disease limited. Enhanced CT images of 57 of these patients from 22 participating centers were collected. Two patients were excluded from this analysis because their post-chemotherapy metastases were too small. Optimal morphologic response was identified in 19 of 55 patients (34.5%). The median PFS was 10.7 months for patients with optimal response and 10.1 months in those with incomplete/no response (log-rank p = 0.96). The median OS was 26.2 and 35.5 months, respectively (log-rank p = 0.062). According to univariate analysis, morphologic response was not associated with PFS or OS, whereas RECIST response was significantly associated with both PFS and OS, with ETS and DpR being associated with significantly longer PFS.

Conclusions: Morphologic response might be neither predictive nor prognostic factor in patients with CLM undergoing chemotherapy containing bevacizumab, whereas RECIST response was significantly associated with both PFS and OS.

Clinical trial identification: UMIN0000022171.

Legal entity responsible for the study: West Japan Oncology Group.

Funding: West Japan Oncology Group.

Disclosure: A. Hosokawa: Honorary: Taiho, Chugai, Takeda, Ono, Novartis, Eisai, Eli Lilly; Research funding: Taiho, Chugai, Ono, Eisai, Yakult. K. Yamazaki: Speakers’ bureau: Chugai, Takeda, Taiho, Yakult, Merck Serono, Eli Lilly, Sanofi, Bayer E. Baba: Speakers’ bureau: Chugai, Eli Lilly; Research funding: Ono, Chugai, Eli Lilly, Takeda, Taiho, Merck Serono. K. Shinozaki: Honorary: Chugai, Takeda, Mochida, Merck Serono, Taiho, Yakult, Astellas, Novartis, Eli Lilly, Shinongi, Kyowa Hakko Kirin, Asahi Kasei, MSD. S. Ueda: Honoraria: Chugai Pharma, Daichii Sankei K. Muro: Honorary: Chugai, Taiho, Bayer, Ono, Eli Lilly, Takeda, Research funding: Ono, MSD, Daichii Sankei, Kyowa Hakko Kirin, Gilead Sciences, Shinongi. All other authors have declared no conflicts of interest.

512P KRAS mutations as a prognostic factor after metastasectomy in colorectal cancer patients

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Background: Different clinicopathological factors have been associated with survival after liver metastasis resection in metastatic colorectal cancer (mCRC) patients. However, there is a need to better identify those patients who may benefit from metastasectomy. In this retrospective study we aimed to analyse clinical outcomes according to KRAS mutational status in a prospective collected series of mCRC patients.

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Results: KRAS mutational status was assessed in 395 mCRC patients, but clinical data were only available in 348 patients. Median age was 66 years old. Two hundred and twenty-six patients were male (65%) and 210 patients (60%) had synchronous metastases at diagnosis. KRAS mutations were detected in 175 tumours (51%). Liver was the most common site of metastasis (210 pts, 60%), followed by lung (133 pts, 33%), lymph nodes (56 pts, 16%) and peritoneum (44 pts, 11%). Lung metastases at diagnosis were more frequent in KRAS mutant tumours (38% vs 27%, p-value = 0.022). We observed different metastasis spread pattern between pts with KRAS mutant and KRAS wt tumours. Risk of lung metastasis after 30 months of follow-up was higher in KRAS mutant tumours (77% vs 60%, p = 0.003). Risk of brain metastases was also higher (18% vs 2%, p = 0.012). Median OS was 37 months, with no differences observed between KRAS mutant and KRAS wt tumours (34 vs 41 months, p-value = 0.70). One hundred thirty-nine patients underwent metastasectomy (39%). In this subgroup of patients, KRAS mutations were associated with worse DFS (13.3 vs 24.5 months, p-value = 0.024).

Conclusions: KRAS mutations were associated with lung metastasis in CRC patients and different pattern spread. Although KRAS mutations were not a prognostic biomarker in the whole set of patients, KRAS mutant tumours had a shorter DFS after metastasectomy. Legal entity responsible for the study: Cancer Institute of Oncology. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Background: The benefit of preoperative chemotherapy (pre-CT) and metastasectomy for pulmonary metastasis (PM) from colorectal cancer (CRC) (PM-CRC) are unclear due to a lack of enough studies. However, there are some patients who receive chemotherapy after PM detection and subsequently undergo metastasectomy in clinical practice. The aim of this study was to investigate the impact of response to pre-CT on the outcome of pulmonary metastasectomy for PM-CRC.

Methods: The subjects were 92 patients, who received pre-CT before metastasectomy for PM-CRC, identified from the 1237 patients whose PM-CRC were curatively resected at 46 institutions in Japan between 2004 and 2008.

Results: Twenty-six (28%) patients initially judged to have inoperable PM underwent chemotherapy before conversion to be resectable and subsequently received metastasectomy. The remaining 66 patients initially judged to have operable PM received pre-CT and subsequently underwent metastasectomy. Fifty-six (61%) patients received fluoropyrimidine based regimens combined with oxaliplatin or irinotecan, and most of the remaining 26 received regorafenib. Pre-CT yielded partial response (PR), stable disease (SD) and progressive disease (PD) in 28 (30%), 20 (28%) and 38 (42%) patients, respectively. At metastasectomy, the proportions of patients with extrathoracic metastasis were 36% (210 pts, 60%), followed by lung (133 pts, 33%), lymph nodes (56 pts, 16%) and peritoneum (44 pts, 11%). Overall, 93 patients met the inclusion criteria: 72 (77%) colorectal (CRC), 13 (14%) appendiceal and primary peritoneal carcinomas (PC) in 17%, colorectal cancer (CRC) in 10.1%, peritoneal mesothelioma (PM) in 9%, and others in 1.6%. Prior surgical Peritoneal Cancer Index (PCI) was 19 (2-29) and 25.2% were exposed to preoperative chemotherapy.

Background: Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis: 10-year experience in a developing country.

Results: Median age at diagnosis was 51–50 (72, 22–78) and 73% (n = 87) were female. Primary origin of the peritoneal carcinomatosis was the appendix in 64%, advanced ovarian and primary peritoneal carcinomas (PC) in 17%, colorectal cancer (CRC) in 10.1%, peritoneal mesothelioma (PM) in 9%, and others in 1.6%. Prior surgical Peritoneal Cancer Index (PCI) was 19 (2–29) and 25.2% were exposed to preoperative chemotherapy.

Conclusions: CRS/HiPEC is an effective treatment for patients with PC providing long-term survival and should be considered as standard of care. Our results, from a specialized center in a developing Latin-American country, are comparable to those from first-world centers, implying the importance of group experience in providing high-quality outcomes. Results showed that patients without relapse at the 5 year follow-up could be considered cured, but should always remain observation.

Legal entity responsible for the study: Fundacion Santa Fe de Bogotá. Funding: Fundacion Santa Fe de Bogotá. Disclosure: All authors have declared no conflicts of interest.

Background: Is important to avoid aggressive treatments in P with OMD with undetermined primary, especially in colorectal cancer. Previous data demonstrated that PET can have a significant clinical impact, especially in colorectal cancer.

Methods: Retrospectively, we review the history of P studied with PET at our unit, from October 2013 to December 2017. We included only P with OMD with a PET done to complete disease extension study in addition to conventional imaging and previously to undergo a potential curative management. Baseline data (age, sex, primary and stage), disease extension and initial strategy before PET were collected. After PET, disease extension, definitive strategy and overall survival (OS) was determined.

Results: Overall, 93 P met the inclusion criteria: 72 (77%) colorectal (CRC), 13 (14%) melanoma, 4 (4%) biliary tract, 2 (2%) oesophageal and 2 (2%) other primaries. The mean age was 64 years (range: 24–85) and 58 (62%) P were male. At debut, 64 (79%) P were non-metastatic, and PET was done at the recurrence. After PET, 47 (51%) P were restaged: 35 (38%) were upstaged and 12 (13%) were downstaged. Final strategy was changed in 43 (46%) P, leading to a non-radical plan in 32 (34%) P. On the radical plan group there was 2 (2.2%) P with no malignant disease after surgery (pulmonary)

Legal entity responsible for the study: Non-profit Organization Tsukuba Cancer Clinical Trial Group. Funding: Non-profit organization Tsukuba Cancer Clinical Trial Group. Disclosure: N. Boku: Honoraria: Ono, BMS, Chugai, Merck Serono, Yakult, Eli Lilly companies. I. Hyodo: Honoraria: Taiho, Chugai, Daiichi-Sankyo, Yakult-Honshu companies. All other authors have declared no conflicts of interest.

Clinical impact of 18F-FDG-PET/CT (PET) in patients (P) with oligometastatic disease (OMD) at a skin and gastrointestinal tumour section

Methods: We evaluated mCRC patients with exon 2 KRAS mutational status assessed between 2010 and 2014. exon 2 KRAS mutational analysis was performed by therascreen® or cobas® assays. We excluded patients (pts) with no clinical data available. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method.

Results: KRAS mutational status was assessed in 395 mCRC patients, but clinical data were only available in 348 patients. Median age was 66 years old. Two hundred and twenty-six (28%) patients were male (65%) and 210 patients (60%) had synchronous metastases at diagnosis. KRAS mutations were detected in 175 tumours (51%). Liver was the most common site of metastasis (210 pts, 60%), followed by lung (133 pts, 33%), lymph nodes (56 pts, 16%) and peritoneum (44 pts, 11%). Lung metastases at diagnosis were more frequent in KRAS mutant tumours (38% vs 27%, p-value = 0.022). We observed different metastasis spread pattern between pts with KRAS mutant and KRAS wt tumours. Risk of lung metastasis after 30 months of follow-up was higher in KRAS mutant tumours (77% vs 60%, p = 0.003). Risk of brain metastases was also higher (18% vs 2%, p = 0.012). Median OS was 37 months, with no differences observed between KRAS mutant and KRAS wt tumours (34 vs 41 months, p-value = 0.70). One hundred thirty-nine patients underwent metastasectomy (39%). In this subgroup of patients, KRAS mutations were associated with worse DFS (13.3 vs 24.5 months, p-value = 0.024).

Conclusions: KRAS mutations were associated with lung metastasis in CRC patients and different pattern spread. Although KRAS mutations were not a prognostic biomarker in the whole set of patients, KRAS mutant tumours had a shorter DFS after metastasectomy. Legal entity responsible for the study: Cancer Institute of Oncology. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Impact of response to preoperative chemotherapy on the outcome of pulmonary metastasectomy for colorectal cancer: Results of a retrospective multicenter study

Background: The benefit of preoperative chemotherapy (pre-CT) and metastasectomy for pulmonary metastasis (PM) from colorectal cancer (CRC) (PM-CRC) are unclear due to a lack of enough studies. However, there are some patients who receive chemotherapy after PM detection and subsequently undergo metastasectomy in clinical practice. The aim of this study was to investigate the impact of response to pre-CT on the outcome of pulmonary metastasectomy for PM-CRC.

Methods: The subjects were 92 patients, who received pre-CT before metastasectomy for PM-CRC, identified from the 1237 patients whose PM-CRC were curatively resected at 46 institutions in Japan between 2004 and 2008.

Results: Twenty-six (28%) patients initially judged to have inoperable PM underwent chemotherapy before conversion to be resectable and subsequently received metastasectomy. The remaining 66 patients initially judged to have operable PM received pre-CT and subsequently underwent metastasectomy. Fifty-six (61%) patients received fluoropyrimidine based regimens combined with oxaliplatin or irinotecan, and most of the remaining 26 received regorafenib. Pre-CT yielded partial response (PR), stable disease (SD) and progressive disease (PD) in 28 (30%), 20 (28%) and 38 (42%) patients, respectively. At metastasectomy, the proportions of patients with extrathoracic metastasis were 36% (210 pts, 60%), followed by lung (133 pts, 33%), lymph nodes (56 pts, 16%) and peritoneum (44 pts, 11%). Overall, 93 patients met the inclusion criteria: 72 (77%) colorectal (CRC), 13 (14%) appendiceal and primary peritoneal carcinomas (PC) in 17%, colorectal cancer (CRC) in 10.1%, peritoneal mesothelioma (PM) in 9%, and others in 1.6%. Prior surgical Peritoneal Cancer Index (PCI) was 19 (2–29) and 25.2% were exposed to preoperative chemotherapy.

Conclusions: Response to pre-CT had some impacts on OS after metastasectomy for PM-CRC, identified from the 1237 patients whose PM-CRC were curatively resected at 46 institutions in Japan between 2004 and 2008.
CRS > 2 in the ER group. Of note, 25% of LTS had CRS > 2. In multivariate analysis, only multiple metastases remain significantly increased in ER (p = 0.016).

Conclusions: Clinical factors are unable to discriminate preoperatively the patients who will benefit of surgery for CRLM from those in whom surgery will be futile. This strongly underlines the need to identify other markers of tumour biology for better individualization of the therapeutic decision.

Legal entity responsible for the study: Vincent Donckier.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

518P Hepatic arterial infusion (HAI) of oxaliplatin with capcitabine in first line treatment of patients (pts) with liver limited metastases from colorectal cancer (LmCRC)

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Background: The hepatic artery accounts for the primary blood supply of liver metastases from CRC.

Methods: First-line therapy with up to 12 series of HAI with oxaliplatin 100 mg/m²/day 1 and capecitabine 3500 mg/m²/day 1-7 every second week. When the hepatic arterial anatomy did not permit a permanent catheter, patients intralesional oxaliplatin 150 mg/ m² day 1 every third week combined with capcitabine 2000 mg/m² day 1-3. A RAS mutation was retrospectively confirmed by next generation sequencing of KRAS Exon (E) 2, codon (C) 12 and 13, E3C59 and 61, E4C117 and 146 and NRAS E2C12 and 13, E3C59 and 61, E4C117 and 146. Pts had a baseline PET/CT scan and was evaluated by liver surgeons for resectability.

Results: Included were 93 pts, 66 had HAI and 27 CAPOX. The groups were comparable with an equal distribution of RAS wildtype (RAS-W) and mutants (RAS-M) tumours. Follow-up was 95-154 mths. Overall response rate (ORR) with complete CR and partial remission (PR) was 89% vs 59% in the HAI vs CAPOX group (P = 0.0008). Progression-free survival (PFS) was independent of RAS status and treatment. Median overall survival (OS) was 6 mths. longer in the HAI vs CAPOX group (HR 1.62, 95% Confidence Interval (CI) 1.0-2.6, P = 0.05). OS was independent of RAS status in the CAPOX group and equal to OS in the HAI RAS-M group. Pts with RAS-W tumours treated with HAI survived double that of all the other groups (HAI-RAS-W vs HAI-RAS-M: HR 1.88, 99%CI 1.1-3.2, P = 0.023, HAI-RAS-W vs CAPOX-RAS-W: HR 1.60 95%CI 1.12-2.27, P = 0.009). Toxicity of HAI was comparable to CAPOX with abdominal pain, neuropathy, and hand foot syndrome as the most common adverse events.

Table: 518P

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<tr>
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<tr>
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<td>27</td>
<td>14</td>
</tr>
<tr>
<td>NA</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>CR</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>6 (22%)</td>
<td>3</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>mCR 1</td>
<td>32 (48-84)</td>
<td>29 (24-35)</td>
</tr>
<tr>
<td>mPFS 1</td>
<td>12 (10-15)</td>
<td>11 (8-15)</td>
</tr>
</tbody>
</table>

Conclusions: ORR and OS was significantly higher when pts with LmCRC was treated with Capecitabine and HAI with oxaliplatin compared to CAPOX. Survival benefit is limited to pts with RAS-W tumours treated with HAI.

Legal entity responsible for the study: Benny Villars Vittrup.

Funding: The Danish Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

517P Clinical factors are unable to accurately predict the absence of benefit of surgery in patients operated for resection of colorectal liver metastasis

A. Bohlok1, H. Tessely2, E. Naets2, F. Bouazza1, D. Germanova3, J.L. Van Laethem4, 1Surgery, Université Libre de Bruxelles, Brussels, Belgium, 2Clinical Risk Score, Université Libre de Bruxelles, Brussels, Belgium, 3Surgery, Erasmus University Medical Centre, Rotterdam, Netherlands, 4Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium

Background: A substantial proportion of patients operated for resection of colorectal liver metastases (CRLM) with curative-intent will rapidly recur after surgery, empha-
sizing the need to improve the current selection process for surgery. The aim of the study is to analyze clinicopathologic prognostic factors that could better identify patients that wouldn’t benefit of surgery.

Methods: A prospective database including patients operated of hepatectomy for CRLM between 2005 and 2017 was analyzed. Within this population, we selected and compared 2 groups: early relapsers (ER), defined as patients with unresectable recurrence ≤1 year postoperatively considered as having not benefited of surgery and long-term survivors (LTS), defined as patients without recurrence ≥5 years after first hepatec-
tomy. In the entire population and in the 2 subgroups, we analyzed potential predic-
tive factors, using uni- and multivariate analysis.

Results: In total population (N = 357), 5 and 10-year disease-free survival (DFS) and overall survival (OS) are 26 and 21.5% and 44 and 25% respectively. In univariate analysis, Fong’s Clinical Risk Score (CRS) > 2, mutated KRAS, major hepatic resection and positive resection margins are significant poor prognostic factors for DFS and OS. In multivariate analysis only mutated-KRAS remains a significant poor prognostic factor for DFS (HR = 1.5 CI 1.06-2.12, P = 0.02) and OS (HR = 1.8 CI 1.19-2.70, P = 0.005). Comparing the 2 subgroups ER group (77 patients) and LTS group (64 patients), repres-
enting respectively 21 and 18% of entire population the univariate analysis showed significantly more synchronous CRLM, multiple metastases, mutated-KRAS and
Background: High microsatellite instability (MSI-H) is a prognostic marker in early colon cancer (CC) identified in retrospective analysis of many trials. However, broad validation in real-life cohorts and its association with clinical and molecular markers is lacking.

Methods: In Sep 2013 the molecular registry trial ColorectalPlus was initiated in 70 German community cancer centers recruiting patients with UICC stage II and III CC. MSI was tested by immunohistochemistry (IHC) of mismatch repair proteins MLH1, MSH2, MSH6 and PMS2. In case of any loss of protein expression fragment length analysis (FLA) was performed, defining MSI high (MSI-H) and MSI stable tumors (MSS). Moreover, mutations in known prognostic factors in CC such as RAS, BRAF, PI3K, and others were determined by next generation sequencing (NGS).

Results: By April 2018, 2102 patients have been recruited: median age 72 yrs., stage II/III: 1108/994 pts. So far, tissue was analysed in 1342 pts. Of these, 377 pts. were IHC negative for one or more mismatch repair proteins. The SACURA trial is a phase III study to evaluate the superiority of 1-α interferon over surgery alone in stage II colon cancer patients. MSI was evaluated by 5 markers; BAT25, BAT26, D2S123, D5S346, and D17S250.

Conclusions: MSI-H was more frequent in this community based registry compared to type status of RAS.

<table>
<thead>
<tr>
<th>Table: 519P</th>
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<tbody>
<tr>
<td>All</td>
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<tr>
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<tr>
<td>1342</td>
</tr>
</tbody>
</table>

Clinical trial identification: DRKS Registry number: DRKS00004305 Release Date: 09-JAN-2013.

Legal entity responsible for the study: Ruhr-University Bochum, Institute of Pathology, Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital.  

Funding: State of North-Rhine Westfalia, Roche Pharma GmbH  
Disclosures: A. Reinacher-Schick: Honoraria: Amgen, Roche, Pfizer, Sanofi-Aventis, Merck-Serono, Shire, Calgene, Lilly, BMS, Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Celgene, Lilly, BMS, Merck-Serono; Studies sponsored by: Roche, Sanofi-Aventis, Celgene, Ipnos. H. Juette: Honoraria: Roche, MSD, BMS, AstraZeneca, Amgen. S. Nooel-Duennbach: Advisory board member: Bexalta, BMS; Studies sponsored by: Roche, Sanofi-Aventis, Celgene, Ipnos. D. Arnold: Honoraria: Bayer, Biosimilars, Lilly, Merck, MSD, Roche, Sanofi, Servier, ISIS; Advisory board member: Roche, Lilly, Merck, Roche, Sanofi, Servier, ISIS, Terminus. Studies sponsored by: Molgen, Roche, Sanofi. C. Teschendorf: Advisory board member: Roche. A. Tannapfel: Honoraria: Amgen, Roche, Pfizer, Merck-Serono, Celgene, BMS, Advisory board member: Amgen, Roche, Pfizer, Sanofi-Aventis, Celgene, BMS, Merck-Serono; Studies sponsored by: Roche, Celgene, Ipnos. All other authors have declared no conflicts of interest.

### Abstracts

519P Microsatellite instability is associated with distinct clinical and molecular characteristics in early colon cancer: Analysis of a molecular registry of the AIO colorectal study group - ColorectalPlus

A. Reinacher-Schick 1, H. Juette 2, S. Nooel-Duennbach 3, D. Arnold 4, N. Basara 5, H. Boerner 1, T. Dahm 1, I. Feder 1, T. Hertzig 1, W. Hiller 1, L. Mueller 1, L. Engel 1, M. Gentilini 1, C. Teschendorf 2, G. Trenn 1, B. Verduett 1, H. Wolters 1, W. Uhl 1, A. Tannapfel 2

1Department of Hematology, Oncology and Palliative Care, St. Josef-Hospital Bochum, Ruhr-University Bochum, Bochum, Germany, 2Institute of Pathology, Ruhr-University Bochum, Bochum, Germany, 3Hematology, Internal Medicine and Palliative Care, Asklepios Klinik Altona, Hamburg, Germany, 4Hematology/Oncology/Internal Medicine, St. Franziskus Hospital Münsterkrankenhaus, Flensburg, Germany, 5Surgical Clinic, Katholische Krankenhaus Dortmund West, Dortmund, Germany, 6General and Visceral Surgery, Katholische Klinikum Bochum - St. Josef-Hospital Bochum, Bochum, Germany, 7General, Visceral and Thoracic Surgery, Klinikum Lippie GmbH, Detmold, Germany, 8Onkologie Uerdingen, Leer Emden Papenburg, Onkologische Schwerpunktklinik Leer-Emden, Leer, Germany, 9Internal Care, Klinikum Nürnberg Nord, Nürnberg, Germany, 10General and Visceral Surgery, Marien Hospital Witten, Witten, Germany, 11Internal Medicine, Katholisches Krankenhaus Dortmund West, Dortmund, Germany, 12Department of Surgery, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany.

Background: High microsatellite instability (MSI-H) is a prognostic marker in early colon cancer (CC) identified in retrospective analysis of many trials. However, broad validation in real-life cohorts and its association with clinical and molecular markers is lacking.

Methods: In Sep 2013 the molecular registry trial ColorectalPlus was initiated in 70 German community cancer centers recruiting patients with UICC stage II and III CC. MSI was tested by immunohistochemistry (IHC) of mismatch repair proteins MLH1, MSH2, MSH6 and PMS2. In case of any loss of protein expression fragment length analysis (FLA) was performed, defining MSI high (MSI-H) and MSI stable tumors (MSM). Moreover, mutations in known prognostic factors in CC such as RAS, BRAF, PI3K, and others were determined by next generation sequencing (NGS).

Results: By April 2018, 2102 patients have been recruited: median age 72 yrs., stage II/III: 1108/994 pts. So far, tissue was analysed in 1342 pts. Of these, 377 pts. were IHC negative for one or more mismatch repair proteins. MSI-H was more frequent in this community based registry compared to type status of RAS.

Table: 519P

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>All</td>
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</tr>
<tr>
<td>1342</td>
</tr>
</tbody>
</table>

| Median age | 73 |
| Female | 677 |
| Male | 665 |
| Stage II | 736 |
| Stage III | 606 |
| Right Colon | 793 |
| Left Colon | 536 |

Conclusions: MSI-H was more frequent in this community based registry compared to randomised trials, possibly related to a higher median age in our cohort. MSI-H was associated with female sex, right-sided primary tumor and BRAF mutations representing a heterogeneous subgroup of CC. First survival data will be presented at the meeting. Association of clinical features with MSI-H in patients with CC (MS status determined by FLA).
mRNA-31 as a prognostic and predictive marker of disease-free survival (DFS) in resected stage III colon cancer: A retrospective analysis of the PETACC-8 trial


Disclosure: All authors have declared no conflicts of interest.

Funding: None.

Distribution of lymph node metastases can have an impact on survival benefit of oxaliplatin-containing chemotherapy in stage III colon cancer

Y. Ozawa1, J.G. Kim1, J.H. Baek2, S.J. Lee3, D.W. Baek2, B.W. Kang2

1Oncology, Kyungpook National University Medical Center, Daegu, Republic of Korea, 2Oncology, Kyungpook National University Hospital, Daegu, Republic of Korea, 3Oncology, Ulsan University Hospital, Ulsan, Republic of Korea

Disclosure: All authors have declared no conflicts of interest.
A. Koumarianou 1

The group of TYMS polymorphisms 2RG/3RG, 2RG/LOH, 3RC/LOH, found to correlate with survival.

an increased risk of death (HR 4.500, p = 0.368, p = 0.029 respectively). The 3'UTR polymorphism ins/LOH was independently associated with increased risk for disease recurrence (HR 0.320, p = 0.02 and HR 0.343, p = 0.013 respectively) and death (HR 0.594). In the multivariate analysis, the addition of oxaliplatin showed no prognostic significance on DFS (p = 0.073) and OS (p = 0.594).

Conclusions: In conclusion, oxaliplatin-containing adjuvant chemotherapy was not found to have a significant effect on survival for stage III CC patients with only PLN.

Legal entity responsible for the study: Jong Gwang Kim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 527P

<table>
<thead>
<tr>
<th>Feature</th>
<th>MLH1 methylated n = 90</th>
<th>MLH1 unmethylated n = 80</th>
<th>P</th>
<th>BRAF mutation n = 24</th>
<th>BRAF wild-type n = 146</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>62y</td>
<td>50y</td>
<td>0.0078</td>
<td>14(2.5)</td>
<td>28(19.2)</td>
<td>0.617</td>
</tr>
<tr>
<td>Synchoric CC</td>
<td>30(3)</td>
<td>8(10.0)</td>
<td>32(40)</td>
<td>0.000</td>
<td>44(30.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>FDR or SDR with LS-related tumor</td>
<td>17(18.9)</td>
<td>14(17.5)</td>
<td>0.011</td>
<td>3(12.5)</td>
<td>106(88.8)</td>
<td>0.962</td>
</tr>
<tr>
<td>FDR or SDR with CRC</td>
<td>12(13.3)</td>
<td>32(40)</td>
<td>0.000</td>
<td>0</td>
<td>44(30.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>FDR with CRC</td>
<td>9(10.0)</td>
<td>27(35.0)</td>
<td>0.000</td>
<td>0</td>
<td>36(24.7)</td>
<td>0.016</td>
</tr>
<tr>
<td>Revised Bethesda guidelines</td>
<td>43(47.8)</td>
<td>69(86.3)</td>
<td>0.000</td>
<td>8(33.3)</td>
<td>104(71.2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

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526P

Results of the national organised colorectal cancer screening program with FIT in Paris

A. Pettiti 1, R. Caritat 2, S. Chaussee 2

1Medical Oncology, Hôpital Saint-Antoine, Paris, France, 2Gastroenterology and Digestive Oncology, Hôpital Cochin, Paris, France

Background: In France, colorectal cancer (CRC) benefits from a nationwide screening program. The faecal immunochemical test (FIT) is being used since April 2015. The test is recommended in asymptomatic patients followed by a colonoscopy if positive for identification and treatment of colorectal lesions. We investigate the CRC national organised screening program using FIT in Paris.

Methods: We performed a retrospective observational study, collecting data from the screening program in Paris using the ADECA75 database. Rates of participation, numbers of positive FIT, detection rates and positive predictive values (PPV) for advanced adenomas (AA) and/or CRC were determined.

Results: Between 01/01/2016 and 30/06/2017, 620.227 Parisians were eligible and 409.340 were invited to participate to the program. A total of 88.796 participants (23%) performed the test with 3.839 positive tests (4.3%). In the positive test population, 2.706 out of 3.839 individuals (70.5%) performed the required colonoscopy with available reports. Histology reports were only available for 2.401 participants (84.7%). Regarding lesions, 753 (30.5%) and 205 patients (8.5%) had AA and CRC, respectively.

Conclusions: Over 18 months of screening with FIT in Paris, the PPV is in line with expected results while the participation rate is below European recommendations.

Legal entity responsible for the study: Gastroenterology and Digestive Oncology Department, Cochin Hospital, Paris.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 527P

Screening strategy of Lynch syndrome for Chinese colorectal cancer patients with MLH1 immunossmals

W. Wang, L. Dong, S. Zou, N. Lu

Pathology Department, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Background: Inactivation of MLH1 due to promoter hypermethylation strongly suggests a sporadic origin, and nearly half sporadic colorectal cancer patients harbor BRAF mutation, providing exclusion criteria for Lynch syndrome (LS). However, there was little evidence from Chinese population. The aim of this study was to compare the util-

ity of two tests, and explore the possibility of substituting BRAF immunohistochemical staining (IHC) for real-time PCR.

Methods: We reviewed MMR expression status of consecutive patients who had undergone surgery for colorectal cancer between 2012.1.1 and 2014.12.30 in Chinese National Cancer Center. Among 317 patients who were identified as dMMR, 170 patients with MLH1 immunomissals were taken into final analysis. MLH1 methylation status was evaluated by MS-PCR(methylation specific PCR). BRAF mutation was tested by IHC and real-time PCR.

Results: 52.9%patients display MLH1 promoter hypermethylation. As for BRAF sta-

tus, the mutation rate tested by IHC and real-time PCR was 14.1%and17.1%, respec-
tively, and the concordance rate was 92.1%. BRAF mutation did better on ruling out patients whose relatives had CRC history. Although patients who had unmethylated CRCs had a notably stronger family history of CRC, there were still 11.3%patients in the hypermethylation group having family history of CRC, indicating a likelihood of LS.
Conclusions: The mutation rate of BRAF in Chinese population with MSI CRCs was significantly lower than that in western countries, leading to a decreased specificity. Thus, BRAF mutation alone was not efficient to be a negative predictor of LS. Due to the high specificity of MLH1 methylation test and the high concordance rate of IHC and real-time PCR for BRAF mutation, patients who have MLH1 hypermethylation, BRAF wild-type tested by IHC and family history of CRC should be recommended for germline mutation testing additional to those with MLH1 unmethylated CRCs.

Legal entity responsible for the study: National Cancer Center, China.

Funding: Chinese Academy of Medical Science.

Disclosure: All authors have declared no conflicts of interest.

Results: A total of 73,685 patients were included, of which n = 1,172,705 = 25,433 had data on microsatellite and KRAS status. Left-sided CRC was an independent predictor of improved OS (vs. right: HR = 0.75, p < 0.001). Rectal cancer had highest OS (2/5-years OS: 43%/10%) compared to cancers of the rectosigmoid junction (HR = 1.07), sigmoid (HR = 1.12), descending colon (HR = 1.19), transverse colon (HR = 1.41), ascending colon (HR = 1.45) or cecum/appendix (HR = 1.45, p < 0.001 respectively). Patients with stable microsatellites (MSS) had improved OS versus MSI (HR = 0.93, p = 0.027); KRAS wildtype showed superior OS over KRAS mutation (HR = 0.88, p < 0.001). CRC location interacted with microsatellite status and KRAS mutation: the prognostic impact of MSS was more pronounced in rectal cancers versus other loca-tions (interaction p < 0.001); the prognostic impact of KRAS wildtype was largest in rec-tal cancers (interaction p < 0.001). In a 3-way interaction model, the largest prognostic impact of MSS and KRAS wildtype was noted for rectal cancer (interaction term p < 0.05). The table summaries 2/4-year OS rates.

Table: S29P Adjusted 2-year and 4-year OS rates by cancer location and mutational status

<table>
<thead>
<tr>
<th>Location / mutational status</th>
<th>Two year OS</th>
<th>Four year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>rectal CRC, MSS, KRAS wildtype</td>
<td>68%</td>
<td>38%</td>
</tr>
<tr>
<td>rectal CRC, MSS, KRAS mutation</td>
<td>56%</td>
<td>29%</td>
</tr>
<tr>
<td>rectal CRC, MSI, KRAS wildtype</td>
<td>66%</td>
<td>39%</td>
</tr>
<tr>
<td>rectal CRC, MSI, KRAS mutation</td>
<td>43%</td>
<td>18%</td>
</tr>
<tr>
<td>other CRC, MSS, KRAS wildtype</td>
<td>60%</td>
<td>31%</td>
</tr>
<tr>
<td>other CRC, MSS, KRAS mutation</td>
<td>52%</td>
<td>24%</td>
</tr>
<tr>
<td>other CRC, MSI, KRAS wildtype</td>
<td>47%</td>
<td>25%</td>
</tr>
<tr>
<td>other CRC, MSI, KRAS mutation</td>
<td>48%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Conclusions: Survival for stage IV CRC shows marked variation depending on loca-tion, MSI and KRAS mutation. The prognostic effects of molecular features varies by CRC location, demonstrating largest impact in rectal cancers.

Legal entity responsible for the study: Hyun S. Kim, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Results: The current literature on stage IV colorectal cancer (CRC) indicates a survival advantage for left-sided CRC. Still, the biological basis remains unclear. We assessed the interaction of cancer location with microsatellite instability (MSI) and KRAS mutation to elaborate how key molecular features modify the effect of cancer location on overall survival.

Methods: The 2010–2015 United States National Cancer Database was searched for stage IV colorectal adenocarcinoma. Overall survival (OS) was assessed via Cox models, implementing 2/3-way interaction terms.

Conclusions: Survival for stage IV CRC shows marked variation depending on location, MSI and KRAS mutation. The prognostic effects of molecular features varies by CRC location, demonstrating largest impact in rectal cancers.

Legal entity responsible for the study: Hyun S. Kim, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Results: A total of 408 synchronous mCC patients, with available data on both PTR status and side, were included (CAIRO: n = 279; CAIRO2 n = 129, excluding patients treated with both bevacizumab and cetuximab). We used mixed effect Cox regression models to study the association between PTR and overall survival (OS) and to estimate hazard ratios (HR). Models were adjusted for age, treatment arm, WHO performance status (PS), serum lactate dehydrogenase (LDH) and year of enrollment as potential confounders. To analyze whether PTR effect was modified by sidedness, we tested the interaction term of PTR status and sidedness.

Conclusions: Survival for stage IV CRC shows marked variation depending on location, MSI and KRAS mutation. The prognostic effects of molecular features varies by CRC location, demonstrating largest impact in rectal cancers.

Legal entity responsible for the study: Hyun S. Kim, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
The EMAST defines a unique molecular subtype of CRC.

Results: Both positive and negative selection of somatic mutations in DNA repeats was observed, leading us to identify the expected driver genes associated with the MSI-driven tumorigenic process. Several coding negatively selected, MSI-related mutational events within microsatellites, while adapting preexisting models to analyze non-repetitive DNA sequences. Negatively selected coding alterations in MSI CRC were investigated for their functional and clinical impact in CRC cell lines and in a third cohort of 164 MSI CRC patients.

Conclusions: The present results shed new light on the main driver somatic mutations acting in MSI-driven tumorigenesis, suggesting that genomic instability in MSI CRC plays a dual role in achieving tumor cell transformation.

Legal entity responsible for the study: INSERM.

Funding: This work was supported by grants from the ‘Institut National du Cancer’ (INCa, PRTK MICROSPLOCTHER, SIRIC, and HTE CoLi, to AD), the Fondation ARC (to AC) and the Canceropole Ile de France (to AC). AD group has the label ‘La Ligue Contre le Cancer’. This work is part of the Cartes d’Identité des Tumeurs (CIT) research program, funded and developed by the Ligue Nationale Contre le Cancer.

Disclosure: All authors have declared no conflicts of interest.

Table: 530P

<table>
<thead>
<tr>
<th>HR (95%CI) for OS after PTR versus no PTR</th>
<th>Right-sided mCC</th>
<th>Left-sided mCC</th>
<th>pinterception</th>
<th>Overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 191)</td>
<td>(n = 217)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariable</td>
<td>0.53 (0.38-0.73)</td>
<td>0.66 (0.49-0.87)</td>
<td>0.31</td>
<td>0.61 (0.50-0.76)</td>
</tr>
<tr>
<td>Multivariable</td>
<td>0.60 (0.42-0.84)</td>
<td>0.72 (0.53-0.96)</td>
<td>0.43</td>
<td>0.69 (0.55-0.87)</td>
</tr>
</tbody>
</table>

Conclusion: The previously reported better survival after PTR among synchronous mCC patients included in the CAIRO and CAIRO2 trials was significant for all mCC patients in our analysis, independent of sidedness. Prospective randomized trials on the prognostic effect of PTR in synchronous mCC, i.e. the CAIRO3 trial, remain valid for mCC patients with both right- and left-sided primary tumours.

Background: The form of microsatellite instability (MSI) affecting tetranucleotide repeats known as EMAST (evaluated microsatellite alterations at selected tetranucleotide repeats) has emerged as a new potential biomarker in multiple cancers. In colorectal cancer (CRC), the clinical implications and mutation spectrum of EMAST mutations remain inconclusive.

Methods: We evaluated 1,605 CRC cases using five EMAST markers (D20S82, D20S85, D8S221, D9S242 and MYCL1) and the Bethesda panel of MMR markers. Most commonly mutations involved in CRC were identified by MassArray assay and DNA repair genes were analyzed by Next-Generation Sequencing (NGS). Clinical characteristics and prognostic relevance were correlated with EMAST. SSIP software (version 16.0) was used to perform all statistical analyses.

Results: Tumors with EMAST-positive were detected in 159 (10.6%) out of 1,505 CRC cases and associated with unique clinical features including female predominance (p < 0.001), higher prevalence of proximal colon tumors (p < 0.001), early stage (< T4b) (p < 0.001), poorly differentiated tumors (p < 0.001), mucinous histology (p = 0.001), and MSI (p < 0.001) and higher incidence of mutations in PIK3CA (p = 0.003), BRAF (p < 0.001), TGFBR (p < 0.001), PTEN (p < 0.001), and AKTI (p = 0.04) compared with EMAST-negative tumors. Compared with EMAST-positive alone or MSI-H alone tumors, EMAST-positive MSI-H tumors had higher rates of MSI-H, MSH3, MSH2, and EXO3 gene mutation (p < 0.001, p = 0.001, and p = 0.027) and MLH1, MSH6, and EXO1 gene mutation (p = 0.019, p = 0.005, and p = 0.046). Finally, EMAST-positive was a good prognostic indicator in early stage CRC (p = 0.002) but not in late CRC (p = 0.920).

Conclusions: The EMAST defines a unique molecular subtype of CRC.

Legal entity responsible for the study: Taipei Veterans General Hospital.

Funding: Taipei Veterans General Hospital, Ministry of Science and Technology.

Disclosure: All authors have declared no conflicts of interest.

Table: 533P

<table>
<thead>
<tr>
<th>Distinct clinicopathological features of hypermutant colorectal cancers with POLE pathogenic mutations. Lynch syndrome and sporadic MSI analyzed over 1,000 colorectal cancer patients</th>
</tr>
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<tr>
<td>T. Nagasaka 1, A. Nyuya 1, H. Taritacl 1, Y. Katsus 1, M. Yokota 1, F. Taraguchi 1, T. Kawa 1, Y. Moriy 1, K. Srgyeayus 1, M. Okawaki 1, Y. Yamaguch 1</td>
</tr>
<tr>
<td>1Medical Oncology, Kawasaki Medical School Hospital, Kurashiki, Japan, 2General Surgery, Kurashiki Central Hospital, Kurashiki, Japan, 3Surgery, Iwakuni Clinical Hospital, Iwakuni, Japan, 4Gastroenterological Surgery, Okayama University Hospital, Okayama, Japan, 5Digestive Surgery, Kawasaki Medical School Hospital, Kurashiki, Japan</td>
</tr>
</tbody>
</table>

Background: POLE proofreading mutations cause ultrahypermutant-phenotype in colorectal cancer (CRC) but the characters of POLE mutations are still obscure in contrast to Lynch syndrome or sporadic microsatellite instability (MSI). Herein, we examined mutation profiles of POLE in 1,039 CRC Japanese patients, and tried to clarify clinicopathological features of hypermutant CRC patients with respect to POLE mutations, Lynch syndrome and sporadic MSI.

Methods: We analyzed POLE pathogenic hotspot (exon9, 13 and 14), BRAF codon 600 and KRAS exon 2 mutations by Sanger sequencing. MSI status was confirmed by a multiplex PCR assay. MSI positive cases were confirmed the four mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and MSH3) expression. Germline mutations were analyzed by Sanger sequencing and a TruSight One Sequencing Panel using a next generation sequencing.

Results: Of 1,039 CRC patients, only four cases showed POLE pathogenic mutations (two P280R, one V411L and one S459F). The four POLE mutant CRCs showed no MSI with MMR deficient (ns-MSI) were observed in 58 cases (5.6%). Of CRCs with MSI, Lynch syndrome was found in 17 cases, but the rest of 41 cases were sporadic MSI. Therefore, we divided 1,039 CRCs into the four subsets: POLE mutant (POLE, n = 4, 0.4%), Lynch syndrome (LS, n = 17, 1.6%), sporadic MSI (MSI, n = 41, 4.0%), and non-hypermutant CRCs (NH; n = 997, 94.0%). Mean age at diagnosis in POLE/LS/MSI/NH was 52.3/35.7/73.6/65.9 years, respectively (P < 0.001). Frequency of female in POLE/LS/MSI/NH was 50.2/33.4/36.1/41.8% (P = 0.03). The primary tumor located at the right colon was observed in 100/35/80/30% of POLE/LS/MSI/NH (P < 0.001). BRAF mutation was observed in 49% of MSI and 4% of NH while KRAS mutation was in 35% of LS and 32% of NH (P < 0.001). Interestingly, 100/82/78% of POLE/LS/MSI tumors were diagnosed at the earlier stage, I or II, while 46% of MSI (P < 0.001). The recurrence free survival rate at 5-years was better in POLE (100%)/LS (86%)/MSI (94%) compared with that in NH (74%).

Conclusions: POLE-mutant CRC was rare, observed in the younger without family history, located at the right colon, and diagnosed at the earlier stage.

Legal entity responsible for the study: The authors.

Funding: The Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Disclosure: All authors have declared no conflicts of interest.
Patterns of germline and somatic mutations in 16 mismatch repair associated genes analyzed with next generation sequencing (NGS) in colorectal cancer with EMASHT or/and MSI-high

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Background: We assume that besides mismatch repair (MMR) genes, next generation sequencing (NGS) of MMR associated genes could detect improvement of driver mutators and clarify the somatic mutation patterns of subtype CRC classified by EMASHT and MSI-high.

Methods: Extracted from a 1505 CRC cases database, 81 cases with MSI-high and EMASHT or/and 78 cases with MSI-low and 72 cases with MSI-high but EMASHT were identified. The tumor and WBC DNA were applied and got from Biobank of Taipei-Veteran General Hospital after approval of IRB. The germline and somatic mutations were analyzed with 16-genes NGS (Illumina HiSeq2500 system).

Results: Totally 284 pathological germline mutations were identified in 161 patients with MSI-high or EMASHT. The most common gene were EPCAM (17.3%), MSH6 (16.9%), followed by MLH1 (15.2%) and AXIN2 (15.2%). Majority of EMASHT and MSI resulted from not only MMR dysfunction, but also germline mutations of AXIN2, POLD1 and TGFBR2. After deduction of 284 germline mutations, there were 1,090 somatic mutations in 161 cases with germline mutations, 445 mutations in 70 cases without germline mutations. Tumors with EMASHT and MSI-high had significantly higher mutation number than those of with only EMASHT or only MSI-high. Besides germline mutations of AXIN2, germline mutations of other genes were similar. With AXIN2 germline mutations, somatic mutation rate was 187.9 ± 8.8 mutations/Mb significantly higher than those of without germline mutations (137.8 ± 84.5 mut/Mb p = 0.002). Besides five major MMR genes, Eleven Axin2, eight POLD1 and six TGFBR2 germline mutations resulted in following MSI-high or EMASHT (+) genotype without other accompany germline mutation. Clinically, patients with germline mutation had significantly higher frequency of proximal tumor location and early stage disease.

Conclusions: Our result showed that NGS could enhance detection of familial CRC. Somatic mutation burdens might be through MSI or EMASHT but not only germline mutation genes themselves. Several genes with germline mutations could explain origin of the familiar CRC. AXIN2 gene was designed to further experiment to confirm its role in WNT pathway and as a hypermutator.

Lower tumor mutational burden (TMB) and hepatic metastases may predict for lack of response to PD-1 blockade in MSI-H metastatic colorectal cancer (mCRC)

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Background: MCRC with microsatellite instability (MSI-H) are associated with cytotoxic lymphocytic infiltration that is counterbalanced by multiple checkpoints. Several prospective clinical trials in chemotherapy-resistant MSH-MCRC have demonstrated a high rate of disease control and a favorable progression free survival (PFS) with PD-1 inhibitors. However, there is a significant discrepancy in response rates (RR) with pembrolizumab and nivolumab (28-52%), likely reflecting patient heterogeneity. We sought to determine the RR to PD-1/PD-L1 targeting in a single center setting.

Methods: All MCRC patients (pts) with MSI-H tumors (by CLIA certified PCR, IHC, or NGS assays) who were treated at City of Hope with PD-1 or PD-L1 inhibitors starting Jan 2016 were identified. RR and PFS were determined by RECIST 1.1. BRAF status, primary tumor location, and metastatic sites were collected on all pts. TMB as determined by FoundationOne on 0.83-1 megabases (Mb) of sequenced DNA was collected, when available.

Results: 17 pts with MSI-H tumors were identified (16 treated with pembrolizumab and 1 with durvalumab). Pts characteristics were: male (10, 59%), age (median 53.7 years, range 33-79), BRAF mutant (6, 35%), right sided (11, 65%), and liver-sparing (8, 47%), 7 (41%) had an objective response, 2 (12%) had stable disease. The median PFS was 9.97 months (mo), and the 6 and 12 mo PFS rates were 53% and 35%, respectively. TMB was available for 9 MSI-H cases (range 8 – 73 mutations/Mb): 1 CR (TMB 73), 1 PR (TMB 71), and 1 SD (TMB 31), and 6 PD (TMB 6, 13, 18, 25, 36). We categorized our patients based on the lowest 10% (TMB < 23.5) and 25% (TMB < 33.06) TMB cutoffs identified from a large Foundation Medicine database of 2811 MCRC. All 44 pts in the lowest TMB decile and 5/6 in the lowest TMB quartile experienced PD. On univariate analysis, only hepatic metastases (p = 0.01) and low TMB (p = 0.02) were associated with poor PFS.

Conclusions: A substantial percentage of pts with MSI-H tumors will progress with PD-1/PD-L1 inhibitors; these patients appear to be enriched for a low TMB status and hepatic metastases. Additional studies should explore TMB as a predictive marker of response to checkpoint inhibition in MSI-H CRC.

Legal entity responsible for the study: City of Hope.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Assessment of local clinical practice for testing of mismatch repair deficiency in metastatic colorectal cancer: The need for new diagnostic guidelines prior to immunotherapy

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Background: Immunologic checkpoint inhibitors (ICIs) have been approved for patients with metastatic colorectal cancer (mCRC) displaying MSI-DMMR (microsatellite mutability, defective mismatch repair). We aimed to evaluate the accuracy of standard immunohistochemistry and PCR methods for the detection of MSHdMMR in mCRC in routine clinical practice.

Methods: The study was performed on a multicenter retrospective cohort of mCRC displaying MSH-DMMR (microsatellite mutability, defective mismatch repair). We evaluated the accuracy of standard immunohistochemistry and PCR methods for the detection of MSHdMMR in mCRC in routine clinical practice.

Results: The study was performed on a multicenter retrospective cohort of mCRC displaying MSH-DMMR (microsatellite mutability, defective mismatch repair). We aimed to evaluate the accuracy of standard immunohistochemistry and PCR methods for the detection of MSHdMMR in mCRC in routine clinical practice.

Legal entity responsible for the study: The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University’s Clinical Cancer Institute of Nanjing University.

Funding: National Natural Science Foundation of China; Nanjing Medical Science and Technique Development Foundation.

Disclosure: All authors have declared no conflicts of interest.

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Legal entity responsible for the study: The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University’s Clinical Cancer Institute of Nanjing University.

Funding: National Natural Science Foundation of China; Nanjing Medical Science and Technique Development Foundation.

Disclosure: All authors have declared no conflicts of interest.
Results: Nine false-positives (9.8%) were found in the retrospective cohort (N = 92). These were initially diagnosed as MSI and/or dMMR by the originating institute but were reclassified as MMR proficient (microsatellite stable in our laboratory (PPV = 90.2%; 95%CI, 83.2 - 96.5)). The PPV in the prospective cohort (N = 39) was 92.3% (95%CI, 79.0 - 98.1), with the 3 false-positive patients experiencing progressive disease with ICIK treatment. Amongst the 119 true-positive mCRCs, the detection rate and sensitivity were respectively 100% and 95.8% for immunohistochemistry, while for pentaplex PCR these were 81.5% and 95.9%. Only the combination of immunohistochemistry and pentaplex PCR methods resulted in 100% detection rate and 100% sensitivity.

Conclusions: Local assessment of MSI/dMMR status in mCRC resulted in misdiagnosis of 9.1% of cases as false positive and subsequently incorrect treatment with ICIK. We recommend new guidelines that mandate dual testing of mCRC samples in experienced diagnostic centers using both PCR and immunohistochemistry.

Legal entity responsible for the study: INSERM.


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Pre-diagnostic anthropometry, sex, and risk of colorectal cancer according to tumor-infiltrating immune cell composition

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Background: Obesity is a well-established risk factor for colorectal cancer (CRC), but whether this risk differs according to CRC subtype defined by the tumor immune microenvironment has been sparsely described. Herein, we examined the relationship between pre-diagnostic anthropometry and CRC risk according to tumor-infiltrating immune cell composition, with particular reference to potential sex differences.

Methods: The density of immune cells expressing PD1, PD-L1 (PD-L1/IC1), CD3, CD8, FoxP3, CD20, CD68, CD163, and tumor cells expressing PD-L1 (PD-L1/IC2) was assessed by immunohistochemistry in tissue microarrays with tumors from 584 incident CRC cases in the Malmo Diet and Cancer Study (n = 28098). Multivariable Cox regression models, adjusted for age, smoking and alcohol intake, were applied to calculate hazard ratios (HR) for CRC risk according to height, weight, body fat %, waist-hip circumference, waist-hip ratio (WHR), body mass index (BMI), and different immune cell subsets.

Results: Obesity, measured as several anthropometric factors, was significantly associated with PD-L1/IC1/low/low, CD8high, FoxP3 low, CD20+ low, and CD68+ low tumors in both sexes, and with PD1+ low tumors in women. A contrasting risk between sexes was seen for PD-L1/IC2 tumors, in that obesity was significantly associated with risk of PD-L1/IC2+ high tumors in women (pinteraction for weight = 0.008, pinteraction for BMI = 0.039) but with risk of PD-L1/IC2+ low tumors in men (pinteraction for weight = 0.003, pinteraction for body fat % = 0.003, pinteraction for waist < 0.003, pinteraction for hip < 0.002, pinteraction for BMI = 0.001, pinteraction for WHR < 0.001). Furthermore, obesity was associated with risk of any CD3+ high or low and any CD68+ high or low tumors in both sexes, and with any PD1+ high or low tumors in men. In age and BMI-adjusted survival analysis, PD1+ high, CD8+ high, CD68+ high were favorable prognostic factors only in women, and FoxP3+ high only in men. High PD-L1- and CD5+ expression was prognostic in both sexes.

Conclusions: Anthropometric factors may influence the immune landscape of colorectal cancer, possibly in a sex-dependent manner. Thus, obesity and sex may be important factors to take into account when stratifying patients for immunotherapy.

Legal entity responsible for the study: Lund University.

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Disclosure: All authors have declared no conflicts of interest.

540P

Monocyte-to-lymphocyte ratio in metastatic colorectal cancer: Prognostic role evaluation and cut-off definition

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Background: Changes in peripheral blood cells composition may reflect tumor immune microenvironment and its role in cancer growth control. High monocyte-to-lymphocyte ratio (MLR) could be a sign of tumor’s recruitment of suppressive cells, showing a prognostic role in many cancer types. This study aimed to evaluate the prognostic role of MLR in metastatic colorectal cancer (MCRG).

Methods: This retrospective study analyzed a consecutive cohort of 392 patients (pts) with metastatic colorectal cancer treated in 2004-2017 at the Oncology Departments of Aviano and Udine (Italy). The prognostic impact of MLR on overall survival (OS) was evaluated with univariate and multivariate Cox regression analyses. The best cut-off value to predict survival was defined through ROC analysis.

Results: Before first line therapy, 269 pts (69%) were aged <70, 120 pts (31%) had a right tumor, 150 pts (38%) was a left tumor and 171 pts (43%) a recanal. Of note, 105 pts (27%) received metastasectomy and 142 pts had >1 metastasis. Metastasis were more frequent in liver (40%), lung (28%) and peritoneum (29%) Overall, 57% had a KRAS mutation (m) and 11% had a BRAFm. At median follow-up of 60 months, median OS was 26 months. At univariate analysis, older age (HR 1.61, p < 0.001), nodes (pN2 HR 1.48, p = 0.036, pN3 HR 2.52, p < 0.001), KRAS (HR 1.36, p = 0.020) and MLR (HR 3.32, p < 0.001) were associated with worse OS. Conversely, sidedness (left HR 0.65, p = 0.003, rectum HR 0.73, p = 0.042), metastasectomy (HR 0.36, p < 0.001) and adjuvant chemotherapy (HR 0.66, p = 0.098) were associated with better OS. By multivariate analysis, sidedness and metastasectomy confirmed a better OS, while MLR (HR 3.20, p < 0.001), nodes (pN2 HR 1.89, p = 0.006, pN3 HR 2.25, p = 0.014), and KRAS (HR 1.50, p < 0.001) were associated with worse OS. The adoption of the cut-off value for MLR (i.e. 0.44) predicted worse OS both in univariate (HR 2.23, p < 0.001) and multivariate (HR 2.41; p < 0.001) analyses. Moreover, MLR was associated with number of metastatic sites (p < 0.001), type of sites (p < 0.001), sidedness (p < 0.001) and LDH level (p < 0.001).

Conclusions: High MLR is an independent prognostic factor associated with worse OS and pathological features of MCRG. Further studies are needed to confirm these data.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Clinical relevance of circulating tumour DNA using amplicon-based deep sequencing panel in colorectal cancer patients with metastasis


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Background: Liquid biopsy system using the detection of circulating tumour DNA (ctDNA) is expected to provide the utility as a novel diagnostic tool for cancers. Methods: We prospectively enrolled a total of 101 colorectal metastatic cancer (mCRC) patients with liver metastasis. We investigated frequency of detectable mutations in cell-free DNA (cfDNA), concordance rate of RAS mutation between tissue and ctDNA, and relationship between allele frequencies (MAFs) and clinicopathological factors. We further investigated the relationship between time course of ctDNA and chemoresponse. Amplicon-based deep sequencing with molecular barcode (including hotspots of 14 genes) was performed to detect the ctDNA.

Results: Mutations in plasma cfDNA were detected in 87.1% (88/101) of patients. The frequencies of plasma ctDNA mutation at TP53, KRAS, APC, and PIK3CA were 68.3%, 36.6%, 23.7%, and 14.8%, respectively. RAS ctDNA concordance rate between tissues and plasma was 76.2% (77/101). MAFs were significantly associated with CEA (P = 0.0001), CA19-9 (P = 0.006), LDH (P = 0.0001) levels and the number of metastatic organs (P = 0.0001). Patients with liver or lymph node metastasis had significantly higher MAF compared with those without metastasis (P = 0.0001, P = 0.008, respectively). The patients with lower MAF at 8 weeks after initiation of chemotherapy showed significantly longer survival than those with higher MAF (>median ≤ median, PFS = 0.001, OS = 0.049). Increase of MAF had been observed earlier than tumour markers before disease progression were confirmed by computed tomography (P = 0.01).

Conclusions: Our results suggested that this ctDNA assay could detect mutations at a high rate of mCRC patients, and could be a useful tool for early detection of chemoresistance as well as a prognostic marker in the clinic.

Disclosure: All authors have declared no conflicts of interest.

542P Droglet digital PCR of circulating tumour DNA for the detection of RAS/BRAF mutation in metastatic colorectal cancer


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Background: We have conducted a phase II trial of 1st-line modified (m)-FOLFOXIRI plus bevazumab (bev) in metastatic colorectal cancer (mCRC) harboring RAS mutation.

543P Gene mutation status in circulating tumor DNA (ctDNA) and first-line FOLFIRI plus bevacizumab (bev) in metastatic colorectal cancer


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Background: We have conducted a phase II trial of 1st-line modified (m)-FOLFOXIRI plus bev for RAS mutant mCRC, which included a biomarker study using liquid biopsies (Uncotarget 2018). There are few reports on monitoring changes in gene mutation (mt) status in mCRC harboring RAS mt. Therefore, the pre-planned analysis was performed to investigate a number of genes in ctDNA during therapy that might be determinants of therapeutic efficacy.

Methods: Sixty-two patients (pts) with resectable/curable measurable tumors received protocol treatment with m-FOLFOXIRI (irinotecan 150 mg/m2, oxaliplatin 85 mg/m2, levofolinate [LV] 200 mg/m2, and fluorouracil 2400 mg/m2 repeated biweekly) plus bev. The phase II trial included objective response rate (ORR) for primary endpoint and progression-free survival (PFS), overall survival, early tumor shrinkage, depth of response (DpR), and safety for secondary endpoints. In 53 pts who enrolled in the biomarker study, plasma samples for extraction of ctDNA were collected at 3 points (pre-, wks 4, and progression) and analyzed for specific KRAS and NRAS variants with real-time PCR assays.

Results: Fifty-three pts had the following clinical data: median age of 61yrs, 57% male, 91% PS0, 28% right-sided tumors, ORR of 72%, median DpR of 49% and median PFS of 10.8 months. RAS mt was detected in pre-treatment plasma in 79% (42/53) of pts. Among pts with mt in ctDNA at pre-treatment, 76% changed to mt-negative 8wks after treatment. ORR and DpR were higher in pts of mt-negative at 8wks compared to pts of mt-positive (81% vs. 50% and 55% vs. 34%, respectively). Median PFS was 11.9 and 8.8 months in pts who were mt-negative and mt-positive, respectively (HR = 0.58, 95%CI 0.25–1.33, P = 0.20). Interestingly, in 26 pts who experienced progressive disease (PD)
and were evaluable for ctDNA analysis. 52% (11/21) of pts with mt at pre-treatment still had no mt in plasma at PD. Pts of mt-negative at PD had longer survival time from PD compared to pts of mt-positive (9.3 vs 7.0 months).

**Conclusions:** Gene mt status in ctDNA during therapy may predict clinical outcome of triplet plus bev treatment in RAS mutant mCRC. Our study suggests that pts with no mt in plasma at PD may have more favorable post-treatment.

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**544P**

cDNA assays identify alterations in RAS, EGFR, and cMET that are unique to RAS-WT patients progressing on anti-EGFR therapy


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**Background:** Circulating tumor DNA (ctDNA) assays and tumor sequencing provide insight to tumor heterogeneity and mechanism of resistance in patients with mCRC. Direct comparisons between Guardant360® (G360) ctDNA panel and the comprehensive FoundationOne® (FO) panel in mCRC patients (pts) are limited.

**Methods:** We identified mCRC pts with FO at diagnosis and subsequent G360 ctDNA assays. Pts were divided into 3 categories based on ctDNA collection date: 1) ctDNA testing prior to any treatment, 2) ctDNA following non-anti-EGFR therapy and 3) ctDNA following anti-EGFR progression (PD). We compared genomic alterations by FO and G360 within the same pts to characterize clonal evolution and its impact on outcome.

**Results:** 43 pts with MCR with FO had at least one ctDNA assay. High concordance between ctDNA and FO was noted in untreated pts (n = 11) for common oncogenic drivers, including RAS and cMET. In total, 13/11 (1/13) of RAS mutations were identified on G360 only: NRAS E31D (unknown significance), and a low frequency G12D (0.3%) which may have been below the reporting limits for FO. Concordance was also noted in pts pre-treated with non-anti-EGFR therapy (n = 11). In contrast, ctDNA assays of RAS-WT pts with PD following anti-EGFR (n = 19) showed a high rate of emerging activating KRAS (Q61H (3/19 (15.8%) and L91V (1/19 DNA 1.01%), EGFR V441G (3/19 ctDNA 6.4%-7.9%), and FGFR2 mutations (2/19 ctDNA 1.0%-2.1%), suggesting that these are common mechanisms of resistance[VR1]. 1 pt had emergence of EGFR V441G mutation without any KRAS or NRAS mutations.

**Conclusions:** In untreated and progressing anti-EGFR naive pts, ctDNA provides an accurate assessment of oncogenic RAS and BRAF status. Clonal evolution is captured on ctDNA in response to anti-EGFR therapy and extends beyond emerging RAS mutations to EGFR mutations and cMET amplification.

**Legal entity responsible for the study:** Marwan Fakih.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
First-line treatment outcomes according to cfDNA analysis of RAS mutation status in metastatic colorectal cancer (mCRC) patients (pts): PERSEIDA study

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Background: Tumour-tissue biopsy testing is the standard of care (SOC) to assess RAS mutation in mCRC pts. However, the analysis of circulating cell-free DNA (cfDNA) has the added advantage of being able to evidence genetic tumour heterogeneity. We explored the correlation of the RAS mutational status assessed in plasma samples with first-line (1L) treatment outcomes in SOC RAS wild type (wt) mCRC pts.

Methods: Prospective, observational, multi-centre study in mCRC pts with RASwt according to tumour-tissue biopsy and treated following standard clinical practice. Plasma samples were collected before starting 1L treatment and sent to Symyx Insmics GmbH for BEAMing analysis. The lower threshold limit was a mutant allele fraction (MAF) > 0.02%. Tumour response (TR) was evaluated approximately every 3 months based on RECIST criteria.

Results: 119 pts were included (61% male; median age: 65 y). 113 received chemotherapy (CT) and 61 anti-EGFR, 4 CT + anti-VEGF and 2 CT alone. Overall response rate (ORR) was 68.1% (95% CI: 58.9-76.3) for all pts and 75% (95% CI: 65.8-82.8) in the 108 pts with TR data. In pts treated with panitumumab (n = 92), the most homogeneous group, 76.3% (n = 70) presented left-sided tumours and 19.6% (n = 18) right-sided; overall ORR was 78.3% (95% CI: 68.4-86.2); 81.4% (95% CI: 73.8-89.7) for left and 72.2% (95% CI: 46.9-90.3) for right-sided pts. ORR in the panitumumab subgroup according to RAS mutational status analysed in cfDNA for the three MA F cut-offs (table) is considered presented in the left.

Table: 546P

<table>
<thead>
<tr>
<th>Mutant allele fraction, RASwt</th>
<th>ORR (not confirmed)</th>
<th>ORR (confirmed)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1% (80 wt/2 mt)</td>
<td>78.9 (69.0 - 86.8)</td>
<td>500 (1.3 - 98.7)</td>
<td>3.7 (0.2 - 62.6) 0.389</td>
<td></td>
</tr>
<tr>
<td>&gt;0.01% (87 wt/5 mt)</td>
<td>79.3 (69.3 - 87.3)</td>
<td>600 (14.7 - 94.7)</td>
<td>2.6 (0.4 - 16.5) 0.297</td>
<td></td>
</tr>
<tr>
<td>&gt;0.02% (80 wt/12 mt)</td>
<td>80.6 (69.8 - 91.2)</td>
<td>66.7 (34.9-90.1)</td>
<td>2.0 (0.5 - 7.3) 0.285</td>
<td></td>
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</tbody>
</table>

*Fisher Test; CI=confidence interval; ORR: Overall Response Rate.

Conclusions: A high ORR was observed in pts treated with panitumumab independently of the localization. ORR in panitumumab treated patients tends to be higher in plasma RASwt. ORR in pts with plasma RASmt increases when a lower MAF cut-off is used. Further investigation is needed to find the optimal clinical cut-off. Study supported by Amgen.

Legal entity responsible for the study: Amgen.

Funding: Amgen.

Disclosure: P. García Alfonso: Consulting fees: Amgen, Bristol, Merck, Sanofi, Roche, Bayer, Servier. M. Valderrama-Ayebes: Research grants: Roche; Consulting fees: Amgen, Roche, Merck, Sanofi, Servier. J.M. Vélez: Research grants: Amgen, Roche; Consulting fees: Amgen, Roche, Servier, Bayer, J.J. Cruz Hernandez; Consulting fees: Amgen, Merck, Roche, BMS. A. Leambil Vila: Full time employee, stocks: Amgen. All other authors have declared no conflicts of interest.

Serial monitoring of circulating tumour DNA in patients with metastatic colorectal cancer to predict the therapeutic response

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Background: Early biomarkers of therapeutic responses could help optimize the treatment of metastatic colorectal cancer (mCRC). This prospective exploratory study was designed to explore the serial changes in plasma-circulating tumor DNA (ctDNA) as an early marker of therapeutic response to systemic treatment in mCRC.

Methods: Forty-seven mCRC patients receiving standard first-line therapy every two weeks were enrolled. Somatic mutations in plasma ctDNA were detected serially before each of the first four cycles via next-generation sequencing, and the mutation of maximal frequency before treatment ctDNA was selected as the candidate mutation for analysis. Radiologic responses were assessed after the fourth cycle.

Results: The results indicated that mutations in pretreatment ctDNA could be detected in 45 (95.7%) patients. Among the 41 patients monitored serially, imaging after four cycles of treatment showed 17 PR, 18 SD, and 6 PD cases. Changes in ctDNA could differentiate patients with progressive disease two cycles (approximately four weeks) earlier than the changes in CEA and CA19-9 levels could, and changes in ctDNA levels as early as prior to cycle 2 predicted the radiologic responses after cycle 4. A log2 value of fold-change in ctDNA after cycle 1 (log2 [C1/C0]) > -0.832 predicted progressive disease, with a sensitivity and specificity of 100.0% (95% CI: 54.1-100.0%) and 85.7% (95% CI: 69.7-95.2%), respectively, and an accuracy of 87.8% (95% CI: 73.8-95.9%). Patients with ctDNA log2 (C1/C0) > -0.832 showed significantly higher progression-free survival than did those with log2 (C1/C0) ≤ -0.832 (median 2.5 versus 9.0 months; P = 0.016).

Conclusions: The present exploratory study suggests that early changes in ctDNA that are detected via targeted sequencing might potentially predict later radiologic responses in mCRC.

Legal entity responsible for the study: Peking Union Medical College Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Cross-platform comparison of NGS and MALDI-TOF for detecting RAS/RAF/PK/RCA mutations in circulating tumor DNA from metastatic colorectal cancer patient plasma

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Background: Evaluating tumor RAS/RAF status is essential for treatment selection and prognosis evaluation in metastatic colorectal cancer (mCRC) patients. Analyzing ctDNA in mCRC patients has many advantages because of its non-invasive nature. However, since the signal of ctDNA is generally low, detection of ctDNA from different platforms need to be carefully interpreted before adapting new technology into routine clinical application.

Methods: 60 mCRC patients under different treatment status were recruited. A cross-platform comparison between MALDI-TOF (UltraSeek) and next-generation sequencing (NGS) was done by examining KRAS/NRAS/BRCA/PK/RCA mutations frequency in plasma from patients. Inconsistent results between two platforms were examined by droplet digital polymerase chain reaction (ddPCR). All results were compared to the mutation status in tissue retrospectively.

Results: In the comparison between NGS and MALDI-TOF, we focused on 65 hotspots, 53.57% and 69.71% of the samples were reported to be positive by NGS and MALDI-TOF respectively. Concordance rate between two platforms was 73.21%. Discrepancy between two platforms was examined by ddPCR, and a reproducible result was then treated as a true positive. The PPA of NGS and MALDI-TOF was 93.94%, 90.91% NPA of NGS and MALDI-TOF was 99.97%, 99.63% respectively. After establishing a ground truth for plasma result, 56 patients were found to have comparable ARMS result from tissue. Apart from 10 patients undertaking chemotherapy or Cetuximab, 95.4% (44/46) patients have their plasma result consistent with that from tissue. For 10 patients undergoing treatment at the time of plasma acquisition, ctDNA status detected by NGS was shown to be an effective biomarker to monitor the response to treatment: 90% (9/10) of patients had a ctDNA status that were consistent with their progression status.

Conclusions: ctDNA detected by NGS was showed to be a reliable signal that reflects tumor burden and informs treatment response. Even challenge exists in detecting variants in low frequency in plasma, appropriate selection of technology allows reliable examination of clinical utility in upcoming clinical studies.

Legal entity responsible for the study: Zhongshan Hospital, Fudan University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
mCRC who converted to wt-RAS status in blood over the course of first-line treatments. As proof of concept, the absence of any clinically relevant mutation of RAS genes in blood has been used as a therapeutically exploitable window. To this purpose five mCRC patients harboring any RAS mutation in tumor tissue and plasma at the time of diagnosis were serially monitored through plasma ctDNA analysis. Eleven patients (73%) switched to a wild-type RAS status in blood during the course of first-line treatments. At disease progression in the first-line setting, 5 of them have received EGFR inhibitors as a second-line treatment, achieving a durable clinical benefit.

**Conclusions:** ctDNA analysis might reveal a therapeutically exploitable window of opportunity, characterized by the prevalence of wt-RAS clones, which can be converted in a clinically meaningful benefit for patients. Our planned KAIROS trial might determine whether the response to EGFR inhibition, in patients with RAS mutant cancers converted to RAS wild-type in course of treatments, might become the rule rather than the exception.

**Legal entity responsible for the study:** Angela Santoni.

**Funding:** No funding.

**Disclosure:** E. Cortesi: Consulting or advisory role: Bristol-Myers Squibb Italia, Sirtex Medical. All other authors have declared no conflicts of interest.

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**Table: 550P**

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<td>1-5%</td>
<td>89.1% (33/37) (p = 0.1336)</td>
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<td>65.1% (41/63) (p &lt; 0.0001)</td>
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Significant differences have been observed in patients with liver and other metastases, except lung, 41/51 (80.4%, p = 0.0044) and patients with lung and other metastases, except liver, 16/24 (66.7%, p = 0.033). **Conclusions:** OncoBEAM demonstrated significantly greater sensitivity for plasma detection of RAS mutations than Idylla. Moreover, these data identify a “gray zone” below 1% MAF where Idylla fails to identify RAS positivity in patient plasma samples. These findings show that liquid biopsy assays with diminished sensitivity may lack the dynamic range to provide accurate and timely RAS mutational status information to lead patient outcomes. Idylla biopsy has emerged as a viable alternative to individualize the management and personalized therapy of mCRC patients. The objective of this study was to provide a head-to-head comparison of the sensitivity of two tests for KRAS mutation detection in plasma from mCRC patients: ddPCR-based OncoBEAM and qPCR Idylla.

**Methods:** Plasma samples from mCRC patients determined to be KRAS-positive using OncoBEAM were re-tested using Idylla. 116 samples with mutant allelic fractions (MAF) below 5% were selected for analysis. The positive percent agreement (PPA) of OncoBEAM were re-tested using Idylla. 116 samples with mutant allelic fractions (MAF) below 5% were selected for analysis. The positive percent agreement (PPA) of OncoBEAM was 0.9% (range 0.1-2%). This significantly decreased over treatment (0.13% week 3 RT, 0.3% final week RT, 0.1% prior to surgery) (p < 0.05). 10 patients had a KRAS mutation in their baseline ctDNA that was not detected in their biopsy, with a median MAF of 0.3% (range 0.1-1.3%). Mutations in NRAS and PIK3CA were identified in 3/27 (11%) and 2/27 (7%) of patients, respectively. NRAS and PIK3CA mutations were identified in the ctDNA of 2/3 (67%) and 1/2 (50%) patients. Post-operative ctDNA samples were available for 13 patients and residual mutations were detected in 10 patients (77%), 3 of whom (30%) had recurrence at median follow up of 20.1 months. There was no recurrence in any patient with negative ctDNA post-surgery.

**Conclusions:** ctDNA can identify clinically relevant biomarkers and could be used as a minimally invasive alternative to repeated tumor biopsies to monitor tumor evolution. ctDNA detection after resection may provide evidence of residual disease and could identify patients at high risk of recurrence.

**Clinical trial identification:** NCT02151019.

**Legal entity responsible for the study:** Cancer Trials Ireland.

**Funding:** St. Luke’s Institute of Cancer Research.

**Disclosure:** A. Santori, D. Irwin: Employee, stock owner: Agena Biosciences. S. Hummel: Employee: Agena Biosciences. All other authors have declared no conflicts of interest.

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553P Dynamic monitoring of KRAS, NRAS, BRAF and PIK3CA mutations in circulating cell-free DNA for metastatic colorectal cancer patients treated with cetuximab

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Background: Genomic heterogeneity affects response to targeted agents. Liquid biopsy is a promising approach to detect genetic mutations in circulating cfDNA (ctDNA) and allows the tracking of treatment-induced genetic evolution in metastatic colorectal cancer (mCRC) patients.

Methods: Longitudinal plasma samples (n = 92) were collected from 15 mCRC patients receiving cetuximab-contained regimen therapy. KRAS, NRAS, BRAF and PIK3CA mutational status relevant to cetuximab resistance were monitored by next-generation sequencing in plasma, which could be reflected by variant allele frequency (VAF). We also included 11 healthy controls to differentiate total ctDNA levels from mCRC patients.

Results: Of these 15 mCRC patients, baseline plasma samples were collected in 8 patients. The average VAF level in treatment naive patients was significantly higher than healthy cohort (p = 0.0004). Moreover, ctDNA levels correlate with the tumor burden before systemic therapy (R² = 0.544). Dynamics of KRAS/NRAS/BRAF/PIK3CA VAF mirrored disease evolution, showing the same trend with partial response, disease progression and relapse. In addition, KRAS/NRAS/BRAF/PIK3CA VAF gradually declined upon cetuximab withdrawal for more than 2 months, and partial response was again achieved when cetuximab was re-used on 1 patient. This provided a molecular explanation for the efficacy of rechallenge therapies based on EGFR blockade.

Conclusions: Dynamic monitoring of KRAS/NRAS/BRAF/PIK3CA mutations in ctDNA is feasible and appears to be useful in early detection of drug resistance to cetuximab in mCRC patients.

Legal entity responsible for the study: Wujia Fang.

Disclosure: All authors have declared no conflicts of interest.

554P KRAS-dependent and independent mechanisms of progressive disease (PD) in colorectal cancer (CRC) patients (pts) with liver metastases (LM) while monitoring on circulating cell free DNA (ctDNA)

A. Kray1, Z. Mihaylova1, V. Petrova1, T. Todorov2, D. Petkova3, A. Gareva2, A. Todorova-Gareva3
1Human Genetics, Independent Medico-Diagnostic Laboratory Genome Centre Bulgaria, Sofia, Bulgaria, 2Department of Medical Oncology, Military Medical Academy, Sofia, Bulgaria, 3Human Genetics, Genetic Medico-Diagnostic Laboratory Genica, Sofia, Bulgaria, 4Medical Chemistry and Biochemistry, Medical University Sofia, Sofia, Bulgaria

Background: KRAS mutational analysis (MA) in plasma (P) ctDNA is an alternative to tissue (T) analysis with concordance rate (ConR) from 30% to 90%. The emergence of KRAS mutation (M) during the course of anti-EGFR therapy is responsible for acquired resistance (AR). We aimed to evaluate the Ras ConR between T and ctDNA in mCRC pts, and to monitor changes in RAS M status.

Methods: All blood samples were collected in ctDNA Preservative Tubes (Norgen Biotek Corp., Canada). ctDNA was extracted within 3 days after sampling, the extraction was performed by commercial kit (P/Seum ctDNA Purification Mini Kit, Norgen Biotek). KRAS (ex 2) M on P ctDNA and tumor T were detected by real-time PCR kits TheraScreen K-RAS Mutation Kit. The other M were detected by Sanger sequencing (BigDye Terminator v3.1 Cycle Sequencing Kit - Thermo Fisher Scientific).

Results: In the ConR evaluation were enrolled prospectively 63 mCRC pts. Only LM had 26,9% (31) pts, from whom - 27,3% (9) pts had primary resectable LM. The median time from T biopsy (primary -99%) to P collection was 275, 7 days (range 26 - 1560). TMA revealed 58,2% (37) pts from whom 78,4% (29) pts had KRAS ex.2 M. ctDNA evaluation showed the distribution of M to wild (W) - 41,8%19% with KRAS ConR of 58,2%. To reduce time between T and P samples MA in the monitoring analysis was included only 31 pts who had primary unresectable LM, with baseline (b) P col-
lection. In 5 pts with KRAS M after converting treatment, LM resection resulted in W type on consecutive cDNAs. In responding pts (16) with W disease on bDNA, there was no change in MA consequently. In non-responders with W type the appearance of KRAS M was noted in 6 pts, while in the rest 3 pts PD was not correlated to KRAS M. In non-responders with KRAS M on bDNA of P pts, monitoring of cDNA revealed no appearance of KRAS M contemporary with mainly LM PD.

Conclusions: The estimated ConR between primary tumor and ctDNA KRAS MA was 58%. TAM emergence of KRAS M in monitoring evaluation of colorectal cancer (CRC). Compared with the classical tumor markers, ctDNA has higher accuracy and specificity while being noninvasive. Based on the phase II work, we explore the role of cDNA methylation in the detection of PCDH18 as a new tumor marker compared with CEA in the clinical diagnosis and progressive evaluation of colorectal cancer (CRC).

Methods: We collected peripheral blood from 60 patients with advanced primary CRC before and after two courses of treatment, as well as from 60 healthy individuals, and the clinicopathologic characteristics were analyzed. The changes of CEA levels before and after treatment were dynamically monitored by electrochemiluminescence (ECL). The methylation status of PCDH18 was detected by qMSP, the correlation between them was also statistically analyzed, and the value of different indexes in the diagnosis and monitoring of tumor progression of CRC were compared.

Results: We found that the percentage of methylation of PCDH18 in plasma of CRC before treatment was significantly higher than that of normal plasma samples. The difference (p < 0.01) suggests that PCDH18 methylation may be involved in the carcinogenesis of CRC. PCDH18 methylation was not significantly correlated with sex, tumor location, histological type, tumor differentiation, TTM or CEA (p > 0.05). To further explore the relationship between the methylation of PCDH18 and the risk of CRC, the results showed that with the increase of methylation level of PCDH18, the risk of CRC and tumor progression increased significantly, while in CEA group, the OR > 1 only in the group with CEA elevation as the dividing point, but the P value was not statistically significant. The sensitivity and specificity of PCDH18 cDNA methylation combined with CEA in the diagnosis of progression of CRC were 90.0% and 67.6%, respectively. The area under the curve (AUC) reached 0.861. Further analysis showed that PCDH18 cDNA methylation was 67.86% while CEA was negative in CRC progression patients, indicating that PCDH18 cDNA methylation could significantly increase the detection of progression in comparison with CEA.

Conclusions: The methylation of PCDH18 cDNA may play an important role in the diagnosis and prediction of tumor progression in CRC as a new tumor marker and can significantly increase the detection of tumor progression in CEA-negative patients. W.-W. Tang, H.-X. An and D. Zhou contributed equally to this work.

Legal entity responsible for the study: Clinical Research Ethics Committee of the First Affiliated Hospital of Xiamen University.

Funding: This study was supported by the National Natural Science Foundation of China (No. 81702414), the Fujian Provincial Health and Family Planning Commission Foundation of Youth scientific research project (No. 2015-3-43) and Xiamen Science and Technology Bureau Foundation of science and technology project for the benefit of the people (No. 3502z20164010).

Disclosure: All authors have declared no conflicts of interest.

555P Correlation between cDNA methylation and CEA in colorectal cancer

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1Department of Medical Oncology, Xiamen Cancer Hospital, The First Affiliated Hospital of Xiamen Medical University, Xiamen, China, 2Oncology, Fujian Medical University, Fuzhou, China, 3Department of Medical Oncology, Jiangyin Hospital of Xiamen University, Xiamen, China, 4Department of Medical Oncology, First Affiliated Hospital of Xiamen University; Xiamen Humanity Hospital, Xiamen, China, 5Key Laboratory of Design and Assembly of Functional Nanostructures, Fujian Provincial Key Laboratory of Nanomaterials, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, Xiamen, China

Background: Compared with the classical tumor markers, cDNA has higher accuracy and specificity while being noninvasive. Based on the phase II work, we explore the role of cDNA methylation in the detection of PCDH18 as a new tumor marker compared with CEA in the clinical diagnosis and progressive evaluation of colorectal cancer (CRC).

Methods: We collected peripheral blood from 60 patients with advanced primary CRC before and after two courses of treatment, as well as from 60 healthy individuals, and the clinicopathologic characteristics were analyzed. The changes of CEA levels before and after treatment were dynamically monitored by electrochemiluminescence (ECL). The methylation status of PCDH18 was detected by qMSP, the correlation between them was also statistically analyzed, and the value of different indexes in the diagnosis and monitoring of tumor progression of CRC were compared.

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Disclosure: All authors have declared no conflicts of interest.
Background: Hepatic Arterial Infusion (HAI) where the cytotoxic agents are administered intrahepatically is an experimental treatment option for patients with colorectal cancer liver metastases (CRCLM). We aimed to investigate the level of cell free DNA (cfDNA) in patients with CRCLM receiving HAI with oxaliplatin and systemic capecitabine. 

Methods: Patients were treated according to a single arm phase II study including patients with liver limited mCRC from November 2004 to May 2010, who were not eligible for any other standard local treatment. Therapy comprised intrahepatic infusion of oxaliplatin 100 mg/sq every second week concomitant oral capecitabine 3500 mg/sq every second week for up to 12 cycles. A pre-treatment plasma sample was used for quantification of cfDNA by a modified fluorescent assay. Survival was analyzed by the Kaplan-Meier method and Cox multiple regression analysis.

Results: Plasma sample data were available from 62 patients. The majority of patients were males (61%), the median age 61.3 years (range 40-87.4) and distribution of colon/rectal cancers 68%/32%. The median level of cfDNA was 0.92 ng/mL (95% CI 0.82-1.06) with no significant differences according to pre-treatment patients characteristics apart from being significantly higher in HDL levels with poor PS (p < 0.001). Plasma cfDNA was significantly lower (0.91 ng/mL, 95% CI 0.76-0.98) in patients who achieved an objective response compared to non-responders (1.79 ng/mL, 95% CI 0.89-2.57, p = 0.02). Patients with a baseline value of cfDNA above the 75th quartile had a median overall survival of 2.4 years (95% CI 7.2-2.8), compared to 3.9 years (95% CI 2.8-5.9) for patients below the 75th quartile (p = 0.02). In multivariate analysis, only increasing baseline level of cfDNA, HR: 1.96, 95% CI 1.0-3.58 (p = 0.03), and mutated KRAS status (HR 3.17, 95%CI 1.67-6.63, p < 0.001) were associated with reduced survival.

Conclusions: Patients with a low baseline level of plasma cfDNA had a favorable outcome from treatment with HAI and capcitabine for CRCLM. Consequently, cfDNA could hold clinically relevant predictive and prognostic information, which needs validation in this setting.

Legal entity responsible for the study: Karen-Lise Spindler.

Funding: Danish Cancer Society Novo Nordisk Foundation.

Disclosure: A.K. Boeyen: Advisory board: Bayer A/S. All other authors have declared no conflicts of interest.

Background: Metastatic colorectal signet ring cell carcinoma (mSRCRC) is a rare entity and data are limited, concerning small number of patients. Chemosensitivity for metastatic disease has never been assessed. This study aims to analyze its chemosensitivity and investigates its clinicopathological, molecular and prognostic characteristics.

Methods: This nationwide retrospective study included patients with mSRCRC from 2003 to 2017 in 31 French centers. They were divided into three groups: curative care (group 1), palliative chemotherapy (group 2) and best supportive care (group 3).

Results: Data on 204 patients were collected. Median age was 63 years. Tumors were more frequent in proximal colon (46%) and rectum (29%). Tumors consisting of both adenocarcinoma and NEC were infrequent in the right-sided colon. Tumors with neuroendocrine tumor (NET) histology comprised 10%. Mucinous components were frequent in proximal colon (38%) and rectum (22%). In 11% of patients, synchronous tumors were noted. Patients with NEC were significantly associated with higher age (p = 0.016). The majority of patients had right-sided (75%) tumors. The most frequent metastatic sites were the liver (64%), lungs (33%) and bone (23%). The median survival was 1.8 months. Patients with metastatic lesions of the liver had a significantly shorter survival than those with central metastases (p = 0.01). There was no difference in PFS between antiVEGF and antiEGFr (p = 0.08) in 1L, and between right-sided (p = 0.275) and left-sided (p = 0.265) tumors.

Conclusions: This large cohort of mSRCRC shows poor prognosis, specific localization and molecular alterations which provides low chemosensitivity. Microsatellite analysis should be done regarding promising results of immunotherapy in MSI-high tumors.

Legal entity responsible for the study: AGEO (Association des Gastroentérologues Oncologues).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
components. We tested the hypothesis that distribution of endocrine tumor marker-positive cells in cancer tissue differ between right- and left-sided colon cancer.

Methods: The study group comprised 354 patients with stage II or III colon cancer who underwent curative resection from 2007 to 2012. Immunostaining was performed using chromogranin A (cgA), synaptophysin, and CD56 as gastrointestinal endocrine tumor markers. Cases in which positive cells were seen in some part of the cancer tissue were evaluated to be positive.

Results: Tumors were located in the right-sided colon in 181 patients (51.1%) and the left-sided colon in 173 patients (48.8%). Immunohistochemical staining was positive for cga in 66 patients (18.6%), positive for synaptophysin in 102 patients (28.8%), and positive for CD56 in 155 patients (35.5%). Immunohistochemical staining was positive for at least one of these markers in 118 patients (33.3%) and for all of the markers in 27 patients (7.6%). The rate of positive staining for cga was 23.7% (43/181) in right-sided colon cancer and 13.2% (23/173) in left-sided colon cancer. The rate of positive staining for synaptophysin was 35.3% (64/181) in right-sided colon cancer and 21.9% (38/173) in left-sided colon cancer. The rate of positive staining for CD56 was 22.6% (41/181) in right-sided colon cancer and 8.0% (14/173) in left-sided colon cancer. The rates of positive staining for cga, synaptophysin, or CD56 were significantly higher in right-sided colon cancer, which may be associated with the high incidence of NEC in the right side of the colon.

Legal entity responsible for the study: Sotaro Sashidori, MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

560P

Prospective DPYD testing in colorectal cancer patients in a real-world UK population

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Background: Polymorphisms within the DPYD gene are present in 7% of Europeans but account for 23% of life-threatening toxicity from fluoropyrimidine (FP) chemotherapy. Four DPYD variants have an adjusted relative risk for toxicity of 1.59 - 4.4. Upfront genotyping is safe and cost effective but not mandated by ESMO guidelines. To reduce the risk of life-threatening toxicity we implemented prospective DPYD testing as standard practice.

Methods: Consecutive colorectal cancer (CRC) patients in a UK cancer centre due to receive FP chemotherapy were genotyped by real time PCR for known clinically relevant DPYD mutations: c.1905>T, c.2846>A, c.1679>T or c.1605>G and from March 2017, c.1236G>A/HapB. We followed published recommendations for dose reduction or alternative drug. Demographics, dose, toxicity and survival data were collected.

Results: Between 1/1/16-31/12/2017, 230 patients were tested. 72% had capecitabine, 24% 5-fluorouracil, and 4% raltitrexed combinations. After dose reduction or alternative therapy, grade 3/4 diarrhoea was similar in wildtype and mutations (10 vs 13%). Dose reductions for DPYD variant allele carriers should also be applied in patients receiving chemoradiation therapy. Four DPYD variant allele carriers were genotyped by real time PCR for known clinically relevant DPYD mutations: c.1905>T, c.2846>A, c.1679>T or c.1605>G and from March 2017, c.1236G>A/HapB. We followed published recommendations for dose reduction or alternative drug. Demographics, dose, toxicity and survival data were collected.

Conclusions: To our knowledge, we are the only UK centre to implement prospective DPYD testing in routine clinical practice for CRC patients. In published data of unselected CRC patients the G3/4 GI toxicity is 15%, but if 2° variant is present this increases to 73%. In the latter population, genotype guided dosing reduces the risk to 28%. Our rate for all variants was 10% but limited by small numbers. Pharmacokinetics in another study showed adequate 5FU exposure with a 50% dose reduction, alleviating underdosing concerns. The growing evidence supports prospective DPYD testing. We have shown it is practical and may mitigate serious toxicities.

Legal entity responsible for the study: Bryony Eccles.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

561P

Standard fluoropyrimidine dosages in chemoradiation therapy result in an increased risk of severe toxicity in DPYD variant allele carriers


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Background: Prospective DPYD genotyping prevents severe fluoropyrimidine-induced toxicity by decreasing initial dosages in DPYD variant allele carriers. However, fluoropyrimidine dosages in chemoradiation therapy are already lower compared to other fluoropyrimidine-containing regimens. It is unknown if recommended dose reductions of pharmacogenetic guidelines are valid for DPYD variant allele carriers receiving fluoropyrimidines in chemoradiation therapy. The aim of this study was to investigate severe toxicity in DPYD variant allele carriers receiving chemoradiation therapy.

Methods: Three databases were used, containing data on patients who received fluoropyrimidine-based chemoradiation therapy. Frequencies of severe (grade ≥3) toxicity in DPYD variant allele carriers (DPYD*2A, DPYD*15, c.2846A>T or c.1236G>A) receiving upfront fluoropyrimidine dose reductions according to current pharmacogenetic dosing guidelines (50 or 75% depending on the variant), and DPYD variant allele carriers receiving full-dose were compared to DPYD wild-type patients receiving standard dose fluoropyrimidines in chemoradiation therapy.

Results: DPYD variant allele carriers treated with standard dosages (N = 34) showed an increased risk of severe gastrointestinal (adjusted OR = 2.58, 95% CI = 1.02-6.53, p = 0.045) or severe haematological (adjusted OR = 4.19, 95% CI = 1.32-13.25, p = 0.015) toxicity compared to wild-type patients (N = 771). DPYD variant allele carriers who received dose reductions (N = 22) showed a comparable frequency of severe gastrointestinal toxicity, but a higher frequency of severe haematological toxicity, compared to wild-type patients. The mean duration of hospitalisation was significantly shorter in DPYD variant allele carriers who received dose reductions compared to DPYD variant allele carriers treated with standard dosages (4 versus 23 days, p = 0.001).

Conclusions: Standard fluoropyrimidine dosages in chemoradiation therapy resulted in an increased risk of severe toxicity in DPYD variant allele carriers. Fluoropyrimidine dose reductions for DPYD variant allele carriers should also be applied in patients receiving chemoradiation therapy.

Legal entity responsible for the study: Leiden University Medical Centre.

Funding: Has not received any funding.

Disclosure: C.A.T.C. Lunenburg. Previously supported by an unrestricted grant from Roche Pharmaceuticals. All other authors have declared no conflicts of interest.

Table: 560P

<table>
<thead>
<tr>
<th>DPYD Heterozygote mutations (No homozygote or compound heterozygote mutations)</th>
<th>Adjusted RR</th>
<th>No. (%)</th>
<th>Mean 1st dose-%</th>
<th>Any grade 3/4 toxicity No. (%)</th>
<th>Grade 3/4 diarrhoea No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1905&gt;G&gt;A</td>
<td>1.59</td>
<td>3 (2%)</td>
<td>77%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>c.2846&gt;A&gt;T</td>
<td>3.02</td>
<td>2 (1%)</td>
<td>100%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>c.1679&gt;T</td>
<td>4.4</td>
<td>0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.1236G&gt;A/HapB</td>
<td>1.59</td>
<td>7 (3%)</td>
<td>76%</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>c.1601G&gt;A</td>
<td>1.52 (Non significant)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Any heterozygote mutation

Wildtype

Total 58% adjuvant 27% neoadjuvant 24% palliative
Background: The toxicity produced by chemotherapy worsens in the presence of mutations in certain enzymes of metabolism or degradation. Such is the case of dihydropyrimidine dehydrogenase (DPYD) in the treatment with fluoropyrimidines. Detection prior to the start of treatment could be beneficial to prevent this increase in toxicity.

Methods: A prospective study in which the DPYD polymorphisms are analyzed, after the first visit in Oncology of patients with a diagnosis of colorectal cancer (CRC), gastrointestinal tumors (GIGT), or breast cancer in the head and neck, that can be treated with fluoropyrimidines as part of chemotherapy. After DNA extraction from the peripheral blood sample the methodology used was: 1. Directed genotyping of variant *2A,* 13 and rs6737698 of the DPYD gene, by analysis of allelic discrimination polymorphisms with TaqMan probes, previous amplification in an ABI Prism 7900 (Applied Biosystems).

Results: We included 374 patients, with an average age of 67a, 62% men, with PS 0 or 1 in 97% of the cases. Localization of the primary tumor was: CRC 85%, GEC 12%, H&N 3%. 47% were adenocarcinomas and 53% squamous carcinoma. The intention of treatment was: adjuvant treatment in 46%, neoadjuvant 17%, a first line of metastatic disease 33%, the second line of metastatic disease 3%. 97% were adenocarcinomas and 3% squamous carcinoma. The intention of treatment was: adjuvant treatment in 46%, neoadjuvant 17%, a first line of metastatic disease 33%, the second line of metastatic disease 3%. Schemes used: combinations of 5FU with oxaliplatin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%), and platin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%). Toxicities G3-4 diarrhea 1.3%, neutropenia 0.8%, rash, 1.3% and mucositis 0.3%.

Conclusions: In our study, we observed that the enzymatic deficit in the metabolic pathways of fluoropyrimidines are rare, and probably do not influence the initiation of chemotherapy treatment. These results will not influence the usual clinical practice, but we think are very important to avoid toxicity to the patient if these are present.

Legal entity responsible for the study: Hospital General Valencia Department of Medical Oncology.

Funding: Has received no funding.

Disclosure: All authors have declared no conflicts of interest.

Results: We included 374 patients, with an average age of 67a, 62% men, with PS 0 or 1 in 97% of the cases. Localization of the primary tumor was: CRC 85%, GEC 12%, H&N 3%. 47% were adenocarcinomas and 53% squamous carcinoma. The intention of treatment was: adjuvant treatment in 46%, neoadjuvant 17%, a first line of metastatic disease 33%, the second line of metastatic disease 3%. Schemes used: combinations of 5FU with oxaliplatin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%), and platin (58%), capecitabine in monotherapy or radiotherapy in neoadjuvant (33%). Toxicities G3-4 diarrhea 1.3%, neutropenia 0.8%, rash, 1.3% and mucositis 0.3%.

Conclusions: In our study, we observed that the enzymatic deficit in the metabolic pathways of fluoropyrimidines are rare, and probably do not influence the initiation of chemotherapy treatment. These results will not influence the usual clinical practice, but we think are very important to avoid toxicity to the patient if these are present.

Legal entity responsible for the study: Hospital General Valencia Department of Medical Oncology.

Funding: Has received no funding.

Disclosure: All authors have declared no conflicts of interest.
placebo (F+P), the combination of mFOLFOX6 plus Nintedanib (F+N) improved mPFS (F+P: 4.6 vs F+N: 8.1 mo; HR 0.65; 95% CI 0.32-1.30; p = 0.2166), mOS (F+P: 9.9 vs. F+N: 17.1 mo; HR 1.03, 95% CI 0.48-2.23; p = 0.9387) and DCR (F+P: 50 vs. F+N: 66.7%; p = 0.2799). ORR was comparable in both arms (F+P: 3.8 vs. F+P: 3.7%). Toxicity was low to moderate without major differences between both arms except G3/4 neutropenia (F+N: 19%, F+P: 12%) and GI disorders (F+N: 23%, F+P: 15%).

Conclusions: Final results suggest a PFS, OS and DCR benefit for mFOLFOX6 + Nintedanib vs. mFOLFOX6 + placebo in the 2nd-line therapy of mCRC. Due to the premature termination of the trial there was no statistical significance demonstrable. Showing no clinically significant PFS-benefit in the 1st-line situation (mFOLFOX6 plus Nintedanib/Bevacizumab, Ann Oncol, 2015) or the last line as single agent, respectively (ESMO 2016) the TRICCC results suggests that Nintedanib could be an interesting therapeutic option for the 2nd-line situation in combination with mFOLFOX6.

Clinical trial identification: NCT01623651.

Legal entity responsible for the study: Martin-Luther-Universität Halle-Wittenberg, Germany.

Funding: Boeringer Ingelheim.

Disclosure: T.J. Ettrich: Research grants: Baxter/Shire; Consulting fees or other remuneration: Merck-Serono, Sanofi, Sirtex, Medical, Novartis, Bayer, Bristol-Myers Squibb, Pfizer. A.W. Berger: Consulting fees: Sanofi. R.D. Hofheinz: Consulting or advisory role: Boehringer Ingelheim. T. Seufferlein: Research Funding: Celgene, Sanofi; Squibb, Pfizer. A.W. Berger: Consulting fees: Sanofi. R.D. Hofheinz: Consulting or advisory role: Celgene, Lilly Pharma, Boehringer Ingelheim, Merck Serono, Angen. All other authors have declared no conflicts of interest.

565P Dose finding and safety study of reovirus (Reo) with irinotecan/ fluorouracil/ leucovorin/ bevacizumab (FOLIRI/B) in patients with KRAS mutant metastatic colorectal cancer (mCRC): Final results

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Background: KRAS mutation is a biomarker of exclusion of anti-EGFR agents in patients with mCRC who have limited options once they progress on oxaliplatin and irinotecan-based regimens. Reo is a naturally occurring, ubiquitous, non-enveloped double stranded RNA virus that selectively replicates in tumor cells harboring KRAS mutations. Reo is synergistic with irinotecan (IRI) in in vitro and in vivo models.

Methods: This was a phase I dose escalation study of FOLIRI/B and Reo to determine maximum tolerated dose (MTD) and recommended phase two dose (RPTD). Eligible pts were adults with oxaliplatin refractory KRAS-mutant mCRC. Both, IRI (150-180 mg/m²) and Reo (1x10¹⁰ TCID₅₀ to 3x10¹⁰ TCID₅₀) were escalated. Reo was given intravenously on one day 1-5 every 4 weeks (wk). FOJIRI/B was delivered every 2 wk as per standard protocol. Pharmacokinetics (PK), on study tumor biopsies, and immune response was studied.

Results: 36 pts enrolled; 23 females (64%), median age 63 years, FOLIRI/B naive (24) and pre-treated (12). At the highest dose of 180 mg/m² of IRI, among FOLIRI pre-treated pts, 2 had dose-limiting toxicity (DLT) in cycle 1; one suffered from grade 4 thrombocytopenia, and another developed febrile neutropenia and urorpeusis. However, in FOLIRI naive patients, none had a DLT. Common (>10%) toxicities included neutropenia, anemia, thrombocytopenia, fatigue, and diarrhea. One patient died of acute renal failure. The MTD was the highest individual dose of FOLIRI/B (180 mg/m² IRI and reovirus (3x10¹⁰ TCID₅₀), and is the RPTD. At this dose, 3 of 6 patients (50%) had a PR and the median progression free survival (PFS) and overall survival (OS) were 65.6 wk and > 98.3 wk (as of May 9, 2018), respectively. There was no PR interaction noted. Immungold staining against viral capsid protein α demonstrated viral “homing” in the tumor cells. Flow cytometry revealed rapid dendritic cell maturation with subsequent activation of cytotoxic T cells.

Conclusions: The combination of reovirus with FOLIRI/B is safe, and well tolerated. The PFS and OS is superior to historic data and this combination deserves further exploration.

Clinical trial identification: NCT01274624.

Legal entity responsible for the study: Sanjay Goel.

Funding: Conquer Cancer Foundation and Oncolytics Inc.

Disclosure: S. Goel, A. Ocean: Oncolytics funding to conduct clinical investigations with reovirus. M. Coffey: Employee, Stock owner: Oncolytics Inc. All other authors have declared no conflicts of interest.
abstracts
multi-cohort study, we evaluated the combination of ADX with standard chemotherapy
in patients with previously untreated mCRC. (Clinicaltrials.gov NCT# 01803282).
Methods: The study enrolled 45 eligible patients (19 female) with measurable disease
and previously untreated mCRC. The median age was 62 years (range 34-78) and 18%
(8/45) of patients had received prior adjuvant chemotherapy. Patients were treated
with 800 mg ADX IV every two weeks plus standard doses mFOLFOX6 and bevacizumab. Safety and efficacy were assessed. Primary endpoints were safety and tolerability.
Exploratory endpoints were investigator-assessed objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Molecular analysis of archival
tumor samples was performed.
Results: As of March 5, 2018, the median duration of ADX treatment was 8.8 months.
Median PFS follow up time was 13.5 months. The most common adverse events were
fatigue (78%), nausea (71%), diarrhea (56%), peripheral sensory neuropathy (49%),
decreased appetite (40%), and neutropenia (40%). 38% of patients reported serious
adverse events (SAEs). Acute respiratory failure and sepsis (both 4%) were the most
common SAEs. Median PFS was 10 months (90% CI 9.0-12.0 months), median duration of response was 8.1 months (90% CI 6.1, 10.4). Overall response rate was 62%
(90% CI 49 – 74%) with 4% complete response rate. The response rate was 50% for
mutated BRAF, 67% for mutated RAS, 67% for right-sided disease. The median OS was
not reached. Study treatment continues in 7% of patients.
Conclusions: Combination of ADX with mFOLFOX6 and bevacizumab was safe and
shows response and PFS similar to historical data with FOLFOX-bevacizumab in firstline treatment of patients with previously untreated mCRC.
Clinical trial identification: NCT 01803282.
Legal entity responsible for the study: Gilead Sciences, Inc.
Funding: Gilead Sciences, Inc.
Disclosure: H.J. Lenz: Consulting/Advisory Role: Bristol Myers Squibb, Roche, Merck
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Vertex, Bayer, Symphogen, Incyte, Pharmacyclics, Karyopharm Theraputics;
Consulting/Advisory Role: Celegene, Symphogen, Genetech/Roche, EMD Serono,
Aduro Biotech, Cornerstone Pharmaceuticals, Five Prime Theraputics, Opsona
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Speakers’ bureau: Bristol Myers Squibb; Travel/Expenses: Bayer, Bristol Myers Squibb,
Sandoz. J. Liu, C. Brachmann, P. Bhargava: Employee and stock ownership: Gilead
Science Inc. Z.A. Wainberg: Research funding: Novartis, Plexxikon, Pfizer, Merck;
Consulting, Advisory role: Sirtex Medical, Amgen, Array BioPharma, Five Prime
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funding: Lilly, Genetech/Roche, Incyte, Gilead Science, Bristol-Myers Squibb, Leap
Theraputics, AstraZeneca/MedImmune, Boston Biomedical, GlaxoSmithKline,
Novartis, Array BioPharma, Taiho Pharmaceutical, Celgene, Oncomed, Daiichi
Sankyo, Bayer, Apexigen, Kolltan Pharmaceuticals, SynDevRX, Merck, Macrogenics,
Five Prime Theraputics, EMD Serono, TG Theraputics, Boehringer Ingelheim, Forty
Seven, Stem CentRx, Onyx, Sanofi, Takeda, Abbott/AbbVie, Eisai, Celldex, Agios,
ARMO BioScience, CytomX Theraputics, Nektar, Ipsen, Merrimack, Tarveda
Theraputics, Tyrogenex, Oncogenex, Marshall Edwars, Pieris Pharmaceuticals,
Mersana, Calithera BioScience, Blueprint Medicines, Gritstone Oncology, Evelo
Therapeutics, Forma Therapeutics, Forty Seven, EMD Serono, Merus. All other authors
have declared no conflicts of interest.
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A phase II study of pemetrexed and erlotinib for metastatic colorectal
cancer refractory to standard chemotherapy

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Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, 5Asan Medical
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Medicine, Department of Internal Medicine, Daegu, Republic of Korea
Background: There are very limited treatment options in metastatic colorectal cancer
(mCRC) after progression on chemotherapy including fluoropyrimidine, oxaliplatin
and irinotecan. This open label, multi-center, phase II study was conducted to investigate the combination of pemetrexed and erlotinib in patients who were refractory to
previous chemotherapy for mCRC.
Methods: Patients were eligible if they had metastatic colorectal cancer that progressed
to standard chemotherapy including fluoropyrimidine, oxaliplatin, and irinotecan.
Each 21-day cycle consisted of intravenous pemetrexed at 500 mg/m2 on day 1 and daily
oral erlotinib at 150 mg (reduced to 100 mg after the first 29 patients).

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Results: Fifty patients were enrolled onto this phase II study. Twenty-seven patients
(54%) had KRAS wild type tumors and 23 patients (46%) did KRAS mutant tumors.
Forty-six patients were evaluable for response; twenty-seven patients (59%) had stable
disease (SD) and 4 patients (9%) achieved prolonged SD for >6 months. No complete
or partial responses were seen. The median progression-free survival was 2.5 months
and the median overall survival was 7.3 months. Clinically significant grade 3 to 4 toxicities included diarrhea (6%), fatigue (6%), ileus (4%), skin rash (2%), and myalgia
(2%); grade 3 or 4 toxicities were reduced with a lower starting dose of erlotinib.
Conclusions: The combination of pemetrexed and erlotinib seems to have limited
activity in refractory mCRC patients. Further research for the regimen is not warranted
without understanding predictive biomarkers.
Clinical trial identification: NCT02723578.
Legal entity responsible for the study: Joong Bae Ahn.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

569P

ISO-CC-005; A phase I/II study of arfolitixorin (MTHF) in combination
with 5-FU, irinotecan, and oxaliplatin 6 bevacizumab in patients with
metastasizing colorectal cancer

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V. Georgoulias6, C. Papadimitriou7, N. Kentepozidis8, D. Boumpas9, L. Skintemo10,
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1
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8
Oncology, 251 Hellenic Airforce General Hospital, Athens, Greece, 9Oncology, University
Hospital Attikon, Chaidari Athens, Greece, 10Clinical Reserach, Isofol Medical AB,
Gothenburg, Sweden, 11Medical, Isofol Medical AB, Gothenburg, Sweden, 12Surgical
Oncology Lab, University of Gothenburg, Goteborg, Sweden
Background: Chemotherapy treatment of Colorectal Cancer, often include 5Fluorouracil (5- FU). 5-FU inhibits the enzyme thymidylate synthase (TS), stopping
the supply of thymidine for DNA synthesis. 5-FU is always combined with a folate,
which enhances the 5-FU effect. Marketed folates such as LV/L-LV are prodrugs needR ) is the natural, biologiing enzymatic conversion. Arfolitixorin (formerly ModufolinV
cally active form of the folates and is expected to be efficacious in a larger proportion of
patients with less inter- and intra-individual variability.
Methods: ISO-CC-005 is a multi-center, phase I/II study in mCRC patients eligible for
5-FU/folate therapy alone or in combination with irinotecan or oxaliplatin 6 bevacizumab. The study investigates safety and tolerability of arfolitixorin at 4 dose levels by
analysing the number and severity of AEs, SAEs and DLTs. Efficacy is evaluated as ORR
after 4 cycles of chemotherapy. Gene expression, deoxyuridine levels as an indirect
marker of TS inhibition and time to death is also investigated. 3-6 patients per cohort
are included. All receives arfolitixorin twice every two weeks during at least 4 cycles of
chemotherapy.
Results: Today, 67 patients have been enrolled and 59 have initiated treatment. 13 are
1st line patients, 16 are in 2nd line, 10 are in 3rd line and 1 is in 5th treatment line. 27
SAEs have been reported in 13 patients, 6 of these were judged as at least possibly related
to arfolitixorin. No SAE were judged as solely related to arfolitixorin. 49 patients have
today been evaluated for efficacy. ORR 1st line patients (n ¼ 14) at 8 weeks All 43% (6
PR, 7 SD, 1PD) Patients with arfolitixorin dose 60 mg/m2 56% (5 PR, 3 SD, 1 PD)
Patients with arfolitixorin dose 60 mg/m2 þ oxaliplatin 60% (3 PR, 1 SD, 1 PD).
Conclusions: The lack of need for metabolic activation makes arfolitixorin a better candidate than LV/L-LV for improved outcome of 5-FU-based chemotherapy regimens in
mCRC. The ISO-CC-005 study evaluates arfolitixorin in combination with 5-FU, irinotecan, oxaliplatin 6 bevacizumab in mCRC patients in 4 countries in Europe. The
results, so far, for both safety and efficacy seems promising.
Clinical trial identification: EudraCT: 2014-001862-84; NCT02244632.
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member is the founder of, have a leadership role, owns shares, have an advisory role,
have conducted funded research, hold patents and have received travel expenses: Isofol
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AB. B. Gustavsson: Founder of, have a leadership role, owns shares, advisory role, conducted funded research, hold patents, received travel expenses: Isofol Medical AB. All
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571P Interim results from a real world European survey on the unmet needs of patients with metastatic colorectal cancer (mCRC)

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Background: With increasing emphasis on patients’ voices, EuroCaColon, a European CRC patient organization, conducted a cross-sectional European survey on unmet needs in mCRC, in 12 countries. The aim was to better understand the challenges, needs and the health-related quality of life (HRQoL). The objective of this work is to report the preliminary results for Hungary (HU), Poland (PL), Serbia (RS) and Spain (ES).

Methods: IRB approval was obtained. Clinicians, and nurses with partner organizations of EuroCaColon recruited patients. The survey had two sections: treatment-related information and HRQol. The former comprised questions on timing of diagnosis/treatment, multidisciplinary team discussion (MDT), type of treatments received, and information on treatments and side-effects. Both paper-based and on-line completion were available. Single data entry was done by EuroCaColon.

Descriptive analyses were carried out in Excel. No imputation of missing data was done.

Results: 548 surveys were analyzed. Completion rates were high. Most responders were treated in public hospitals and 85-92% in HU, ES and PL and 57% in RS were under treatment at the time. Most patients (82%) received treatments within 3 months after diagnosis with CRC, 16% within first 2 weeks. 60% underwent MDT discussion and were informed about the outcome. Proportions however varied between countries, with lowest for PL (46%) and highest for RS (74%). Proportion of patients feeling their views were considered prior starting treatment varied (30% in RS to 83% in HU). Most patients had surgery and chemotherapy (63% and 91%), 21% radio- and 9% targeted therapy. Specific therapies however were not given in >23% of cases. Patients were relatively informed about side effects (73%). A fifth of patients received molecular test, from a low 6% in RS up to 34% in PL.

Conclusions: Among mCRC patients in HU, ES and RS the degree of information varies. Patients know about MDT and are informed about potential side effects.

Legal entity responsible for the study: EuroCaColon.

573P Influence of not having children on mortality in patients with metastatic (mCRC) colorectal cancer

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Background: Although there is evidence that parents live longer than non-parents, prognostic effect of parenthood in cancer patients is not well established. We previously noted that palliative use of chemotherapy in patients with mCRC significantly varied in those with and without children and use of chemotherapy was 3-fold lower in patients with mCRC than in children (2018 GCS Cancers Symposium). In this study we examined if childless individual with mCRC have higher mortality than patients with children.

Methods: Patients with mCRC diagnosed in 2016-2018 in Saskatchewan were assessed. Cox proportional hazard multivariate analyses were performed to determine correlation between not having children and mortality.

Results: 569 patients with median age 69 yrs (IQR 59-77) and M:F was 59:41 were identified. Of 569 patients, 461 (81%) had children. Significant differences were noted between the group with children and the group with no children with respect to being married/partnered (74 vs. 32%, p < 0.001), performance status >2 (53 vs. 45%, p = 0.02), distance to travel to cancer center > 100 km (45 vs. 69%, p = 0.007), law

Legal entity responsible for the study: Hyun S. Kim, MD.
albumin (70 vs. 85%, p = 0.001), anemia (68 vs. 87%, p < 0.001), and use of chemotherapy (64 vs. 31, p < 0.001 respectively). On Cox proportional multivariate analysis adjusted for other variables, not having children (HR 1.4; 95%CI: 1.10-1.90), not having chemotherapy (3.6, 2.8-4.6), no metastasectomy (2.15, 1.60-2.91), intact primary tumor (1.91, 1.56-2.33), leukocytosis (1.53, 1.07-1.70), elevated alkaline phosphatase (1.32, 1.07-1.62), performance status ≥2 (1.30, 1.01-1.60), right colon cancer (1.28, 1.04-1.57), grade III cancer (1.28, 1.05-1.56) and stage IVb disease (1.25, 1.04-1.30) were correlated with poor survival.

Conclusions: The present study demonstrated that not having children was independently associated with an increased risk of mortality in patients with metastatic colorectal cancer. Future studies are warranted to confirm the finding and to determine underlying etiology.

Legal entity responsible for the study: Shahid Ahmed.

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Disclosure: All authors have declared no conflicts of interest.

<p>| Table: 574P |
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<td>84.3 (7.9)</td>
<td>81.8 (25.4)</td>
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Mean fatigue and pain symptom scores were lower in HU/ES and higher in RS/PL. This was maintained in nausea, insomnia, appetite loss, constipation, but not in dyspnea, diarrhea. Differences could be affected by the patients’ place in the treatment pathway. Global health scores for RS and PL were lower, and symptom scores were higher than reported in mCRC trials.

Conclusions: mCRC has an important effect on HRQoL, which can differ among real-world mCRC patients and those in clinical trials. Variations across countries and comparisons to HROQL in trials require further analysis.

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Disclosure: All authors have declared no conflicts of interest.
significant difference. Among the pts who required surgery, SBO was caused by adhe-
sion to the midline incision in 1 patient (7.7%) in the Splenill™ group and in 2 pts
(10.5%) in the control group. This difference was also not significant. Multivariate
analysis showed that a history of laparotomy was an independent risk factor for
SBO and the use of Splenill™ was unrelated to the incidence of SBO.

Conclusions: A midline incision was an infrequent cause of SBO in pts who underwent
surgery for colon cancer. It was unclear whether the placement of Splenill™ can
reduce the incidence of SBO.

Legal entity responsible for the study: Sotaro Sadahiro, MD.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

577P Short- and long-term outcomes of high- vs low-grade lymph nodes in colorectal cancer: a single center study
K.L. Li

Background: Controversy is ongoing on the level of inferior mesenteric artery (IMA) ligation in sigmoid colon or rectal cancer surgery. In the present study, we aimed to reevaluate the mortality and morbidity especially for anastomotic leakage of low grade lymph nodes. A total of 1895 patients with sigmoid colon or rectal cancer were included in this study. After PSM, LT-LND and HT-LND patients were comparable. Ultimately, 277 patients were ligated at the origin of IMA and 277 patients experienced the preservation of left colic artery plus lymph node dissection around IMA. The survival outcomes and clinicopathological characteristics were reviewed from the database retrospectively.

Results: The median follow-up period was 13.7 months (range from 1 to 69 months). There were no differences in terms of postoperative complication rate and overall survival (OS) as well as disease-free survival (DFS). In the LT group and LT-LND group, the 5-year OS rates were 90.8% and 90.0%, respectively, whereas the 3-years DFS rates were 78.3% and 75.9%, respectively. Further, LT-LND was associated with prolonged operation time and less blood loss.

Conclusions: LT-LND seems to be less invasive and is not inferior to HT from the point of oncological safety. Further prospective studies and long-term follow-up data are needed.

Legal entity responsible for the study: Xinzhang Li.
Funding: This work was supported by the National Natural Science Foundation of China (Grant NO. 81772599).
Disclosure: The author has declared no conflicts of interest.

578P Mesenteric vs. antimesenteric colorectal cancer: A single center study

Background: We investigated the possible correlation between the prognosis and cir-
cumferential location of the tumor according to the cancer involvement on the mesen-
teric side. This study is based on the hypothesis that mesenteric tumors, which are
closer to blood and lymphatic vessels, could spread more aggressively and rapidly com-
pared to the antimesenteric tumors.

Methods: We reviewed the retrospectively collected data of 251 patients treated during
the period of October 2008 to May 2012. 162 patients with mesenteric side involving
tumors were included in the mesenteric group and 89 patients with antimesenteric
tumors were included in the antimesenteric group. The analyzed information included
gender, location, size of the main lesion, extent of lymph node metastasis, patho-
logic features, metastasis, complication, TNM stage, recurrence and 5-year survival. We
retrospectively studied the survival of patients by examining of our 5-year follow-
up archive. Data were analyzed using Pearson-Chi square test and Kaplan-Meier curve
analysis.

Results: There was no statistical difference between the two groups regarding age, gen-
der, location, extent of lymph node metastasis, pathologic features, complication, and
TNM stage. The size of the main tumor was statistically larger in the mesenteric group
compared to the antimesenteric group. (P value = 0.03). The mesenteric group showed
statistically higher rate of distant metastasis and carcinomatosis than the antimesenteric
group. (P value = 0.02) In addition, the mesenteric group showed lower 5-year survival
rate than the antimesenteric group.

Conclusions: In conclusion, mesenteric tumors have significantly larger size of main
tumor, higher rate of distant metastasis and worse 5-year survival than antimesenteric
tumors. This difference implies that colorectal cancers should be regarded differently
according to the circumferential location and more careful follow up is necessary with
mesenteric side involving colorectal cancer patients.

Legal entity responsible for the study: Jong Woo Kim.
Funding: Has not received any funding.
Disclosure: The author has declared no conflicts of interest.

579P The SLICE study: The prognostic role of visceral fat in metastatic colorectal cancer

Background: Body composition, more specially the excess of body weight, was estab-
lished as a risk factor of the colorectal cancer initiation and progression. Aim of this
study was to investigate the prognostic role of adiposity, especially visceral fat (VAT),
in metastatic colorectal cancer (MCRC).

Methods: This retrospective study analyzed a consecutive cohort of 71 patients (pts)
with MCRC treated between 2013 and 2017 at the Oncology Department of Aviano
National Cancer Institute (Italy). VAT area was measured as crossed-sectional (cm²)
area at the L3 level divided by the square of the height (m²). A ROC analysis was performed
to define a threshold capable to identify distinct prognostic categories of patients
according to VAT. Subsequently, the value of VAT in predicting overall survival (OS)
and progression free survival (PFS) was evaluated with uni- and multivariate Cox
regression analyses. Survival outcomes were estimated with Kaplan-Meier curves.

Results: Before first line therapy, 19 pts (27%) were aged>70, 14 pts (20%) had a right
tumor, 21 pts (30%) a left tumor and 36 pts (50%) a rectal one. Of note, 59 pts (83%)
underwent primitive tumor resection and 24 pts (33%) received metastasectomy.
Interestingly, 40 pts (56%) had a body mass index (BMI)>25 and 42 (59%) had medium
VAT of 51.94. LHD level >= 480 U/L was recorded in 12 pts (27%) reflecting the
inflammatory response. The obtained cut-off for VAT was 44. Median OS was 30.97
months. At univariate analysis, older age (HR 2.46, p = 0.013), primary tumor resec-
tion (HR 0.40, p = 0.029), VAT>44 (HR 2.85, p = 0.011), metastasectomy (HR 0.22,
p = 0.005), were significantly associated with OS. Multivariate analysis, only
VAT>44 (HR 2.64, p = 0.030) was significantly associated with OS. Conversely, VAT
showed no prognostic impact in terms of PFS.

Conclusions: This exploratory study supported the prognostic role of adiposity evalua-
tion in patients with MCRC. In particular, high values of VAT were predictors of worse
outcome. These encouraging preliminary data merit to be validated through prospec-
tive investigations.

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

580P Safety and outcomes of self-expandable metal stents (SEMS) versus emergency surgery for acute colonic obstruction in metastatic colon cancer patients treated with bevacuzimab (BV)

Background: Colorectal cancer presents with malignant bowel obstruction in about
10% of cases. SEMS can be an alternative for immediate surgery but long-term data is
limited regarding clinical outcomes and safety of BV in this subset of patients.

Methods: We performed a retrospective review of 2850 cases of colon cancer from
January 2012 to October 2017, and identified metastatic patients with malignant bowel
obstruction initially treated with SEMS or emergency surgery. Differences in proce-
dure-related morbidity and overall survival (OS) were assessed.

Results: We selected 119 cases, 79 treated with SEMS and 40 with surgery. Median age: 76.
Median follow-up time: 11 months. No differences in sidedness or RAS status between
cohorts. SEMS and surgery had a similar rate of complications (35.5% vs 32.9%, p = 0.45) and showed longer time to complication (18m vs 1m, p = 0.004). In patients treated with BV, complications were similar in SEMS and surgery (40% vs 31%, RR 1.28, p = 0.5) and perforation was also similar (13% vs 19%, RR 1.46, p = 0.4). The incidence of perforation in the SEMS group was similar between BV and chemotherapy alone (13% vs 9%, p = 0.2). In patients without systemic therapy, complications were higher in the surgery group compared to SEMS (30% vs 29%, RR 1.34, p = 0.01), also the incidence of perforation (20% vs 6%, RR 3.33, p = 0.02), but not statistically significant. SEMS and surgery showed similar OS (14m vs 15m, p = 0.5). Treatment with BV increased OS in SEMS group (18months vs 7months, p = 0.001) and surgery group (20 months vs 4 months, p = 0.001) compared to patients without subsequent medical treatment. In the multivariate analysis, patients treated with subsequent medical treatment showed a statistically significant longer OS [HR 0.43, 95% 0.19-0.94, p = 0.02] and patients who had complications, showed a shorter OS (HR 2.45, 95% 1.7-5.12, p = 0.01).

Conclusions: Bevacizumab-based therapy increased survival in metastatic colon cancer and, was not associated with a higher risk of perforation in patients with SEMS. Emergency surgery and SEMS showed a similar incidence of complications and perforations, with no differences between both strategies in patients treated with BV.

Legal entity responsible for the study: Hospital Universitario La Princesa, Instituto de Investigación Sanitaria La Princesa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

581P

Metronomic capcitabine plus cyclophosphamide in unresectable or relapsed pseudomyxoma peritonei

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Background: The standard treatment of Pseudomyxoma Peritonei (PMP) is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). No consensus was reached on treatment of unresectable or recurrent disease. PMP is considered chemoresistant for its low mitotic index but non-randomized series showed promising results with regimens for gastrointestinal tumors. Metronomic schedules may be preferred for their antiangiogenic and immunomodulatory activity.

Methods: We conducted a single center prospective single arm trial. Inclusion criteria were histologically confirmed PMP, unresectable or relapsed after CRS/HIPEC, in progression to surgery or previous treatments. Patients received continuous metronomic capcitabine (625 mg/m2 q.d.i.d) plus cyclophosphamide (30 mg/day) until progression, disease-unacceptable toxicity or consent withdrawal. The primary end-point was progression free survival (PFS); secondary endpoints were disease control rate (DCR), overall survival (OS) and safety profile. Ion Torrent® next generation sequencing technology (Hot-spot Cancer Panel) was used to characterize molecular activity.

Results: 23 consecutive patients were enrolled from April 2015 to October 2017. At a median follow up of 13.5 months, median PFS was 9.5 months and 1-year OS rate 73.7%. A complete response (CR) was seen in 43% patients for CA19.9, 22% for CA125 and 20% for CA19-9. A partial response (PR) was seen in 47% patients for CA19.9, 30% for CA125 and 20% for CA19-9. At each evaluation, disease reduction was observed in 78% patients reported GI2 drug-related adverse events, only 17% G3 and none G4-G5. As expected, the main toxicities were anemia, neutropenia, nausea, diarrhea, fatigue and hand foot syndrome. Only 17% patients required dose reduction. Molecular profile was available in 15/23 cases: KRAS mutations were found in all cases and GNAS mutations in 47%.

Conclusions: Metronomic capcitabine plus cyclophosphamide is an active and well tolerated regimen in unresectable or recurrent PMP, with a safety profile comparable favorably with historical data. Further studies are needed to identify predictive biomarkers for novel treatment strategies.

Legal entity responsible for the study: Istituto Nazionale dei Tumori di Milano, Fondazione IRCCS.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

582P

Utility of carcinoembryonic antigen (CEA) in appendiceal carcinoma

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Background: Primary cancers of the appendix are rare and are frequently diagnosed after surgery for appendicitis. There is no designated staging system or evidence-based guideline for treatment. The staging and treatment of appendiceal adenocarcinoma mirror that of colon cancer. Elevated serum carcinoembryonic antigen (CEA) has been strongly associated with poor prognosis in colorectal cancer, so our study aims to first compare appendiceal cancers with tumors of the ascending colon, and then evaluate the prognostic value of CEA in appendiceal carcinoma.

Methods: We performed a retrospective analysis of all patients (n = 2,614) diagnosed with appendiceal adenocarcinoma from 2004 to 2014 in the National Cancer Institute’s Surveillance, Epidemiology and End Results database.

Conclusions: Though appendiceal cancers are rare, they are increasing in incidence. They are less likely than colorectal cancers to have the CEA test ordered despite CEA elevation odds ratio having no significant difference between the two cancers. Elevated CEA in appendiceal cancers is associated with later stage and higher grade. CEA levels should be checked in all appendiceal cancer patients to assist in the development of treatment strategies.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

583P

Thromboembolic risk and survival with Khorana score in resected colorectal cancer patients: Subgroup analysis from the adjuvant TOSCA trial

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Background: The risk of venous thromboembolic events (VTE) during adjuvant chemotherapy for colorectal cancer (CRC) is unknown. We aim to evaluate if the Khorana score (KS) can predict this risk of VTEs and overall survival (OS) in a randomised phase III, noninferiority, open-label trial of different durations of adjuvant chemotherapy in resected stage II-III CRC.

Methods: Data were obtained using a TOSCA [‘Randomised trial investigating the role of FOLFOX-4 vs XELOX (three versus six months) regimen duration as adjuvant therapy for patients with stage II/III colon cancer’] study. A logistic regression model was used to test the associations between the risk of VTEs and the KS. The results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). To assess the effect of the KS on OS, multivariate analyses using Cox regression models was performed. The results are expressed as hazard ratios (HR) with 95% CI.

Results: Among n = 1,380 CRC patients with available data, the VTE risk (n = 72 events: 5.2%) was similar in the three- and six-month duration arms (5.5% vs 4.9%) with 0.2% of patients belonging to the high-risk KS group. Rates of VTE were similar in the low- and intermediate-risk groups (4.8% vs 6.4%). KS did not represent an independent predictive factor for VTE risk, with a low positive predictive value and accuracy (64.4% and 74.1%). Chemotherapy duration was not associated with VTE risk. Also, KS was not associated with OS in multivariate analysis (HR = 0.92, 95% CI, 0.63–1.36, P = 0.68).

Conclusions: The use of the KS was not a predictor of VTEs in a low–moderate thromboembolic risk population as CRC. These data did not support the use of KS to estimate the occurrence of VTE during adjuvant chemotherapy, and suggest that other assessment tools must be evaluated.

Legal entity responsible for the study: GISCAD.
Background: Surveillance after curative resection for colorectal cancer with computed tomography (CT) of abdomen, pelvis and chest is a standard practice, but the optimal interval of surveillance CT is unclear. Usually recommended interval is 6 to 12 months, but in South Korea, earlier follow-up CT during adjuvant chemotherapy for stage II or III disease is a common practice. This study aimed to show clinical utility of early follow-up CT (EFCT) within 6 months after surgery.

Methods: The medical records of patients with stage II or III colorectal cancer who received oxaliplatin-based adjuvant chemotherapy between January 2011 and December 2014 in Asan Medical Center were retrospectively reviewed. Those who started adjuvant chemotherapy beyond 3 months after surgery and who were lost to follow-up before 6 months after surgery were excluded. Information on the results of EFCT and subsequent treatment was obtained.

Results: In a total of 678 patients, 597 (88%) underwent EFCT. EFCT was associated with advanced stage: 79% (749/95) of stage II, 88% (317/359) of low-risk stage III (pT1-3 and N1), and 92% (206/224) of high-risk stage III (pT4 or N2) checked EFCT (p = 0.002). EFCT revealed recurrence in 6 (1%) of stage II, 1 (0.3%) of low-risk stage III, and 3 (2.4%) of high-risk stage III (p = 0.132). Only 1 of 6 patients with recurrence underwent surgical resection of curative intent. There were no differences in overall survival (OS), disease-free survival (DFS), and cumulative occurrence of local treatment for DFS events according to undergoing EFCT with adjustment to age, gender, and stage.

Conclusions: Early recurrence within 6 months after surgery occurred in 1% of patients who were treated with oxaliplatin-based adjuvant chemotherapy, mostly in high-risk stage III disease. The practice of EFCT was associated with advanced stage but did not affect OS, DFS, or cumulative occurrence of local treatment. Clinical utility of EFCT seems to be low and should be discouraged especially in stage II or low-risk stage III disease.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
primary Left location. The use of Immunotherapy was minimal, with these pts tested for either MSI or PD-1/L1 expressed.

Background: Recent studies suggest that primary tumour location (PTL) has a prognostic value in patients (pts) with metastatic colorectal cancer (CRC), while its role in early stage disease remains unclear. The aim of this analysis is to investigate the relationship between PTL and the development of metachronous metastasis.

Methods: We performed a population-based study from Modena Cancer Registry collecting data of pts (with early stage disease; stage I, II, III) who underwent surgery from 1995 to 2010. We hypothesized a potential impact of PTL on the postoperative recurrence rate. Fisher’s exact test, univariate and multivariate Cox regression analysis were performed.

Results: During the study period, 1570 pts with left-sided colon cancer (LCC) and 841 pts with right-sided colon cancer (RCC) were registered. In the entire cohort, 268 of 1576 pts (17%) with LCC and 100 of 841 pts (11.2 %) with RCC developed metachronous metastasis, for a total of 368 of 2411 pts (15%). Comparing LCC and RCC clinical and pathological status we found no statistically significant difference in lymph-node status (p = 0.737) but an increasing rate of G3 cancers in RCC vs LCC (p = 0.010). Median overall survival (OS) from early stage disease diagnosis for LCC pts was 45 months versus 35 months for RCC pts, with no significant difference in relapse free survival between the two groups (23.8 Vs 23.0 months). When relapsed, time to death resulted to be significantly longer in LCC group than in RCC group (14.7 vs 6.3 months, HR 1.46, 95% CI 1.36-1.86, p = 0.001). In the multivariate Cox regression analysis adjusted for grading and stage at diagnosis, we confirmed a statistically significant impact of the primary tumour sidedness on OS in the relapsed setting (HR 1.48, 95% CI 1.15-1.89, p = 0.001).

Conclusions: In accordance to literature, our registry data confirm the prognostic role of PTL in advanced colorectal cancers: in particular, right-sided tumours have lower recurrence rate but poor prognosis once relapsed. Other investigations are necessary to better understand the substantial heterogeneity within the molecular biology of RCC and LCC in order to provide a better post-operative surveillance and to select the most effective treatment strategies after relapse.

Legal entity responsible for the study: Modena University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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The prognostic value of KRAS, NRAS, BRAF and DNA mismatch repair (MMR) status in left- and right-sided metastatic colorectal cancer (mCRC): A Belgian population-based study

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Background: In recent years, various studies have convincingly shown that mCRC patients with left-sided primaries have a significantly better prognosis than those with right-sided tumours. More research is required to identify the biomarkers that cause this difference in survival. Furthermore, these conclusions are mostly based on data of clinical trials and therefore selected patients. Confirmation in population-based studies is necessary. Therefore, the aim of current study is to compare the impact of biomarkers on survival rates in left- and right-sided mCRC in the (non-selected) Belgian population.

Methods: In Belgium, data on patient and tumor characteristics of all new diagnosed cancers are collected in the Belgian Cancer Registry. A random sample of 1035 patients diagnosed with mCRC in 2014 was included in our analysis. We obtained information on age, sex, primary tumor location, biomarker data (MMR status and BRAF, KRAS and NRAS mutational status) and survival. We constructed a logistic regression model, using location, age, gender and biomarkers as independent variables and survival as dependent variable.

Results: After exclusion of 177 patients with a second tumor, the study included 858 mCRC patients: 268 (31.24%) with right-sided mCRC, 352 (41.03%) with left-sided mCRC, 212 (24.71%) with rectal cancer and 26 (2.03%) with an overlapping lesion or unknown localization. KRAS and BRAF mutations were more frequently observed in right-sided tumours compared to left-sided tumours, whereas NRAS mutations were more frequently observed in left-sided CRC compared to right-sided CRC. Microsatellite instability (MSI)-high tumours were more frequently observed on the right side of the colon. Detailed overall survival data according to tumor location and biomarker status will be available at the congress.

Conclusions: We present the survival data of 1035 Belgian mCRC patients according to age, sex, tumor location and biomarker status. Currently, we can conclude that in Belgian patients left-sided mCRC has a better prognosis than right-sided mCRC, regardless of biomarkers status.

Legal entity responsible for the study: University of Antwerp.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

S89P Increase in tumor-infiltrating FoxP3-positive regulatory T cells in left-sided colorectal cancer tissues after 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 (CT) for colorectal cancer (CRC). Immunotherapy (IT) such as pembrolizumab are being approved and developed for the treatment of CRC with high microsatellite instability which is specific to right-sided CRC. We previously showed that the increases in the gene expressions of the IT targets, CTLA4 and LAG3, after UFT/LV CT were specific to left-sided CRC (ESMO2017). In this study, we examined the amount of tumor infiltrating lymphocytes (TILs) and the subtype of TILs in tumor tissues after and without UFT/LV CT.

Methods: In 90 patients with CRC, UFT (300 mg/m²/day) and LV (75 mg/day) were administered for 2 weeks before surgery (UFT/LV group), and in the other 170 patients with CRC, no CT was treated before surgery (control group). The amounts of TILs were quantitatively evaluated using HE-stained tumor tissue. The subtypes of TILs were evaluated by immunohistochemical analyses (IHA) of the surface markers of lymphocytes (CD3, CD4, CD8 and FoxP3). The patients were divided into low and high groups of the expressions of the markers using the appropriate cutoff values.

Results: The rate of TIL-high patients in UFT/LV group was significantly higher than in control group (43.4% vs. 35.3%, p = 0.0008). In IHA of TILs, the rate of FoxP3-high patients in UFT/LV group was significantly higher than in control group (41.1% vs. 22.4%, p = 0.0024). No differences were observed in other lymphocytic markers, CD3, CD4 and CD8. In left-sided tumors, the rates of TIL- and FoxP3-high patients in UFT/LV group were significantly higher than in control group (45.8% vs. 14.3%, p < 0.0001 and 43.8% vs. 20.9%, p = 0.0066, respectively). In right-sided tumors, there were no differences in both groups.

Conclusions: The increases in TILs, especially FoxP3-positive regulatory T cells, after UFT/LV CT may be specific to left-sided CRC, suggesting that the combination therapy of UFT/LV and immune checkpoint inhibitors or the sequential therapy of immune...
Background: The incidence of colorectal cancer in patients(pts) under the age of 50 has been steadily rising over the last two decades. This is in sharp contrast to average onset CRC where there has been a decline. Little is known about clinical behavior and biology of metastatic CRC in the young VO population.

Methods: We defined VO as < 45 yo and AO as > 50 yo. To better understand the differences in biology of early onset rectal tumors, we tabulated the clinical characteristics, genomics using next generation sequencing(MSK-IMPACT), treatments and outcomes in 175 metastatic pts with VO CRC treated at Memorial Sloan Kettering Cancer Center between 2014 and 2017 and compared these cases to a cohort of VO M CRC cases (n = 413) with CRC related hereditary syndromes such as Lynch Syndrome and inflammatory bowel disease were excluded.

Results: We analyzed 175 in the VO cohort. Age at diagnosis was between 17-35yo in 46 and between 36-45 in 129 pts. Among VO patients, there were 50.2% males, 27.7% smokers and the median BMI was 25.5. Comparing to AO, VO pts have significantly more right sided tumors (22.8% vs 33%; p = 0.01). Treatment choices did not differ among VO vs AO groups; systemic chemotherapy (46.7% vs 42.6%; p = 0.40) and metastectomy (34.6% vs 49.4%; p = 0.83). Overall survival was 59months in the VO vs 63.9 for the AO (p = 0.149). Among genetic characteristics mutational burden and DNA mismatch repair (MMR) defects were more frequent in VO vs AO (65% vs 63%; p = 0.60). VO pts also had a significantly worse overall survival compared to AO (HR 6.42, p = 0.005).

Conclusions: Our series describes a comprehensive clinical and genomic profile of VO mCRC. In contrast to prior reports VO does not appear to be associated with more aggressive disease and there was no difference in treatment modalities. Detailed genomic and clinical characteristics will be presented.

Legal entity responsible for the study: Andrea Cercek.

Disclosure: All authors have declared no conflicts of interest.

Funding: Has not received any funding.

593P The SENEA study: Prognostic role of serum biomarkers in elderly metastatic colorectal cancer patients

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Background: Aging induces meaningful changes in immune system and inflammation response with increase in monocyte-lymphocyte ratio (MLR) and serum lactate dehydrogenase (LDH) levels. Notably, high levels of these serum biomarkers are associated with poor prognosis in many tumours. We aim to explore the prognostic role of baseline (i.e. before first line chemotherapy) MLR and LDH levels in elderly patients (pts) with metastatic colorectal cancer (mCRC).

Methods: A retrospective analysis of a consecutive cohort of 120 elderly (>70 years) pts treated for mCRC between 2014 and 2017 at the Oncology Department of Aviano National Cancer Institute and University Hospital of Udine (Italy), was conducted. The prognostic role of MLR and LDH levels on overall survival (OS) was investigated through uni- and multivariate Cox regression analyses.

Results: At a median follow-up of 50.85 months, median OS was 19.96 months. Overall, 46 pts (38%) presented a right cancer, 43 pts (36%) a left cancer and 30 pts (29%) a colorectal one. In 8 (8%) and 47 (50%) pts a mutation of BRAF or KRAS was detected, respectively. Liver (36%), lymph-nodes (22%), peritoneum (22%) and lung (17%) were the most frequent sites of metastasis. Noteworthy, 22 pts (18%) had undergone a metastectomy. High levels of LDH (>480 U/L) and MLR (>45, obtained with ROC curve) were discovered in 23 (32%) and 51 (42%) patients respectively. By univariate analysis, high levels of LDH (HR 2.81, p = 0.001), MLR (HR 2.26, p < 0.001) or both (HR 6.42, p = 0.001) and node involvement at diagnosis (pN2 vs. pN0 HR 2.15, p = 0.019) were associated with worse OS. Metastectomy (HR 0.47, p = 0.009), tumor resection (HR 0.30, p = 0.010) and left sidedness (HR 0.53, p = 0.01) were associated with better OS. By multivariate analysis, high levels of LDH (HR 2.64, p = 0.004), MLR (HR 2.21, p = 0.019) or both (HR 4.19, p = 0.019) were independently associated with worse OS.

Conclusions: High baseline levels of LDH, MLR or both are unfavorable independent prognostic factors in elderly pts treated with first line chemotherapy for mCRC. These preliminary results emphasize the need of prospective studies to validate this cost-effectiveness biomarkers in this subgroup of pts.

Legal entity responsible for the study: University of Udine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Methods: This is a retrospective series of consecutive pts affected by mCRC treated with first line chemotherapy. The pts included were treated from 1/1/2005 to 15/03/2017 at University Hospital of Udine and IRCCS CRO of Aviano, Italy. A “drug holiday” was defined as 56 or more consecutive days without chemotherapy during first-line. Upfront metastasectomy were excluded. Logistic regression was used to find association between predictors and “holiday offer” in univariate and multivariate analysis.

Results: A total of 648 pts were included. In detail, 215 received a drug holiday (33.2%) while 433 (66.8%) received continuous treatment. In univariate analysis, the variables associated with holiday were: non-upfront metastasectomy (OR 11.1, IC 95% 6.62-22.6, p < 0.001), thrombosis (OR 6.08, IC 95% 3.19-11.58, p < 0.001), primary tumor (OR 2.79, IC 95% 1.79-4.34, p < 0.001), G3-G4 pathological grade (OR 1.49, IC 95% 1.01-2.19, p = 0.046), adjuvant CT (OR IC 95% 1.34, IC 95% 0.96-2.33, p = 0.032). Adjuvant RT (OR 1.62, IC 95% 0.99-2.62, p = 0.031) showed a trend towards association. More than one metastatic site at diagnosis (OR 0.59, IC 95% 0.42-0.83, p = 0.003) and nodal involvement (OR 0.57, IC 95% 0.34-0.95, p = 0.032) were associated to continuous treatment. In multivariate analysis, only first line non-upfront metastasectomy (OR 9.89, IC95% 4.38-22.33, p < 0.001), thrombosis (OR 4.48, IC95% 1.97-10.19, p < 0.001) and primary tumor resection (OR 2.43, IC95% 1.14-5.19, p = 0.022) were independently associated with drug holiday.

Conclusions: In our cohort, clinicians were more prone to propose a drug holiday in pts who had received non-upfront metastasectomy or thrombo-ablation or were treated on their primary tumor. Having more than one site of metastasis at the beginning of 1st line and nodal involvement favored continuous therapy.

Legal entity responsible for the study: ASUUD - Azienda Ospedaliero-Universitaria di Udine, Dipartimento di Oncologia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

5907P Predictive value of in vitro testing anti-cancer therapy sensitivity on 3D micro-tumors (tumouroids) from patients with metastatic colorectal cancer: A feasibility study


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Background: The treatment of cancer may be improved by testing the chemo sensitivity of cancer cells obtained from the patient’s tumor. 3D culture represents a promising method for modeling of patient tumors in vitro. The purpose of this study was to test the feasibility of a clinical trial offering patients with metastatic colorectal cancer treatment based on in vitro testing anti-cancer therapy sensitivity.

Methods: Main inclusion criteria were stage IV colorectal cancer, PS 0-1, previous exposure to 5FU, oxaliplatin, irinotecan, bevacizumab and, if RAS/Raf wild-type, an EGFR inhibitor. Fresh cancer tissues from metastases were cultivated as tumouroids. The culturing protocol which was originally developed for resected tissue was optimized for the smaller tissue amounts received from needle biopsies. Ten patients were to be included and at least five of them to have clinically applicable results in order for the procedure to be feasible.

Results: Ten patients were included from September to December 2017 in one institution. Biopsies were from liver (6), peritoneum (2), retroperitoneum (1) and lung (1). Rebiopsies were allowed and a total of 19 biopsy sessions were performed with ultrasound (14), CT (3) or sigmoidoscopy (2). In seven cases, the biopsy tumourpheresphere formation and sensitivity testing was successful. Median time from biopsy to result was 34 days (range 19-30). A notable challenge was obtaining sufficient viable tumor tissue resulting in increased culture times or the need for re-biopsies.

Conclusions: This is the first clinical study of its kind. The method of selecting last-line of colorectal cancer based on fresh biopsies was feasible as results were obtained in seven out of ten cases. The trial is now extended to a phase II trial with PFS as the primary endpoint.

Clinical trial identification: NCT03251612.

Legal entity responsible for the study: Lars Henrik Jensen.

Funding: 2cureX.

Disclosure: L.H. Jensen: Travel grants: Roche, Amgen, Bayer. G. Høgel, H. Harling, O. Thastrup: 2cureX. All other authors have declared no conflicts of interest.

5908P Macrophage migration inhibitory factor overexpression is a mechanism of acquired resistance to anti-EGFR inhibitor cetuximab in human colorectal cancer cell line


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Background: The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab are effective in a subset of RAS/RAF wild-type (WT) metastatic colorectal cancers (mCRCs) patients. Despite an accurate RAS-driven selection, not all patients will respond to EGFR inhibitors and the onset of secondary resistance limits their clinical benefit.

Methods: With the aim of developing effective preclinical models for testing possible strategies to overcome acquired resistance to EGFR blockade, we have generated a series of human colon cancer cell lines with in vitro and in vivo acquired resistance to anti-EGFR inhibitors. To better investigate the differentially expressed proteins involved in EGFR resistance, we applied an advanced quantitative proteomic approach based on TMT isotopic labeling and nano-liquid chromatography coupled with high resolution tandem mass spectrometry (MS/MS).

Results: To evaluate changes in protein expression we have used human CRC cell line cetuximab-sensitive GEO, as well as its derived cell line with acquired resistance to cetuximab GEO-CR. By MS/MS, we have identified and quantified 2455 proteins; 53 proteins were found to be differentially expressed in GEO-CR compared to GEO cells. Only 11 proteins were found to be high regulated in GEO-CR, among these we focused our attention on the inhibition factor of macrophage migration (MIF) for its relevance in CRC tumorigenesis. To explore its involvement in resistance to cetuximab in CRC cell line, we have performed an MTT assay with two MIF-antagonists, ISO1 a cell-permeable inhibitor of MIF taumomerase and 4-IPP, a selective MIF inhibitor that blocks MIF and its receptor, CD74, internalization. GEO-CR cell line was treated with two MIF-antagonists alone and in combination with cetuximab. Only the combined treatment with cetuximab and 4-IPP induced a synergistic antiproliferative and apoptotic effects.

Conclusions: These results suggest that MIF overexpression is involved in acquired resistance to cetuximab and the inhibition of EGFR and MIF could be a strategy for overcoming anti-EGFR resistance in patients with CRC.
Efficacy and safety of a recombinant soluble human thrombomodulin (ART-123) in preventing oxaliplatin induced peripheral neuropathy (OIPN): Results of a placebo-controlled, randomized, double-blind phase II study

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Background: OIPN is a common adverse event leading to early discontinuation of oxaliplatin. This was the first exploratory trial for proof of concept of whether ART-123 prevented OIPN.

Methods: Patients with stage II or III colon cancer who planned adjuvant chemotherapy with mFOLFOX6 were randomly allocated to the following 3 groups in a double-blind manner: placebo group (placebo saline on day 1-3, 1-day ART-123 group (ART-123 380U/kg on day 1 and placebo on day 2-3), and 3-day ART-123 group (ART-123 on day 1-3)). Study drug was given intravenously for 30 min immediately before oxaliplatin. The severity of OIPN was evaluated using NCI-CTCAE by physicians and FACT/GOG-NTX-12 (score range 0-48, lower values more severe) by patients. NCI-CTCAE was assessed at baseline, day 1-3 of every cycle, and 14 and 42 days after the last treatment with oxaliplatin. FACT/GOG-NTX-12 was assessed at baseline, day 1 and 8 of every cycle, and 14 and 42 days after the last treatment with oxaliplatin.

Results: Eighty patients were randomized, and 79 (28 placebo, 27 day 1-ART-123, and 24 3-day ART-123) patients were analyzed. Both 1-day and 3-day ART-123 tended to reduce the cumulative incidence of NCI-CTCAE grade 2 or higher OIPN and prevent worsening of FACT/GOG-NTX-12 scores, compared to placebo (Table). No substantial differences in other adverse events were noted.

Conclusions: ART-123 showed promising efficacy in delaying and reducing OIPN without serious safety concerns.

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<td><strong>Placebo</strong></td>
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<td><strong>(n = 28)</strong></td>
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<td>Sensory neuropathy</td>
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<td>NCI-CTCAE Baseline at 6th cycle</td>
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<td>1% (grade 2 or higher) at 12th cycle</td>
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<td>Overall scores in FACT/GOG-NTX-12 (the least square mean (SE))</td>
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<td>Baseline at 6th cycle</td>
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<td>NTX-12 (the least square mean (SE))</td>
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<td>Median total dose of oxaliplatin (mg/m²)(range)</td>
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Legal entity responsible for the study: Asahi Kasei Pharma Corporation.

Funding: Asahi Kasei Pharma Corporation.


Development of a nomogram for predicting survival in microsatellite stable patients with resected colorectal cancer

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Background: The benefits of adjuvant chemotherapy remain controversial in microsatellite stable (MSS) stage II resected colorectal cancer (CRC) patients. In this study, we constructed an overall survival (OS) prediction model for this subgroup, integrating a combination of molecular and clinical predictors.

Methods: Variables with p-values < 0.05 were entered into multivariate analyses using Cox stepwise regression model to select independent predictors as input for OS prediction nomogram. A final model was selected using a backward step-down process, which used Akaike Information Criterion as a stopping rule. The probability of 3-year and 5-year survival can be obtained by summing up the total score and locating it on the total point scale.

Results: We performed targeted sequencing on surgically resected tumor tissue of 122 stage II MSS patients, defined as having less than 15% length-instable loci, using a panel which allows for simultaneous detection of MSI status and mutation in 41 CRC-related genes. Among them, 23, 30 and 69 patients were diagnosed with proximal, distal and rectal cancer, respectively. To predict the probability of 3-year and 5-year survival, we constructed a nomogram incorporating the significant prognostic factors, including APC, ATM, BRAP, PTFEN, TP53 (LOF), mutation count (high > 5, low: < 5), age, CEA, and the location of the tumor. The actual and predicted survivals were in an excellent agreement, reflected by a C-index of 0.887 (95% CI: 0.816-0.957). Furthermore, Kaplan-Meier curves for survival outcomes showed significant distinction (p < 0.001) after stratifying our cohort into low, median and high risk groups according to total score obtained from our nomogram. Our data also demonstrated high risk patients who received adjuvant chemotherapy are associated with a better OS (p = 0.049). Low and median risk patients did not benefit from adjuvant chemotherapy, reflected by comparable OS.

Conclusions: We developed a nomogram model for predicting survival of MSS patients with stage II resected CRC. It can potentially serve as complementary method for clinicians to identify subgroups necessitating adjuvant therapy.

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Disclosure: T. Hou, H. Han-Zhang, H. Liu, J. Xiang, L. Zhang: Burning Rock Biotech. All other authors have declared no conflicts of interest.

Germline mutations in Chinese colorectal cancer patients with mismatch repair deficiency

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Background: Mismatch repair deficiency (dMMR) due to germline mutations in DNA repair genes including MLH1, MSH2, MSH6 and PMS2, or somatic aberrant silencing of MLH1, is a well-established feature for Lynch syndrome, a major type of hereditary colorectal cancer (CRC). The purpose of this study is to derive prevalence of germline MMR gene mutations in Chinese population with dMMR CRC.

Methods: ColonCore panel is designed for simultaneous detection of microsatellite instability (MSI) status of 22 regions and mutations in 38 CRC-related genes. Whole exons of the 38 genes were covered by the panel. The MSI phenotype detection method was a read-count–distribution-based approach. It utilized the coverage ratio of a specific set of repeat lengths as the main characteristic of each microsatellite locus, and categorized a locus as unstable if the coverage ratio was less than a given threshold. The MSI status of a sample was determined by the percentage of unstable loci in the given sample.

Results: Among 1394 postsurgical CRC patients whose MMR status were detected by ColonCore panel, there were 175 samples with dMMR (12.6%). Among these patients harbored pathogenic germline MMR gene mutations, their first cancer was diagnosed ranging from 22 to 69 years old.
Kynurenic 3-monooxygenase as a potential biomarker for colorectal cancer

C. Liu, X. Mao: Employee of Burning Rock Biotech. All other authors have declared no conflicts of interest.

Background: Colorectal cancer (CRC) is the third most common cancer and the cause of cancer-related deaths worldwide. Due to the lack of highly sensitive and specific biomarkers, colorectal cancer often identified at the late stages in most patients when diagnosed. Identifying the potential cancer marker and understanding the mechanisms of metastasis and progression behind colorectal cancer is crucial for human CRC. Kynurenic 3-monooxygenase (KMO) is a monooxygenase participating in tryptophan metabolism. Previous studies showed that KMO related to metastasis and proliferation in hepatocellular carcinoma. However, the biological role of KMO in human CRC is still unclear.

Methods: The expression level of KMO in patients with CRC was examined using immunohistochemistry (IHC). The correlation between KMO expression and patient survival rate was analyzed using The Cancer Genome Atlas (TCGA) database. CRC cell lines were used to perform functional assays. UPF 648, a potent KMO inhibitor, and RNAi against KMO and luciferase were used for in vitro studies. Cell viability was analyzed by MTT assay. Cell motility was examined by transwell assay. Stemness properties were assessed by sphere assay and the expression of cancer stem cells markers.

Results: IHC data showed that the expression of KMO was upregulated in CRC tumor tissues compared with normal counterparts of CRC. Furthermore, higher level of KMO transcript was associated with worse overall survival in CRC patients in TCGA database. Knockdown of KMO inhibited the expression of cancer stem cells markers, including CD44 and Nanog, as well as abilities of migration and invasion of CRC cells. Furthermore, the effect of KMO activity inhibition in cell viability was cell lines specific whereas the abilities of cell migration, invasion and sphere formation in CRC cells were significantly suppressed by UPF 648 treatment.

Conclusions: Our data suggest that KMO may serve as a potential biomarker and play a tumor-promoting role in CRC.

Legal entity responsible for the study: Chun-Yu Liu.

Funding: Has not received any funding.

Disclosure: C. Liu, X. Mao: Employee of Burning Rock Biotech. All other authors have declared no conflicts of interest.

Induction chemotherapy plus chemoradiotherapy with or without aspirin in high risk rectal cancer (IGC)

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Background: Induction chemotherapy followed by chemoradiation is an attractive approach, with more favorable compliance and toxicity profiles. Furthermore, the benefit of aspirin in cancer of the colon and rectum is already known. Recently, it was described its potential activity during chemoradiotherapy. The aim is to evaluate the efficacy of total neoadjuvant treatment and the aspirin use during chemoradiotherapy for high-risk rectal cancer.

Total design was randomized trial to evaluate induction treatment with XELOX and Capecitabine-based chemoradiotherapy with or without aspirin in a high risk population selected by MRI. High risk will be defined by presence of at least one of the following criteria on high-resolution thin-slice MRI: tumors within 1 mm of or beyond the mesorectal fascia; tumor extending >5 mm or more into perirectal fat; resectable cT4 tumors; lower third; nodal involvement; extramural vascular invasion. Primary objective is to evaluate the tumor downstaging after total neoadjuvant treatment with or without aspirin. All the patients enrolled in the study will receive XELOX every 21 days for four cycles, unless unacceptable toxicity or progression is detected. After this treatment, patients will be randomized to receive Capecitabine-based chemoradiotherapy with aspirin or placebo (Capecitabine 850 mg/m2 5 days per week combined with radiotherapy with total dose of 50.4 Gy in 28 days). Random assignment of treatment will be stratified by MRI tumour regression grade. After 8-10 weeks, they will be evaluated by MRI. Patients with complete clinical response will be managed with “watch and wait” approach. The sample size was calculated to Simon’s optimal two-stage design. Accordingly, 11 patients must be included in each group during the first stage. If 3 patients or fewer show downstaging, the trial will be stopped (interim efficacy analysis). Inclusion of patients will continue until 31 patients are included, in order to detect a difference of 26% or greater in downstaging. A treatment regimen will be considered effective if more than 10 patients of the total 31 show downstaging (final analysis), reaching 90% power with an alpha of 0.05 level of significance.

Clinical trial identification: NCT03170115.

Legal entity responsible for the study: INCA - Instituto Nacional de Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Phase II study of surgery after S-1 + oxaliplatin + bevacizumab therapy for unresectable rectal cancer by organ-preserved TME

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Background: For unresectable locally advanced rectal cancer (ULARC), long-course preoperative neoadjuvant chemotherapy (NACRT) was recommended by ESMO guideline. However, ULARC had the risk of not only local recurrence but also subsequent metastatic disease. In these circumstances, preoperative neoadjuvant intense chemotherapy without radiotherapy (NAC) are being investigated in multiple trials. The recent trials suggested equivalent local down staging and pCR rates of NAC using doublet + bevacizumab as compared with standard NACRT. On the other hands, the addition of bevacizumab could be associated with anastomotic insufficiency or rectal perforation. Therefore, the strategy of the safe and sufficient introduction of preoperative doublet therapy + bevacizumab has been recommended for ULARC.

Trial design: Primary end point: 1. down-staging rate (The rate of pT0, pT1a, pT1b and pT1c) Exclusion criteria: 1. Clinical stage T3 or T4, any N without distant metastases. 2. Unresectable rectal cancer by organ-preserved TME which was judged by high resolution MRI. The features include CRM c < 1 mm, T4b, and lateral lymph node metastasis. 3. The patients had thromboembolism or significant abnormal electrocardiogram or cardiovascular disease. Protocol: 5–6 is administered orally at 80mg/m²/day for 14 consecutive days followed by a 7 day rest. L–OHP is given intravenously on days 1, at a dose of 135mg/m²/day. Bevacizumab is given intravenously on days 1, at a dose of 5mg/kg/day. 21 days are assumed 1 course, and chemotherapy consisted of 4 courses. Surgery is carried out in 8 to 12 weeks after the end of chemotherapy. The type of surgery was defined by high resolution MRI after preoperative chemotherapy within 2 weeks before the date of surgery. Target sample: 32 patients Features of this trial: Paying attention to the safety and efficacy of bevacizumab compared with prior trials according to the following points: 1. long interval between surgery and the administration of bevacizumab. 2. The transverse loop colostomy is required before NAC in case of stenosis. 3. The diverting stoma are necessary after intestinal resection.

Clinical trial identification: UMIN Clinical Trials Registry: UMIN000031626.

Release date: 2018/03/08.

Legal entity responsible for the study: Aomori Colorectal Cancer Study (ACCS) group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
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and surgery. In these circumstances, we designed a preoperative doublet + bevacizumab therapy in high-risk patients such as synchronous liver metastasis before simultaneous resection of primary and liver metastasis.

Trial design: Primary endpoint: Disease-free survival. Inclusion criteria: 1. Clinical T3 and T4 lesions with only liver metastases. Exclusion criteria: 1. Over 75 years old. 2. The patients had thomboembolism or significant abnormal electrocardiogram or cardiovascular disease. Protocol: S-1 is administered orally at 80mg/m²/day for 14 consecutive days followed by a 7-day rest. Oxaliplatin (L-OHP) was given intravenously on days 1, at a dose of 130mg/m²/day. Bevacizumab is given intravenously on days 1, at a dose of 7.5mg/kg/day. 21 days were assumed 1 course, and chemotherapy consisted of 4 courses. Surgery was carried out 8 to 12 weeks after the end of chemotherapy. Adjuvant chemotherapy of S-1 at 80mg/m²/day for 14 consecutive days followed by a 7-day rest was initiated within 6-8 weeks after surgery. Target sample: 28 patients. Features of this trial: Paying attention to the safety and efficacy of bevacizumab compared with prior trials according to the following points: 1. Long interval between surgery and the administration of bevacizumab. 2. Preoperative chemotherapy was administered prior to resection of primary colorectal cancer in order to increase the intensity of chemotherapy. 3. The loop ostomy is required before neoadjuvant chemotherapy in case of toxicity.

Clinical trial identification: UMIN000032102, release date: 2018/04/04.

Legal entity responsible for the study: Authors Colorectal Cancer Study (ACCS) Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Randomized phase II study of FOLFIRI plus ramucirumab (Rmab) versus FOLFIRI plus Rmab as first-line treatment for patients with metastatic colorectal cancer (mCRC): WJOG921G6


Background: Rnmb, an anti-VEGFR-2 antibody, inhibits VEGF-A, -C, -D, and binding endothelial cell proliferation, while bevacizumab (Bmab) binds to and blocks circulating VEGF-A. The TRIBE trial demonstrated that FOLFOXIRI plus Bmab improved overall response rate (ORR), progression-free survival and overall survival compared with FOLFOXIRI plus Bmab plus induction therapy followed by maintenance therapy with Bmab (5-FU, leucovorin (L-V) and Bmab). However, little is known about the role of Rmab in first-line setting and the comparison of induction followed by maintenance therapy with continuous therapy continued until progressive disease (PD) or unacceptable toxicity.

Trial design: WJOG921G6 is an open-label, randomized phase II study evaluating FOLFIRI plus Rnmb until PD (arm A) versus FOLFIRI plus Rmab for 8 to 12 cycles followed by maintenance therapy with 5-FU, LV and Rmab (arm B) for patients with mCRC.

Eligibility criteria include histologically confirmed unresectable colorectal adenocarcinoma, age of 20-75 years, ECOG PS of 0 or 1, without UGT1A1 *1/*1, *1/*28 or *1/*28/*28, no history of prior chemotherapy for mCRC, and adequate organ function. Stratification criteria are institution, RAS status, history of adjuvant chemotherapy, and primary tumor location. Arm A comprises Rnmb 8 mg/kg, irinotecan (IRI) 180 mg/m², 5-FU 200 mg/m², and bolus 5-FU 600 mg/m² given by a 46-hour continuous infusion (ci) of 5-FU 2400 mg/m² every 2 weeks until PD. Arm B consists of 8 to 12 cycles of FOLFIRI plus Rmab (Rnmb 8 mg/kg, IRI 165 mg/m², oxaliplatin 85 mg/m², 5-FU 200 mg/m², and 5-FU 800 mg/m²) as induction therapy followed by 5-FU, LV and Rmab until PD. Primary endpoint is ORR, and main secondary endpoints are PFS, PFS2, OS and safety. Sample size was calculated to be 120 (60 patients per arm), with a one-sided alpha of 10% and a power of 80%, assuming ORR of 50% in arm A and 70% in arm B. This study has enrolled 23 patients as of April 28th, 2018.


Legal entity responsible for the study: West Japan Oncology Group.

Funding: Eli Lilly Japan K.K.

Disclosure: H. Yasu: Honorary: Taiho Pharmaceutical, Chugai Pharma, Yakult Honsha, Bristol-Myers Squibb Japan, Takeda, Kyowa Hakko Kirin, Medicinon, Ono Pharmaceutical, Daiichi SANKYO, Lilly Japan, Merck Serono, Terumo, Becton Dickinson, Nihonkayaku, H. Hara: Consulting or advisory role: Ono Pharmaceutical, Chugai Pharma, Merck Serono, and MSD, Honoraria from Chugai Pharma, Taiho Pharmaceutical, Merck Serono, Yakult Honsha, Lilly, Ono Pharmaceutical, Takeda, Author’s institution has received research funding: Asta Zeneca, Chugai Pharma, Merck Serono, MSD, Ono Pharmaceutical, Taiho Pharmaceutical, Takeda, Boehringer Ingelheim, Daiwippon Sumitomo Pharma, Daiichi Sankyo, Lilly, Pfizer, LSX BioPharma, Eisai, Incyte. E. Baba: Honoraria: Chugai Pharma, Lilly Pharma, Author’s institution has received research funding: Chugai Pharma, Lilly Pharma, Taiho Pharmaceutical, Taiho Pharmaceutical, Takeda, Merck Serono Ltd. K. Yoshimura: Honoraria: Chugai Pharma, Lilly, Astra Zeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Takeda, Eisai. S. Hironaka: Consulting or advisory role. Astra Zeneca, Honoraria: Lilly, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Taiho Pharmaceutical, Yakult Honsha, Daiichi Sankyo. K. Muro: Honoraria: Takeda, Chugai Pharma, Lilly, Yakult Honsha, Merck Serono, Taiho Pharmaceutical, Lilly, Ono Pharmaceutical, Research funding: Ono Pharmaceutical, MSD, Daiichi Sankyo, Shionogi Pharma, Kyowa Hakko Kirin, Gilead Sciences. K. Yamazaki: Honoraria: Chugai Pharma, Daiichi Sankyo, Yakult Honsha, Takeda, Bayer, Merck Serono, Bristol-Myers Squibb Japan, Taiho Pharmaceutical, and Lilly. Author’s institution has received research funding: Taiho Pharmaceutical. All other authors have declared no conflicts of interest.

60ISTIP BIG BANG study: A multicenter phase II study of the MEK inhibitor binimetinib + BRAF inhibitor encorafenib + anti-EGFR antibody cetuximab in patients with BRAF non-V600E mutated metastatic colorectal cancer (EPOCH 1703)


60ISTIP Background: While BRAF mutations occur in 10-15% of metastatic colorectal cancer (mCRC), BRAF Non-V600E mutations is recently reported with range 2.2-5.2%. We have reported that BRAF Non-V600E could be a negative impact on survival outcome as well as anti-EGFR antibody treatment for pretreated mCRC patients (Shinozaki E, et al. JIT Cancer 2017). In addition, simultaneous inhibitions of MEK, BRAF and EGFR exhibited most potent anti-tumor activities in BRAF Non-V600E mutant cell lines and xenografted models (unpublished data).

Trial design: BIG BANG study is a multicenter phase II study to assess efficacy, safety and proof-of-concept of the triple combinations of binimetinib (BINI) + encorafenib (ENCO) + cetuximab (CEXTU) in patients with BRAF Non-V600E mutated mCRC, identified by either tumor tissue-based analysis (primary analysis cohort) or circulating tumor DNA (ctDNA) analysis (liquid biopsy cohort). Key eligibility criteria includes ECOG PS ≤ 1, mCRC with BRAF Non-V600E mutant and non-silent type; refractory or intolerant to at least one fluoropyrimidine-based regimen (including irinotecan or oxaliplatin) and no prior history of anti-BRAF or anti-EGFR antibody and regorafenib. The primary end point is ORR for primary analysis cohort. A sample size of the primary analysis cohort is calculated to be 21 on the hypothesis that the threshold ORR is 6% and expected ORR is 30%, with a significant level of 2.5% (one-sided) and power of 80%. Furthermore, paired tissue and blood samples will be obtained for pharmacodynamic analysis before study treatment, pre-dose of second cycle, and after disease progression. To our best knowledge, this is the first study targeting BRAF Non-V600E mutated mCRC.

Clinical trial identification: UMIN000031857 and UMIN0031860.

Legal entity responsible for the study: Hideaki Bando.

Funding: The Japan Agency for Medical Research and Development.

Background: BRAF V600E mutations are present in 5-10% of metastatic colorectal cancer (mCRC) patients, associated with aggressive biology and limited response to standard chemotherapy, especially in second line and beyond. BRAF V600E mutant CRCs have different patterns of gene expression from the BRAF wild-type, and preclinical evidence suggests that microtubule inhibitors have a potential antitumor effect on CRCs with BRAF V600E mutations. In addition, we observed two arms study with intermittent PAN plus FOLFIRI compared to the same toxicities of anti-EGFR monoclonal antibodies (moAbs). This issue is of particular interest given the dermatologic toxicities of anti-EGFR moAbs and the emergence of drug resistant clones. In mCRC pts recent data suggest a molecular adaptation of tumor to an intermittent drug schedule with anti-EGFR moAbs. On this basis, we designed a multicenter phase II randomized two arms study with intermittent PAN plus FOLFIRI compared to the same regimen given continuously until disease progression (PD) in the first line treatment of pts with WT RAS and BRAF unresectable mCRC, with a prospective genetic analysis of both tumor tissue and cfDNA.

Trial design: PFS on treatment (PFSOT) at 12months is the primary endpoint. Assuming a p0 of 30% (corresponding to a median PFS of 7months), and a p1=43% (corresponding to a median PFS of 10months), setting the significance level at 10% with a power of 80% a total of 68 pts will be enrolled in each arm. At the time of enrollment, pts will be immediately randomized to one of the two arms: standard continuous or exploratory intermittent treatment. All pts will receive an induction treatment with 8 cycles of PAN plus FOLFIRI, given every two weeks, at the standard dosage. After the induction treatment, non-progressing pts will receive continuous PAN plus FOLFIRI until PD, unacceptable toxicity or informed consent withdrawal (Standard ARM) or observe a treatment free interval until PD followed by up to 8 cycles of PAN plus FOLFIRI (Experimental ARM). Treatment cycling will continue till any PD on treatment.


Legal entity responsible for the study: Istituto Nazionale Tumori Fondazione G. Pascale - Naples, Italy.

Funding: Amgen; Istituto Nazionale Tumori Fondazione G. Pascale - Naples, Italy.

Disclosures: A. De Stefano: Advisory boards: Amgen, Roche; C. Rosati: Advisory role: Amgen, Roche, Bayer, Merck Serono. S. Leo: Scientific advisory board: Amgen, Roche, Bayer, Merck Serono, Sanofi. C. Mastroianni: Advisory role: Roche, Amgen, Celgene, Sanofi; Research funding: Bayer. All other authors have declared no conflicts of interest.
Background: Colorectal cancer (CRC) is one of the most common malignancies, and a leading cause of cancer death worldwide. Surgery is the only curative therapy available for locally advanced colon cancer (LACC), however, the disease is associated with a significant recurrence rate and even with surgery the therapy its prognosis is far from satisfactory. Preoperative treatment strategy is an attractive concept in LACC because it has the theoretical advantages to eradicate micrometastases, to reduce tumor cell shedding during surgery, to allow the assessment of initial tumor response and could be better tolerated than adjuvant treatment. The results of the recently reported FOxTROT trial has shown that preoperative chemotherapy in LACC is feasible with no increase in surgical morbidity or mortality. The immune contexture of solid tumors has become an emerging hallmark of cancers. Recent evidences indicate that immune infiltrate is an informative prognostic indicator in LACC. Moreover, it was demonstrated that immune checkpoint inhibitor are also a stronger predictor of patient survival than microsatellite instability. Based on these considerations, we designed a window of opportunity study to determine the feasibility of nivolumab in the preoperative setting in pts with LACC.

Trial design: Pts will receive nivolumab at a flat dosage of 240 mg every two weeks on Day 0 and Day 14 (+/- 1 day) prior to planned surgery on Day 0 or up to 7 days. An initial 6-pts safety run-in cohort will be followed by an expansion cohort, with a planned accrual of 16 pts. Postoperatively, standard adjuvant chemotherapy will be administered as recommended by guidelines. Primary objective is to determine the safety and feasibility of Nivolumab in the preoperative setting. The exploratory primary objective is the rate of pathological complete tumor regression, as well as correlative studies to determine molecular and immunophenotypic changes in tumor and peripheral blood samples as potential biomarkers of toxicity/efficacy. Secondary objective are tumor response rate defined by RECIST, postoperative complications, relapse-free survival, overall survival and metabolic response changes evaluated by FDG-PET-CT scan prior to surgery.

Clinical trial identification: EudraCT: 2017-003739-12.

Legal entity responsible for the study: Società Campana di Immunoterapia Oncologica (SCITO).

Funding: Società Campana di Immunoterapia Oncologica (SCITO) with funding from IMS.

Disclosure: All authors have declared no conflicts of interest.


Disclosures: All authors have disclosed no conflicts of interest.

Legal entity responsible for the study: Grupo Español Multidisciplinar de Melanoma.

Funding: Merck.


Legal entity responsible for the study: Celyad SA.

Funding: Celyad SA.

Disclosure: A. Flament, F.F. Lehmann, C. Lonez: Employee: Celyad SA. All other authors have declared no conflicts of interest.

Legal entity responsible for the study: Celyad SA.

246TP Pembrolizumab showed clinical benefit in patients with microsatellite instability (MSI) in mCRC but not in MSS patients. Cancer vaccines with ADC could be a complementary therapeutic approach to CHKPTN. We previously conducted a negative randomized phase II trial in mCRC patients refractory to standard therapy, with ADC compared to the best supportive care (Eur J Cancer 64:167-74, 2016). A phase I-II multicentric trial withavelumab (anti-PD-L1) plus ADC vaccine in pre-treated MSS mCRC patients began in April 2018 (NCT03152565).

Trial design: The study is designed to evaluate the safety, tolerability, pharmacodynamics and anti-tumor effects of the combination in pre-treated MSS mCRC patients. In the phase I, patients are assigned using a standard 3x3 de-escalation criteria (level -1 if dose limiting toxicity (DLT) with avelumab 3 mg/kg every 2 weeks) to receive avelu-
mab at a dose of 10 mg/kg every 2 weeks combined to ADC vaccine at days 1, 14, 28, 42 and 56, and thereafter every 6 months until disease progression (maximum of 6 additional doses) or unacceptable toxicity. Biopsies to prepare tumour lysate will be obtained from primary tumour or metastatic disease. The primary objective is to determine the maximum tolerated dose (MTD) and the efficacy of the combination. To detect at least a 20% difference in PFS at 6 months (from 20% to 40%), 33 patients are needed (80% power, alpha equals 5%, two sided). An interim analysis (Simon’s two stage) when the first 18 patients are accrued is planned. Secondary objectives includes pharmacodynamics (a) NanoString 360 gene immune-signature from archival biopsy, at study entry and at 2 months therapy (b) cytokine and chemokine determination (at study entry and at 2 months therapy) and (c) Autologous tumour mixed leucocyte reaction to test the polarisation of the immune response against the combination (at study entry and at 2 months therapy).

Clinical trial identification: NCT03152565.

Legal entity responsible for the study: The French National Comprehensive Cancer Network (CCNE).

Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.

Clinical trial identification: NCT03152565.

Legal entity responsible for the study: Celyad SA.

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Legal entity responsible for the study: Celyad SA.

Disclosures: All authors have declared no conflicts of interest.

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Legal entity responsible for the study: Celyad SA.

Funding: Celyad SA.
Serum levels of interleukin 8 (IL-8) and other cytokines as predictors of the efficacy of aflibercept in combination with FOLFIRI in metastatic colorectal cancer patients: The FLIBER study

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Background: The VELOUR study (Van Cutsem, et al 2012) showed that the addition of aflibercept to irinotecan-based chemotherapy (FOLFIRI) in patients with metastatic colorectal cancer (mCRC) refractory to oxaliplatin-based chemotherapy was associated with improved progression-free and overall survival. IL-8 enhances cell proliferation and survival and promotes tumor angiogenesis (Lee, et al 2012). In the randomized phase II AFFIRM study, conducted in mCRC patients treated with oxaliplatin-based chemotherapy with or without aflibercept, high serum levels of circulating IL-8 were significantly associated with reduced PFS (Lambrechts, et al 2015). While in patients treated without aflibercept, PFS was independent on IL-8 levels, patients treated with aflibercept with IL-8 levels ≤ vs. > 19 pg ml⁻¹ presented a median progression free survival of 9.3 (7.52–11.10) vs. 4.1 (2.33–8.54) months. The FLIBER trial aims to explore the predictive value of serum levels of IL-8 and other cytokines in a population of mCRC patients receiving aflibercept plus FOLFIRI.

Trial design: The FLIBER trial is a phase IV single arm study which plans to enroll 124 patients with mCRC resistant to or progressed after an oxaliplatin-containing regimen who are planned to start aflibercept in combination with FOLFIRI as per standard clinical practice and decision by their treating oncologist. Patients will be assessed for a serum cytokine panel at baseline, after 2 months of treatment and at radiologic progression. The primary end point is progression free survival (PFS), with the objective to estimate the difference in PFS between the two groups defined on the basis of their baseline IL-8 levels (≥ vs. < than median). The secondary endpoints are Radiologic Response Rate (rRR), Overall Survival (OS) and safety profile and their relationship with IL-8 levels and the other cytokines assessed. Assessed cytokines include PDGF, IL-1β, IP-10, IL-1α, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Epitaxin, MGF, GCSF, GMPCF, IFNg, MCP1, MIP1a, MIP1b, RANTES, TNFa and VEGF, VEGFa, T-cad, VEGFR3, SAP, VDRF, neuropilin1, CRBP, endoglin, PGF.


Legal entity responsible for the study: Fondazione Ricerca Traslazionale (FoRT).

Funding: Sanofi Genzyme.

Disclosure: C. Buonerba: Research support to Institution, Consultancy. All other authors have declared no conflicts of interest.
**GASTROINTESTINAL TUMOURS, NON-COLORECTAL**

**6150** Randomized phase III study of gemcitabine, cisplatin plus S-1 (GCS) versus gemcitabine, cisplatin (GC) for advanced biliary tract cancer (KHBO1401-MITSUBA)


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**616PD** Quality-of-life (QoL) results from RAINFALL: A randomized, double-blind, placebo (PL)-controlled phase III study of cisplatin (Cis) plus capicitabine (Cape) or 5FU with or without ramucirumab (RAM) as first-line therapy for metastatic gastric or gastroesophageal junction (G-GEJ) cancer


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A phase III study of nivolumab (nivo) in previously treated advanced gastric or gastric esophageal junction (G/GEJ) cancer (ATTRACT-2): Two-years update data


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Progression-free survival and recurrence results for AGITG DOCTOR: Pre-op cisplatin, 5FU & DOcetaxel +/-radiotherapy after poor early response to cisplatin & 5FU for resectable oesophageal adenocarcinoma


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620PD Influence of enteral nutrition on nutritional status, treatment toxicities, and short-term outcomes in esophageal carcinoma patients treated with concurrent chemoradiotherapy: A prospective, multicenter, randomized controlled study

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621PD Phase II trial of tepotinib vs sorafenib in Asian patients (pts) with advanced hepatocellular carcinoma (HCC)


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622PD Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP) following first-line sorafenib: Patient reported outcome results across two phase III studies (REACH-2 and REACH)

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623PD The nationwide cancer genome screening project in Japan, SCRUM Japan GISCREEN: Efficient identification of cancer genome alterations in advanced biliary tract cancer


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Preliminary results of a phase 2a study to evaluate the clinical efficacy and safety of erdafitinib in Asian patients with biomarker-selected advanced cholangiocarcinoma (CCA)


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Pembrolizumab for advanced biliary adenocarcinoma: Results from the multicohort, phase II KEYNOTE-158 study

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Randomized, phase III trial comparing adjuvant gemcitabine (Gem) versus Gem plus chemoradiation (CCRT) in curatively resected pancreatic ductal adenocarcinoma (PDAC): A Taiwan cooperative oncology group study

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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-small-cell lung cancer (NSCLC) patients. The purpose of the esophagus. Using a custom-built device, digital annotations of whole slide images were transferred to a hematoxylin-stained slide, which was subsequently deparaffinized. Marked tumor areas were scraped for RNA extraction and qPCR.

Methods: We included all patients with esophageal adenocarcinomas between 2004 and May 2013 in the AMC. Paired tumor samples were obtained before start of neoadjuvant chemoradiation therapy according to the CROSS regimen and at surgical resection.

Results: Of the 220 aEC samples analyzed, the proportion of sample and histology type is followed: surgical specimen 52.1%, squamous cell carcinoma 29.6%, adenocarcinoma 16.7%, and small cell carcinoma 1.8%. Five patients with druggable genomic alterations (PIK3CA(n=3), EGFR(n=1)) were enrolled for clinical trials of targeting therapies.

Conclusions: This study is ongoing with the participation of 23 major cancer centers. The nationwide screening system is efficient to detect rare gene alterations in aEC. This novel knowledge provides an intriguing background to investigate new target approaches in these patients and to progress precision medicine. Clinical trial information: UMIN00016344 (Non-CRC).

Clinical trial identification: UMIN00016344

Legal entity responsible for the study: SCRM JAPAN.

Funding: 15 SCRM-Japan collaborating pharmaceutical companies, AMED, NGC.

Disclosure: K. Kato: Other: 15 SCRM-Japan collaborating pharmaceutical companies; Grants: AMED; Other: NCC, during the conduct of the study; Grants: Shionogi, Ono Pharmaceutical, Pfizer, GlaxoSmithKline, MSD, Astellas, Bayer, Chugai, Taiho, Chugai, Astellas, Eisai.

N. Nomura 14, T. Kuwata 15, S. Fujii 16, W. Okamoto 17, K. Shitara 18, A. Ohtsu 18, T. Yoshino 18
**Hypoxia gene expression defines a poor prognostic sub-group in oesophageal adenocarcinoma**

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**Background:** The incidence of Oesophageal Adenocarcinoma (OAC) has risen 6-fold in the western world in the last forty years but survival is poor. Increased molecular understanding of this heterogeneous disease is needed to improve treatment selection and develop novel therapies. This study uses gene expression data to perform unbiased molecular subtyping and identify prognostic subgroups in OAC.

**Methods:** Transcriptional profiling of 274 treatment naïve OAC biopsies was performed using the Almac Diagnostics Xcel array (13). All patients received platinum-based neo-adjuvant chemotherapy prior to surgical resection at four United Kingdom centres between 2004-2012. Iterative semi-supervised clustering based on gene expression level variability was performed followed by functional enrichment using DAVID. Cluster membership was assessed for independence of known prognostic factors using Cox proportional hazards regression for relapse-free (RFS) and overall survival (OS). Clustering was repeated with a published 51-gene hypoxia signature with validation in the TGCA OAC (n = 65) and oesophageal squamous cell carcinoma (n = 45) cohorts.

**Results:** Patients were clustered into two groups with significantly different RFS (HR = 0.54, p = 0.05) and OS (HR = 0.52, p = 0.04). There were no significant differences in known prognostic factors such as pathological response, lymphovascular invasion and resection margin. Pathway analysis revealed the PI3K-AKT, p53, Tumour Necrosis Factor and Hypoxia Inducible Factor 1 (HIF-1) signalling pathway to be upregulated in the poor prognostic group. To further investigate the role of the HIF-1 pathway, a hypoxia 51-gene signature was applied. Patients were stratified into hypoxia low and high groups with improved RFS (HR 0.64, 95% CI: 0.42-0.97; p = 0.04) and OS (HR 0.67, 95% CI: 0.44-1.02; p = 0.08) in the hypoxia-low group. Increased OS for the hypoxia-low group was also observed in the TCGA cohort (HR 0.49, 95% CI: 0.24-0.97; p = 0.04). There was a significant association between membership of the poor prognostic and hypoxia-low cluster groups (p < 0.001).

**Conclusions:** Molecular stratification and application of a hypoxia gene signature identifies a poor prognostic group of OAC patients characterised by upregulation of hypoxia signalling.

Legal entity responsible for the study: Queen’s University Belfast.

**Funding:** Northern Ireland Health and Social Care Research and Development Division.

**Disclosure:** R.D. Kennedy: Global VP of Biomarker Development for Almac Diagnostics and have patent declarations. All other authors have declared no conflicts of interest.

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**630P**

**Neoadjuvant radio-chemotherapy for esophageal cancer: A multicenter European study comparing paclitaxel/carboplatin, 5FU/cisplatin and FOLFOX**


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**Background:** The incidence of Oesophageal Adenocarcinoma (OAC) has risen 6-fold in the western world in the last forty years but survival is poor. Increased molecular understanding of this heterogeneous disease is needed to improve treatment selection and develop novel therapies. This study used gene expression data to perform unbiased molecular subtyping and identify prognostic subgroups in OAC.

**Methods:** Patients operated from January 2004 to December 2014 who underwent neo-adjuvant radio-chemotherapy were included. Different regimens of neoadjuvant radio-chemotherapy are concurrently used prior to surgery for resectable, locally advanced esophageal cancer. Comparative data are scarce and to some extent conflicting, regarding toxicity and long-term outcomes when treating different subtypes. This study aimed to assess clinical tolerances and long-term survival of three commonly used combinations of neoadjuvant therapies.

**Results:** Of the 143 eligible patients, 429 patients were analysed following propensity score matching (caliper 0.2) using pre-treatment variables (age, gender, year of treatment, tumour length and site, and clinical T stage), we compared the impact of the treatments on pathological outcomes, patient recurrence and overall survival.

**Conclusions:** The concurrent chemoradiotherapy followed by surgery is the standard treatment for locally advanced esophageal cancer (LAECC) and the role of induction chemotherapy (IC) remains unclear. We aimed to study if the addition of IC to standard treatment increases the rate of pathologic complete response (pCR).

Legal entity responsible for the study: The University of Queensland.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**631P**

**Neoadjuvant therapy for esophageal adenocarcinoma: A propensity score-matched comparison of paclitaxel and carboplatin chemotherapy with cisplatin and 5-fluorouracil-based chemotherapies.**


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**Background:** Multimodality treatments of patients with esophageal adenocarcinoma (EAC) improve survival, but the optimal treatment strategy remains undetermined. This study aimed to compare response, local recurrence and survival outcomes in patients undergoing neoadjuvant paclitaxel and carboplatin chemoradiotherapy with 41Gy (CROSS) with neoadjuvant cisplatin and 5-fluorouracil (CF)-based chemoradiotherapy with 45Gy (CFRT) or CF chemotherapy followed by oesophagectomy for EAC.

**Methods:** Patients who underwent CROSS, CFRT or CF followed by surgery for EAC were identified from two single institution prospective databases from Australia and the Netherlands (2000-2018) and included in this study. After pair-wise propensity score matching (caliper 0.2) using pre-treatment variables (age, gender, year of treatment, tumour length and site, and clinical T stage), we compared the impact of the treatments on pathological outcomes, patient recurrence and overall survival.

**Conclusions:** The concurrent chemoradiotherapy followed by surgery is the standard treatment for locally advanced esophageal cancer (LAECC) and the role of induction chemotherapy (IC) remains unclear. We aimed to study if the addition of IC to standard treatment increases the rate of pathologic complete response (pCR).

Legal entity responsible for the study: The University of Queensland.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Methods: We performed a retrospective analysis of patients (pts) diagnosed with LAEC and treated with neoadjuvant chemoradiotherapy followed by esophagectomy (CRT+T), preceded or not by IC, between 2009 and 2017. Patients’ characteristics, tumor variables and treatment outcomes were evaluated. Kaplan-Meier method was used to estimate overall survival and Cox proportional hazard model to evaluate prognostic factors.

Results: 103 pts were studied, with a median age of 62 years (range 37-84). Seventy-five pts (73%) were male, 67 (65%) had squamous cell carcinoma and 31 (30%) adenocarcinoma. Forty-two pts (41%) received IC followed by CRT+T (IC+CRT+T). The most frequent IC consisted of paclitaxel and platinum (38 pts – 90%) and the median number of cycles was 2 (range 1-6). All pts received CRT+T. Concurrent chemotherapy was a combination of paclitaxel and platinum in 94 pts (91%). The median radiation dose was 41.4 Gy (range 39.6-104). There was no statistically significant difference in pCR between the IC group and the standard CRT+T group. The pCR was 41.9% and 46.7% in the IC+CRT+T and standard CRT+T group (p = 0.628, respectively). In the multivariate analysis, pCR was an independent prognostic factor for failure free survival (FFS) (HR 0.35, 95% CI 0.14-0.85, p = 0.021), but not for overall survival (OS) (p = 0.863). The factor that significantly affected OS in the multivariate analysis was positive lymph node (HR 5.9, 95% CI 1.23-28.27, p = 0.026). IC, histology, histologic grade, radiation dose, T stage were not identified as independent prognostic factors for neither OS nor FFS.

Conclusions: Our data suggest that the addition of IC to standard CRT+T does not increase the pCR rate in LAEC. No difference in OS was observed between pts that received or not IC. Regardless of the treatment received, pts achieving a pCR presented improved FFS.

Legal entity responsible for the study: Guillaume Harada.

Disclosure: All authors have declared no conflicts of interest.

Background: Neoadjuvant chemoradiation (nCRT) followed by surgery is the preferred treatment for locally advanced ESCC. But a recent trial suggested close observation might be a reasonable option in patients achieving clinical complete response (cCR) to nCRT. For this strategy, accurate clinical assessment for predicting pathologic CR (pCR) is essential. In NCCN guidelines PET/CT is recommended as response assessment, whereas endoscopy is optional after nCRT.

Methods: In 234 patients who received nCRT (46–50.4Gy) plus surgery for locally advanced ESCC at Asan Medical Center from 2007 to 2014, the performance of endoscopy and PET/CT which were done 4-8 weeks after nCRT for predicting pCR was evaluated. A subjective CR (sCR) was defined as complete resolution of EDX uptake within all lesions, making them indistinguishable from surrounding tissue, and endoscopic CR (eCR) as no residual mucosal lesions except for scar change.

Results: sCR (ypT0N0) was achieved in 108 patients (46.2%), and ypT0N+ in 17 (7.3%). Among patients who underwent PET/CT (n = 231), mCR was obtained in 102 (44.2%), and non-mCR in 81 (35.1%), whereas metabolic response could not be assessed due to diffuse esophagitis in 48 (20.8%). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mCR for pCR was 56.6%, 46.4%, 58.8%, and 71.6%, respectively. Among patients who underwent endoscopy (n = 229), eCR was obtained in 42 (18.3%), and the sensitivity, specificity, PPV, and NPV of eCR for pCR was 45.1% (95% CI 29.0 - 59.5%), 82.7%, 94.3%, 85.4%, and 54.1%, respectively. When adding endoscopic response to metabolic response, the sensitivity, specificity, PPV, and NPV of eCR or mCR for clinical CR (cCR) was 29.5%, 94.4%, 85.7%, and 54.0% respectively. In the multivariate analysis, cCR was associated with age, histology, and IC treatment. The positive likelihood ratio (PLR) for clinical CR (cCR) was 4.9 (95% CI 2.2-10.6).

Conclusions: The addition of endoscopic evaluation to metabolic response can improve specificity and PPV for cCR compared to metabolic response alone, which could help in applying surveillance strategy without immediate surgery in patients achieving clinical CR after nCRT for ESCC.

Legal entity responsible for the study: Asan Medical Center.

Disclosure: All authors have declared no conflicts of interest.

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Legal entity responsible for the study: Asan Medical Center.

Disclosure: All authors have declared no conflicts of interest.

Background: Sarcopenia, a decrease in skeletal muscle mass and strength, is associated with poor outcomes in many malignancies. To improve outcomes, we characterized sarcopenia in patients with esophageal adenocarcinoma treated with neoadjuvant chemotherapy.

Methods: We retrospectively collected data on DLT from 197 OAC patients treated with neoadjuvant chemotherapy at a single institution between August 2009 and September 2016. CT scans were visualised using the Worldmatch software package. Sarcopenia was defined as a lean mass index (LMI) <12.03 cm²/kg, and skeletal muscle index (SMI) <74.5 cm²/m². The chi-squared test was used to analyse differences in toxicity between groups.

Results: In 197 OAC patients treated with neoadjuvant chemotherapy, 115 (58%) patients achieved a clinical complete response (cCR). Sarcopenia was observed in 81% of patients. There was no correlation with age and BMI (r = 0.1). Average BMI was greater in men than women (40.2 cm²/m² versus 37.3 cm²/m², male versus female). Sarcopenic patients had a worse overall survival than non-sarcopenic patients (median OS, 28.0 months versus 19.3 months, p = 0.0225). In contrast patients with sarcopenic obesity showed no difference in OS, in keeping with...
638P Prognostic value of pretreatment diffusion weighted magnetic resonance imaging based texture in concurrent chemo-radiotherapy of esophageal squamous cell cancer

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Background: We prospectively enrolled 82 cases with ESCC into a cohort study which underwent DWI before CRT. AB MR examinations included axial T2WI, T1WI and diffusion-weighted images (b = 0, b = 600 s/mm²). Two groups of tumor features were examined: (1) clinical features (eg, TNM stage, age and gender) and demographic, (2) spatial texture features of apparent diffusion coefficient (ADC), which characterize tumor intensity range, spatial patterns and distribution and associated changes resulting from CRT. A reproducible and no redundant feature set was statistically filtered and validated. The prognostic value of each parameter for overall survival was investigated using Kaplan-Meier and Cox regression models for univariate and multivariate analyses, respectively.

Results: Both univariate and multivariate Cox model analyses showed that the radiation dose, FHST, energy, m_contrast, l, m_clustershade, 2, Diff, Clu/Trendency, 2, Diff, Homogeneity_2, m_inversevariance_2, high intensity small zone emphasis (HISE) and low intensity large zone emphasis (LILE) associated significantly with survival. Our study showed seven 3D texture features extracted from ADC maps could distinguish high, median and low risk groups (Log-rank c² = 13.5, P = 0.0073).

Conclusions: The ADC 3D texture features can be useful biomarkers to predict the survival of ESCC patients who received CRT. The combination of DWI texture and conventional prognostic factors can be used to generate robust predictive models for survival rate.

Legal entity responsible for the study: Shandong Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

639P Volume reduction rate of the primary tumor of esophageal squamous cell carcinoma after neoadjuvant chemotherapy: Could this measurement be a surrogate end point for survival before surgery?

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Background: Neoadjuvant chemotherapy (NAC) followed by surgery is regarded as a standard treatment for Stage II and III resectable thoracic esophageal squamous cell carcinoma (ESCC) in Japan. In general, therapeutic effect of NAC against the primary tumor is estimated microscopically with resected specimen after surgery. Then, this microscopic assessment is validated as surrogating survival. However, as this assessment needs resected specimen, therapeutic effect could not be evaluated before surgery. The aim of this study was to investigate whether therapeutic effects in imaging findings obtained by calculating tumor volume reduction could be a surrogating survival or not.

Methods: This retrospective study examined the patients who fulfilled the following criteria: (1) thoracic ESCC, (2) underwent esophagectomy following NAC between outcome data available. Negative CRM status was correctly identified on post chemo MRI in 17/19 (89%) cases; positive CRM in 3/9 (33%) cases. When compared to pathological staging there was concordance between MRI T staging in 36 cases, with over-staging in 43% and under-staging in 21%. Concordance between MRI and CT for T/N staging was 66% and 77% respectively. Tumour size reductions and ADC increases were observed during chemo. Local sites predicted significantly more CRM involve- ment than central review (48 vs 19%).

Conclusions: This represents the first prospective, multi-centre, national trial of MRI in oes cancer and is the first report of interobserver variability between treatment centres. Although limited by small numbers, MRI showed promising specificity to identify negative surgical margins and reasonable correlation with pathological outcome. Discrepancy between local and central review was observed, suggesting that more standardised methods of MRI assessment in oes cancer are required.

Clinical trial identification: EudraCT: 2006-000811-12.

Legal entity responsible for the study: Medical Research Council, UK.

Funding: Cancer Research UK, Clinical Trials Awards Advisory Committee.

Disclosure: D. Cunningham: Research funding: Amgen, AstraZeneca, Bayer, Celgene, Merck-Serono, Medimmune, Merrck, Novartis, Roche, Sanofi. N. Starling: Research funding: AZ, BMS, Merck; Honoria: AZ. All other authors have declared no conflicts of interest.

636P Survival benefit of re-irradiation in esophageal cancer patients with locoregional recurrence: A propensity score matched analysis

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Background: To investigate the prognostic factors of esophageal squamous cell carcinoma (ESCC) with locoregional recurrence and to explore whether re-irradiation(re-RT) improves outcomes.

Methods: We retrospectively analyzed 87 ESCC patients with locoregional recurrence. All patients received radiotherapy in the initial treatment. The failure patterns were classified into regional lymph node recurrence only (LN) and local failure with/without regional lymph node recurrence (LF). A propensity score model was utilized to balance baseline covariates: RT group (n = 33) comprising patients who underwent re-RT and non-LF group (n = 33) without re-RT. Outcome measures including overall survival (OS) and toxicities.

Results: Median follow-up was 87 months (range 2-206). Of the 87 included patients, 39 received re-RT. Failure pattern and re-RT were the independent prognostic factors of OS (P = 0.004 and 0.015) by Cox multivariate analysis. Further subgroup analysis did not demonstrate a survival benefit with re-RT combined with chemotherapy as compared to re-RT alone (P = 0.70). After propensity score matching, no differences were found between two groups’ characteristics by Chi-square tests. Similarly, Cox model demonstrated failure pattern and re-RT as the prognostic factors, with hazard ratio (HR) 0.319 (95% confidence interval [CI] 0.117-0.869, P = 0.025) and HR 0.375 (95% CI 0.201-0.701, P = 0.002) in the matched cohort. Also, significant differences in OS (P = 0.004) were presented in failure pattern (LN vs. LF, P = 0.004) and re-RT (RT vs. non-RT, P = 0.001). In terms of toxicities, there were 9.09% and 3.03% of tracheoe-osophageal fistula, 15.15% and 3.03% of pericardial/pleural effusion in the RT and non-RT group, respectively (P > 0.05). The RT group had a higher rate of radiation pneumonitis (24.24% vs. 6.06%, P = 0.039), but no pneumonitis related deaths occurred.

Conclusions: Re-irradiation might improve the long-term prognosis of locoregional recurrent ESCC with a radiation history. Though the radiation pneumonitis is more frequent, re-irradiation is well tolerated.

Legal entity responsible for the study: Junxun Wu.

Funding: National Clinical Key Specialty Construction Program.

Disclosure: All authors have declared no conflicts of interest.

637P Magnetic resonance imaging in oesophageal (oes) cancer: Results from the ST03 MRI subsity

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Background: A key aim of neoadjuvant therapy in oes cancer is to increase the chance of complete R0 resection. Microscopic residual disease after surgery is reported in around 30% cases, mainly involving the circumferential resection margin (CRM), with current staging techniques unable to accurately identify pts at risk of residual tumour at the CRM. Previous small single site studies have shown that high res T2-weighted MRI achieving detailed imaging of oes anatomy and has the potential to serve as an additional non-invasive staging modality.

Methods: As part of the UK ST03 trial pts from participating centres with operable lower oes and type I/II OGG adenca were enrolled in the MRI observational sub-study. All pts underwent standard staging investigations, with additional MRI scans pre and post neoadjuvant chemo, followed by surgery. MRI parameters were consistent across sites and included CRM, T/N staging and apparent diffusion coefficient (ADC) assessment. Scans were reviewed locally and centrally to assess interobserver variability. Chemo response and association with pathological outcome were recorded.

Results: Between Aug 2011 and Mar 2015 57 pts were recruited from 11 sites. Of these 32 had matched pre and post chemo scans and 28 had corresponding pathological

previous data. There was no significant difference between rates of DLT in patients with sarcopenia and those without (16.4% and 13.2% respectively, P > 0.05). There was a non-significant trend towards increasing rates of completion of 6 cycles of perioperative chemotherapy in non-sarcopenic patients (47% Vs 39%).

Conclusions: In our large homogeneously treated cohort of patients undergoing neoadjuvant chemotherapy for OAC sarcopenia was associated with poorer OS confirming recent studies of smaller mixed populations.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

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January 2011 and December 2015, and (3) clinical Stage II or III. Tumor volume was calculated by multiplying length and thickness in the lateral view of esophagography. The reduction rate of tumor volume was calculated as follows: \( \text{pre NAC tumor volume} - \text{post NAC tumor volume} / \text{pre NAC tumor volume} \). The cut off value of volume reduction ratio was determined as 50%, 60%, and 70% respectively. Patients were divided into an effective group and an ineffective group in each cut off value, and examined relationship with 3-year relapse-free survival (3yRFS). The hazard ratio (HR) for 3yRFS in each cut off value was estimated for selecting optimal cut off for curative surgery.

**Results:** In total, 93 patients were included in this study. 3yRFS of the effective group/ ineffective group and HR of ineffective group for effective group in each cut off were 70.2% / 39.4% (HR = 0.469 [95% CI = 0.253 - 0.861], \( p = 0.016 \)) in 50%, 73.5% / 40.3% (HR = 0.418 [95% CI = 0.216 - 0.890], \( p = 0.07752 \)) in 60%, and 80.4% / 42.8% (HR = 0.427 [95% CI = 0.199 - 0.916], \( p = 0.02435 \)) in 70%.

**Conclusions:** Therapeutic effect of NAC evaluated by imaging finding was reflected in 3-year relapse free survival. Especially for optimal surrogate of 3yRFS, the optimal cut off point was 60% volume reduction after NAC.

**Legal entity responsible for the study:** Kanagawa Cancer Center.

**Funding:** Has not received any funding.

**Disclosure:** T. Hayashi: Personal fee: MDS, Chugai, Ono. T. Yoshikawa: Personal fee: MDS, Chugai, Ono, Taiho. All other authors have declared no conflicts of interest.

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**Annals of Oncology**

Results: Expression of PD-L1 was detected in 35/39 patients (90%) with at least 1% tumor cell expression. Median treatment duration was 6.1 (range, 2.0–40.0) weeks; treatment was ongoing in 4 pts with 3 responses ongoing per RECIST (DOR, 1.4 months). The origin of samples included the primary site of 65.4%, metastatic site of 34.6%. The tumors were analyzed. The sequence was successfully performed in 136 tumors (65.1%). The detected genomic variant data were classified according to genetic drivers of cancer, and alterations were KRAS (91.9%), TP53 (62.5%), CDKN2A (14.0%), SMAD4 (10.3%), GNAS (4.4%), TET2 (4.4%), PIK3CA (3.7%), ATM (2.9%), STK11 (2.9%), BRCA2 (2.2%). Most frequently detected CNVs (>7 copies) was MYC (2.9%), and no gene fusion was detected. We will show the clinical outcome based on certain key cancer genome alterations.

Conclusions: This nationwide screening system is effective to detect rare gene alterations in aPC. This novel knowledge provides an intriguing background to investigate new targeted approaches in these patients and to progress medicine precision.

Clinical trial identification: UMIN000016344.

Legal entity responsible for the study: SCRUM-Japan GI-Screening. Funding: 15 SCRUM-Japan collaborating pharmaceutical companies, AMED, NCC.


Spatial genomic heterogeneity from multi-region endoscopic biopsies in primary gastric cancer: Implications for precision therapy

**Methods:** Patients with newly diagnosed advanced GC underwent endoscopic mapping and pre-determined 8-region biopsy of the primary with concurrent plasma cfDNA sampling. Biopsy samples were subjected to NGS using a 32-gene custom panel and plasma cfDNA analysis via 28-gene cfDNA assay. Clinopathologic features and genetic alterations (GA) were abstracted and descriptive statistics were used to compare samples.

**Results:** All six initial patients underwent multi-region biopsy and NGS. Within a given patient the average number of GA observed in all biopsies (shared GA) was 3.3 with an average of 12.8 non-shared alterations (p < 0.05). There was no significant difference in the average mutant allele frequency (MAF) or MAF variability between shared and non-shared GA in the primary tumor (p > 0.05). Cell-free DNA analyses identified GA not found in each respective case’s multi-region primary tumor analysis, likely due to heterogeneity score in prospective trials may inform optimal patient selection, particularly in targeted therapies. Standardized methods to determine intra and inter-tumoral heterogeneity are needed and stratification by heterogeneity score in prospective trials may inform optimal patient selection, particularly in targeted therapies.

**Legal entity responsible for the study:** Samsung Medical Center.

**Funding:** Samsung Medical Center.

**Disclosure:** S.J. Klemperer: Consulting, Advisory: Lilly Oncology, Boston Biomedical, Astellas, Merck. J. Chao: Consulting: Advisory: Boston Biomedical, Merck, Five Prime Therapeutics. All other authors have declared no conflicts of interest.

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**Table: 646P OS and PFS by arm and EGFR amp**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>EGFR</th>
<th>Median OS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>&lt;2</td>
<td>12.5 (9.5-15.7)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>7 (11.5)</td>
<td>1.2 (0.5-2.8)</td>
</tr>
<tr>
<td>Plasma</td>
<td>&lt;2</td>
<td>163 (11.0-14.6)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>4 (11.5)</td>
<td>1.6 (0.5-5.0)</td>
</tr>
<tr>
<td>EOX-P OS</td>
<td>Tissue</td>
<td>&lt;2</td>
<td>120 (7.6-4.8)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>7 (6.6)</td>
<td>1.4 (0.6-3.2)</td>
</tr>
<tr>
<td>Plasma</td>
<td>&lt;2</td>
<td>163 (7.1-2.8)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>4 (6.5)</td>
<td>1.2 (0.4-3.2)</td>
</tr>
<tr>
<td>EOX-P FS</td>
<td>Tissue</td>
<td>&lt;2</td>
<td>113 (8.0-9.7)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>10 (5.7)</td>
<td>1.3 (0.7-2.4)</td>
</tr>
<tr>
<td>Plasma</td>
<td>&lt;2</td>
<td>169 (9.7-3.11)</td>
<td>Ref</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>18 (7.8-1.9-12.9)</td>
<td>1.6 (0.8-3.1)</td>
</tr>
<tr>
<td>EOX-P FS</td>
<td>Tissue</td>
<td>&lt;2</td>
<td>113 (5.4-6.3)</td>
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<td>≥2</td>
<td>10 (2.7)</td>
<td>1.2 (0.6-2.3)</td>
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<tr>
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<td>169 (6.9-6.08)</td>
<td>Ref</td>
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<tr>
<td></td>
<td>≥2</td>
<td>18 (5.3-2.6)</td>
<td>1.28 (0.8-2.1)</td>
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</tbody>
</table>

**Conclusions:** Liquid biopsy using ddPCR can detect EGFR amp in advanced OGA patients; higher levels of EGFR tissue amp may predict plasma status. EGFR amp appears to be negatively prognostic, however due to low biomarker prevalence this difference was not significant.

**Clinical trial identification:** NCT00824785.

**Legal entity responsible for the study:** Royal Marsden.

**Funding:** Royal Marsden National Institute for Health Research Biomedical Research Centre.

Background: Fibroblast growth factors (FGF) and their receptors are complex intracellular pathways that control cellular proliferation and tumour growth and invasion. FGFR alterations have been shown to be associated with the initiation and progression of gastric cancer (GC). We investigated the correlations of the FGFR2 amplification and expression with clinicopathological characteristics and outcomes in advanced/metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine.

Methods: FFPE tumor samples were obtained from patients with advanced/metastatic gastric cancer who received systemic chemotherapy based on fluoropyrimidine chemotherapy on fluoropyrimidine diagnosed at 2 cancer centers between 2010 and 2016. FGFR2 gene copy number was assessed by FISH method using probes specific for the 10q26 locus and the chromosome 10 centromere (CE10N). FGFR2 amplification was defined as FGFR2/CE10N ≥2.0. FGFR2 protein expression was determined by immunohistochemistry. Overexpression was defined as complete membrane staining intensity ≥2+ (graded from 0 to 3+) in cancer cells.

Results: From the cohort consists of 186 GC patients, FFPEs were available from 123 pts. FGFR2 amplification was found in 4/123 (3.3%) patients with FGFR2/CE10N median 1.16, IQR 1.77 and range 0.8-20.0. FGFR2 overexpression was observed in 5/123 (4.1%) patients. FGFR2 amplification had no significantly impact on overall survival (OS) and progression free survival (PFS) in compare those without FGFR2 amplification (HR 0.5961 and HR 1.27, 95%CI 0.52 to 3.15, respectively). There was no prognostic significance observed for FGFR2 overexpression on OS and PFS (respectively, HR = 1.27, 95%CI 0.52 to 3.15, p < 0.0063 and HR = 2.44, 95%CI 0.88 to 6.78, p = 0.0863).

Conclusions: The rate of GC patients with tumors positive for FGFR2 amplification or overexpression was consistent with the data published in the literature. However, FGFR2 amplification and overexpression have no prognostic significance in advanced/metastatic gastric cancer patients who received systemic chemotherapy based on fluoropyrimidine. There is a further investigation on a larger population is required.

Legal entity responsible for the study: Celon Pharma.

Funding: National Centre for Research and Development (Poland); Celon Pharma.

Disclosure: M.M. Skupinska, J. Pieczykolan, A. Stanczak: Employee: Celon Pharma. M. Wieczorek: CEO: Celon Pharma. All other authors have declared no conflicts of interest.
Background: Based on a comprehensive molecular characterization of gastric cancer, Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) can be classified as one of the four subtypes of gastric cancer (GC). Several studies have shown significantly better prognosis of EBVaGC compared with EBV-negative GC (EBVnGC). However, no published study has yet investigated the clinical significance of standard adjuvant chemotherapy in patients with resected EBVaGC. Accordingly, the present study analyzed the prognostic differences between EBVnGC and EBVaGC, and their survival impact on standard adjuvant chemotherapy.

Methods: This study retrospectively reviewed 773 patients with gastric cancer who underwent surgical resection at Kyungpook National University Chilgok Hospital, between January 2011 and December 2017. The patients were enrolled according to the following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosed with primary gastric adenocarcinoma, 2) the presence of test using EBV-encoded RNA in situ hybridization, 3) stage II/III following criteria: 1) pathologically diagnosis of EBVaGC and EBVnGC, respectively. One hundred twenty-nine (46.7%) patients were classified as stage II and 147 (33.3%) were as stage III. As for adjuvant chemotherapy, 87 patients (31.3%) received capcitabine and oxaplatin (XELOX), while 189 (68.7%) received S-1, respectively. With a median follow-up duration of 21.3 months (2.4-89.0), the estimated 3-year disease-free survival (DFS) and overall survival (OS) rates were 74.8% and 83.0%, respectively. In a univariate analysis and multivariate analysis using a Cox proportional hazard model, EB-positivity was not significantly associated with disease-free survival (p = 0.630) for all patients and XELOX or S-1 group.

Conclusions: In conclusion, EB-positivity was not found to be associated with prognosis in patients with curatively resected gastric cancer who received standard adjuvant chemotherapy. Accordingly, the standard adjuvant chemotherapy can be used for patients with EBVaGC.

Legal entity responsible for the study: Jong Ong Kim.

Funding: Has not received any funding.

Disclosures: All authors have declared no conflicts of interest.
Merck & Co, Inc., BMS, Arog Pharmaceuticals, AstaZeneca. H.C. Chung: Advisory board member: Taiho, Celtrion, MSD, Eli Lilly, Quintiles, BMS, Merck-Serono; Speakers’ bureau: Merck-Serono, Lilly, Foundation Medicine; Institution research funding: Lilly, GSK, MSD, Merck-Serono, BMS-GO; Taiho. C. Feinn: Employee of Novant Health; Travel expenses, accommodations: Aducro Biotech, M.J. Savage, W. Zhou, S.A. Peter: Employee, Stock owner: Merck & Co, Inc, T. Wu: Employee of Merck & Co, Inc., at the time the analysis was conducted for this abstract. J.A. Ajani: Institution research funding: BMS, Merck & Co, Inc., Taiho, Deltaply, Gilead. All other authors have declared no conflicts of interest.

Background: Microsatellite instability (MSI), mainly caused by dysfunction of mutL homolog 1 (MLH1), was classified as one of distinctive molecular subtype of gastric cancer. MSI was also reported to be associated with high PD-L1 expression and high Immunoscore (IS), a density analysis of tumor-infiltrating lymphocytes. This study aimed to investigate the association between MLH1, PD-L1 expression, and IS and chemosensitivity in patients with gastric cancer.

Methods: A total of 271 patients who underwent gastrectomy (R0/1) for gastric cancer between 2008 and 2016 in our institution were retrospectively analyzed. Immunohistochemistry was performed to evaluate MLH1 and PD-L1 expression. IS was evaluated by the density of CD3+ and CD8+ lymphocytes in the center and invasive margin of tumor and classified into two groups, IS-High or IS-Low. The relation between these markers and the pathological effect of neoadjuvant chemotherapy (NAC) was examined in patients with NAC, and recurrence-free survival (RFS) was compared separately with and without NAC.

Results: Low MLH1, high PD-L1 expression, and IS-High was observed in 29 (11%), 70 (26%), and 114 (42%) patients, respectively. Low MLH1 expression was significantly associated with high PD-L1 expression (P = 0.006) and IS-High (P = 0.04). In patients with NAC (n = 114), low MLH1 expression was significantly associated with low chemosensitivity (lower proportion of pathological effect Grade ≥1b, P = 0.006), although PD-L1 expression and IS were not associated with chemosensitivity (P = 0.99, P = 0.08). In patients without NAC (n = 157), low MLH1 expression and IS-High were significantly associated with better RFS (HR = 0.02, P < 0.001), however not associated in patients with NAC (P = 0.78, P = 0.07). While, PD-L1 expression was not associated with RFS in both patients with and without NAC (P = 0.28, P = 0.53). Multivariate analysis revealed that high MLH1 expression and IS-low were one of the independent risk factors for RFS (HR 2.9 [1.3-6.9] P = 0.014, HR 1.9 [1.2-3.0] P < 0.001).

Conclusions: Although low MLH1 expression and IS-high may be associated with better prognosis, low MLH1 expression may be also associated with low chemosensitivity. Legal entity responsible for the study: Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Prognostic significance of lymphocyte-activation gene-3 expression in chemoradiotherapy-naive esophageal and gastric adenocarcinoma

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Background: Neoadjuvant and/or adjuvant treatment has led to improved survival in patients with resectable esophageal and gastric adenocarcinoma (GEAC). Nevertheless, survival rates remain poor and, hence, there is a great need to identify novel treatment strategies and relevant complementary diagnostics. Immunotherapies targeting the PD-1/PD-L1 checkpoints have shown promising results, but simultaneous inhibition of other fundamental checkpoints, such as lymphocyte-activation gene-3 (LAG-3), may further improve clinical outcome. The expression and prognostic significance of LAG-3 in GEAC has however not yet been described. Herein, we examined the expression of LAG-3 in tumour-infiltrating immune cells (TIC) in chemoradiotherapy-naive GEAC and paired lymph node metastases, with particular reference to its relationship with PD-1 and PD-L1 expression, mismatch repair (MMR) status, and survival.

Methods: Immunohistochemical LAG-3 expression was analysed in tissue microarrays with 165 tumour primaries and 72 paired lymph node metastases from a retrospective consecutive cohort of patients with chemoradiotherapy-naive resected GEAC. LAG-3 expression was denoted in categories of negative (0), low (1-10) and high (>10). PD-1, PD-L1 expression and MMR status had been previously analysed.

Results: The distribution of LAG-3 expression in primary tumours was 55.8% negative, 28.5% low, and 15.8% high. The corresponding figures in lymph node metastases were 48.6% negative, 37.5% low, and 13.9% high. LAG-3 expression did not differ by tumour location. Positive LAG-3 expression in primary tumours was an independent factor for prolonged overall survival in the entire cohort (HR = 0.64, 95% CI 0.43-0.96), and in gastric cancer (HR = 0.35, 95% CI 0.17-0.74). LAG-3 expression in primary tumours was significantly associated with PD-L1 expression in both tumour cells and TIC, and with PD-1 expression in TIC, but not with MMR status. Conclusions: LAG-3 is expressed in a considerable proportion of GEAC, with a similar distribution in primary tumours and lymph node metastases. Positive LAG-3 expression is an independent favourable prognostic factor, particularly in gastric cancer. Legal entity responsible for the study: Lund University.

Funding: The Swedish Research Council, The Swedish Cancer Society, University Hospital Research Grant, Mrs Berta Kamppan Foundation, Swedish Government Grant for Clinical Research (ALF).

Disclosure: All authors have declared no conflicts of interest.
Can preoperative diagnosis select therapeutic target of neoadjuvant chemotherapy for gastric cancer?

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1Gastroenterological Surgery, Kanagawa Cancer Center, Yokohama, Japan, 2Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan, 3Gastroenterology Surgery, Kanagawa Cancer Center, Yokohama, Japan, 4Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

Background: Precise clinical staging by diagnostic imaging is essential for determination of initial treatment for gastric cancer. Indeed, T3 and T4 diseases with lymph node metastasis (T3-4N+) were candidate of neoadjuvant chemotherapy (NAC) followed by gastrectomy, defined as cStageIII in 8th edition of AJCC/UICC TNM classification. However, pathological T3-4N+ diseases could contain some cases that were underestimated as cStageII and excluded from target of NAC. This study aims to examine the accuracy of preoperative diagnosis and the prognosis from each cStage in pathological T3-4N+ gastric cancers.

Methods: The study analyzed gastric cancer patients who received gastrectomy and diagnosed as pathological T3-4N+ diseases between Jun 2000 and Jun 2012 at Kanagawa Cancer Center. The clinical and pathological data were analyzed retrospectively. Patients who received preoperative chemotherapy were excluded. The proportion of each cStage was investigated based on the 8th edition of AJCC/UICC, and 5-year overall survival rate (5yOS) for each cStage was calculated using the Kaplan-Meier method.

Results: In total, 337 patients were diagnosed as pathological T3-4N+ diseases and included in this study. In clinical staging, 48 patients (14.2%) were diagnosed as cStageI, 10 patients (3.0%) as cStageIIA, 109 patients (32.3%) as cStageIIIB, 159 patients (47.2%) as cStageIIIC, 6 patients (1.8%) as cStageIVA, and 5 patients (1.5%) as cStageIVB. Significance for cStageIIB, cStageIIIC, and cStageIVB at 5yOS (as each cStage) was examined using the Kaplan-Meier method.

Conclusions: Among pathological T3-4N+ diseases, the underestimation as cStageIIB and cStageIIIC was acceptable, because of relative low frequency and good prognosis without NAC. Meanwhile, the underestimation as cStageIIIC could not be ignored, because pathological disease as cStageIIIC occupied one third of pathological T3-4N+ disease and had poor prognosis comparable to cStageIII. We need to consider underestimation of preoperative diagnosis, when we determine target of NAC for advanced gastric cancer.

Legal entity responsible for the study: Kentaro Hara.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Avelumab (anti–PD-L1) in Japanese patients with advanced gastric or gastronephropathic junction adenocarcinoma (GC/GEJC): Updated results from the phase I/II JAVELIN solid tumour JPN trial

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Background: Avelumab, a human anti–PD-L1 IgG1 monoclonal antibody that can induce innate effector function against tumor cells in preclinical models, is an approved treatment for metastatic Merkel cell carcinoma in various countries and platinum-treated advanced urothelial carcinoma in the US and Canada. We report updated results from the dose-expansion part of a phase I/II trial of avelumab in Japanese patients (pts) with advanced GC/GEJC (NCT01943461).

Methods: Pts had stage IV GC/GEJC adenocarcinoma and progression after 1 or 2 prior lines of chemotherapy including a platinum and fluoropyrimidine agent (initially enrolled pts) or progression after platinum/fluoropyrimidine followed by a taxane or irinotecan (later pts). Pts received avelumab 10 mg/kg Q2W by IV infusion until confirmed progression, unacceptable toxicity or withdrawal. PD-L1 expression was assessed using the Dako PD-L1 IHC 73-10 assay (≥1% tumor cell cutoff).

Results: At data cutoff on Aug 18, 2016, 40 pts had received avelumab (median treatment duration 2.7 mo; range 0.5–21.4); 21 pts (52.5%) had received ≥3 prior lines of therapy for advanced disease. The objective response rate (ORR) was 10.0% (95% CI 2.8–23.7), including complete response in 1 pt and partial response in 3 pts. 17 pts had stable disease as best response and the disease control rate was 52.5%. Median progression-free survival was 2.5 mo (95% CI 1.4–2.8). Median overall survival (OS) was 9.1 mo (95% CI 7.2–11.2) and the 12-mo OS rate was 31.0% (95% CI 15.6–47.8). In evaluable pts with PD-L1 + (n = 11) or PD-L1 − (n = 27) tumors, ORR was 27.3% and 3.7%, respectively. Treatment-related adverse events (TRAEs) of any grade occurred in 32 pts (80.0%), including infusion-related reaction (27.5%, all grade 1/2), pruritus (15.0%), pyrexia (12.5%) and rash (10.0%) ≥10% of pts. Grade 3 TRAEs occurred in 3 pts (7.3%; ALT increase, anemia and neutropenia); no pt had a grade ≥4 TRAE. 5 pts had an immune-related AE (all grade 1/2), the most common were pruritus (n = 3) and maculopapular rash (n = 2).

Conclusions: Avelumab showed acceptable safety and clinical activity in Japanese pts with advanced GC/GEJC progressed after chemotherapy.

Clinical trial identification: E9810070-002 (NCT01943461).
Safety and efficacy of a DKK1 inhibitor (DKN-01) in combination with pembrolizumab (P) in patients (Pts) with advanced gastrointestinal cancer (GE) malignancies

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Background: Dickkopf-1 (DKK1) is a modulator of the Wnt and PI3K/AKT signaling pathway and contributes to an immunosuppressive tumor microenvironment by activating MDSCs and Treg cells. DKN-01 (D), an mAb against DKK1, acts on innate immune cells, and in preclinical studies demonstrates upregulation of both PD-L1 and IFN-γ, related cytokines, suggesting a role for immune checkpoint combination. Anti-PD-1 plus DKN-01 have shown antitumor effects in the B16 syngeneic mouse model; clinical studies are underway. GE cancers commonly overexpress DKK1 and harbor Wnt pathway alterations.

Methods: Phase 1b study to evaluate dose, safety and efficacy of D (150 mg or 300 mg on Days 1 & 15) plus P (200 mg on Day 1) of each 21-day cycle in pts with advanced GE cancer. Safety, efficacy, and correlative analyses (cytokines, PBMC immunophenotyp- ing, tumor genomics and intratumoral DKK1/PD-L1) are ongoing.

Results: Pts enrolled in 2 cohorts: D (150 mg [n = 2] or 300 mg [n = 11]) + P. All 13 pts had adenocarcinomas (4 pts: EC, 6 pts: GEJ, 3 pts: GC). Pts were refractory to prior checkpoint inhibitor, and only 1 pt was known to be PD-L1 + at study entry. No DLTs or treatment related SAEs were observed. Most TEAE were Grade 1/2 and commonly gastrointestinal disorders. ≥ Grade 3 TEAE included hypotension & anorexia (each 2 pts), lymphopenia, transfusion reaction, G3 bleeding, abdominal pain, dehydration, weight loss, thrombocytopenia & anemia (each 1 pt); only lymphopenia related to D. Among 9 evaluable patients there was one confirmed PR, 5 SDs in 3 pts (including one IO-refractory pt with minor response) and PD in 3 pts. The 6-week disease assessment showed a median duration of 4.1, 7.3, and 9.0 mo. There were 4 PDs that had a confirmed objective response based on investigator assessment (ORR, 22.6%; DCR, 38.7%). There were 5 partial responses (2.4, 3.6, 4.1, 8.3, and 9.7+ mo) and 2 complete responses (0.3- and 9 mo). The initial assessment of PD-L1 expression (22C3 assay) does not hint towards predictive for ORR.

Conclusions: M7824 monotherapy had a manageable safety profile in heavily pretreated Asian pts (74% ≥ 3 prior therapies) with GE. Early signs of clinical efficacy, with an ORR of 22.6% and long lasting responses, are encouraging. Updated data will be presented.

Clinical trial identification: NCT02699515.

Disclosure: Y.J, Bang: Consultancy (Includes expert testimony): AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BMS, Eli Lilly, Merck Serono, FivePrime, Taiho, Ono, ADC Therapeutics, GreenCross, Syangiam Biopharm; Research funding (institution): AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GSK, BMS, Pfizer, Eli Lilly, Boehringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD Pharma, Ono, Ontaka, Taiho, Takeda, BiotGene, Hanmi, Green Cross, Caris, Daiichi Sankyo, Astellas, T. Doi. Consultancy (Includes expert tes- timony): Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Amgen, Sumitomo Dainippon, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly Japan, Chugai Pharma, Kyowa, Hakko, Kirin, Daiichi Sankyo, Kyowa Hakko Kirin, Daiichi Sankyo, and GSK.


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Background: Objective response rates (ORRs) in patients (pts) with gastric cancer (GC) treated with anti-PD-L1 antibodies range from 11.2% (PD-L1 unselected) to 15.5% (PD-L1 +) for second line therapy. Inhibiting the transforming growth factor β (TGF-β) pathway, which plays a key role in tumor immunosuppression, may enhance the response to anti-PD-L1 treatment. We report results for M7824, an innovative first-in-class bifunctional fusion protein composed of a monovalent antibody against PD-L1 fused with the extracellular domain of TGF-β (receptor II (TGF-β “trap”) in pts with GC.

Methods: Pts in Asia with recurrent GC or gastrointestinal junction adenocarcinoma for whom standard therapy does not exist or has failed were enrolled in this expansion cohort of the ongoing, phase 1, open-label trial NCT02699515 and received M7824 1200 mg q2w until disease progression, unacceptable toxicity, or trial withdrawal. The primary objective is to assess safety/tolerability; secondary objectives include assessment of best overall response (BOR) per RECIST v1.1.

Results: As of February 15, 2018, 31 heavily pretreated pts with advanced GC (74.2% received ≥3 prior therapies) received M7824 for a median duration of 10.1 (range, 2- 52) wks; 4 pts remained on treatment. 6 pts (19.4%) had grade 3 treatment-related adverse events (TRAEs): anemia (2), diarrhea (1), abdominal hypertension (1) and rash (2). No grade 4 TRAEs occurred. 1 grade 5 AE of death occurred after 5 doses with suspected rupture of pre-existing thoracic aortic aneurysm as per investigator’s assess- ment. 7 pts had a confirmed objective response based on investigator assessment (ORR, 22.6%; DCR, 38.7%). There were 5 partial responses (2.4, 3.6, 4.1, 8.3, and 9.7+ mo) and 2 complete responses (0.3- and 9 mo). The initial assessment of PD- L1 tumor expression (22C3 assay) does not hint towards predictive for ORR.

Conclusions: M7824 monotherapy had a manageable safety profile in heavily pretreated Asian pts (74% ≥ 3 prior therapies) with GC. Early signs of clinical efficacy, with an ORR of 22.6% and long lasting responses, are encouraging. Updated data will be presented.

Clinical trial identification: NCT02699515.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

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Disclosure: Y. J. Bang: Consultancy (Includes expert testimony): AstraZeneca, Novartis, Genentech/Roche, MSD, Pfizer, Bayer, BMS, Eli Lilly, Merck Serono, FivePrime, Taiho, Ono, ADC Therapeutics, GreenCross, Syangiam Biopharm; Research funding (institution): AstraZeneca, Novartis, Genentech/Roche, MSD, Merck Serono, Bayer, GSK, BMS, Pfizer, Eli Lilly, Boehringer-Ingelheim, MacroGenics, Boston Biomedical, FivePrime, CKD Pharma, Ono, Ontaka, Taiho, Takeda, BiotGene, Hanmi, Green Cross, Caris, Daiichi Sankyo, Astellas, T. Doi. Consultancy (Includes expert tes- timony): Lilly Japan, Chugai Pharma, Kyowa Hakko Kirin, MSD, Daiichi Sankyo, Amgen, Sumitomo Dainippon, Taiho Pharmaceutical; Research funding: Taiho Pharmaceutical, Novartis, Merck Serono, Astellas Pharma, MSD, Janssen, Boehringer Ingelheim, Takeda, Pfizer, Lilly Japan, Chugai Pharma, Kyowa, Hakko, Kirin, Daiichi Sankyo, Kyowa Hakko Kirin, Daiichi Sankyo, and GSK.

Y. J. Bang, T. Doi, S. Kondo, H.C. Chung, K. Muro1, J. Dussault, C. Helweg2, M. Chandar1, Y.K. Kang3
Biomarker-guided enrichment of the antimetastatic activity of margetuximab (M) plus pembrolizumab (P) in patients with advanced HER2+ gastric adenocarcinoma (GEA)


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Background: Transmutanab (T) + chemostat is standard 1st line therapy (tx) for HER2+ GEA patients (pts). Pts typically progress in 6-8 months, with loss of HER2 positivity in J. Baughman, J. Muth, A. Wynter-Horton, T. Wu, J. Wigginton, J.K. Davidson-Mondon, Y. J. Ban.

Methods: HER2+. PD-L1-unselected, 2nd line GEA pts post T progression received M (15 mg/kg Q3) + P (200 mg Q3). Safety, objective response rate (ORR), median overall and progression-free survival (mOS, mPFS), disease control rate (DCR), circulating-tumor DNA (ctDNA), and tumor PD-L1 expression were assessed.

Results: At data cutoff, 60 GEA pts were dosed in cohort expansion; 16.7% had treatment-related adverse events ≥ Grade 3. Overall, 21.6% had objective response (OR), 10 confirmed and 3 unconfirmed. DCR was 55% and mOS was 15.6 mos (95% CI: 7.26, NR). In GC pts, OR occurred in 10 of 34 (29.4%), mPFS was 4.24 mos (95% CI: 1.68, 5.62), and mOS was not reached. Notably, only 31 of 56 (51%) of pts with baseline ctDNA testing showed ERBB2 amplification; 21 of 30 (70%) of pts with fresh tumor biopsy were HER2 + by IHC (86% concordance). Tumors were PD-L1+ in 13 of 24 (54%) pts treated with higher rates in pts with GC. The presence of ERBB2 amplification by ctDNA and tumor PD-L1 expression by IHC were both associated with increased probability of OR: 33% vs. 10.5% (p = 0.0984) and 43.8% vs. 16.7% (p = 0.0097), respectively. ORR was 35% vs. 8.62% (5.3%) in ERBB2 amplified/PD-L1+ pts. In pts with activating HER2 mutations DCR was 11/15 (73%), indicating ADCC.

Conclusion: Consistent with prior tissue-based reports, many GEA pts progressing on T have lost ERBB2 amp. ERBB2 status by ctDNA NGS post-T could help identify patients more likely to respond to M+P particularly in PD-L1+ pts. Our results suggest that M+P is well tolerated and has encouraging preliminary activity in 2nd line HER2+ GEA. Biomarker selection may further enrich for responding pts, advancing a potential chemos-free regimen in this population.

Clinical trial identification: NCT02689284.

Legal entity responsible for the study: MacroGenics, Inc.

Funding: MacroGenics, Inc.

**Results:** As of 15 Feb 2018, 100 pts were enrolled in the expansion cohorts, 97 of whom were treated. Mean age was 58 ± 11 years, M/F 267/4, ECOG PS 0/1/1/3 (1 missing). Pts received 1 median of 2 MCLA-128 cycles (range 1–27). Common related AEs were infusion-related reactions (3%), diarrhea (17%), asthenia/fatigue (13%), nausea (6%), and decreased appetite (5%). Four (4%) pts had suspected grade 3–4 AEs. No clinically significant LVEF decline (>10% from baseline and LVEF <50%) was seen. Mean F12 was ~100 (n = 89). Steady state serum concentrations of MCLA-128 were achieved after 2 cycles. As of 25 Mar 2018, 25 GC/GEJ pts were evaluable for response, with a median 3 metastatic sites (range 1–6), and progression on 1–2 prior anti-HER2 agents. They received a median of 2 MCLA-128 cycles (range 1–17). 1 pt had a confirmed CR (8+ cy); 5 pts had SD (sustained: 4, 5, 6, 12, 17 cy); CBR was 24% (6/25 pts). Based on central analysis variable HER2 levels were observed by HER2 IHC, and HER2 amplification was confirmed by FISH in all CBR patients. 4 of the 6 CBR pts had HER2 IHC ≥ 3+.

**Conclusions:** MCLA-128 is very well tolerated with mainly grade 1/2 AEs. Promising single agent antitumor activity was seen in heavily pretreated GC/GEJ pts progressing on anti-HER2 therapy. Further clinical exploration of MCLA-128 in GC/GEJ pts is warranted.

**Clinical trial identification:** EuadrCT: 2014-003277-42.

**Editorial acknowledgement:** Dr Sarah MacKenzie, Oncology Therapeutic Development.

**Legal entity responsible for the study:** Merus NV.

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66SP  **NRF2 activation via PI3K/akt/mTOR/RPS6 causes resistance to anti-HER2 agents among HER2 amplified gastric cancer**

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**Background:** Personalized treatment for gastric cancer (GC) represents a big challenge. HER2 is an important driver in 7–34% of cases, playing a relevant role in cell growth and survival. Trastuzumab (T), when combined with chemotherapy, improves survival. No further anti HER2 drugs demonstrated clinical benefit. Resistance to treatment is a serious problem.

**Methods:** OE 19 and NC3 NMY, HER2 + GC cell lines, were treated with increasing doses of Lapatinib (L) and T to obtain resistant clones. These were isolated and characterized by performing mutational analysis by Sequon mass/Array and Western blot (WB) to evaluate protein expression. Genome-wide expression profile was conducted. Inhibition of the altered pathways was performed with specific drugs and siRNA to verify if those alterations were responsible for resistance. In vivo experiments was performed to corroborate the obtained results. A retrospective cohort of HER2 amplified patients treated with T was also analysed. Clinical characteristics and outcomes were collected.

**Results:** T and resistant clones were obtained. Protein expression underlined the activation of PI3K pathway and of its downstream effector RPS6 protein. Data obtained by microarray were analysed, identifying a large number of genes regulated by NFR2, a transcriptional regulator involved in oxidative stress, detoxification, and drug resistance. NRF2 expression was detected by WB and immunofluorescence. Cells were treated with GS048 (G), a dual PI3K/TORCH1/2 inhibitor, showing a decrease in cell growth. siRNA of both RPS6 and NR2 confirmed the decrease of proliferation and when treatment with antiHER2 was administered, sensitivity was restored. Interestingly after inhibiting PI3K pathway NRF2 expression decreases. In xenografts L and G were tested. G reduced both the expression of pRPS6 and NRF2. Patients with high HER2 expression treated with T, experienced worse outcome, suggesting that hyperactivation of the PI3K pathway may make anti HER2 treatment less effective.

**Conclusions:** Activation of NR2 in PI3K seems to be consistently related to anti HER2 resistance in HER2 amplified GC.

**Legal entity responsible for the study:** INCLIVA Biomedical Research Institute.

**Funding:** INCLIVA Biomedical Research Institute.

**Disclosure:** All authors have declared no conflicts of interest.

667P  **A phase II study of trastuzumab with S-1 plus oxaliplatin for HER2-positive advanced gastric cancer (HIGHSOX)**

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**Background:** Trastuzumab with cisplatin and fluoropyrimidines (FUs) improved the overall survival of patients with human epidermal growth factor receptor type 2 (HER2)-positive advanced gastric cancer (AGC). S-1 plus oxaliplatin (SOX) is one of the standard regimen for HER2-negative AGC especially in Japan. However, to date, few studies have evaluated the efficacy and safety of trastuzumab combined with SOX in patients with HER2-positive AGC.

**Methods:** This is a multi-center, phase II study that is conducted in 10 Japanese institutions. Patients with HER2-positive AGC received S-1 (80mg/m²) twice a day orally on days 1–14, oxaliplatin (130mg/m²) intravenously on day 1, and trastuzumab (course 1, 8mg/kg; course 2–6, 6mg/kg) intravenously on day 1 of a 21-day cycle. The primary end point was confirmed response rate (cRR); secondary end points included overall survival (OS), progression-free survival (PFS), and adverse events. The sample size was determined to be 75 cases based on a hypothesis of threshold RR of 50% and an expected RR of 65%, 90% power, with an alpha value of 0.1 (one-sided) using the binomial trial.

**Results:** From June 2015 to January 2018, a total of 78 patients were screened, of whom 75 were enrolled and eligible. The median age was 64 years. ECOG PS 0/1/2/3 (3%); resectable/recurrence; 66/9, Gastric/EcG; 64/11, pathology(tub)±(tub/por)/sig; 13/33/24/ 5, metastatic sites(LN/liver/peritoneum/lung/bone/others); 40/35/20/9/3. The proportion of HER2+ was 73.3%. In the full analysis set of 75 patients as of March 2018, cRR was 65.2% (95% confidence interval (CI): 52.4–76.3); n = 66: excluding unconfirmed 9 cases; and the disease control rate was 89.4% (95% CI 79.4–95.6). Median OS,
PSF were estimated as 20.6 (95% CL: 14.8-30.6) and 9 (95% CL: 7.4-14.7) months, respectively. Major grade 3 or 4 adverse events included sensory neuropathy (14.7%), neutropenia (9.3%), diarrhea (6.7%), and anemia (6.7%). There were no treatment-related deaths.

Conclusions: Trastuzumab in combination with SOX showed promising activity with well-tolerated toxicities in patients with HER2-positive AGC as well as other platinum and PSF. Final analysis based on confirmed response will be reported at the conference.

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Legal entity responsible for the study: The authors

Funding: Japanese Foundation for Multidisciplinary Treatment of Cancer.


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Annals of Oncology

668P Updated analysis of a phase II study of SOX plus trastuzumab for the patients with HER2 positive advanced or recurrent gastric cancer: KSCC/HGCSG/COCOR/SERUIS5101B

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Background: Trastuzumab (T)-combined with cisplatin and fluoropyrimidines is the standard first line treatment for the patients with HER2-positive advanced gastric cancer (AGC). We conducted first phase II trial to assess the efficacy and safety of T-combined with 5 and oxaliplatin (HER-SOX130) for HER2-positive or recurrent gastric cancer.

Methods: Patients with IHC 3 + or IHC 2 + /FISH positive received 80 mg/m2 (80-120 mg/body) S-1 per day orally on days 1-14, 150 mg/m2 oxaliplatin intravenously on day 1, and T (4-mg/kg loading dose and 2-mg/kg thereafter) intravenously on day 1 of a 21-day cycle until one of the criteria for withdrawal of the study treatment occurred. The primary end-point was the response rate (RR). The secondary end-points were disease progression-free survival (PFS), overall survival (OS), time-to-treatment failure (TTF), duration of treatment, time to failure of strategy (TFS) and dose intensity. Adverse events were recorded based on the CTCAE Ver 4.0.

Results: 42 patients were enrolled from June 2013 to May 2016. Efficacy and safety analyses were conducted in the full analysis set of 39 patients. The data cut-off specific to the survival status was February 19, 2018. The proportion of patients with IHC 3 + was 87%. The incidence of grade 3 or 4 adverse events (>10%) were plasteat count decreased (12.9%), neutropenia (10.3%), and hypertension (10.3%). The confirmed RR achieved by the independent review committee was 82.1% (32/39) (95%CI: 67.3-91.0), and the disease control rate was 87.2% (34/39) (95%CI: 73.3-94.4). 9 cases underwent curative surgery after HER-SOX130. Median PFS, TTF and OS was 7.0 (95%CI: 5.3-14.4), 7.5 (95%CI: 4.6-7.0) and 27.7 (95%CI: 15.6-) months, respectively.

Conclusions: HER-SOX130 demonstrates promising response and survival with a favorable safety profile. HER-SOX130 should be considered for the patients with HER2-positive AGC.

Clinical trial identification: UMIN000017552, 2015/05/29.

669P Differences in outcome according to chemotherapy backbone and maintenance treatment in HER2 positive metastatic gastric cancer (GC) or gastroesophageal junction (GEJ)

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Abstracts

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Background: Although the TOGA study used cisplatin plus capecitabine (XP) or fluorouracil (FP), oxaliplatin schedules (CAP/FOLFOX) are commonly used. There is also a discrepancy in the no. of cycles and the maintenance treatment with trastuzumab (T). Methods: We conducted an observational, retrospective, multicentric study of patients with metastatic HER2 GC or GEJ treated at 6 Spanish hospitals belonging to Galician Research Group on Digestive Tumors (G1Ud). Demographic, clinic and pathological data were retrospectively collected and correlated with overall survival (OS) and progression-free survival (PFS). Results: 91 pts treated between May 2010 to January 2018 were recorded. Median age was 68 years (range 38-94 years), 74.7% were male, 39.6% GEJ location, 82.9% intestinal/neuroendocrine type, 66.8% well differentiated, 82.4% synchronous disease and 24.2% primary tumor resection. Median of metastatic locations was 2 (range 1-4). Chemotherapy backbone: FP 47%, XP 21.2%, CAPOX 17.6%. With a median follow up of 45.6 months, 85 pts were evaluable for efficacy. Median OS was 14.2 months (CI 95% 10.3-18.1 months) and median first line PFS was 8.9 months (CI 75% 7.7-10.1 months). Overall response rate 57.6% and disease control rate 78.9%. Median cycle of induction treatment was 6 (range 1-18). No PFS differences were found according to the platinum (p = 0.579) or fluoropirimidine used (p = 0.955). Of 47 non-progressive patients after 6 months the majority received maintenance treatment for a median of 6.5 cycles (range2-77 with T plus fluoropirimidine (21 and 16 pts) while 10 discontinued treatment. Post-induction PFS favors those who continued treatment with a PFS of 7 vs 5 months (p = 0.033), without differences between schemes (p = 0.890). Primary tumor surgery (HR 0.380; p = 0.010, neutrophil to lymphocyte ratio > 518.061) and primary tumor surgery < 200 (HR 0.357; p = 0.030) were associated with prolonged OS. Conclusions: Maintenance treatment with T has a benefit in terms of PFS even in patients who received T during induction. The practice of continuing the fluoropirimidine during maintenance does not appear to add any PFS benefit in our series.

Legal entity responsible for the study: Galician Research Group on Digestive Tumors. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.
Methods: Patients received oral S-1 40-60 mg twice daily on days 1 to 14 every 3 weeks plus intravenous oxaliplatin 130 mg/m² on day 1 every 3 weeks for 3 courses, followed by gastrectomy with D2 lymphadenectomy. The primary endpoint was pathological response rate (pRR) according to the proportion of necrosis in the tumor: grade 0, no necrosis; grade 1, <1/3 necrosis; grade 1b, 1/3–<2/3 necrosis; grade 2, >2/3 necrosis; grade 3, all necrosis; and grade 3, all parts of the tumors affected by necrosis. A sample size of 46 was set according to one-sided significance level of 0.05 and power of 80% based on an exact binomial distribution, and assuming the null hypothesis of a 50% pRR and an alternative hypothesis of a 30% pRR. The incidence of anastomosis leakage in EGC was the main secondary endpoint. Other secondary endpoints were R0 resection rate, overall survival, relapse free survival and safety.

Results: Between 2016 April and 2017 July, 47 patients (24 EGC, 23 LAGC) were enrolled in this study. All patients were eligible for analysis. 42 patients (89.4%:95%CI 76.9-96.5) underwent surgery, and curative resection was performed in 41 patients. The rate of postoperative treatment completeness was 42 patients (89.4%:95%CI 76.9-96.5%). pRR, the primary endpoint (grade 1b to 3), was 25 cases (59.5%:95%CI 45.7-72.3%) of primary lesions. The main toxicities of neoadjuvant chemotherapy were grade 3/4 thrombocytopenia (10.6%), neutropenia (6.4%), anemia (4.3%), grade 3/4 anaorexia (12.8%). The number of anastomosis leakage so as to 20 EGC according to the Clavien–Dindo classification was 2 for grade IIa, 2 for grade Ib, and 1 for grade IV (25.0%-95%CI 10.4-45.6%). Survival data will be updated in further investigation.

Conclusions: The S-1 and oxaliplatin was well tolerated and is promising as a preoperative chemotherapy regimen for patients with LAGC and EGC.

Clinical trial identification: UMIN000021061.

Legal entity responsible for the study: KSCC.

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A multicenter phase II trial of perioperative capcitabine plus oxaliplatin for clinical stage III gastric cancer (OGG16101)

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Background: D2 gastrectomy followed by postoperative S-1 is the standard therapy for the patients (pts) with stage III gastric cancer (GC) in East Asia, but 40% of the pts develop a recurrence. We hypothesize that the perioperative capcitabine and oxaplatin (Capox) might improve survival for clinical stage III GC.

Methods: In this phase II trial, the eligibility criteria included pathologically confirmed clinical stage IIIA, B, N0, M0 GC according to Japanese Classification of GC [JCCGC]. 3rd English Edition. Perioperative Capox Patients consisted of three cycles of Capox (capcitabine: 2,000 mg/m² for 14 days, oxaliplatin: 130 mg/m² day 1) every 3 weeks as neoadjuvant chemotherapy (CT), followed by five cycles of adjuvant Capox after the D2 gastrectomy. The primary endpoint was the pathological response rate (pRR) according to JCCGC (≥ Grade Ib). The planned sample size was 34 pts calculated on the hypothesis that the expected pRR was 65% and the threshold was 40%, with one-sided alpha of 0.05 and power of 90%.

Results: Thirty-seven pts were enrolled from Apr. 2016 to May. 2017, and fully eval-
uated for efficacy and toxicity. R0 and R1 resection were achieved in 29 and 3 pts, respectively. One pt underwent R2 resection, and four pts could not undergo surgical resection. Sixteen pts underwent total gastrectomy, and 17 pts underwent distal gastrectomy. The pRR was 54.1% (one-sided p = 0.058, 95%CI: 36.9-70.5). The relative dose intensity (RDI) of Capcitabine and Oxaliplatin were 97.6% and 92.0%, respectively. Twenty-seven pts received adjuvant chemotherapy, and the RDI of capcitabine and oxaliplatin were 80.9% and 63.4%, respectively. Grade 3/4 toxicities of neoadjuvant CT included neutropenia (8%), thrombocytopenia (8%), and anorexia (8%). Grade 3/4 toxicities of adjuvant CT included neuropathy (29%), diarrhea (8%), and anorexia (3%). Grade IIIA surgical complications included intraabdominal abscess (3%), bowel obstruction (3%) and anastomotic leakage (5%).

Conclusion: This phase II trial of perioperative Capoxs showed favorable antitumor activity with an acceptable safety profile for stage III GC, although pRR as primary endpoint did not meet the prespecified threshold.

Clinical trial identification: UMIN000021641.

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Clinical trial identification: Chinese Clinical Trial Registry (ChiCTR-OPC-16010061).

Legal entity responsible for the study: Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai Institute of Digestive Surgery, Shanghai Key Laboratory of Gastric Neoplasms.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

674P

**The efficacy and safety of (neo)adjuvant therapy for gastric cancer: A network meta-analysis**

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**Background:** Alternatives in treatment-strategies exist for resectable gastric cancer treated with curative intent including: perioperative chemotherapy, adjuvant chemoradiotherapy and adjuvant chemotherapy. Our aims were (1) to assess the benefit of peri-operative, neoadjuvant and adjuvant treatment-strategies and (2) to determine the optimal adjuvant regimen for gastric cancer treated with curative intent.

**Methods:** PubMed, EMBASE, CENTRAL, and ASCO/ESMO conferences were searched up to August 2017 for randomized controlled trials on curative treatment for resectable gastric cancer. We performed two network-meta-analyses (NMA). NMA-1 compared perioperative, neoadjuvant and adjuvant strategies only if there was a direct comparison. NMA-2 compared different adjuvant regimens with chemotherapy or chemoradiotherapy after curative resection. Overall-survival (OS) and disease-free-survival (DFS) were analyzed using random-effects NMA on the hazard ratio (HR) scale and calculated as combined HRs and 95% credible intervals (95%CrI).

**Results:** NMA-1 consisted of 9 direct comparisons between strategies for OS (14 studies, n = 4,187 patients). NMA-2 consisted of 16 direct comparisons between adjuvant chemotherapy/chemoradiotherapy regimens for OS (37 studies, n = 10,761) and for DFS (30 studies, n = 9,714 patients). Compared to taxane-containing perioperative chemotherapy surgery-alone (HR = 0.58, 95%CrI = 0.38-0.91) and perioperative-chemotherapy with oxaliplatin-fluoropyrimidine (HR = 0.79, 95%CrI = 0.58-1.15) were inferior in OS. Compared to surgery-alone, adjuvant chemoradiotherapy was non-significant (HR = 1.00, 95% CrI = 0.67-1.47). After curative-resection, the doublet oxaliplatin-fluoropyrimidine (for one-year) was the most efficacious adjuvant regimen in OS (HR = 0.47, 95%CrI = 0.28-0.80). The addition of radiotherapy to chemotherapy did not improve OS and DFS.

**Conclusions:** For resectable gastric cancer treated with curative intent, (1) taxane-containing perioperative chemotherapy is the preferred treatment strategy; and (2) adjuvant oxaliplatin-fluoropyrimidine is the optimal regimen after curative resection.

Legal entity responsible for the study: Academic Medical Center.

Funding: Has not received any funding.

Disclosure: S.S. Gisbertz: Consultant; Medtronic; Unrestricted research grant: Olympus. M.G.H. van Oijen: Unrestricted research grants: Bayer, Lilly, Merck Serono, Nordic, Roche. H.W.M. van Laarhoven: Consultant: Philips, Celgene, Lilly, Nordic; Unrestricted research funding: Philips, Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. All other authors have declared no conflicts of interest.

675P

**Irinotecan, oxaliplatin, 5-fluorouracil/leucovorin (FOLFIRINOX) as first-line therapy in advanced HER2-negative gastric or gastroesophageal adenocarcinoma (G/GA)**

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**Background:** G/GA is relatively chemosensitive, but triplet chemotherapy (CT) regimens with docetaxel have the most efficacy with overall response rate (ORR) 37-58%, median progression free survival (MPS), 9.2-14.7 months. The disease control rate was 90.3%. For this reason, we introduced mFOLFIRINOX regimen. The main toxicities Grade (G) 3-4 in pts included neutropenia - 47.2%, febrile neutropenia - 5.6%, diarrhea - 5.6%; we noted else thrombocytopenia gr 1-2 - 29.6%, asthenia gr 1-3 - 87%, hepatotoxicity - 25%/gr 0-3, neurotoxicity - 15%/gr 1-2. 31(28.7%) pts received G-CSF on 8,5% cycles. There were no deaths and treatment discontinuation due to toxicity. After the complete regression of distant metastases 11 pts were operated (D2 gastrectomy). For these pts MPCR was 18,47 mo, MOS - 29.33 mo.

**Conclusions:** mFOLFIRINOX showed remarkable ORR, PFS and OS in patients with advanced gastroesophageal or gastric adenocarcinoma in the first-line setting. This regimen may be one more reasonable therapeutic option for these pts. We recommend mFOLFIRINOX for Phase III clinical trial compared with FLOT regimen.

Legal entity responsible for the study: Besova N.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

676P

**Efficacy and safety for apatinib combined with oxaliplatin and S1 in initially treated metastatic gastric cancer: A single-center observational study**

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**Background:** Currently, S-1 combined with oxaliplatin (SOX) is widely used in the first-line treatment of advanced gastric cancer in China. Apatinib has demonstrated encouraging anti-cancer activity in gastric cancer within both in vitro and in vivo models. We evaluated the efficacy and safety of apatinib combined with SOX in initially treated patients with metastatic gastric cancer.

**Methods:** In this single arm study, patients with unresectable metastatic gastric adenocarcinoma was enrolled to received chemotherapy with apatinib (500mg, once daily) and SOX regimen. Oxaliplatin was administered at a dose of 130 mg/m2 on day 1, and 5-1 (40-60 mg depending on patient’s body surface area) was given weekly twice daily for 2 consecutive weeks followed by a 1-week rest. The primary end point was response rate. Secondary endpoints were safety, median progression-free survival and median overall survival.

**Results:** Thirty-one eligible patients were enrolled between January 2016 and September 2017. Two patients achieved a complete response and 19 patients had partial response. The objective response rate was 67.7%. Seven patients had stable disease and the disease control rate was 90.3%. Disease progression was seen in 3 cases (9.7%). Progression-free survival was 5.9 months (95% confidence interval: 3.2-12.6) and median overall survival was 15.6 months (95% confidence interval: 7.3-22.1). The most common grade 3 to 4 hematologic adverse events (AE) were leukopenia (12.9%), neutropenia (38.7%), thrombocytopenia (6.5%) and anemia (25.8%), nonhematologic AE were nausea (12.9%), anorexia (32.3%), hand-foot syndrome (6.5%), hyper-tension (9.7%) and proteinuria (5.2%). No treatment-related death was documented during the drug administration.

**Conclusions:** Apatinib plus SOX is effective for initially treated metastatic gastric cancer with more favorable safety.

Editorial acknowledgement: Approved by the hospital ethics committee of the first affiliated hospital of Sun Yat-sen University (SYX).

Legal entity responsible for the study: Peng Jianjun.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

677P

**Apatinib in combination with cisplatin and 5-fluorouracil (5-FU) as first line treatment in inoperable gastric and gastro-esophageal junction (G/EJ) cancer: A phase II study by the Hellenic Cooperative Oncology Group**

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**Background:** Inoperable gastric and GEJ cancer is usually treated with platinum- and fluoropyrimidine-based combination chemotherapy. Targeting of the epidermal growth factor family of receptors has been unsuccessful except in the case of HER2 targeting with trastuzumab. Apatinib, has shown activity in preclinical models of gastric cancer and has been combined with cisplatin and 5-FU in phase I studies.

**Methods:** Patients (pts) were treated with the combination of cisplatin (75 mg/m2, day 1), 5-FU (750 mg/m2, continuous infusion days 1-4) and apatinib (40 mg/day, week1: days 1-3, weeks 2, 3: days 1-5), in an effort to optimize therapy efficacy and tolerability. Primary endpoint was the objective response rate (ORR) in the intention to treat (ITT) and the per-protocol (PP) population. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety profile.

**Results:** Among the 55 pts (median age 64, range 20-77) enrolled (ITT), the ORR was 34.5% (44.2% in PP pts; N = 43). After a median follow-up of 33.3 months, median PFS and OS were 9.3 (95% CI 6.4-11.5; 43 deaths) months, respectively. Median relative dose intensities administered were 0.97 for 5-FU, 0.96 for cisplatin and 0.94 for apatinib. Grade 3 adverse events (AEs) occurred in 34 pts (61.8%) and 9 pts (16.4%), respectively. Most common grade 3/4 AEs were:
neutropenia (27.3%), anemia (12.7%), hypokalemia (10.9%), diarrhea (5.4%), infections (5.4%). Acenocoumarol grade 1/2 was noted in 20% of pts, while there were 4 (7.3%) thromboembolic events (grade 1-3). There were no treatment related deaths. Pts with GEJ cancer had worse OS than pts with gastric cancer (p = 0.03).

**Conclusions:** The combination of atezolizumab with cisplatin (3/5 FU) in pts with inoperable gastric/GEJ cancer has modest activity, however atezolizumab benefited pts and prolonged OS.

**Clinical trial identification:** NCT01743365 (December 6, 2012).

**Legal entity responsible for the study:** Hellenic Cooperative Oncology Group.

**Funding:** Hellenic Cooperative Oncology Group.

**Disclosure:** All authors have declared no conflicts of interest.

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**678P** Treatment patterns and changes in quality of life during first-line palliative chemotherapy in Korean patients with advanced gastric cancer


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**Background:** The purpose of this study was to evaluate chemotherapy patterns and changes in quality of life (QOL) during first-line palliative chemotherapy for Korean patients with unresectable or metastatic/recurrent gastric cancer (GC).

**Methods:** This was a non-interventional, multi-center, prospective, observational study of 527 patients in Korea. QOL assessments were conducted using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-STO22) every 3 months over a 12-month period during first-line palliative chemotherapy. The specific chemotherapy regimens were selected by individual clinicians.

**Results:** Most patients (91.2%) received combination chemotherapy (mainly fluoropyrimidine plus platinum) as their first-line palliative chemotherapy. The median progression-free survival and overall survival were 8.2 and 14.8 months, respectively. Overall, a ‘little’ change (differences of 5-10 points from baseline) were observed in some of the functioning or symptom scales; none of the QOL scales showed either ‘moderate’ or ‘very much’ change (i.e., >11 point difference from baseline). When examining the best change in each QOL domain from baseline, scales related to some aspects of functioning, global health status/QOL, and most symptoms revealed significant improvements (p < 0.05). Throughout the course of first-line palliative chemotherapy, most patients’ QOL was maintained to a similar degree, regardless of their actual response to chemotherapy.

**Conclusions:** This observational study provides important information on the chemotherapy patterns and QOL changes in Korean patients with advanced GC. Overall, first-line palliative chemotherapy was found to maintain QOL, and most parameters showed an improvement compared with the baseline at some point during the course.

**Legal entity responsible for the study:** Kwon-Hee Lee.

**Funding:** Sanofi-Aventis Korea Co., Ltd.

**Disclosure:** All authors have declared no conflicts of interest.

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**679P** Meta-analysis of biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer


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**Background:** Biweekly CPT-11 plus CDDP (BIRIP) and CPT-11 alone are both expectable options for treating advanced gastric cancer (AGC) in second-line setting.

Recently, two randomized phase III trials (TCOG GI-003 and ECRIN TRILS) employing the same regimes have been reported. Both trials did not demonstrate the survival benefit of BIRIP due to underpowered. Therefore, we conducted a meta-analysis to compare the efficacy and safety of these two regimes in patients who have been enrolled in these two randomized trials.

**Methods:** Individual patient-level data from these two trials were collected for this study. In these two trials, patients with metastatic or recurrent gastric cancer refractory to S-1 based chemotherapy were randomly allocated to BIRIP (CPT-11, 60mg/m²; CDDP, 50mg/m², q2w) or CPT-11 (150mg/m², q2w). Overall survivals (OS) and progression-free survivals (PFS) were described using Kaplan-Meier methods. Tumor responses were evaluated using RECIST ver. 1.0. Adverse events were evaluated using CTCAE ver. 3.0.

**Results:** Cumulative data from eligible 280 patients from these two trials were evaluated. OS were 12.3 (95% confidence interval [CI]: 10.5–14.1) in BIRIP group and 11.3 (95% CI: 10.0–13.2) months in CPT-11 group (hazard ratio 0.87; 95% CI: 0.66–1.12, P = 0.272). PFS was significantly longer in BIRIP group (4.3months [95% CI: 3.3–5.1]) than in CPT-11 group (3.3months [29.4–41.9], HR 0.77; 95% CI: 0.61–0.98, P = 0.035). The response rate was 20.9% (95% CI: 13.3–27.7) in BIRIP group and 16.0% (95% CI: 9.6–22.4) in CPT-11 group (P = 0.461). The disease control rate was significantly better in BIRIP group (72.1% [95% CI: 64.2–80.1]) than in CPT-11 group (59.2% [95% CI: 50.6–67.8]) (P = 0.032). The incidences of grade 3 or worse adverse events did not differ between the two groups, for example neutropenia (35.9% vs. 32.4%) and elevation of serum creatinine (0.7% vs. 0.7%). The incidences of anemia (16.6% vs. 10.3%) was higher for BIRIP than for CPT-11. But diarrhea (1.4% versus 4.1%) was more common in CPT-11 group. The difference of the incidence of diarrhea (1.4% versus 4.1%) was more common in CPT-11 group.

**Conclusions:** BIRIP significantly prolonged PFS as compared with CPT-11 alone and was tolerated as second-line treatment for AGC, but did not demonstrate the survival benefit.

**Clinical trial identification:** UMIN 000125367.

**Legal entity responsible for the study:** The non-profit organization Epidemiological & Clinical Research Information Network (ECRIN).

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**680P** A phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (KCGG ST10-01)


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**Background:** Although emerging treatments have been introduced to patients with metastatic or recurrent gastric cancer (MRCG) as second-line therapy, paclitaxel or irinotecan are still viable options. This phase III study compared the efficacy and safety of...
Impact of adding ramucirumab to paclitaxel in patients with advanced gastric cancer according to the level of ascites: A multicenter retrospective study

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Background: Adding ramucirumab (Ram) to paclitaxel (PTX) improved the overall survival (OS) in patients with advanced gastric cancer (AGC) in the RAINBOW trial, which excluded patients with high levels of ascites. This retrospective study included patients with AGC who received PTX alone or PTX+Ram as a 2nd-line treatment from Nov. 2013 to Nov. 2016. Selection criteria were ECOG PS of 0–2, refractory or intolerant to fluoropyrimidines, and no prior use of taxane or Ram. The level of ascites was classified as low (no or limited to either the pelvic cavity or upper abdomen) or high (extended from the pelvic cavity to the upper abdomen). An adjusted HR (aHR) for progression-free survival (PFS) and OS was calculated by a multivariate Cox model that contained variables with \( p \leq 0.126 \). There was no difference in response rate (\( p = 0.783 \)) between paclitaxel (15.8%) and irinotecan (13.6%). Among toxicities of \( >^\text{grade 3} \), neutropenia (11.9%) was the most common toxicity, followed by peripheral neuropathy (7.7%) in the paclitaxel group, and neutropenia (34.3%) followed by nausea, vomiting and anemia (8.6%, respectively) in the irinotecan group.

Conclusions: Although paclitaxel showed numerically longer PFS and OS compared with irinotecan, this was statistically insignificant. Both irinotecan and paclitaxel are valid second-line treatment options in MRGC.

Disclosure: All authors have declared no conflicts of interest.

Table 682P: Prognostic factors associated with apatinib treatment

<table>
<thead>
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<th>Metastatic site</th>
<th>n</th>
<th>mPFS, mos</th>
<th>p</th>
<th>mOS, mos</th>
<th>p</th>
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<tr>
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<td>3.6</td>
<td>0.0003</td>
<td>8.0</td>
<td>0.0031</td>
</tr>
<tr>
<td>Yes</td>
<td>266</td>
<td>3.8</td>
<td>&lt;0.0001</td>
<td>7.7</td>
<td>0.0059</td>
</tr>
</tbody>
</table>

Conclusions: The real world study confirms that apatinib is safe and effective for advanced gastric cancer pts. Factors associated with better prognosis were \( \leq 2 \) metastatic sites, ECOG PS 0/1, dose \( >300 \) mg, and occurrence of proteinuria, hypertension, hand-foot syndrome, or leukopenia.


Legal entity responsible for the study: Jiangsu Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

682P Identification of patients who benefit from apatinib in advanced gastric cancer: Data derived from a real-world study

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Background: A prospective, multicenter, non-intervention registered study of apatinib is being conducted in advanced gastric cancer patients (pts). The result of interim analysis on efficacy and safety was released in ESMO 2017 Congress (695P). Herein, we mainly aimed to identify pts who benefit from apatinib treatment.

Methods: Pts with advanced or metastatic adenocarcinoma of stomach or gastro-esophageal junction who received apatinib administration were included in this real world study. The subgroup analyses were stratified by numbers of metastatic sites, ECOG PS, dosage of apatinib, and occurrence of adverse events (AEs).

Results: As of January 2018, data on 212 pts were available for final analysis. The median progression free survival (mPFS) and median overall survival (mOS) were 4.0 mos and 8.2 mos, respectively. 239 pts (74.9%) reported AEs. Main AEs were proteinuria (17.1%), hypertension (15.9%), and hand-foot syndrome (8.7%). As in table, the mPFS and mOS of pts with \( <^2 \) metastatic sites were longer than those of pts with \( \geq^2 \) metastatic sites (mPFS: \( p = 0.0087 \), mOS: \( p = 0.0016 \)). For pts with ECOG PS 0, 1, and \( \geq^2 \), the differences among groups were significant (mPFS: \( p < 0.0001 \), mOS: \( p = 0.0316 \)). Among different dose groups, dose \( \geq 300 \) mg got longer mPFS (\( p < 0.001 \)) and mOS (\( p = 0.0039 \)). What’s more, pts who reported proteinuria, hypertension, hand-foot syndrome, or leukopenia had longer mPFS (\( p < 0.001 \)) and mOS (\( p < 0.003 \)) compared with those who didn’t.

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Conclusions: The real world study confirms that apatinib is safe and effective for advanced gastric cancer pts. Factors associated with better prognosis were \( \leq 2 \) metastatic sites, ECOG PS 0/1, dose \( >300 \) mg, and occurrence of proteinuria, hypertension, hand-foot syndrome, or leukopenia.


Legal entity responsible for the study: Jiangsu Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

paclitaxel versus irinotecan in patients with MRGC who failed to first-line chemotherapy.

Methods: Patients were randomized to receive either paclitaxel (70 mg/m\(^2\), days 1, 8, 15, every 4 weeks) or irinotecan (150 mg/m\(^2\) b.i.w.). The primary endpoint was progression-free survival (PFS).

Results: This study was stopped early due to low accrual rate. A total of 112 patients were enrolled, of which 54 were allocated to paclitaxel, and 58 to irinotecan. Median PFS of paclitaxel or irinotecan group were 3.5 and 2.1 months, respectively [hazard ratio (HR) 1.27; 95% confidence interval (CI), 0.86–1.88; \( p = 0.234 \)]. Non-inferiority of irinotecan to paclitaxel was not proven according to the predefined upper margin of non-inferiority (1.32). Median overall survival (OS) was 8.6 months in the paclitaxel group, and 7.0 months in the irinotecan group (HR, 1.39; 95% CI, 0.91–2.11, \( p = 0.126 \)). There was no difference in response rate (\( p = 0.783 \)) between paclitaxel (15.8%) and irinotecan (13.6%). Among toxicities of \( >^\text{grade 3} \), neutropenia (11.9%) was the most common toxicity, followed by peripheral neuropathy (7.7%) in the paclitaxel group, and neutropenia (34.3%) followed by nausea, vomiting and anemia (8.6%, respectively) in the irinotecan group.

Conclusions: Although paclitaxel showed numerically longer PFS and OS compared with irinotecan, this was statistically insignificant. Both irinotecan and paclitaxel are valid second-line treatment options in MRGC.

Disclosure: All authors have declared no conflicts of interest.
Background: Apatinib, a small molecule VEGFR TKI, has been approved in the treat-
ment of advanced or metastatic gastric cancer (GC) in China. We performed a real
world study to observe the current status, efficacy and safety of apatinib treatment in
clinical practice, and preliminarily define patients (pts) who could benefit from
apatinib.

Methods: From September 2017, pts (age ≥18 yrs) with pathologically or histologically
diagnosed GC who were given apatinib treatment met the inclusion criteria. The target
sample size is 1000.

Results: As of April 2018, 651 pts from 37 centers were eligible. There are 491 (75.4%)
male and 160 (24.6%) females. The median age was 62.5 yrs. The majority pts were at
stage IV (399, 61.3%), had prior surgery (370, 56.8%) and chemotherapy (341, 52.4%).
Pts with ECOG PS 0–2 were 520 (79.9%), and ECOG PS 1 was most common (403,
61.9%). Metastases were detected in 370 (56.8%) pts, which mainly were hepatic and
pulmonary metastases. Pts received apatinib monotherapy or in combination with che-
motherapy. The dose of apatinib in most pts (79.0%) was 500 mg qd. Apatinib was
used in perioperative treatment for 269 (41.3%) pts. 382 (58.7%) pts with unresectable
locally advanced, recurrent, or metastatic disease received apatinib as different lines of
systemic therapy; among whom, 284 pts were evaluable for response, and 113 pts
obtained complete clinical efficacy and safety assessment. 12 achieved partial response,
79 had stable disease and 22 got progressive disease. Thus, the objective response rate
(ORR) and disease control rate (DCR) were 10.6% and 80.5%. 78.8% pts reported
adverse events (AEs). The incidence of grade 3-4 AEs was 22.1%. Main apatinib-related
AEs were hypertension (20.3%), and hand-foot syndrome (26.5%). There were tenden-
cies that prognostic factors related with higher ORR were lines of apatinib (>3, 9.5%),
duration of medication (< 90 days, 7.1%; 90-120 days, 6.7%; >120 days, 11.9%).

Conclusions: In the real world, GC pts receiving apatinib therapy are mainly elderly
men, stage IV, and ECOG PS 1. Apatinib is confirmed to be effective and safe for GC
pts. Further analysis is needed to identify pts who obtain benefits from apatinib

treatment.

Clinical trial identification: NCT03339967.

Legal entity responsible for the study: The First Affiliated Hospital of Anhui Medical
University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: There is growing consensus that host immunity, of which lymphocytes are well-known as an indicator, plays important roles against the development of malignancy. Based on this concept, many studies reported the prognostic value of pre-operative lymphocyte counts and representative markers associated with lymphocytes in predicting overall survival (OS) in patients with gastric cancer. Methods: A total of 177 consecutive patients who underwent curative gastrectomy for stage II disease. NS GEP demonstrated 4 distinct molecular signatures, A-D. Group D exhibited the greatest downregulation of distinct molecular signatures, A-D. Group D exhibited the greatest downregulation of immune signaling. We conducted a retrospective analysis of resected GAs to gain insight into the immune landscape in gastric cancer. Results: Elevated pre- and postoperative lymphocytes, especially postoperative lymphocytes, were significantly associated with better OS (p < 0.001) and PNI (p < 0.007). The correlation of OS and PPS was strong (s correlation coefficient of 0.8705). As the RECIST categories worsened, the correlation of OS and PPS was moderate with a Spearman’s correlation coefficient of 0.611. The correlation of OS and PFS was strong with a Spearman’s correlation coefficient of 0.7805. As the RECIST categories worsened, OS, PFS, PPS shortened. The median OS for the responders and non-responders (357 days, 272 days p-value < 0.005) was significantly longer than non-responders (316 days, 179 days p-value < 0.005). Conclusions: Although there are limitations, the analysis shows positive linear correlation between OS and PFS as well as OS and PPS. Patients in better RECIST categories have longer time to OS, PFS and PPS. From the correlation observed, response rate may be a surrogate endpoint to OS, PFS and PPS in gastric cancer patients will be analyzed and presented using joint modeling of the survival data.

Clinical trial identification: UMIN000019519.

Legal entity responsible for the study: Japan Clinical Cancer Research Organization (JACRBO).

Funding: Japan Clinical Cancer Research Organization (JACRBO).


686P

Immune gene expression profiling (GEP) of resected gastric adenocarcinomas (GAs) to identify biomarkers associated with immune checkpoint inhibitor (ICP) response in early stage disease

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3Department of Medicine, Samsung Medical Center, Seoul, Republic of Korea

Background: Clinical trials of ICPs in early stage GA are ongoing. Nanostri NGEP allows for simultaneous interrogation of a wide range of genes involved in immune signaling. We conducted a retrospective analysis of resected GAs to gain insight into the immune landscape in this setting. Methods: We profiled 45 archival GAs treated with upfront surgery (pT2N0 to pT4N3 ASCC) using a 770-gene immune profiling panel on the NS platform. Clinopathologic data were abstracted and overall survival (OS) was analyzed using Kaplan-Meier methods. Results: The majority of patients (44/45) had stage II disease. NS GEP demonstrated 4 distinct molecular signatures, A-D. Group D exhibited the greatest downregulation of pro-inflammatory genes relative to the other 3. Grouping was not correlated to tumor location, Lauren histology, or stage. When applying an analogous 18 gene T-cell

Table: 686P

<table>
<thead>
<tr>
<th>NS GEP (n)</th>
<th>Median OS (mo)</th>
<th>Log-rank Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell inflamed (10)</td>
<td>Not reached (NR)</td>
<td>p = .52</td>
</tr>
<tr>
<td>Non-T-cell inflamed (35)</td>
<td>59.9</td>
<td></td>
</tr>
<tr>
<td>Group B+c (24)</td>
<td>NR</td>
<td>p = .07</td>
</tr>
<tr>
<td>Group A+D (21)</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>High B score (23)</td>
<td>NR</td>
<td>p = .02</td>
</tr>
<tr>
<td>Low B score (22)</td>
<td>33.0</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: This data supports ongoing trials of ICPs in early stage GA. ICPs alone are unlikely to be sufficient for the majority of patients, necessitating biomarkers to guide addition of ICPs to current multimodality approaches. Subsequent GAs are quantifiable by NS GEP to exhibit pre-existing CD8+ T-cell infiltration or B-cell signaling and more favorable prognosis. This suggests ICPs alone or chemotherapy de-escalation evaluated for each of the RECIST categories and responders were defined as patients with complete response (CR) or partial response (PR).

687P

Significant prognostic markers related to lymphocytes in gastric cancer

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2Division of Cancer Research, Graduate School of Medicine, Osaka University

Background: Significant prognostic markers related to lymphocytes in gastric cancer are not defined in early stage gastric cancer. Methods: We profiled 45 archival GAs treated with upfront surgery (pT2N0 to pT4N3 ASCC) using a 770-gene immune profiling panel on the NS platform. Clinopathologic data were abstracted and overall survival (OS) was analyzed using Kaplan-Meier methods. Results: The majority of patients (44/45) had stage II disease. NS GEP demonstrated 4 distinct molecular signatures, A-D. Group D exhibited the greatest downregulation of pro-inflammatory genes relative to the other 3. Grouping was not correlated to tumor location, Lauren histology, or stage. When applying an analogous 18 gene T-cell

infamed signature from the KEYNOTE-059 trial, 10/45 GAs matched this signature, indicative of higher likelihood of response to single agent ICI. OS did not differ between T-cell inflamed vs. non-T-cell inflamed (Table). Comparing signatures associated with greatest (B+c) vs. least (A+D) CD8+ T-cell gene expression as a surrogate for T-cell infiltration, OS favored groups B+c. We also observed a gene (MDS1A1, CD19, BLK, TNFRSF17) B-cell signature significantly favored high vs. low expressions for OS.

Table: 687P

<table>
<thead>
<tr>
<th>NS GEP (n)</th>
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<td>33.0</td>
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</tbody>
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Conclusions: This data supports ongoing trials of ICPs in early stage GA. ICPs alone are unlikely to be sufficient for the majority of patients, necessitating biomarkers to guide addition of ICPs to current multimodality approaches. Subsequent GAs are quantifiable by NS GEP to exhibit pre-existing CD8+ T-cell infiltration or B-cell signaling and more favorable prognosis. This suggests ICPs alone or chemotherapy de-escalation evaluated for each of the RECIST categories and responders were defined as patients with complete response (CR) or partial response (PR).

Legal entity responsible for the study: City of Hope.

Funding: NIH.

Disclosure: J. Chao: Research funding: Merck, Novonco Therapeutics; Consulting, Advisory roles: Lilly, Five Prime Therapeutics, Boston Biomedical, Merck; Speaker’s bureau: Merck. S.M. Klimpfer: Research funding: Leap Therapeutics; Consulting, Advisory roles: Lilly, Boston Biomedical, Astellas Pharma; Speakers’ bureau: Foundation Medicine. R. Pillai: Consulting, Advisory roles: Qiagen. All other authors have declared no conflicts of interest.
**Table: 688P Main CP differences between MSS and MSI groups and survival outcomes**

<table>
<thead>
<tr>
<th>SEX</th>
<th>MSS 110 (79.7%)</th>
<th>MSI 38 (25.7%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEX M F</td>
<td>77 (70) 33 (30)</td>
<td>18 (47.4) 20 (52.6)</td>
</tr>
<tr>
<td>STAGE (TNM)</td>
<td>19 (17.3) 26 (23.6)</td>
<td>13 (34.2) 13 (34.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>I II III</td>
<td>65 (31.6) 12 (31.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NODAL</td>
<td>26 (23.6) 84 (76.4)</td>
<td>16 (42.1) 22 (57.6)</td>
<td>0.029</td>
</tr>
<tr>
<td>METASTASES NO YES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (months)</td>
<td>16.1</td>
<td>44.7</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusions:** MSI is an independent PD in GC and identifies a subset of pts with better OS and specific CP characteristics, including high expression of PDL-1. MSI could be a promising biomarker to select pts for CT vs IT in ES of GC.

Legal entity responsible for the study: ASST Cremona.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**689P** Neutrophil-lymphocyte ratio (NLR) as an important prognostic factor for paclitaxel as a second line chemotherapy in advanced gastric cancer (AGC): Results from phase III DREAM study

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1Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, 2Division of Hematology/Oncology, Internal Medicine Department, Korea University Guro Hospital, College of Medicine, Korea University, Seoul, Republic of Korea, 3Hematology-Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, 4Department of Oncology, Kyungpook National University Medical College, Daegu, Republic of Korea, 5Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea, 6Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea, 7Clinical Trial Team. Daehwa Pharmaceutical Co., Ltd., Seoul, Republic of Korea

Background: Paclitaxel is the most commonly used second-line chemotherapy in AGC. Recently, the DREAM phase 3 study (NCT01389773) have demonstrated that the efficacy and safety of DHP107, an oral paclitaxel, is comparable to those of intravenous (i.v.) paclitaxel. This post-hoc analysis was conducted to evaluate whether NLR is related with the treatment outcomes for both oral and i.v. paclitaxel.

Methods: In the DREAM study, pts were randomized 1:1 to DHP107 (200 mg/m² orally twice daily on days 1, 8, 15, every 4 weeks) or i.v. paclitaxel (175 mg/m² on day 1, every 3 weeks). High vs low NLR was defined by the baseline median. With comparable efficacy between two arms in the original DREAM study, all the patients (n = 236) enrolled in the DREAM study were included in this post-hoc analysis for NLR.

Results: Median age was 59 years (range, 27–83) and 185 pts (78.4%) were male. The median for NLR was 2.08. Thirty-four (28.6%) out of the 118 pts with low NLR (<2.08) achieved a complete or partial response, while 17 (14.4%) out of the 118 pts with high NLR (>2.08) showed responses (p = 0.007). With a median follow up duration of 10.8 months (range, 0.4–27.8) in surviving pts, median progression-free survival (PFS) was 4.1 months (95% confidence interval [CI], 2.8–4.3) with low NLR and 1.6 months (95% CI, 1.4–2.5) with high NLR (p = 0.0012); and median overall survival (OS) was 12.0 months (95% confidence interval [CI], 9.7–14.5) with low NLR and 7.1 months (95% CI, 5.4–9.1) with high NLR (p = 0.0004). With a multivariate analysis including important clinical factors, low NLR remained an independent factor for better PFS (HR 0.66, 95% CI 0.49–0.89, p = 0.0065) and OS (HR 0.57, 95% CI 0.42–0.78, p = 0.0005).

Conclusions: The current study demonstrates that low NLR is correlated with better treatment outcomes for both oral and intravenous paclitaxel as a second-line chemotherapy in AGC.

Clinical trial identification: NCT01389773

Legal entity responsible for the study: Daehwa Pharmaceutical Co., Ltd.

Funding: Daehwa Pharmaceutical Co., Ltd.

Disclosure: Y K Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daehwa, LSK Biopharma. All other authors have declared no conflicts of interest.

**690P** Combination versus single-agent as palliative chemotherapy for gastric cancer: Significance of age and platelet-to-lymphocyte ratio

M S Ahn, Y W Choi, H Lee, S Y Kang, J H Choi

Hematology-Oncology, Ajou University School of Medicine, Suwon, Republic of Korea

Background: Although combination chemotherapy (CC) is generally recommended in recurrent or metastatic gastric cancer, the results of randomized trials are conflicting.

Methods: A retrospective review was conducted on 687 patients who received palliative chemotherapy for recurrent (n = 304) or primary metastatic (n = 383) gastric cancer. We compared the overall survival (OS) between CC and single-agent chemotherapy (SC) among these patients, while analyzing clinicopathological characteristics affecting outcome including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

Results: While 521 (75.4%) patients underwent CC, SC was more frequently performed in older age (>70) (57.6%) and ECOG performance status (PS) 2/3 (65.8%) patients (p = 0.0001, both). The median OS of patients who received CC was significantly longer than that of patients who received SC (11 vs. 8 months, p < 0.0005). Although patients with CC showed better OS in the majority of subgroups, no difference in OS between CC and SC was observed in patients with old age (p = 0.599), ECOG PS 2/3 (p = 0.821), signet ring cell histology (p = 0.40), palliative surgical resection (p = 0.407), and high PLR (p = 0.137), with a significant interaction between age and type of the regimen (CC vs. SC) (p = 0.011). Multivariable analysis revealed that palliative resection and ≥2nd line chemotherapy were independently associated with favorable OS (p < 0.0001, both); whereas ECOG PS 2/3 (p = 0.004), poorly differentiated and signet ring cell histology (p = 0.02, p = 0.0001), peritoneal metastasis (p = 0.045), high NLR (p = 0.001), and high PLR (p = 0.028) were independent prognostic factors of poor OS. In patients who underwent palliative resection before chemotherapy, there was a significant interaction between PLR and type of the regimen (p = 0.017), without significant difference in OS between CC and SC in patients with high PLR (p = 0.306).

Conclusions: Although CC is the standard of care in recurrent or metastatic gastric cancer, SC can be considered as a reasonable option in certain subgroups, such as elderly patients or those with high PLR after palliative resection.

Legal entity responsible for the study: Department of Hematology-Oncology, Ajou University School of Medicine.

Funding: Samsung Biopharmaceuticals Corporation.

Disclosure: All authors have declared no conflicts of interest.
Venous thromboembolism (VTE) is a common complication in patients with cancer. Gastric cancer (GC) has been associated with one of the highest risks of VTE. Risk factors for VTE in GC have mainly been investigated in Asian populations and/or in metastatised setting and include: gender, age, body mass index (BMI), stage, primary tumour localisation and chemotherapy, in particular cisplatin. Limited data is available on risk factors for VTE in resectable GC in Western patients. The aim of this study was to identify risk factors for VTE during preoperative chemotherapy in resectable GC patients. In addition, we addressed the question whether VTE was a risk factor for not proceeding to surgery.

Methods: Patients with resectable GC selected from the CRITICS trial (stages Ib-IVa; American Joint Cancer Committee, sixth edition; no distant metastasis) should previously be treated with 3 cycles of 3-weekly epirubicin, cisplatin/oxaliplatin and capecitabine (ECC or EOC). Inclusion criterion for this analysis was start of at least 1 chemotherapy cycle. VTE was defined as any thrombus in the venous system, excluding superficial and/or device related VTE. Risk factors of interest were fitted in a multivariable logistic regression model: age, gender, BMI, ECC/EOC and tumour localisation.

Results: A total of 781 patients were included in this analysis of whom 78 (10%) developed a VTE during the preoperative period. Results of the multivariable analysis are shown in the table. Seventy four patients with VTE proceeded to surgery (95%), compared to 666 patients (95%) without VTE (p = 0.99).

Conclusions: High BMI (≥ 30) was the only independent risk factor for developing VTE in resectable GC, preoperatively treated with ECC/EOC. Cisplatin was not identified as a significant risk factor for VTE in this cohort. A diagnosis of VTE did not influence the clinical decision to proceed to surgery.

Clinical trial identification: NCT00497186.

Legal entity responsible for the study: Netherlands Cancer Institute.

Funding: Dutch Cancer Society, Dutch Colorectal Cancer Group, and Hoffmann-La Roche.

Disclosure: All authors have declared no conflicts of interest.

Table: 691P Multivariable analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>No VTE (n = 703)</th>
<th>VTE (n = 78)</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>287</td>
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<td>28</td>
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<td>60-69</td>
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<td>70-80</td>
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<td>16</td>
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<td>≥80</td>
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<td>&lt;25</td>
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<td>25-30</td>
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<td>≥30</td>
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<td>Tumour localisation</td>
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<td>11</td>
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<tr>
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<tr>
<td>Proximal L</td>
<td>150</td>
<td>94</td>
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<td>6</td>
</tr>
<tr>
<td>Proximal M</td>
<td>121</td>
<td>90</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

* reference, BMI unknown (n = 1); OR= Odds; Ratio; CI= Confidence Interval

692P

The difference of risk factor for gastric cancer surgery between elderly and non-elderly patients

T. Masuda1, T. Ohshima1, K. Han1, Y. Shimoda1, M. Nakaazao1, S. Nagasawa1, Y. Kamazu1, T. Yamada1, Y. Rino1, M. Masuda1, T. Ogata1, T. Yoshikihaka1

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Background: The risk factor for gastric cancer surgery is expected to be characteristic feature of elderly in comparison to non-elderly due to decline in organ function and co-morbidities related to aging. However, the differences in the risk factors for gastric cancer surgery between elderly and non-elderly have not been evaluated. The aim of this study was to identify characteristics of risk factors of gastric cancer surgery for elderly.

Methods: This retrospective study examined 2500 patients who underwent gastrectomy with D1, D1+, D2, or D3 lymphadenectomy during 2000 to 2016 at Kanagawa Cancer Center hospital with curative intent. Patients were divided into two groups according to age, more than 75 years old (n = 406), E group; and less than 75 years old (n = 2094), Y group. Multivariate logistic regression analysis was performed to assess the independent contribution of variables to postoperative complication in each group.

Results: Mean age was 61.3 y.o. in Y group and 78.3 y.o. in E group. Charlson Index (0/1/2) was 152/557/14 in Y group, and 228/173/5 in E group (p < 0.001). ECOC-PIS was 0/1/23 was 191/187/21 in Y group, and 345/89/11 in E group (p < 0.001). Extent of the stomach resection (total/proximal/distal) was 76/37/129 in Y group, and 149/42/25 in E group. Stage (III/IIIIV) 1227/323/311 in Y group, 223/56/ 86/57 in E group. Postoperative complications were observed in 267 patients (13%) in Y group and 84 patients (21%) in E group. The most frequent complication was pancreatic fistula (n = 41), followed by anastomotic leakage (n = 36 in Y group, and pulmonary embolism (n = 20), followed by anastomotic leakage (n = 19) in E group. Multivariate analysis identified male sex (odds ratio: 1.87), and total gastrectomy (odds ratio: 1.58) as independent predictors of postoperative complications in Y group, and male sex (odds ratio: 3.01), stage IV (odds ratio: 2.54), and Charlson score > 1 (odds ratio: 1.76) in E group.

Conclusions: In elderly patients, co-morbidity more strongly affects postoperative complications compared with non-elderly patients. Co-morbidities especially in major organ function should be taken into consideration for future trials evaluating gastric cancer surgery for elderly patients.

Legal entity responsible for the study: Kanagawa Cancer Center.

Funding: Has not received any funding.

Disclosure: T. Hayashi: Personal fee, Lectual fee Chugai, Ono, MSD. T. Yoshikihaka: Personal fee, Lectual fee Taiho, Chugai, Yakult, Ono, MSD. All other authors have declared no conflicts of interest.

693P

Gastric cancer in young patients

M.M. Seker1, A. Bahceci, T. Kacan

Medical Oncology Department, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Background: The majority of gastric cancer-related studies include elderly patients. Studies have shown that gastric cancer carries more poor prognostic factors in younger patients.

Methods: In this study we retrospectively reviewed the results of gastric cancer patients under age 30 who had diagnosed and treated at our hospital. Statistical analysis of the study was done by the Kaplan-Meier test, Log Rank test and Cox regression analysis in the SPSS17 statistical program.

Results: 824 patients had diagnosed with gastric cancer at our clinic. Of these, 30 (3.6%) patients were under 30 years of age. 17 of them were women (56.6%) and 13 of them were men (43.4%). Of these, the results of 22 patients, 9 males and 13 females, whose data were available, had evaluated. At the time of diagnosis, 5 patients (23%) were stage 1, 2, 6 patients (27%) were stage 3, and 11 patients (50%) had metastatic disease. R0 resection was performed in 10 patients (90.9%) and R2 resection was performed in 1 patient (9.1%). Palliative surgery had performed in 4 (36.3%) of 11 metastatic patients. The tumor was grade 1 in 5.5% of patients, grade 2 in 16.6%, grade 3 in 77.8%. The tumor was diffuse type in 83.3% of patients and intestinal type in 16.6% of patients. The median follow-up was 11 months (2-101 months). Median progression free survival (PFS) was 3 months in metastatic patients, but median PFS was not achieved in non-metastatic patients. The 1 year PFS was 58% (p = 0.001) in non-metastatic patients (Figure 1A). Median overall survival (OS) was 6 months in metastatic patients, and median OS was not achieved in non-metastatic patients (p = 0.001). The estimated OS was 67 months in non-metastatic patients (Figure 1B). Turor grade, histopathological subtype, presence of lympohovascular and perinear invasion and chemotherapy regimens were not correlated with PFS and OS. There was no correlation between OS and serum CE, A, AFP, CA19-9 and CA125 levels at the time of diagnosis.

Conclusions: The ratio of gastric cancer under age 30 varies between 1-2% in the literature. In our study, the ratio of patients under 30 years old was 3.6%. Although young patients have more poor prognostic criteria such as diffuse type, proximal location, high grade, and lymphovascular invasion, the survival rates were similar to the elderly patients, according to the other studies in the literature.
694P Differences in presentation and outcomes among young and old patients with gastric cancer


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Introduction: Gastric cancer (GC) incidence is increasing in young patients (YP). During the last decades, there was a shift from surgical to non-surgical therapy. This has resulted in a better survival of YP, however, the clinical presentation and outcomes are less known.

Methods: We performed a retrospective analysis of patients with GC from all Dutch tertiary hospitals from 2008 to 2016. Patients were divided in YP (<65 years) or older patients (OP) and compared in terms of demographics, risk factors, clinical and histopathological characteristics, stage at diagnosis and survival. Multivariate analysis was performed to determine independent clinical and pathological factors associated with survival.

Results: A total of 167 YP and 455 OP were analyzed. YP were younger (mean age 43.2 vs 65.3 years, p<0.001). There were more males compared to 72.2% in OP, p<0.001. YP presented with symptoms earlier (50.6% vs 15.7% for OP, p<0.001). The overall survival was 78.5% for YP versus 63.5% for OP, p=0.0057.

Conclusions: Compared to their older counterparts, YP with GC tend to present with more epigastric pain and less likely to be smokers. Significant differences were found in demographics, risk factors, and outcomes between YP and OP. More research is needed to further understand the risk of GC among YP.

Legal entity responsible for the study: Ministry of Health of Kuwait.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

695P Prospective observational cohort study of oesophago gastric cancer patients (POCOP): A Dutch nationwide cohort


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Background: POCOP is a prospective observational study including oesophago gastric cancer patients, initiated by the Dutch Upper GI Cancer Group (DUCG) to stimulate multidisciplinary research. Within POCOP treatment and diagnostic strategies as well as prognostic and predictive factors for outcome can be evaluated on a population-based level. We present the design and current proceedings.

Methods: All patients with oesophago gastric cancer in the Netherlands are eligible. Patients need to provide consent for: 1) the reuse of clinical data collected by the Netherlands Cancer Registry (NCR), 2) longitudinal collection of patient reported outcomes (PROs), receiving future information on new interventional studies (including cohort multiple randomized controlled trials (cmRCTs)), and/or 3) linkage with Dutch databases e.g. the Dutch Upper GI Cancer Audit, the biobank of The Parelsnoer Institute and general practitioner databases. Funding: Dutch Cancer Society (UVA 2014-7009).

Results: Thus far, clinical data is being collected from almost all Dutch patients with oesophago gastric cancer diagnosed from 2015 onwards. Clinical data mainly consist of patient, tumour and multidisciplinary sequential treatment characteristics. The collection of longitudinal PROs started in 2016. Of all patients who gave consent (N = 1000), 92% also participated in the PRO-registry. PRO compliance was 87%, 67% and 46% (not accounted for death or drop-out) at diagnosis, 3 and 6 months follow up, respectively. 81% of patients consented to receive future information on new interventional studies, including cmRCTs. Collaborations with phase II/III trials and other cohort studies were established to reduce patient burden regarding completion of PROs and trial registration burden. Obtained data is being governed by the DUCG scientific committee which includes members of participating hospitals, the study team and the NCR.

Conclusions: POCOP provides real world population-based data to stimulate (international) multidisciplinary research and provides the opportunity to perform novel tri- als within the established infrastructure. Researchers can acquire data by submitting a research proposal to the scientific committee of the DUCG (www.ducg.nl).

Legal entity responsible for the study: Dutch Upper GI Cancer Group.

Funding: Dutch Cancer Society.

Disclosure: J.W.B. de Groot: Advisory role: BMS and MSD. T. van Voorthuizen: Travel, accommodations, expenses: Ipsen, Astellas M. van Berge Henegouwen: Consulting/advisory: Olympus, Covidien; Research funding: Olympus; Travel, accommodations, expenses: Johnson&Johnson M.G.H. van Oijen: Research funding: BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Roche. H.W.M. van Laarhoven: Consultancy: Celgene, Lilly, Nordic. Research funding: Bayer, Lilly, Merck Serono, Roche. All other authors have declared no conflicts of interest.

696P A phase I, open-label, multi-center, dose-escalation study of codiruzumab, an anti-glypican-3 monoclonal antibody, in combination with atezolizumab in patients with locally advanced or metastatic hepatocellular carcinomas


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Background: Codiruzumab (Cod) is a recombinant humanized monoclonal antibody against Glypican-3 (GPC3). GPC3 is over-expressed in hepatocellular carcinoma (HCC). Cod elicits antibody-dependent cellular cytotoxicity against human HCC cell lines and shows more potent anti-tumor activity when combined with anti-PD-L1 antibody in syngeneic mouse model. This is a phase I dose-escalation study to evaluate safety/tolerability and pharmacokinetics in combination with the anti-PD-L1 antibody, atezolizumab (Atezo) in advanced HCC patients.

Methods: This study is composed of a 3 + 3 dose-escalation part and an expansion part. Patients with advanced or metastatic HCC who had failed prior systemic therapy, GPC3 high expression, ECOG PS 0-1, Child-Pugh A-B7 were eligible. Cod given intravenously 800 to 1600 mg on Day 1, 4, then weekly from Day 8 compared with 1200 mg every 3 weeks dosing of Atezo until disease progression/toxicity. The objectives were to determine MTD of Cod and Atezo combination primarily, to assess safety, antitumor effect (RECIEST 1.1) and pharmacokinetics secondarily, and to assess biomarkers exploratory.

Results: Ten patients each were enrolled in dose-escalation and expansion parts, respectively. There were 16 men/4 women, median age 58, all Asian, HBV/HCV/negative 11/45, ECOG 0/1 5/5. No dose limiting toxicities were observed in dose-escalation part. The most frequently observed adverse event (AEs) was pyrexia (80%), fatigue (50%), decreased appetite (30%), the mean atorvastatin was increased, lymphocyte count decreased (25%), constipation, cough, nausea/pharyngitis (20%). Grade 3 or higher AEs (>2 patients) were aspartate aminotransferase increased, lymphocyte count decreased (20%), anemia (15%), and ascites (10%). There was confirmed PR, 1 SD (including 1 unconfirmed PR) among 18 evaluable patients and 6 of them had SD for more than 6 months before progression.

Conclusions: Cod + Atezo combination was well-tolerated and showed antitumor activity in this advanced, previously treated and GPC3 highly expressed HCC patients.

Clinical trial identification: JapicCTI-163325 Registered date: 22/07/2016.

Legal entity responsible for the study: Chugai Pharmaceutical Co., Ltd.

Funding: Chugai Pharmaceutical Co., Ltd.
**Annals of Oncology**

**698P** Phase II efficacy and safety data for the MET inhibitor tepotinib in patients (pts) with sorafenib-treated advanced hepatocellular carcinoma (HCC)


**Background:** MET is a potential therapeutic target in advanced HCC, tepotinib is a highly selective MET inhibitor. Here we report final analysis results from a single-arm multicenter phase 2 study investigating the efficacy and safety of tepotinib in pts with sorafenib-treated advanced HCC (NCT02113573).

**Methods:** Adults with advanced HCC > Child-Pugh Class A, Eastern Cooperative Oncology Group performance status 0–1, and > 24 weeks of prior sorafenib therapy were eligible for treatment. MET status was assessed by immunohistochemistry (IHC) (≥ 3+ or ≥ 3+ and mts in hybridization. Pts received tepotinib at the recommended phase 2 dose (RP2D) of 500 mg once-daily. The primary endpoint was progression-free survival (PFS) at 12 weeks; secondary endpoints included safety and other efficacy parameters.

**Results:** 49 pts had received treatment; median (range) duration of therapy was 3.02 (0.03–16.49) months. Median (range) age was 66 (19–82) years and most patients were male (83.7%). The null hypothesis that the rate of progression-free subjects at 12 weeks was not significantly different from its null hypothesis was rejected (p = 0.018). One pt (2%) died from treatment-related adverse events (AEs): anorexia (15.6%) and pruritus (15.8%), nausea (13.1%), liver dysfunction (13.1%), grade 3 diabetes. There was no HBV reactivation (0.0%). Partial response was observed in 6 patients (ORR 7.9%) and they all are on nivolumab therapy for ≥ 4.1 months. Disease control rate was 99.5%. The most common adverse events (AEs) were anorexia (13.1%) and fatigue (13.1%). Liver dysfunction (21.4%) and fatigue (7.9%). However, these were almost grade 1 or 2 except for two cases of grade 3 liver dysfunction and grade 3 diabetes. There was no HBV reactivation observed.

**Conclusions:** Compared to phase III study of nivolumab (CheckMate 040), our real-world data showed lesser ORR and DCR. Move advanced disease status, liver dysfunction and short follow-up duration might explain it. However, nivolumab showed a manageable safety profile even in transplanted patients.

**Legal entity responsible for the study:** Samsung Medical Center.

**Disclosure:** All authors have declared no conflicts of interest.

**Funding:** Has not received any funding.

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**700P** Stemness in hepatocellular carcinoma reduced by inhibition of WEE1 expression

K.U. Park 1, M.J. Ko 2, H.M. Ryu 2, Y.H. Lee 2

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**Background:** Chemotherapy targets proliferating cells, not cancer stem cells (CSCs). Targeting agents, e.g. sorafenib for hepatocellular carcinoma (HCC), do not seem to target CSCs as evidenced by frequent tumor relapse and resistance after therapy. Identification and characterization of signaling pathways and biomarkers associated with CSC biology are priorities for developing new paradigms of molecular cancer therapeutics. Increase of WEE1 kinase activity through an epigenetic regulation plays an important role in the development of HCC. However, the functional role of WEE1 in HCC progression remains to be clarified.

**Methods:** HCC cell lines were transfected with WEE1 siRNA and tested for growth inhibition, apoptotic induction, molecular changes in both RNA and protein levels, and changes in CSC phenotype using various methods such as MTS, FACS, microscopic analysis, Real-time PCR, Western blotting, sphere forming assay. To find the molecular changes in response to WEE1 knockdown, global changes in gene expression were examined using RNA sequencing.

**Results:** We demonstrated that WEE1 siRNA silencing caused inhibition of HCC cell growth through blockade of cell cycle progression and induction of apoptosis. The anti-proliferative effects were driven by a subset of molecular alterations including the upregulation of alk inhibitor p21 and the downregulation of AKT, CDK2, cyclin B1, PARP1 and GIPAM which are functionally involved in control of cell cycle, apoptosis and lipid metabolism. WEE1 silencing resulted in a strong inhibition of lipidogenesis and caused a marked decrease in fat accumulation. Knockdown of WEE1 dramatically reduced the portion of liver CSC population through co-downregulation of cancer stemness genes, weakened the capacity of sphere formation and cancer cell migration. The systemic delivery of a modified WEE1 siRNA encapsulated in lipid nanoparticles inhibited human HCC growth in murine xenograft models, and increased survival.

**Conclusions:** Our findings suggest that the epigenetic modifier WEE1 functionally involves to HCC lipid metabolism and CSC-like phenotype maintenance and that molecular targeting of WEE1 may be an effective systemic therapy for prevention of tumor recurrence via elimination of CSCs in liver tumor microenvironment.

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**Disclosure:** All authors have declared no conflicts of interest.

**Funding:** Has not received any funding.

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**References:**

1. KU. Park, M.J. Ko, H.M. Ryu, Y.H. Lee. 2Oncology, Dongtan Medical Center Kemyung University Hospital, Daegu, Republic of Korea. 3Department of Hematology/Oncology, Kemyung University School of Medicine, Daegu, Republic of Korea, 4Hematology/Oncology, Daegu Catholic University, Daegu, Republic of Korea. 5Department of Molecular Biology, Kemyung University School of Medicine, Daegu, Republic of Korea.

**Background:** Chemotherapy targets proliferating cells, not cancer stem cells (CSCs). Targeting agents, e.g. sorafenib for hepatocellular carcinoma (HCC), do not seem to target CSCs as evidenced by frequent tumor relapse and resistance after therapy. Identification and characterization of signaling pathways and biomarkers associated with CSC biology are priorities for developing new paradigms of molecular cancer therapeutics. Increase of WEE1 kinase activity through an epigenetic regulation plays an important role in the development of HCC. However, the functional role of WEE1 in HCC progression remains to be clarified.

**Methods:** HCC cell lines were transfected with WEE1 siRNA and tested for growth inhibition, apoptotic induction, molecular changes in both RNA and protein levels, and changes in CSC phenotype using various methods such as MTS, FACS, microscopic analysis, Real-time PCR, Western blotting, sphere forming assay. To find the molecular changes in response to WEE1 knockdown, global changes in gene expression were examined using RNA sequencing.

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**Conclusions:** Our findings suggest that the epigenetic modifier WEE1 functionally involves to HCC lipid metabolism and CSC-like phenotype maintenance and that molecular targeting of WEE1 may be an effective systemic therapy for prevention of tumor recurrence via elimination of CSCs in liver tumor microenvironment.
Background: Regorafenib is a multikinase inhibitor that improved overall survival (OS) and time to progression (TTP) in patients with HCC who progressed during sorafenib treatment in the phase 3 RESORCE trial. This exploratory analysis evaluated the impact of SNPs on regorafenib treatment benefit (OS and TTP) and the occurrence of hand–foot skin reaction (HFSR) in the RESORCE trial.

Methods: Genotyping of 187 SNPs was performed on whole blood DNA from 330/573 (58%) patients from RESORCE using a custom NimbleGen™ kit and sequencing libraries that were made using NimbleGen™ KAPA HYPER-construction kits. The prognostic and predictive effects of the SNPs, as well as the impact on the occurrence of grade ≥1 HFSR, were assessed using Cox proportional hazards regression with Breslow tie handling or logistic regression, respectively. Models were adjusted for clinical covariates as determined by Akaike information criterion (AIC)-based selection and adjusted for population stratification. P values were corrected for multiple testing using Bonferroni correction and deemed significant at an adjusted p < 0.05.

Results: The overall RESORCE and biomarker cohorts were generally similar for demographic variables (except the latter had a smaller proportion of C vs P patients) and outcomes. None of the assessed SNPs were prognostic or predictive of OS. In contrast, 6 SNPs (positioned in the UGT1A1, VEGFC, and TIE2 genes) were prognostic for TTP; SNP rs1547651 in the VEGFA gene showed a significant prognostic effect on the occurrence of grade ≥1 HFSR (odds ratio (OR) 0.04, 95% CI 0.01–0.19; adjusted p = 0.037), while the rs11601547 SNP, also in the VEGFA gene, showed a predictive effect (OR 26.23, 95% CI 3.9–197.96; adjusted p = 0.038).

Conclusions: These exploratory results suggest that the detected SNP biomarkers may be candidates for future research to gain deeper understanding of the biological mechanisms determining clinical benefit of regorafenib treatment in HCC.

Clinical trial identification: NCT01774544.

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Legal entity responsible for the study: Bayer.

Funding: Bayer.


Unselected abstracts: Gastrointestinal tumours, non-colorectal | Volume 29 | Supplement 8 | October 2018

Table: 702P

<table>
<thead>
<tr>
<th>Baseline AFP, ng/mL</th>
<th>Patients, N</th>
<th>HR C vs P (95% CI)</th>
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<tr>
<td>&lt;20</td>
<td>139</td>
<td>0.97 (0.67–1.40)</td>
</tr>
<tr>
<td>≥20</td>
<td>331</td>
<td>0.67 (0.54–0.84)</td>
</tr>
<tr>
<td>&lt;200</td>
<td>242</td>
<td>0.83 (0.63–1.10)</td>
</tr>
<tr>
<td>≥200</td>
<td>228</td>
<td>0.70 (0.54–0.91)</td>
</tr>
<tr>
<td>&lt;400</td>
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<td>0.81 (0.62–1.04)</td>
</tr>
<tr>
<td>≥400</td>
<td>192</td>
<td>0.71 (0.54–0.94)</td>
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</tbody>
</table>

Conclusions: C improved OS and DFS vs P in patients with previously treated advanced HCC across a range of baseline AFP levels. High AFP levels were associated with a larger treatment benefit with C vs both OS and DFS.

Clinical trial identification: NCT01774544

Legal entity responsible for the study: Exelixis, Inc.

Funding: Exelixis, Inc.

Disclosure: R. K. Kelley: Consulting or advisory role: Genentech for IDMC (self), Bayer, BMS, AstraZeneca, DobiPharm, Agios (institution); Research funding: Adaptimmune, Agios, Astra Zeneca, Bayer, Bristol Myers Squibb, Celgene, Exelixis, Eli Lilly, Merck, Novartis, Regeneron, Sanofi, Taiho, Target Pharma Solutions, Tekmira. A. R. El-Khoueiry: Honorary: BMS, Bayer, Exelixis, EMD Serono, Eisai, Roche, Cytoxim, Merck; Consulting or advisory role: BMS, Bayer, Research funding: AstraZeneca, Ascent; T. Meyer: Consulting or advisory role: Bayer, Eisai, BMS, BFC, Ipsen; Research funding: Bayer, L. Rimassa: Consulting or advisory role: Lilly, Bayer, Sirtex Medical, Italmarmaco, Sanofi, Arquile, Baxter, Ipsi, Exelixis, Amgen, Travel accommodations expenses: Amgen, Ipsi, S. L. Chan; Consulting or advisory role: AstraZeneca, MSD; Research funding: MSD, Pfizer, Sirtex, A. Tran; Consulting or advising role: Gilead, Abbvie, MSD; Speakers’ bureau: Gilead, Abbvie, MSD; Travel accommodations: expenses: Gilead, Abbvie, MSD, V. C. Tam: Honorary: Celgene, Apolligene, Travel accommodations expenses: Amgen. D. W. Markby, D. O. Clary: Employee, Stock ownership: Exelixis, A. L. Cheng: Consulting or advisory role: Bayer, Schering Pharma, Bristol-Myers Squibb, Eisai, Merck Serono, Novartis, Ono Pharmaceutical, ONXEO; Speakers’ bureau: Novartis; Research funding: Sanofi. G. K. Abou-Alfa: Self consulting: Agios, Amgen, Antengene, Aptus, Astalan, Astrella, Astra Zeneca, Bayer, BMS, Boston Scientific, Caragam, Celgene, Casa, Daiichi, Dcho, Delcat, Eisai, Exelixis, Halozyme, Inovio, Ipsen, Merck, OncoRx, PCL Biotech, Roche, Sanofi, Servier, Sillaie, Sirtex, Yakult Immediate; Family member consulting: Celgene, Cytoxim, Gilead, Halozyme, Sanofi, Silenseed; Institutional research: Agios, Array, Astra Zeneca, Bayer, BMS, Casi, Celgene, Exelixis, Genentech, Jnccyte, Lilly, Malvax, Medimmune, Momenta, Novartis, OncoMed Pharmaceuticals, Roche. All other authors have declared no conflicts of interest.

Exelixis, San Francisco, CA, USA; Medical Oncology, USC/Norris Comprehensive Cancer Center, Los Angeles, CA, USA; Medical Oncology, Royal Free Hospital, London, UK; Oncology, Humanitas Cancer Center, Milan, Italy; Hepatology, Groupement Hospitalier Lyon Nord, Lyon, France; Clinical Oncology, The Chinese University of Hong Kong, Shatin, Hong Kong, China; Hepatology, Groupe Hospitalier L’Archet, Nice, France; Oncology, Adelaide Cancer Centre, Adelaide, Australia; Medical Oncology, University of Calgary, Calgary, AB, Canada; Diseases of the Digestive System - Hepatology, CHRU Lille, Lille, France; 1Medical Affairs, Exelixis Inc., San Francisco, CA, USA; 2National Taiwan University Hospital, Taipei, Taiwan; 3Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Background: Extrahepatic spread (EHS) and macrovascular invasion (MVI) are poor prognostic factors in HCC. In the phase III CELESTIAL trial (NCT01908426), C, improved over all survival (OS) and progression-free survival (PFS) vs P in patients with previously treated advanced HCC. Median OS was 10.2 mo with C vs 8.0 mo with P (HR, 0.76; 95% CI, 0.63–0.92; P = 0.0049). Median PFS was 5.2 mo with C versus 1.9 mo with P (HR, 0.44; 95% CI, 0.36–0.52; P < 0.001). Here, we analyze OS and PFS based on (i) EHS, (ii) MVI, and (iii) the sum of target lesion diameters (SOD) at baseline.

Methods: A total of 707 pts, stratified by disease etiology, geographic region, and the presence of EHS and/or MVI, were randomized 2:1 to receive C, 60 mg once daily (C) or placebo (P) irrespective of the extent of the disease. Eligible pts had a pathologic diagnosis of HCC, Child-Pugh score A, and ECOG performance status ≤2. Pts received prior sorafenib and ≤2 lines of prior systemic therapy. Tumors were assessed every 8 weeks by investigator.

Results: In the overall population, 78% pts had MVI and 85% had EHS and/or MVI. Among pts with EHS, 50% had metastasis to the lung, 40% to lymph nodes and 17% to bones. C improved OS (HR = 0.75; 95% CI 0.54–1.03) vs P in pts with or without MVI (Table). C also improved OS over P in pts with EHS or high SOD. PFS was improved with C irrespective of the extent of the disease.

Conclusions: C generally improved OS in pt subgroups defined by extent of disease burden. The presence of MVI, EHS, or high SOD at baseline was associated with shorter OS in both treatment groups.

Clinical trial identification: NCT01908426.

Legal entity responsible for the study: Exelixis.

Funding: Exelixis, Inc.

Disclosures: J.F. Blanc: Consulting or advisory role: Bayer, SP; BMS, Ipsen, T. Meyer: Consulting or advisory role: Bayer, BTG, Ipsen; Research funding: Bayer, BTG, A-L. Cheng: Consulting or advisory role: Bayer Schering Pharma, Bristol-Myers Squibb, Eisai, Merck; Novartis, Otsu Pharmaceutical, Ono; Speakers’ bureau: Bayer, Elixirix, MSD Sanoﬁ, Eisai, Roche, CytomX, Merck; Consulting or advisory role: AstraZeneca, Astex.

Table: 703P

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<th>Median PFS, mo</th>
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Table: 704P

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Clinical trial identification: NCT01908426

Legal entity responsible for the study: The authors.

Funding: Exelixis, Inc.

Disclosure: A-L. Cheng: Honoraria; Consulting, Advisory role; Speakers’ bureau: Bayer, Eisai, Ono, Genentech, Novartis, BMS, Merck. M.S.I. T. Meyer: Consulting, Advisory role; Bayer, BMS, Merck. T. Hoang: Honoraria; Consulting, Advisory role; BMS, Ono, Genentech, Advisory role: BMS, Ono, Bayer, Eisai, Midatech, Roche. H.-J. Klumper: Travel, accommodations and expenses to the ENETS knowledge network, sponsored by Ipsen. J. Knox: Honoraria; Novartis; Consulting or advisory role: Lilly, Merck; Research funding, AstraZeneca. M. Patel: Employee, Stock ownership: Exelixis, Genentech/Roche. A.B. El-Khoueity: Honoraria: BMS, Bayer, Exelixis, EMD Serono, Eisai, Roche, Cytxom, Merck; Consulting or advisory role: BMS, Bayer, Research funding: AstraZeneca, Asten. R.K. Kelley: Consulting or advisory role: Genentech for IMC; (eold), Boeing, BMS, AstraZeneca, Debiopharm, Agios; Research funding: Adaptimmune, Agios, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Exelixis, Eli Lilly, Medimmune, Merck, Novartis, Regeneron, Sanofi, Taiho, Target Pharma Solutions, Tekniria. G.K. Abou-Alfa: Self Consulting: Agios, Amgen, Antengene, Aptus, Astellas, AstraZeneca, Bayer, BMS, Boston Scientific, Caragen, Celgene, Casi, Daichi, Debeo, Delarch, Eisai, Exelixis, Halosyne, Inovio, Ipsen, Merck, Onexio, PCl Biotech, Roche, Sanofi, Servier, Silajum, Sirius, Yakuhi Immediate; Family member consulting: Celgene, Cytxom, Gilead, Halosyne, Sanofi, Sileesed Institutional Research Agios, Array, AstraZeneca, Bayer, BMS, Cass, Celgene, Exelixis, Genentech, Incyte, Lilly, Malus, Medimmune, Momenta, Novartis, OncodMed Pharmaceuticals, Roche. All other authors have declared no conflicts of interest.

### 705P Clinico-pathological evaluation of skin lesions (SL) in patients with hepatocellular carcinoma (HCC) treated with sorafenib

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**Background:** Dermatologic adverse events (DAE) are frequently experienced in patients under sorafenib. Although the majority appear as rash or hand-foot reaction, some patients may present SL requiring biopsy or local procedures that may impact in the treatment. While there are series of patients with melanoma and BRAF inhibitors presenting SL, there is no information on HCC patients with sorafenib.

**Methods:** We analyzed a prospective database of patients with HCC treated with sorafenib. Patients who developed biopsed SL were included and the pathology samples were reviewed.

**Results:** Between oct-2007 and jan-2018, 313 patients were treated with sorafenib (54.6% BCLC-C, 48.7% ECOG-PS0 and 83.6% CPA), 88 (28.1%) presented DAE in the first 60 days (eDAE) and 24 (7.7%) developed SL submitted to excisional biopsy. From the 24 patients, 33 SL were biopsied and 5 patients presented more than 1 SL. Most of the patients with SL were male (79.2%), CPA (87.5%), HCV infection (87.5%) and 2 had liver transplantation. The median time from sorafenib initiation until SL biopsy was 8.5 months (IQR 4.1 to 18.1). SL are described in the table. Lymphocyte proliferation at the interface between the SL and dermis was noted in 61.1%. The median treatment duration (MTD) and OS in the whole cohort were 6.5 months (IQR 3.3-13.9) and 13.6 months (IQR 9.2-22.0) for the subgroup with SL, the MTD and OS was 12.5 (IQR 9.3 - 22.0) and 26.5 months (IQR 17.0 - 43.9), respectively. For those with both eDAE and SL, the MTD and OS was 17.9 months ([7.7-28.9] and 26.5 [22.0-51.6] respectively. There was no permanent discontinuation related to the SL.

**Table: 705P SL subtypes**

<table>
<thead>
<tr>
<th>SL Type</th>
<th>Patients (n)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor SL</td>
<td>22</td>
<td>66.7%</td>
</tr>
<tr>
<td>Keratoacanthomas</td>
<td>7</td>
<td>21.2%</td>
</tr>
<tr>
<td>Squamous cell carcinomas</td>
<td>5</td>
<td>15.2%</td>
</tr>
<tr>
<td>Basal cell carcinomas</td>
<td>3</td>
<td>9.1%</td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
<td>3</td>
<td>9.1%</td>
</tr>
<tr>
<td>Hypertrophic keratoma</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Sebaceous hyperplasia</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Pilomatrixoma</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Trichilemmal cyst</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Non-Tumor SL</td>
<td>7</td>
<td>21.2%</td>
</tr>
<tr>
<td>Suppurative folliculitis</td>
<td>2</td>
<td>6.1%</td>
</tr>
<tr>
<td>Interphase dermatitis</td>
<td>2</td>
<td>6.1%</td>
</tr>
<tr>
<td>Subacute spongiform dermatitis</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Septal panniculitis / Erythema nodosum</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Conclusions:** This is the largest series on patients with HCC and sorafenib that presented biopsed SL similar to other tumors treated with BRAF inhibitors, patients with HCC and sorafenib are in risk of developing SL. Interestingly, the majority presented lymphocyte proliferation. This reinforces the need to understand the immune modula
tion by sorafenib.

Legal entity responsible for the study: BCLC group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

### 706P Relationship between ethnicity and overall survival (OS) in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib (S): Results from a Canadian multi-centre HCC database

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**Background:** The SHARP and Asia-Pacific (AP) trials showed that S improves OS compared to placebo in advanced HCC. However, OS was worse in the AP trial, which included predominantly East Asian (EA) patients. The purpose of this study was to determine whether ethnicity affects OS in patients with advanced HCC, being treated with S.

**Methods:** Patients who received S for the treatment of HCC between 01/01/08 and 30/06/16 in the provinces of British Columbia and Alberta, as well as Princess Margaret Cancer Centre and Sunnybrook Odette Cancer Centre in Toronto, Ontario were included. Patient demographics and clinical variables were retrospectively collected. Patients were dichotomized by ethnicity as either EA or not according to a validated list of surnames. Survival outcomes were assessed with Kaplan-Meier curves and compared with the log-rank test. A Cox-proportional hazard model was constructed with ethnicity and relevant clinical characteristics to assess their impact on survival.

**Results:** A total of 757 patients were included. Mean age was 64 years. 81 men, 36 East Asian, and 86% Child-Pugh (CP) A at initiation of S. Underlying cause of liver disease was 31% hepatitis B Virus (HBV) and 30% hepatitis C Virus (HCV). Majority of patients had a performance status of 0 (30%) or 1 (36%). EA compared to non-EA were more likely to have HBV (68 vs 11%) and less likely to have HCV (13 vs 39%), p < 0.01. Median OS was 8.6 months for EAs and 9.6 months in non-EAs (p = 0.89). On multivariate analysis, ethnicity (HR 1.01, 95% CI 0.82 - 1.27, p = 0.89) was not a significant prognostic factor for OS. However, no previous localized treatment (HR 1.66 95% CI 1.39 - 1.99, p < 0.01), higher ECOG (HR 1.63 95% CI 1.34-1.97, p < 0.01), CP B at initiation of S (HR 1.72 95% CI 1.54 - 2.03, p < 0.01) and HBV compared to HCV (HR 1.39 95% CI 1.08-1.80, p = 0.01) were associated with worse survival.

**Conclusions:** Ethnicity does not affect OS in HCC patients treated with S. However, patients treated with S who have a history of HCV appear to have a better OS than those with HBV. Higher baseline ECOG, no previous localized treatments and CP B liver function appear to negatively affect OS.

Legal entity responsible for the study: CHORD consortium.

Funding: Department of Oncology, University of Calgary.

Disclosure: J.M. Davies: Advisory capacity: Bayer. All other authors have declared no conflicts of interest.

### 707P Efficacy and safety of sorafenib (SFN) in elderly patients with hepatocellular carcinoma (HCC)

L. Gomes Da Fonseca1, J. Guedes Matos1, M.I. Baghiroli1, P. M. Hoff1, J. Sabbaga2

**Background:** The second leading cause of cancer-related deaths worldwide. Sorafenib (SFN) has been the backbone of advanced HCC treatment over the past decade. Since the mean age of HCC presentation is between 50 and 60 years, data on SFN use in the elderly patients (pts) remain scarce due to underrepresentation of this population in pivotal clinical trials. Thus, the treatment of elderly HCC pts represents a
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clinical challenge given the concomitance of advanced age with chronic hepatopathy, raising concerns about clinical benefit and increased toxicity in this subgroup. We analyzed a cohort of HCC pts with advanced HCC treated with SFN was retrospectively evaluated. Pts were divided into 2 groups: (A) those younger than 70 years-old (y-o) and (B) those who were 70 y-o or older at the time of SFN initiation. Survival (OS) was calculated from the first day of SFN to death or last data record. Time to treatment failure (TTF) due to disease progression or toxicity was calculated from the first to the last day on SFN. TTF and OS were estimated using Kaplan-Meier and curves were compared by log-rank test.

Results: We analyzed 226 HCC pts treated with SFN from Oct 2007 to Jan 2017. Group B was comprised of 37 (16.4%) pts, median age 73.5 years (70-85), 75.7% male, 29.7% had HCV, 86.3% Child-Pugh A, 37.8% had extrapathic spread. Reduced starting dose SFN (< 800 mg/d) was more common in Group B than in Group A (27% vs 11.8%, p = 0.026). No statistically significant differences in OS (7.9 vs 9.8 months, p = 0.534) or TTF (3.5 vs 4.3 months, p = 0.962) were detected between Groups A and B. The incidence of dermatologic adverse events (36.6% vs 34.1%, p = 0.596) and hypertension (7% vs 9%, p = 0.641) did not differ significantly between Groups A and B, respectively. Intolerance leading to SFN discontinuation occurred in 11% and 9.3% of pts in Groups A and B, respectively (p = 0.780).

Conclusions: Our findings suggest that the efficacy and the incidence of adverse events were similar in elderly HCC pts treated with SFN when compared to younger pts. Thus, age alone should not be used to determine the therapy of pts with advanced HCC being considered for SFN.

Legal entity responsible for the study: Instituto do Câncer do Estado de São Paulo.

Funding: Has not received any funding.


Funding: Speaker’s bureau: Roche, Bayer, MSD; Travel expenses: Bayer. All other authors have declared no conflicts of interest.

Table: 708P

<table>
<thead>
<tr>
<th>Observed AFP change during 1L</th>
<th>N</th>
<th>Median OS (95% CI), months</th>
<th>Cross ratio</th>
<th>Kendall’s Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease (↓) to &lt; 400 ng/mL from &gt; 400 ng/mL</td>
<td>20</td>
<td>14.3 (4.8-30.9)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 20 ng/mL</td>
<td>85</td>
<td>7.4 (5.7-11.9)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 7 ng/mL/month</td>
<td>68</td>
<td>6.8 (5.0-12.7)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 20%</td>
<td>98</td>
<td>11.1 (7.3-13.2)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>51</td>
<td>12.2 (7.3-18.2)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increase (↑) to ≥ 400 ng/mL from &lt; 400 ng/mL</td>
<td>18</td>
<td>5.9 (3.6-7.4)</td>
<td>1.506</td>
<td>0.202</td>
</tr>
<tr>
<td>≥ 20 ng/mL</td>
<td>140</td>
<td>4.8 (3.7-5.5)</td>
<td>1.902</td>
<td>0.311</td>
</tr>
<tr>
<td>≥ 7 ng/mL/month</td>
<td>124</td>
<td>4.5 (3.1-5.2)</td>
<td>2.006</td>
<td>0.335</td>
</tr>
<tr>
<td>≥ 20%</td>
<td>141</td>
<td>5.2 (4.1-6.5)</td>
<td>1.841</td>
<td>0.296</td>
</tr>
<tr>
<td>≥ 50%</td>
<td>109</td>
<td>5.4 (4.5-6.9)</td>
<td>1.755</td>
<td>0.274</td>
</tr>
</tbody>
</table>

Conclusions: Increases and decreases in AFP during 1L, regardless of AFP change definition, were generally associated with shorter and longer OS, respectively. Conclusions are limited by the risk of immortal time and selection bias, as not all patients had multiple AFP measures recorded.

Legal entity responsible for the study: Eli Lilly and Company.

Funding: Has not received any funding.

Disclosure: L.M. Hess, Z.L. Cui, A. Girvan, P.B. Abada: Employee: Eli Lilly and Company. All other authors have declared no conflicts of interest.

Table: 709P

Antiviral therapy improves outcomes after radiofrequency ablation for HBV-related hepatocellular carcinoma: A propensity score matching analysis


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Background: We intended to explore hepatitis B virus (HBV) reactivation after percutaneous radiofrequency ablation (PRA) for HBV-related hepatocellular carcinoma (HCC) and the impact of antiviral therapy (AVT) on post-PRA outcomes.

Methods: Data on 538 consecutive patients who underwent PRA for HBV-related early HCC at the Eastern Hepatobiliary Surgery Hospital between 2007 and 2011 were studied. Propensity score matching (PSM) analysis was used to compare the outcomes between the study groups. Recurrence free survival (RFS) and tumor recurrence were endpoints. Post-PRA viral reactivation, hepatitis, and patterns of tumor recurrence were also observed. Logistic regression, Kaplan-Meier method and Cox proportional regression were used during the analysis.

Results: Viral reactivation developed in 10.8% of patients who underwent PRA. Patients with HBV reactivation had higher 1-, 3-, and 5-year tumor recurrence rates than patients without viral reactivation after PRA (46.9%, 81.6% and 81.6% vs 36.0%, 63.5% and 65.4, P = 0.004). AVT reduced viral reactivation rate (P < 0.001) and decreased 1-, 3-, and 5-year tumor recurrence rate when compared with the no-AVT (30.2%, 58.6% and 61.4% vs 44.1%, 72.6% and 73.0%, P < 0.001). The local recurrence of tumor after PRA was only associated with tumor diameter (P = 0.010), however, viral reactivation (P = 0.015) and AVT (P < 0.001) were independent risk factors of intrahepatic distant recurrence.

Conclusions: HBV could be reactivated after PRA. Viral reactivation and AVT had opposite impact on intrahepatic distant recurrence but not local tumor progression of HCC patients after PRA.

Legal entity responsible for the study: Fen Shen MD.

Funding: State Key Project on Infectious Diseases of China (2012ZX10002-011,016 to FS).

Disclosure: All authors have declared no conflicts of interest.

708P

Relationship between change in α fetoprotein (AFP) and patient (pt) survival in hepatocellular carcinoma (HCC): A real-world electronic medical records (EMR) database study

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Background: Serum AFP levels are used as a diagnostic and prognostic marker for pts with HCC. Assessment of the clinical relevance of changes in AFP over time outside of clinical trials is lacking. This study was designed to explore the relationship between changes in AFP levels and overall survival (OS) in a real-world setting.

Methods: This retrospective analysis used the IMS Oncology EMR database (US patients, 12/01/2007-12/31/2014). Eligible pts were diagnosed with HCC, 18+ years old, had ≥ 1 AFP test recorded 60 days prior to 180 days after diagnosis, and received anticaner therapy ≤ 180 days after diagnosis. Survival analyses were by Kaplan-Meier method. The gamma-frailty model was used to correlate AFP change utilizing previously-reported definitions of AFP change (above/below 400 ng/mL, ≥ 20 ng/mL/month, ≥ 7 ng/mL/month, ≥ 20% increase, ≥ 50% decrease) and OS.

Results: A total of 907 pts met eligibility criteria (77.3% male, median 65 years of age). Of 687 pts with AFP prior to start of first-line therapy, the 453 (65%) with a baseline AFP < 400 ng/mL had an OS of 4.2 months and the 244 (35%) with ≥ 400 ng/mL had an OS of 2.9 months. An increase in AFP was associated with a decrease in OS in the 278 pts with AFP measures recorded.

Conclusions: Of 697 pts with AFP prior to start of first-line therapy, the 453 (65%) with a baseline increase in AFP levels had a shorter OS than the 244 (35%) with a baseline decrease in AFP levels.
TACE is commonly used in patients (pts) with unresectable HCC (uHCC).

Methods: OPTIMIS is an international, prospective, non-interventional study of
uHCC pts for whom the decision to treat with TACE was made prior to enrollment. Here we report practice patterns, subsequent treatments, and liver deterioration data from Europe and Canada (Eur/Can) and the global population. TACE eligibility was defined using international and regional guidelines.

Results: Overall, 1650 enrolled pts received TACE including 497 from Eur/Can (n = 447 Eur, n = 50 Can). Of those, 40% of pts in Eur/Can and 39% globally were TACE ineligible according to guidelines (Table). After exclusion of pts with prior sorafenib use, 35% of pts in Eur/Can and 31% globally became TACE ineligible during the study (to be assessed for primary endpoint). Of those, 8% in Eur/Can and 9% globally received sorafenib immediately after TACE eligibility. At inclusion, most pts were BCLC stage B, and the presence of extrahepatic spread and portal vein thrombosis was lower in Eur/Can vs globally (Table). In pts with available laboratory values, chronic liver function deterioration (worsening in CTCAE grade 30–90 days post TACE) after first TACE was noted in Eur/Can and the global population: ALT 19% and 19%, albumin 30% and 29%, AST 25% and 24%, bilirubin 9% and 11%, and INR 15% and 14%, respectively.

Conclusions: Adherence to TACE eligibility guidelines appear to be similar in Eur/Can and the global population. In the Eur/Can subgroup, chronic deterioration of liver function was observed. These results also suggest that systemic therapies are not commonly used after TACE eligibility in Eur/Can clinical practice.

Clinical trial identification: NCT01939945.

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Legal entity responsible for the study: Bayer.

Funding: Bayer.

BRCAness analysis in PDAC patients was possible with the MLPA method. Conclusions: BRCAness is advantageous in being a low-cost method that allows for analysis within a small specimen, thereby providing a strong rationale for improved first line trial design.
significantly associated with OS, but CA19-9 and IL-6 along with higher age, PS, stage and presence of liver metastases were associated with shorter OS.

Conclusions: Plasma cDNA concentrations measured with a simple assay was higher in PC patients than in healthy individuals. High plasma cDNA levels were associated with a short OS. Adjusted for a number of known prognostic parameters cDNA was not statistically significantly associated with OS.

Legal entity responsible for the study: Julia Sidenuis Johansen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Cell free tumor-DNA can predict treatment outcome in advanced PDAC
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Background: Determination of chemotherapy response in pancreatic cancer (PDAC) relies on imaging such as CT or MRI scan, where reliable results can be obtained not earlier than 12 weeks after treatment start. Herein we report, that determination of cell-free DNA (cDNA) can improve treatment monitoring and may allow prediction of treatment response after administration of the first cycle of chemotherapy.

Methods: 26 patients with advanced PDAC were treated with the FOLFIRINOX regime. Cell-free DNA (cDNA) was determined from blood samples before treatment start and before each cycle (d1 and d15) for 3 months. In a subset, cDNA was also determined during first FOLFIRINOX administration after infusion of osaplatin and irinotecan (8hrs). Tumor status was evaluated before treatment start and after 3 month by CT scan. cDNA was extracted from at least 2 mL of plasma and ≥10ng total cDNA was used for sequencing library preparation. Sequencing reads, obtained with a NextSeq500 (Illumina) were mapped to the reference genome (HG19) and read counted in 701 bins of autosomes, with an average size of 5.5Mb. After normalization and transformation into log2 ratios, Z-values were calculated versus a healthy reference group (133 cDNA samples). Z-Scores of bins significantly different from the reference were summed to generate the CNI-score.

Results: The risk of patients (n=11) with an elevated pre-therapeutic CNI-Score (Z> 200 for not responding to chemo) was 82%. Patients with CNI-Score above the 95thpercentile of the reference population (CNI > 24) after cycle 3, had a significantly higher risk to progress (90%), with a 73% accuracy of prediction (p = 0.03). The prediction of therapy failure was even better after 4 cycles with a 90% predictive value and an overall 83% accuracy (p = 0.02). In 13 patients CNI-score was determined after 8hrs of initiation therapy to assess a possible cytolytic tumor burst. Only patients showing a significant increase of CNI-scores, compared to pre-therapeutic values were responders (n=2), one of three stable patients had a borderline burst, whereas all progressive patients (n=8) did not show any sign of tumor burst.

Conclusions: Determination of cell-free DNA represents a powerful tool to predict outcome very early during medical treatment of advanced PDAC.

Legal entity responsible for the study: Alexander König.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Germline and somatic DNA damage repair gene mutations and overall survival in metastatic pancreatic ductal adenocarcinoma patients treated with FOLFIRINOX
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Background: Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with lack of predictive biomarkers. We conducted a study to assess DNA damage repair gene mutations (DDRGM) as a predictive biomarker in PDAC patients treated with FOLFIRINOX.

Methods: Indiana University Simon Cancer Center pancreatic cancer database was used to identify patients with recurrent metastatic PDAC, treated with FOLFIRINOX and had tissue available for DNA sequencing. Baseline demographic, clinical and pathologic information was gathered. DNA isolation and targeted sequencing was performed using the Ion AmpliSeq protocol. Chi-square or t-test was used for univariate analyses. Overall survival (OS) analyses was conducted by Kaplan-Meier method, logis- tic regression (OS categorized as above and below 3rd quartile) and Cox proportional hazard model. Multivariate models were adjusted for age, gender, margin status, CA 19-9, adjuvant chemotherapy, tumor and nodal stage.

Results: Overall, 36 patients were sequenced. DDRGM were found in 12 patients. Mutations were seen in BRCA1 (N = 7), BRCA2 (N = 5), BRCA1/2 (N = 3), PALL2 (N = 3), MSH2 (N = 1) and FANCF (N = 1) of all the DDR genes sequenced (BRCA1, BRCA2, PALB2, CHEK1, CHEK2, RAD51, MLH1, MSH2, ERCC1, ERCC4, PARP1, FANCD, ATR and MDM2). Median age was 65.3 years, 58% were male, 97.2% were Caucasian and 51.6% had any family history of cancer. There were no significant differences between those with DDRGM present and absent except age (64.6 vs. 66.0 years, p = 0.002). The median OS was near significantly superior in those with DDRGM present vs. absent (14 vs. 5 months; HR 0.58 0.29-1.14), log-rank p = 0.085. Multivariate logistic (OR 1.47 1.04-2.06, p = 0.04) and Cox regression (HR 0.37 0.15-0.94, p = 0.04) showed presence of DDRGM was associated with improved OS. Similar analyses limited to only germline BRCA1/2 mutations also showed significantly improved OS with the presence of BRCA1/2 mutations.

Conclusions: In a single institution, retrospective study, we found that the presence of germline and somatic DDRGM as well as germline BRCA1/2 mutations are associated with improved OS in PDAC patients treated with FOLFIRINOX.

Legal entity responsible for the study: Indiana University Institutional Review Board.

Funding: Walther Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

A three-gene signature to predict lymph node metastasis of pancreatic cancer
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Background: Pancreatic cancer, specifically pancreatic ductal adenocarcinoma (PDAC), represents one of the most aggressive malignancies. Lymph node (LN) status is considered as one of the most significant risk factors for survival of PDAC patients, and it is of great importance for making reasonable therapeutic strategies to individual patients. Imaging techniques are widely used in the evaluation of LN status in PDAC patients, however, their application are limited because of the inconsistent sensitivities and specificities findings.

Methods: Gene Set Enrichment Analysis (GSEA) and leading edge analysis were used to analyze the data from The Cancer Genome Atlas (TCGA) on 177 PDAC patients to identify genes associated with LN metastasis. The identified genes with LN metastasis were indexed by Spearman’s rank-correlation test to construct the risk score model. Risk scores were used to predict LN metastasis and overall survival (OS). For validation, we used 80 specimens from patients with PDAC diagnosed at Fudan University Shanghai Cancer Center.

Results: A risk model consisting of three genes (MAPK9, ITGA5, AKT2) was developed. This model could correctly predict the LN metastasis evaluated by receiver operating characteristic (ROC) curves (area under curve (AUC) = 0.668, P = 0.001), and risk score positively associated with the number of metastatic lymph node (MLN). Spearman r = 0.3309, P < 0.001, especially in the PDAC with greatest dimension ≤ 4 cm and total lymph nodes dissected (TLN) > 12 [AUC = 0.80, P = 0.003; Spearman r for MLN ≤ 4237, P = 0.0004; Spearman r for lymph node rate (LNR) ≤ 0.3171, P = 0.0089]. In the set of PDAC patients with TLN ≥ 12, patients with high risk had a worse OS than that with low risk with hazard ratio (HR) of 2.657 (P = 0.0044) for all stage and HR of 2.548 (P = 0.043) for stage I and II. Patients from stage I and stage IIA with high risk scores had a similar OS with stage IIIB (median survival = 21.13 months vs. 20.23 months, P = 0.8227). In the validation set, high risk scores could also effectively predict the LN metastasis and poor prognosis in resectable PDAC.

Conclusions: Our findings highlight three-gene signature with effective capacity for identification of PDAC patients with poor prognosis that are likely to suffer from LN metastasis.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: National Science Foundation for Distinguished Young Scholars of China.

Disclosure: All authors have declared no conflicts of interest.
Background: Pancreatic cancer (PC) remains a disease difficult to treat. Afatinib, a
novel, oral irreversible Erbb family blocker has shown efficacy in non-small cell lung
cancer bearing driver mutations of the epidermal growth factor receptor. This open-
label, multicenter, randomised phase II trial evaluated the efficacy and safety for gemci-
tabine/afatinib vs. gemcitabine in metastatic PC.

Methods: Patients with historically proven metastatic PC were randomised in a 2:1
ratio of gemcitabine/afatinib vs. gemcitabine alone as first-line treatment for metastatic disease. Overall survival (OS) was the primary endpoint.

Results: Between April 2013 and January 2017, 119 patients from 25 German centers
were randomised (79 patients for gemcitabine/afatinib and 40 for gemcitabine), of
which 115 received at least one dose of study medication and 108 were eligible for the
primary analysis. Median OS was 7.3 months for gemcitabine/afatinib vs. 7.4 months
for gemcitabine, HR 1.06 (95% CI 0.80–1.40), p = 0.80. Median progression free sur-


growth: 1000mg or 1250mg nelfinavir bd continuously during CRT. Six design. 7 patients received 1250mg nelfinavir and no DLTs were observed. During

GEMBAX, common grade ≥3 toxicities among participants were neutropenia (30%),
fatigue (22%), and diarrhea (15%). During CRT, grade ≥3 toxicities included fatigue
(6%) and anorexia (6%). No grade 5 adverse events were reported in Stage 1. Survival
analysis will be presented.

Conclusions: 1250mg nelfinavir was recommended for combining with capcitabine-
CRT in the ongoing randomised component of the trial (Stage 2).

Clinical trial identification: SRCTN50883238.

Legal entity responsible for the study: University of Oxford, UK.

Funding: Cancer Research UK, Celgene.

Disclosure: S. Mukherjee, P.G. Corrie: Research funding: Celgene. J. Bridgewater:
Consultancy: Celgene. N. Patel: Part-time employee of GSK. All other authors have
disclosed no conflicts of interest.

Background: In Japan, gemcitabine based chemotherapy has been a standard regimen
as one of the first-line treatment for unresectable pancreatic cancer. FOLFIRINOX was
introduced in the second-line treatment for the gemcitabine-refractory pancreatic can-
cer of patients with an ECOG performance status score of 0 or 1. However, FOLFIRINOX
requires dose monitoring and must be limited to patients with good performance
status because of significant toxicity. Further FOLFIRINOX requires a central

Results: Among the 12 patients enrolled, dose-limiting toxicity was observed in
a patient at level 1 (irinotecan 100 mg/m² on day 1, S-1 was administered orally at 80
mg/m² twice daily for 7 days) and oxaliplatin was administered as per the rolling-

6. N. Patel: Part-time employee of GSK.
oxaliplatin 85 mg/m² on day 1), and in two patients at level 2 (irinotecan 100 mg/m² on day 1, 5-fluorouracil 425 mg/m² weekly, and oxaliplatin 85 mg/m² on day 1). The MTD was established as level 2. The RD was established as level 1. The most common grade 3–4 toxicity was neutropenia (33.9%). The overall response rate was 9.0%. The overall disease control rate was 45.4%.

**Conclusions:** Based on the present results, the RD was determined as level 1 (irinotecan 100 mg/m² on day 1, 5-fluorouracil 425 mg/m² weekly, and oxaliplatin 85 mg/m² on day 1). IRISOX was well tolerated and showed antimetastatic efficacy in the second-line treatment for the gemcitabine-refractory pancreatic cancer in a phase 1 study.

**Clinical trial identification:** UMIN000022964.

**Legal entity responsible for the study:** Kitasato University School of Medicine, Japan.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 722P**

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<th>Gem + nab (n = 63)</th>
<th>FOLFIRINOX (n = 91)</th>
<th>PANOPTIMOX (n = 92)</th>
<th>FIRMEG (n = 90)</th>
<th>FIRGEMAX (n = 64)</th>
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<tbody>
<tr>
<td>mITT - ORR (%)</td>
<td>25 (p = 0.11)</td>
<td>36</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Median ITT - PFS (mo)</td>
<td>4.2 (p = 0.12)</td>
<td>6.0</td>
<td>7.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Median ITT - OS (mo)</td>
<td>11.3 (p = 0.09)</td>
<td>12.4</td>
<td>12.2</td>
<td>13.0</td>
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</tbody>
</table>

*Overall Log-rank test + Chi2 test.

**Conclusions:** FOLFIRINOX seems confirmed as a reference treatment for mPDAC. These exploratory analyses show no major differences between the different treatment options offered in these 2 studies except for the FIRGEM sequential strategy that seems both in ITT and preplanned PP analyses less efficient than the other options. The addition of nab-paclitaxel to this sequential strategy seems to dramatically improve patients’ oncological outcomes.

**Clinical trial identification:** NCT02352337 and NCT02872701.

**Legal entity responsible for the study:** FFCED.

**Funding:** Celgene.

**Disclosure:** J. Taebi: Consulting or advisory role: Roche, Merck KGaA, Amgen, Celgene, Lilly, Basaltia, Servier, Sirtex Medical, Speakers’ bureau: Amgen, Basaltia, Servier, Roche/Gentech, Sanofi, Merck, Lilly. J.M. Phelip: Consulting or advisory role: Roche, Merck, Amgen, Sanofi, Lilly, Bayer, Servier; Travel accommodations expenses: Roche, Merck, Amgen, Sanofi, Lilly, Bayer, Servier. O. Bouché: Consulting or advisory role: Roche, Merck, Amgen, Bayer; Speaker’s bureau: Lilly, Pierre Fabre, Novartis, Servier; Travel accommodations expenses: Lilly, Roche, Merck. F. Khemissa: Consulting or advisory role: Roche, Merck, Amgen, Bayer; Speaker’s bureau: Lilly, Pierre Fabre, Novartis, Servier, Sanofi, C. Ibos: Consulting or advisory role: Advanced Accelerator Applications; Travel accommodations expenses: Amgen, Novartis, Ipsen, Bayer, Honoraria: Novartis, E. Francois: Consulting or advisory role: Roche, Merck Travel, accommodations expenses: Roche, Merck, Servier. L. Dahan: Honoraria: Sanofi, Amgen. All other authors have declared no conflicts of interest.

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**Table: 723P**

| First-line (1L) full dose (f) and modified (m) FOLFIRINOX and gemcitabine+nab-paclitaxel (GN) treatment (tx) for metastatic pancreatic adenocarcinoma (mPDAC) patients (pts) in routine clinical practice across Europe |
|-----------------|-----------------|-----------------|-----------------|
| Gem + nab (n = 63) | FOLFIRINOX (n = 91) | PANOPTIMOX (n = 92) | FIRMEG (n = 90) | FIRGEMAX (n = 64) |
| mITT - ORR (%)    | 25 (p = 0.11)     | 36                 | 34             | 23               | 40               |
| Median ITT - PFS (mo) | 4.2 (p = 0.12) | 6.0               | 7.7            | 7.5              | 6.3              | 7.6              |
| Median ITT - OS (mo) | 11.3 (p = 0.09) | 12.4              | 12.2           | 13.0             | 9.8              | 15.8             |

*Overall Log-rank test + Chi2 test.

**Conclusions:** FOLFIRINOX and GN have shown superior OS but with increased toxicity in fitter and younger pts vs gemcitabine. In routine practice, FOLFIRINOX is often modified at start (eg no FU bolus). No randomized phase III data are available and real world data are scarce.
In this large retrospective chart review, pt characteristics and outcomes of mFOLFIRINOX were seen. f/FOLFIRINOX pts were a little more often dose adjusted. Of FOLFIRINOX/GN compared with FFOLFRINOX, more mFOLFIRINOX pts were >65 y and female. FOLFIRINOX pts had somewhat lower OS/PFS; 41.5% vs 41.8% (12/7 mo for GN). mFOLFIRINOX (16/10 mo) had similar outcomes vs FOLFIRINOX (15/10 mo). On average, 1.5 reasons were reported to stop tx. Most common for FOLFIRINOX/GN were: radiological PD (59/34%), clinical PD (24/32%), tx completed as planned (36/18%) and toxicity (13/9%). No overall benefit of continued tx by 12/7 mo for GN. mFOLFIRINOX (16/10 mo) had similar outcomes vs FOLFIRINOX (15/10 mo). In 2 studies that reported OS based on ECOG PS, the median OS for pts with ECOG PS 0/1 was 12.1 and 14.1 mo for nab-P/G vs 11.4 and 13.7 mo for FFX. Overall response rates ranged from 10% to 41% for nab-P/G and 6% to 34% for FFX (4 studies), and disease control rates ranged from 50% to 92% and 56% to 89%, respectively (5 studies). Safety outcomes were heterogeneously reported in 1667 pts (10 studies) receiving nab-P/G or FFX (Table). Conclusions: Several real-world studies have compared the effectiveness of nab-P/G vs FFX, highlighting the clinical significance. A systematic review of these studies shows that nab-P/G and FFX have comparable effectiveness in mp/PC. Differences were observed in the toxicity profiles for the 2 regimens, which may drive treatment decisions. Table. Studies reporting OS, PFS, and safety.

Legal entity responsible for the study: Celgene Corporation.

Funding: Celgene Corporation.


Legal entity responsible for the study: The authors.

Funding: No funding sources.

Disclosure: All authors have declared no conflicts of interest.

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<table>
<thead>
<tr>
<th>First-line treatment</th>
<th>N</th>
<th>% pts with dose adjustment</th>
<th>% pts &gt;65 year</th>
<th>% female pts</th>
<th>% pts 0-1 ECOS Performance Score</th>
<th>% pts received 2L</th>
<th>Median OS/PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>gemcitabine+nab-paclitaxel (GN)</td>
<td>660</td>
<td>20.5%</td>
<td>44.8%</td>
<td>43.2%</td>
<td>76.5%</td>
<td>67.4%</td>
<td>12/7</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>912</td>
<td>23.9%</td>
<td>35.2%</td>
<td>87.2%</td>
<td>89.0%</td>
<td>78.0%</td>
<td>15/10</td>
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<td>mFOLFIRINOX</td>
<td>164</td>
<td>6.7%</td>
<td>41.5%</td>
<td>86.8%</td>
<td>78.1%</td>
<td>78.1%</td>
<td>15/10</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>748</td>
<td>26.1%</td>
<td>18.3%</td>
<td>92.6%</td>
<td>66.7%</td>
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<tr>
<td>FOLFIRINOX modified in cycle 2/3</td>
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<td>25.9%</td>
<td>48.1%</td>
<td>88.1%</td>
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<tr>
<td>FOLFIRINOX modified in cycle 3+</td>
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<td>27.4%</td>
<td>41.1%</td>
<td>77.4%</td>
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<tr>
<td>FOLFIRINOX never modified</td>
<td>553</td>
<td>24.4%</td>
<td>32.7%</td>
<td>86.1%</td>
<td>78.9%</td>
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</table>

Background: Current guidelines recommend chemotherapy with nab-P/G or FXX as the preferred first-line (1L) treatment for metastatic (m)PC pts with good performance status. However, no clinical trial has directly compared 1L nab-P/G vs FXX in mp/PC or APC. We conducted a systematic review of the real-world comparative effectiveness of nab-P/G vs FXX in this setting.

Methods: Embase, Medline, and ASCO GI 2018 were searched through January 2018 for real-world, retrospective studies directly comparing 1L nab-P/G vs FXX in mp/PC or APC. We searched clinicaltrials.gov, the Cochrane Library, and relevant conferences for ongoing studies. A total of 308 patients with mPC who were treated with AG (n = 149) or FFX (n = 159) as first-line treatment between January 2013 and December 2016 at Asan Medical Center, Seoul, Korea were included. Treatment outcomes including survivals, response rates and toxicities of each regimen were evaluated.

Results: Patients treated with AG were older (62 vs. 60 years, p = 0.02) and they had higher Charlson Comorbidity Index (CCI) score (2.9 vs. 4.63%, p = 0.02). There were no significant differences between the two groups in terms of other baseline characteristics. The response rates (43% vs 34%, p = 0.08) and median progression-free survival (PFS) (6.8 vs 5.1 months, p = 0.19) were comparable, but median overall survival (OS) was significantly better with AG (11.4 vs 9.6 months; p = 0.002). In subgroup analyses, PFS with AG was longer in patients with age ≥ 65 years, peritoneal metastasis, and higher CCI than that with FXX. While grade 3-4 peripheral neuropathy was more frequent in the AG group (10% vs 3%), grade 3 nausea was more frequent in the FXX group (2% vs 17%). granulocyte colony-stimulating factor was required only in the FXX group (n = 27, 18%). Conclusions: AG was well tolerated and showed comparable efficacy outcomes with FXX. Of note, AG might be preferentially considered as the first-line treatment in mPC patients with peritoneal metastasis, comorbid medical conditions or old age. As both regimens are feasible as first-line treatment for mPC, further investigations are needed for the personalized uses of these regimens.

Legal entity responsible for the study: The authors.

Funding: No funding received.

Disclosure: All authors have declared no conflicts of interest.

Efficacy and safety of nab-paclitaxel plus gemcitabine (AG) vs. FARLIRINOX (FFX) as first line chemotherapy for metastatic pancreatic cancer (mPC): Retrospective analysis


OncoDec, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Background: Nab-Paclitaxel plus Gemcitabine (AG) and FARLIRINOX (FFX) have been established as standard first-line treatment in metastatic pancreatic cancer (mPC) based on the superior efficacy compared to gemcitabine monotherapy. Although FXX is recommended for patients with relatively young age and good performance status (PS), there is lack of data for optimal choice between these two regimens. We performed retrospective analysis comparing the efficacies and safety of AG and FXX in mPC patients as first line therapy.

Methods: A total of 308 patients with mPC who were treated with AG (n = 149) or FXX (n = 159) as first-line treatment between January 2013 and December 2016 at Asan Medical Center, Seoul, Korea were included. Treatment outcomes including survivals, response rates and toxicities of each regimen were evaluated.

Results: Patients treated with AG were older (62 vs. 60 years, p = 0.02) and they had higher Charlson Comorbidity Index (CCI) score (2.9 vs. 4.63%, p = 0.02). There were no significant differences between the two groups in terms of other baseline characteristics. The response rates (43% vs 34%, p = 0.08) and median progression-free survival (PFS) (6.8 vs 5.1 months, p = 0.19) were comparable, but median overall survival (OS) was significantly better with AG (11.4 vs 9.6 months; p = 0.002). In subgroup analyses, PFS with AG was longer in patients with age ≥ 65 years, peritoneal metastasis, and higher CCI than that with FXX. While grade 3-4 peripheral neuropathy was more frequent in the AG group (10% vs 3%), grade 3 nausea was more frequent in the FXX group (2% vs 17%). granulocyte colony-stimulating factor was required only in the FXX group (n = 27, 18%). Conclusions: AG was well tolerated and showed comparable efficacy outcomes with FXX. Of note, AG might be preferentially considered as the first-line treatment in mPC patients with peritoneal metastasis, comorbid medical conditions or old age. As both regimens are feasible as first-line treatment for mPC, further investigations are needed for the personalized uses of these regimens.

Legal entity responsible for the study: The authors.

Funding: No funding received.

Disclosure: All authors have declared no conflicts of interest.

725P
<table>
<thead>
<tr>
<th>Study</th>
<th>n (1L)</th>
<th>Median 1L OS, mo</th>
<th>Median 1L PFS, mo</th>
<th>Grade ≥ 3 AEs</th>
<th>AE</th>
<th>nab-P/G</th>
<th>FFX</th>
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<tr>
<td></td>
<td>Median</td>
<td>Median</td>
<td>Nab-P/G</td>
<td>Nab-P/G</td>
<td>Nab-P/G</td>
<td>Nab-P/G</td>
<td>FFX</td>
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<tr>
<td>Beyer 2016 (mPC)</td>
<td>19</td>
<td>57</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Park 2016 (mPC)</td>
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<td>Capronnetto 2017 (mPC)</td>
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<td>Javed 2017 (mPC)</td>
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<td>90</td>
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<td>Kasi 2017 (aPC)</td>
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<td>Mañes-Sevilla 2017 (mPC)</td>
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<td>15</td>
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<td>11.4</td>
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<td>86 (70)</td>
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<td>NR</td>
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<td>Hwang 2018 (mPC)</td>
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<td>Total</td>
<td>1363</td>
<td>1528 (1253, 1528 (1306)</td>
<td></td>
<td></td>
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</tbody>
</table>

- Study: 724P
- n (1L): number of patients in the first-line setting
- Median 1L OS, mo: median overall survival in months for the first-line setting
- Median 1L PFS, mo: median progression-free survival in months for the first-line setting
- Grade ≥ 3 AEs: grade ≥ 3 adverse events
- AE: adverse event
- nab-P/G: nab-paclitaxel/gemcitabine
- FFX: FOLFIRINOX

*Reported as database persistence, a proxy for OS.
†For pts with ECOG PS 0/1, OS was 12.1 mo for nab-P/G and 11.4 mo for FFX.
‡aPC includes mPC. The numbers in parentheses are for pts with mPC.
§Biomarker study observing homologous recombination deficiency low vs high in each treatment regimen with data presented here as a range.
*Modified FFX (no bolus 5-FU and reduced dose irinotecan).
††For pts with ECOG PS 0/1, OS was 14.1 mo for nab-P/G and 13.7 mo for FFX.
‖Represents minimum as some studies did not report the number of pts. The numbers in parentheses are for pts with mPC. 1L, first line; AE, adverse event; aPC, advanced pancreatic cancer; FFX, FOLFIRINOX; mPC, metastatic pancreatic cancer; nab-P/G, nab-paclitaxel/gemcitabine; NR, not reported; OS, overall survival; PFS, progression-free survival.
Background: There are concerns about more severe toxicities of FOLFIRINOX use in case with recurrent disease after pancreatic resection, because a certain number of these patients suffer from malnutrition, weight loss, and diabetes mellitus induced by pancreatic exocrine or endocrine insufficiency. Today, FOLFIRINOX is widely adopted also in recurrent disease after resection beside metastatic disease studied in the ACCORD trial, which examined multi-institutional experience with FOLFIRINOX use in pancreatic cancer by registration study. We focused on toxicity and tolerance of FOLFIRINOX use in patients with recurrent disease after resection.

Methods: This study was carried out as an incidental research of JASPAC 06 study which examined multi-institutional experience with FOLFIRINOX use in pancreatic cancer by registration study. We focused on toxicity and tolerance of FOLFIRINOX use in case with recurrent disease after pancreatic resection, and correlated them with those of locally advanced or metastatic disease group.

Results: From Nov. 2014 to May 2015, 399 patients were registered in JASPAC 06, 80 patients (20%) had recurrent disease, 78 (20%) had locally advanced disease, and 241 (60%) had metastatic disease. There were no difference in background such as age, sex, ECOG PS, pathology and CA19-9 level between recurrent disease group and locally advanced disease group. FOLFIRINOX was initiated as modified manner in 69% of recurrent group and 67% of locally advanced or metastatic group. The major grade 3-4 toxicities observed in recurrent group and locally advanced or metastatic disease group were neutropenia (68% vs 63%), febrile neutropenia (4% vs 15%, p = 0.007), thrombocytopenia (4% vs 3%), anemia (8% vs 10%), fatigue (4% vs 3%), anorexia (14% vs 14%). The median treatment duration and median treatment cycle in recurrent group and locally advanced or metastatic group was 2.9 months vs 1.1 months, and 6 vs 1 cycle. There was no difference in relative dose intensity between two groups.

Conclusions: Toxicity and tolerance of FOLFIRINOX use in recurrent disease after pancreatic resection were similar to those of use in locally advanced or metastatic disease.

A phase II study of nab-paclitaxel and gemcitabine in Korean patients with metastatic pancreatic cancer


Background: Nab-paclitaxel (nab-P) in combination with gemcitabine (G) significantly improved overall survival in patients with pancreatic cancer and is considered as standard first-line therapy. However, the efficacy and safety data in Korean patients are lacking as the phase III study was done only in Western countries.

Methods: This open-label, multicenter, phase II, single-arm study was conducted at seven hospitals in South Korea (NCT02426281). Patients with pathologically confirmed metastatic pancreatic cancer were enrolled. Patients received nab-P (125mg/m²) followed by G (1000mg/m²) on days 1, 8, and 15 every 4 weeks until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Through a randomized phase III trial, Von Hoff et al. observed a median PFS of 3.7 months from the G-alone arm and 5.5 months from the nab-P + G arm. This study is to confirm this outcome from the Korean population. We will not be interested in the combination therapy of nab-P + G if its median PFS is 3.7 months or shorter and will be highly interested in it if its median PFS is 5.5 months or longer. (90% of power and by the one-sample log-rank test with a one-sided alpha = 5%).

Results: A total of 65 patients were enrolled between May 2015 and November 2016. The median age of patients was 60 years (range 43-83), 75% of patients were male, and all had an ECOG performance status of 0 or 1. The median PFS was 7.0 months (95% CI, 5.6-8.3), which met primary endpoints. Median overall survival was 12.9 months (95% CI, 10.1-15.6) and the objective response rate was 41.5% (95% CI, 29.3-53.5) according to RECIST v1.1. The median relative dose intensity was 84% for nab-paclitaxel and 88% for gemcitabine. Grade 3-4 adverse events included neuropathy (62%), anemia (14%), neutropenia (12%) and febrile neutropenia (9%). There was one treatment-related death of septic shock.

Conclusions: In Korean patients with metastatic pancreatic cancer, nab-paclitaxel plus gemcitabine regimen showed comparable efficacy and safety profile to previous phase III study of Western countries. Based on this result, we are conducting a phase II trial with the nab-P + G in an expansion cohort of locally advanced pancreatic cancer.

Clinical trial identification: NCT02426281.

A pooled meta-analysis

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Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: About 80%-85% of patients with pancreatic cancer are unresectable at first diagnosis. Several studies have examined nab-paclitaxel plus gemcitabine (NG) in patients with locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer (MPC). The objective of this analysis was to evaluate the effectiveness of NG as first-line treatment in this specific patient population.

Methods: We searched Pubmed for eligible studies from the day of inception to April 16th, 2018 for studies of chemoradiation/therapy-naive patients who accepted NG as first-line treatment of unresectable pancreatic cancer (UPC). Overall objective response rate (ORR), 1-year overall survival (OS) and 6-month progression free survival (PFS) rates were estimated by randomized-effect model. Subgroup analyses were conducted in LAPC and MPC.

Results: Of 890 patients included from 16 studies, 53 patients were LAPC and 837 patients were MPC. Median OS from the start of NG of all patients ranged from 8.7 months to 20.0 months with a 1-year survival rate of 50.9% (95%CI 40.1% to 61.8%). Median PFS ranged from 2.2 months to 8.4 months with a 6-month PFS rate of 52.8% (95%CI 33.2% to 72.3%). In single arm analysis, the overall ORR in unresectable pancreatic cancer was 34.4% (95%CI 25.3% to 43.5%). In patients with LAPC, 80.6% (48/ 53) underwent surgery and the R0 resection rate was 81.2% (ranging from 70% to 100%), achieving a 1-year survival rate of 97.9%. In patients with MPC, the ORR was 30.8% and the 1-year survival rate was 44.6%. Five hundred and fifty six grade 3/4 adverse events and no death caused by toxicity were reported in 15 studies consisting of 871 patients.

Conclusions: This is the first meta-analysis to evaluate the effectiveness of NG for UPC. More than 50% of patients with UPC treated with NG survived longer than 12 months. NG showed favorable tumor reduction with acceptable toxicity profile. Randomized controlled trials are needed to confirm the efficacy of NG in patients with LAPC.

A pooled meta-analysis of patients with metastatic pancreatic cancer (mPC) treated with first-line nab-paclitaxel plus gemcitabine (AG)


Background: AG is standard first-line chemotherapy for patients with mPC. However, prognostic factors for patients with mPC treated with AG are largely unknown. This retrospective analysis was performed to identify the prognostic factors including
inflammation-based prognostic scores in mPC patients treated with AG as first-line treatment.

Methods: A total of 203 patients with histologically confirmed recurrent (n = 55) or metastatic (n = 148) pancreatic cancer who were treated with first-line AG in Asian Medical Center, Seoul, Korea, between January 2013 and January 2018, were included in this analysis. As inflammation-based scores, baseline Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR) and modified Glasgow prognostic score (mGPS) were tested. Cox-proportional hazards model were used to identify prognostic factors in univariate and multivariate analyses.

Results: Median age was 62 years (range, 32-82) and 116 patients (57%) were male. With median follow-up duration of 21.5 months (range, 0.5-34.3), median overall survival (OS) and progression free survival (PFS) in overall patients were 15.5 (95% CI 12.6-17.6) and 7.1 (95% CI, 6.2-8.0) months, respectively. In multivariate analysis, elevated CA19-9 level (HR 1.75, p = 0.008), liver metastasis (HR 1.8, p = 0.001), distant lymph node metastasis (HR 1.4, p = 0.04), and high mGPS (≥ 5 vs < 5 HR 1.6, p = 0.005) were significantly associated with poorer OS. For PFS, poor performance status (PS) (ECOG PS 2 vs 0/1: HR 2.1, p = 0.048), liver metastasis (HR 1.4, p = 0.05), distant lymph node metastasis (HR 1.5, p = 0.02), and elevated CA 19-9 level (HR 1.1, p = 0.02) were significantly related with poorer outcomes. Neither NLR nor PLR was significantly associated with PFS or OS.

Conclusions: CA 19-9 level, liver and distant lymph node metastasis were independent prognostic factors in mPC, patients treated with first-line AG. Among the inflammation-based prognostic scores, mGPS may be the reliable indicator for the prediction of OS.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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Table: 730P

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Conclusions: Intermediate analysis shows R is safe and effectively prevents TE events in patients receiving PAG. Responses and disease control rate are encouraging in this tumor HA-level unselected patient population. Updated safety and efficacy data will be reported.

Clinical trial identification: NCT02921022.

Legal entity responsible for the study: Memorial Sloan Kettering Cancer Center.

Funding: Halozyme Therapeutics, Inc.

Disclosure: All authors have declared no conflicts of interest.

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731P

Phase II clinical trial of gemcitabine plus oxaliplatin combination therapy (GEMOX) in patients with advanced adenocarcinoma with a family history of pancreatic/breast/ovarian/prostate cancer (FABRIC study)

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Background: Presence of family/personal history of breast/ovarian/pancreatic cancer has been reported to be a useful predictive marker in patients with pancreatic adenocarcinoma (PA) receiving platinum-based chemotherapy (Fogelman D. 2015). We planned a prospective phase II study to evaluate the efficacy and safety of platinum-based chemotherapy in this population.

Methods: Eligible patients were those with chemotherapy-naive metastatic PA with one or more of the following: 1) family history of pancreatic (P)/breast (B)/ovarian (O)/prostate (PR) cancer in a first-degree relative, 2) at least two family members with P/B/O/PR cancer within third-degree relatives, and 3) personal history of B/O/PR cancer. Patients received gemcitabine, 1,080 mg/m2 and oxaplatin 100 mg/m2 every two weeks (GEMOX). The primary endpoint was the one-year survival rate, and the outcome in 19 of 43 patients (pts) (44%) were died. The target sample size was determined as 43, with a one-sided alpha of 5% and a power of 80%.

Results: A total of 45 pts were enrolled. The first consecutive 43 pts were included in the efficacy analysis. The one-year survival rate (90% confidence interval) was 27.9% (17.0-41.3) and did not meet the expected threshold. The response rate was 27.9%. A tendency towards prolonged survival was observed in patients with two or more family histories of P/B/O/PR cancer (HR 0.65, 95% CI 0.34-1.23). Presence of a family/personal history of B/O/PR cancer tended to be associated with a better response and longer survival. In this study population, patients with a family history of pancreatic cancer seemed to show a poorer response. The most common adverse events of grade 3 or higher severity were neutropenia (36%), leukopenia (27%) and thrombocytopenia (23%).

Conclusions: GEMOX did not show expected efficacy in patients with metastatic PA with a family/personal history of P/B/O/PR cancer. Selection of GEMOX based on family/personal history alone is not recommended, especially in patients with a family history of P cancer.


Legal entity responsible for the study: National Cancer Center Hospital.

Funding: Japan Agency for Medical Research and Development (AMED), National Cancer Center Research and Development Fund.

1 termoblation and 3 explorative laparotomy), 1 patient became sicker but refused surgery. The overall resectability rate was 25%, while the R0 resection rate was 12.5%. Toxicity to GEMOX was similar to that reported elsewhere. Radiotherapy was well tolerated and the minor side effects encountered were moderate nausea and vomiting, abdominal pain and fatigue. At a median follow-up of 50 months, the median progression-free survival and overall survival were 9.3 (95% CI 6.2-14.9) and 15.8 (95% CI 8.2-25.4) months, respectively.

Conclusions: Our results show the feasibility of using accelerated hypofractionated radiotherapy on tumor volume and locoregional lymph nodes in LAPC. Treatment was well tolerated and survival rates are promising.

Clinical trial identification: EudraCT7 | RS02010-003079-22.

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

733P NAPOLI-1 phase III trial outcomes by prior surgery, and disease stage, in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC)

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Background: The NAPOLI-1 phase 3 trial (NCT01494506) reported significantly increased median OS with nal-IRI + 5-FU/LV vs 5-FU/LV (6.1 mo vs 4.2 mo; HR = 0.67; p = 0.012) in mPDAC patients who progressed after gemcitabine-based therapy. We report subgroup analysis outcomes in NAPOLI-1 patients who had undergone prior surgery and by disease stage at diagnosis.

Methods: This post-hoc analysis investigated outcomes with or without prior surgery, and by disease stage at diagnosis (stage IIA, IIB, or III vs IV). P values are descriptive.

Results: In the NAPOLI-1 trial, OS and PFS were increased in ITT patients who had undergone prior surgery compared to those who did not (Table). In patients with prior surgery receiving nal-IRI + 5-FU/LV (n = 40), OS and PFS were increased vs 5-FU/LV (n = 43) (HR = 0.84 and 0.72). Patients without prior surgery had significantly increased OS and PFS with nal-IRI + 5-FU/LV vs 5-FU/LV (n = 76) (HR = 0.66, p = 0.003 and HR = 0.47, p < 0.001). OS was significantly increased in ITT patients with disease stages IIA (n = 36, HR = 0.59, p = 0.013), IIB (n = 77, 0.54, < 0.001), and III (n = 75, 0.57, < 0.001) vs stage IV (n = 213). A consistent OS increase was also seen in patients treated with nal-IRI + 5-FU/LV: stage IIA (HR = 0.65, n = 38) IIB (HR = 0.50, p = 0.024) and stage III (HR = 0.43, p = 0.021) vs stage IV.

Conclusions: OS and PFS were increased in ITT patients who had undergone surgery prior to trial inclusion. Patients treated with nal-IRI + 5-FU/LV showed a consistent increase in OS and PFS in ITT patients with stages IIA, IIB, and III than with stage IV disease. Treatment with nal-IRI + 5-FU/LV showed a survival benefit across disease stages IIA, IIB, and III vs stage IV. Limited patient numbers should be taken into consideration when interpreting these findings.

Clinical trial identification: NCT01494506.

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Legal entity responsible for the study: Merrimack Pharmaceuticals.

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Disclosure: G. Bodoky: Consulting, Advisory role: Bayer, Ipsen, Janssen, Lilly, Novartis, Pfizer, Roche; Support for travel, accommodation and expenses: Jansen, Lilly, Novartis, Pfizer, Roche, J. Siewe: Consulting, Advisory role: Merckxam Pharmaceuticals, Baxalta (now part of Shire), Celgene, Lilly; Research funding: Celgene, Bristol-Myers Squibb, 4SC, Novartis, Boehringer Ingelheim; Travel, accommodation, expenses: Roche, Celgene, Shire, J. Chen, F. de Jong; Employee: Stockholder: Shire, B. Mitakuhi: Employee: Ipsen; Stockholder: Ipsen, GlaxoSmithKline; A. Dean: Honoraria: Specialised Therapeutics Australia; Consultant/Advisor: Baxalta (now part of Shire). L-T. Chen: Honoraria, Consultant, Advisor: Bristol-Myers Squibb, Ono Pharmaceutical, Lilly, MSD; Pharmacology, Merckxam Pharmaceuticals, TTY Biopharm, SynCorBio, Five Prime, Novartis; Patent: HumilTech Technology; Research funding: Novartis, GlaxoSmithKline, Merck Serono, TTI Biopharm, Polaris, SynCorBio, Pfizer, Celgene. All other authors have declared no conflicts of interest.
Impact of dose reduction or dose delay on the efficacy of liposomal irinotecan (nal-IRI) + 5-fluorouracil/leucovorin (5-FU/LV): Survival analysis from NAPOLI-1

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1Internal Medicine, National Health Research Institutes – National Institute of Cancer Research, Taichung, Taiwan, 2Vall d’Hebron Institute of Oncology (VHI), Vall d’Hebron University Hospital (HUV), Barcelona, Spain, 3CHU Bordeaux, Groupe Hospitalier Pau-Léonest, Pessac, France, 4Medical Affairs, Ipsen Biopharmaceuticals,Inc., Basking Ridge, NJ, USA, 5Medical Affairs, Shire GmbH, Zug, Switzerland, 6Immunology R&D, Ipsen Biopharmaceuticals,Inc., Basking Ridge, NJ, USA, 7Internal Medicine, Division of Hematology/Medical Oncology, Mayo Clinic, Phoenix, AZ, USA, 8Division of Solid Tumor Translational Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany

Background: Chemotherapy dose modifications to manage adverse events (AEs) is common in clinical practice. In NAPOLI-1 (NCT01494506), a randomized phase 3 study in patients with metastatic pancreatic cancer previously treated with gemcitabine-based therapy, nal-IRI + 5-FU/LV improved overall survival (OS; primary end-point) vs 5-FU/LV (6.1 mos vs 4.2 mos; HR = 0.67, 95% CI 0.49–0.92; P = 0.012). The study protocol permitted dose modifications (reduction or delay) to address toxicity. In this exploratory post-hoc analysis, we evaluated the impact of nal-IRI dose modifications on overall survival (OS) and progression-free survival (PFS).

Methods: All pts enrolled under protocol v2 who received nal-IRI + 5-FU/LV during the first 6 wks were included in the analysis. Pts were grouped according to those with dose modification or those without dose modification. Dose reduction was defined as any decrease from initial dose, delay as any dosing delay < 3 days from target date. Pts without dose modification received the first 3 scheduled doses of nal-IRI + 5-FU/LV without qualifying delay/reduction. OS and PFS (Kaplan-Meier estimates) were calculated using Cox regression.

Results: Among pts in the nal-IRI + 5-FU/LV arm (n = 93), 40 pts had no dose modification and 53 had a dose modification (delay, n = 49; reduction, n = 34). Within the nal-IRI + 5-FU/LV arm, there was no significant difference in median OS or PFS between pts with vs without dose modification (Table). No significant impact on OS or PFS compared to patients without dose modifications. This suggests that tolerability-guided dose modification of nal-IRI does not adversely affect efficacy outcomes.

Conclusions: Dose modification of nal-IRI + 5-FU/LV in the first 6 wks does not significantly impact OS or PFS compared to patients without dose modifications. This suggests that tolerability-guided dose modification of nal-IRI does not adversely affect efficacy outcomes.

Table: 733P

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Clinical trial identification: NCT01494506.
Results: Between Jun. 2013 and Oct. 2015, a total of 54 patients were included, with median age of 59 y/o, ECOG PS = 1 in 82%, and the presence of liver metastases in 66.7%. At the cut-off Feb.01, 2017, nine patients remained alive and their median follow-up time was 21.5 months. The ORR was partial response in 22 patients (ORR=40.7%, 95% CI: 28.5-53.5) and stable diseases in 19 patients (35.2%). Long-term disease control rate (stable disease ≥16 weeks) was 64.8% (95% CI: 51.7-77%). The median progression-free survival and overall survival was 7.6 (95% CI: 4.4-10.7) and 11.4 (95% CI: 6.1-16.3) months, respectively. One-year and two-year survival rates were 46% and 17%, respectively. The most common treatment-related grade 3-4 adverse events included neutropenia (40.7%), anorexia (14.8%), nausea (11.1%), thrombocytopenia (9.3%), and diarrhea (7.4%).

Conclusions: Current study demonstrated SLOG is a highly active regimen with manageable and favorable safety profiles for mPDAC patients. A randomized phase II trial comparing SLOG vs. modified FOLFIRINOX in advanced PDAC patients is ongoing.

Clinical trial identification: NC10143713

Legal entity responsible for the study: Taiwan Cooperative Oncology Group, National Health Research Institutes.

Funding: National Health Research Institutes.

Disclosure: J.-S. Chen: Honoraria: Ono, Eli Lily, MSD, TTY, Novartis. Y.-Sh. Shan: Honoraria: TTY, PharmaEngine. L.-T. Chen: Research funding: Novartis, Merck-Serono, TTY, Polaris, Syncere Pharm, BMS; Honoraria: Ono, Eli Lily, MSD, PharmaEngine, TTY, Syncere Pharm, Novartis, Astra Zeneca. Ipsen; Patents & royalties: ENO-1 mAb/HuniLife; Membership on any entity’s Board of directors or advisory committees: PharmaEngine. All other authors have declared no conflicts of interest.


737P A phase II trial of gemcitabine, S-1 and LV combination therapy in patients with advanced pancreatic cancer

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Background: The aim of this single center, open label, single arm phase II trial was to assess the efficacy and toxicity of gemcitabine, S-1 and leucovorin (LV) combination therapy for advanced pancreatic cancer (UMIN-CTR 000010678).

Methods: Chemotherapy-naive patients with histologically or cytologically proven advanced pancreatic cancer were enrolled. Gemcitabine was administered at a dose of 1,000 mg/m² by 30 min infusion on days 1, 8, 14 and 21, and LV 25mg orally twice daily on days 1 to 7 every 2 weeks. Primary end point was progression free survival (PFS), and secondary endpoints were overall survival (OS), response rate, disease control rate and adverse events.

Results: A total of 49 patients with advanced pancreatic cancer (19 locally advanced and 30 metastatic) were enrolled between May 2013 and March 2017. Median age was 68 (range: 44-84) and PS was 0 in 26 and 1 in 23. Overall response rate and disease control rate were 32.7% and 87.8%. The median PFS and OS were 10.8 (95% confidence interval [CI], 7.4-13.5) and 20.7 (95% CI 13.0-NA) months with 1-year survival rate of 73.4%. The median PFS of locally advanced and metastatic diseases was 12.7 and 7.4 months, and the median OS of locally advanced and metastatic diseases was 26.1 and 18.8 months, respectively. Conversion surgery was performed in 2 patients among 19 locally advanced diseases. The reasons for treatment failure was disease progression in 31, unacceptable toxicities in 4, deteriorated general conditions in 6, consent withdrawn in 3, others in 3. A second line chemotherapy was introduced in 29 patients. Major Grade 3-4 toxicities were neutropenia (22.4%) and mucositis (14.3%). No toxicity related death was observed.

Conclusions: In this phase II trial, gemcitabine, S-1 and LV combination therapy was tolerable and can potentially be a treatment option for advanced pancreatic cancer. Legal entity responsible for the study: The University of Tokyo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

738P Antibiotics may enhance the efficacy of gemcitabine treatment for advanced pancreatic cancer


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Background: It has been reported that bacteria can metabolize gemcitabine (gem) into its inactive and contribute to the drug resistance. It was also reported that the resistance was abrogated by cotreatment with antibiotics (Geller LT, et al. Science 2017, in which, many of human pancreatic ductal adenocarcinoma samples contained causal bacteria which potentially mediates tumor resistance to gem. We therefore hypothesized the use of antibiotics may affect clinical outcomes of gem therapy in patients (pts) with pancreatic cancer (PC).
Results: One hundred twenty-four pts were treated with gem alone as first-line therapy and had the following characteristics: median age of 72 yrs, 59% male, 39% 55-64/4% 65-74 yrs, 14% 75 + yrs; 60% PS0/1/2/3; 35%/46%/19% of primary tumor of head/body/tail; median of PPS of 3.4 months, and median OS of 7.7 months. In 124 pts, 59% used antibiotics before treatment with gem. One hundred pts discontinued due to disease progression, while 24 pts due to toxicity or pts’ wish. 4 pts who received antibiotics had significantly longer PPS than those who did not receive antibiotic (4.2 vs 2.1 months, HR 0.64, 95%CI 0.43-0.96; P = 0.029). The association was not statistically significant after multivariate analysis adjusted for PS, tumor location, and number of metastatic sites (HR 0.73, 95%CI 0.43-1.17; P = 0.19). Median OS was numerically longer in pts with use of antibiotics than in pts without antibiotic (8.0 vs 5.5 months).

Conclusions: Our study indicated that antibiotic use before gem therapy was associated with favorable outcome in pts with advanced PC treated with gem. These findings warrant further exploratory studies and suggest scientific approach to identify antibiotics as an enhancer for gem.

Annals of Oncology
Background: Few studies have evaluated HRQoL in patients with ESCC and compared PROMs in A/NAC for ESPC. HRQoL scores were compared with reference values (ie, norms) and assessed longitudinally when possible. Minimally important difference (MID) estimates for the most frequently used PROMs were also assessed.

Methods: Studies Depression Scale (n = 2) and assessed longitudinally when possible. Minimally important difference (MID) estimates for the most frequently used PROMs were also assessed.

Results: Of 645 identified records, 37 PROMs and HRQoL outcomes were studies were retained. The EORTC QLQ-C30 and/or QLQ-PAN26 were used in 31 studies; other PROMs were used in 11 studies, including the Functional Assessment of Cancer Therapy (n = 4), 36-Item Short Form Survey (n = 3). The Center for Epidemiologic Studies Depression Scale (n = 2). At baseline (before and/or immediately after surgery), EORTC QLQ-C30 global health status/QoL scores for patients with ESCC were similar to reference values for PC but lower than those for all cancers. Among studies that reported QoL outcomes, QoL trends varied: 4 studies reported improvement from baseline to 3 mos post-resection, 1 study reported no change, and 1 study reported worsening.

Conclusions: The EORTC QLQ-C30 and QLQ-PAN26 are the most commonly used PROMs for ESCC and the most frequently used PROMs in A/NAC for ESPC. The EORTC QLQ-C30 is recommended for use in future studies of HRQoL in patients with ESCC.

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Disclosure: M. Reni: Grants, Personal fees, Non-financial support: Celgene; Grants and personal fees: Basilca, Merck, Serono, Heusin; Personal fees: Lilly, Pfizer, Basilca, Merck, Serono, Astra Zeneca, Novocure, Halomyze, Novartis, Shire, outside the submitted work. M.A. Temporero: Consultant: AbbVie, Advance Medical, BioPharm Communications, BMS, Celgene, Eisai, Iqvita, Pharmacys, Pharmacyt Biotech, Tocagen, Inc.; Ad Boards: AstraZeneca, CPRIT, Immunovia, Research contract: Halomyze. M.F. Botteman: Grants: Personal fees: Celgene; Personal fees: Roche, Shire, outside the submitted work. E. Lucas: Grants: Celgene, during the conduct of the study; Grants: Personal fees: Pharmaceutical and device manufacturers, outside the submitted work. All other authors have declared no conflicts of interest.

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Legal entity responsible for the study: Celgene Corporation.

Funding: Celgene Corporation.
Results: Initial treatment and mOS for all 4161 pts.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts, No</th>
<th>mOS, months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection*</td>
<td>466</td>
<td>17.5</td>
<td>15.4-20.1</td>
</tr>
<tr>
<td>N-</td>
<td>215</td>
<td>36.9</td>
<td>28.6-44.7</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gem</td>
<td>958</td>
<td>5.1</td>
<td>4.8-5.6</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>414</td>
<td>10.0</td>
<td>8.9-11.0</td>
</tr>
<tr>
<td>GemCap</td>
<td>125</td>
<td>8.4</td>
<td>6.8-9.8</td>
</tr>
<tr>
<td>GemS1</td>
<td>111</td>
<td>9.0</td>
<td>7.2-10.3</td>
</tr>
<tr>
<td>GemPac</td>
<td>85</td>
<td>7.1</td>
<td>5.5-9.7</td>
</tr>
<tr>
<td>Others</td>
<td>53</td>
<td>9.3</td>
<td>8.2-14.0</td>
</tr>
<tr>
<td>BSC</td>
<td>1696</td>
<td>1.6</td>
<td>1.5-1.8</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval, N: lymph node status, without – or with +, Gem: gemcitabine, FOLFIRINOX: 5-flourouracil, leukovorin, irinotecan and oxaliplatin, Cap: capecitabine, S1: tegafur/gimeracil/oteracil, Pac: nab-paclitaxel, others: other regimens. *There were 38 pts without histopathological reports on lymph node status.

Conclusions: The initial resected lymph node negative pts had the longest survival; double that of lymph node positive pts. Pts initially treated with chemotherapy had slightly shorter mOS than found in randomized trials, reflecting patient characteristics in an unselected population. The outcome of gemcitabine monotherapy was poor, possibly reflecting less treatment effect and selection of less fit pts. The BSC group was larger than expected and further investigations, particularly in early diagnosis of PC are of utmost importance.

Legal entity responsible for the study: The authors.

Funding: The Axel Muusfeld foundation.

Disclosure: All authors have declared no conflicts of interest.

| 744P | Trends of care of non-metastatic pancreatic cancer patients in Ireland |

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Background: Surgery offers the only chance of cure in non-metastatic pancreatic cancer. However, chemos- and radiotherapy also play important roles in pancreatic cancer care. How each of these different modalities of treatment impact on pancreatic cancer outcome is unclear. The National Cancer Registry (NCRI) is a publicly appointed body, established to collect and classify information on all cancer cases which occur in Ireland. We analysed these data with the objective to examine the trend of care of stage 1 to 3 pancreatic cancer in Ireland.

Methods: Pancreatic cancer data have been collected by NCRI since 1994. Only those with stage 1 – 3 adenocarcinoma of the pancreas (PDAC) were included in the final analyses. Descriptive statistics, Pearson chi-square test and survival analysis using Kaplan Meier curve with log-rank test and cox regression was performed.

Results: Between Jan 1994 and Dec 2013, of the 8230 patients with pancreatic cancer identified from the NCRI database, 4298 pts had histologically proven adenocarcinoma. Among these, 1177/272% of patients (pts) had stage 1 – 3 disease. 52% were male and 74% of pts were over 60 years of age. Stage 1, 2 and 3 disease comprised 25%, 32% and 42% of pts respectively. Overall 48% of pts had surgery, 44% had chemotherapy and 21% had radiotherapy. 364, 31% pts did not have any therapy at all. Compared to those who did not have any treatment, there was an incremental benefit in overall survival (OS) with the more number of different modalities of treatment involved (Table). OS was 3 mos with no treatment, 8 mos with either chemo or radiotherapy (HR 0.57), 11 mos with chemo and radiation (HR 0.46), 18 mos with surgery only (HR 0.27) and 20 mos with surgery with chemo and/or radiation therapy (HR 0.24).

Table: 744P

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>364</td>
<td>3 months</td>
<td>0.24 (95% CI: 0.20 – 0.28)</td>
</tr>
<tr>
<td>Multimodality therapies including surgery</td>
<td>287</td>
<td>20 months</td>
<td>0.27 (95% CI: 0.22 – 0.32)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>245</td>
<td>18 months</td>
<td>0.46 (95% CI: 0.36 – 0.58)</td>
</tr>
<tr>
<td>Multimodality therapy (no surgery)</td>
<td>179</td>
<td>8 months</td>
<td>0.57 (95% CI: 0.48 – 0.69)</td>
</tr>
</tbody>
</table>

Conclusions: Multimodality therapy with surgery improves OS in non-metastatic pancreatic cancer with incremental benefit seen from even single modality therapy.

Legal entity responsible for the study: Rozana Abdul Rahman, Ray McDermott.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

| 745P | Anti-hypertensive medication, sRAGE, and risk of pancreatic cancer: Results from the women’s health initiative study |

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Background: Pancreatic cancer is the 4th leading cause of cancer death in the United States. With its anti-inflammatory property, soluble receptor for advanced glycation end product (sRAGE) has been associated with lower risk of pancreatic cancer. Anti-hypertensive - (anti-HT) medications were shown to modulate sRAGE levels and AGE/RAGE signaling pathway. However, few large-scale population based study have evaluated the associations between antihypertensive medications and risk of pancreatic cancer.

Methods: A total of 145,551 postmenopausal women aged 50 to 79 years with no prevalent cancer from Women Health Initiative (WHI) were included with a mean follow-up of 13.8 year. Medication data including product and generic name, duration of use, and dosage form were collected at baseline recruitment (1993-98). We examined four anti-HT drugs including B-blockers, diuretics, angiotensin converting enzyme inhibitors (ACEI) and calcium channel blockers (CCB). Serum levels of sRAGE were measured in a subset of 1,466 study participants using immunoassay. Cox proportional hazard regression model was performed to obtain hazard ratio (HR) and its 95% confidence interval (CI) for each anti-HT medication use and its duration of use in association with risk of pancreatic cancer.

Results: By August 29, 2014, a total of 841 incident pancreatic cancer cases were ascertained through annual self-administered questionnaires and confirmed by central adjudication. Increased risk of incident pancreatic cancer was found among ever users of short-acting CCB (HR = 1.66, 95% CI: 1.20-2.29) and long-term (> 3 years) users of short-acting CCB (HR = 2.07, 95% CI: 1.42-3.02) compared to ever users of other anti-HT medications. Average sRAGE levels were lower in short-acting CCB ever users than those who took other anti-HT medication (1,158 pg/ml versus 1,446 pg/ml, P = 0.032).

Conclusions: We found a positive association between short-acting CCB use and risk of incident pancreatic cancer in postmenopausal women. Future studies are warranted to confirm these findings and elucidate potential mechanisms by which short-acting CCBs may influence development of pancreatic cancer, such as modulating RAGE signaling pathway.

Legal entity responsible for the study: Li Jiao.

Funding: National Cancer Institute.

Disclosure: All authors have declared no conflicts of interest.
Usefulness of the first screening using apolipoprotein A2 isoforms as the enrichment strategy for pancreatic cancer and its risk diseases

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Background: We recently reported the usefulness of apolipoprotein A2 isoforms (apoA2-α) as a plasma/serum biomarker for the early detection of pancreatic cancer (PC) and its risk diseases, and the level of apoA2-α/AT, which is one of apoA-α, is significantly decreased in early stage PC and risk diseases. To evaluate the possibility of usefulness as the screening biomarker, we prospectively tested the performance of apoA2-AT/AT as a first screening method for PC and its risk diseases in general population.

Methods: Study participants were prospectively enrolled from the subjects of medical checkup at 6 institutions between Oct 2015 and Jan 2017. We measured the plasma level of apoA2-AT/AT by using ELISA, and all participants with the positive results from the level of apoA2-AT/AT (<35 μg/mL) were recommended for 2nd examination with contrast enhanced-CT (CECT), MRI, or EUS.

Results: Among a total of 5,120 participants registered in this study, 83 were positive (Positive rate: 1.6%). In the 83 subjects with the positive results, 55 (66.3%) underwent 2nd examination. In total, 14 pancreatic diseases were detected in 23 (41.8%) of 55. They included a 1 PC, 12 pancreatic cystic lesions (PCL), and 3 chronic pancreatitis (CP). Furthermore, 14.3% of apoA2-AT/AT positive subjects had abnormal ultrasonographic findings in the pancreas, while the subjects with ultrasonographic abnormalities of the pancreas under a medical checkup were 3.2% of the participants who underwent endoscopic ultrasonography. Taken together, apoA2-AT/AT could significantly accumulate the subjects with abnormal ultrasonographic findings by 4.53 times in comparison with a normal medical checkup for general population.

Conclusions: Plasma apoA2-AT/AT as a first screening method in general population could improve an efficiency of detection of PC and its high-risk diseases.

Legal entity responsible for the study: Kobe University Graduate School of Medicine, Department of Gastroenterology.

Funding: Japan Agency for Medical Research and Development.

Disclosure: All authors have declared no conflicts of interest.

Survival-associated factors and a prognostic nomogram in resected pancreatic cancer: A large international population-based cohort study

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Background: Pancreatic cancer (PaC) remains extremely lethal worldwide even after resection. This large international population-based study aimed at exploring factors associated with survival in resected PaC, and at developing and globally validating a survival-predicting nomogram.

Methods: Data of PaC patients resected in 2003–2014 were obtained from multiple European national cancer registries and the US SEER-18 Program. Multivariable Cox proportional hazards models were constructed to investigate the associations of patient and tumor characteristics with overall survival. Prognostic factors remaining after backward selection in the Cox model were used to build a nomogram, which was cross-validated to bootstrap internal validation and external validation using the European databases. Predictive accuracy was assessed using the concordance-index.

Results: Totally 24,863 resected PaC patients were included, with median survival of 12.9 months and 5-year survival rates of 14%–28%. In main analysis, patient age, tumor T, N, and M stages, histology, and differentiation were significantly associated with survival, with country-specific association patterns and strengths. Additionally, hospital type, tumor size, number of positive nodes, performance status, and certain comorbidities were associated with survival in countries with available informa-

Conclusions: In these international population-based cohorts, resected PaC patients have distinct characteristics independently associated with survival. A personalized postoperative survival-predicting nomogram is established and internationally validated, which would be practical and helpful clinically and aid to patient stratification in international studies.

Legal entity responsible for the study: Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ).

Funding: German Cancer Aid (Deutsches Krebsfonds).

Disclosure: All authors have declared no conflicts of interest.

Predicting survival of pancreatic cancer using supervised machine learning

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Background: Pancreatic cancer is one of the major deadliest cancers, ranking fourth among causes of cancer-related deaths. Pancreatic cancer patients suffer from a poor prognosis with a 5-year survival rate of only 6%. Predicting pancreatic cancer survival is challenging due to different tumor characteristics, treatments and patient populations. Reliable predictions can help in achieving more personalized and targeted management. In this study we test the ability of machine learning to predict pancreatic cancer survival.

Methods: Pancreatic cancer patients were identified through the Surveillance, Epidemiology and End Results database (2010–2014). Clinical data for patients were extracted including: age, sex, race, tumor site, tumor histology, grade, cancer sequence number, TNM stage, surgery, tumor size, tumor extension, and survival months. Patients’ records were randomly divided into a training set (80%) and a validation set (20%) to predict survival at 6, 12, and 24 months. Different supervised machine learning models were tested to identify models with best predictions.

Results: We identified 14631 patients with median survival of 13 months. Random Forest algorithm achieved better results compared to other tested models. For evaluating model performance, the Area Under the Receiver Operating Characteristic Curve (AUC) of survival prediction was calculated. The trained model yielded AUCs of 85.3% at 6 months, 84.6% at 12 months and 83.2% at 24 months. The most important characteristics which influenced model prediction were: age at diagnosis (19.9%), tumor size (18.5%), surgery (14.6%), and tumor extent (8.4%).

Table 748P Performance metrics of the trained machine learning model

<table>
<thead>
<tr>
<th>Area Under Curve (AUC)</th>
<th>Precision (positive predictive value)</th>
<th>Accuracy</th>
<th>Recall (sensitivity)</th>
<th>F1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months Survival</td>
<td>85.3%</td>
<td>81%</td>
<td>81.6%</td>
<td>82%</td>
</tr>
<tr>
<td>12-months Survival</td>
<td>84.6%</td>
<td>78%</td>
<td>77.8%</td>
<td>78%</td>
</tr>
<tr>
<td>24-months Survival</td>
<td>83.2%</td>
<td>80%</td>
<td>80.1%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Conclusions: Predicting survival of patients with pancreatic cancer can be achieved using machine learning with good performance of prediction. Improved survival prediction can help in making better treatment decisions and planning social and care needs.

Legal entity responsible for the study: Mohamed H. Osman.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

The prognostic value of the modified glasgow prognostic score (mGPS) in predicting overall survival (OS) in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) receiving liposomal irinotecan (nal-IRI)+5-fluouracil and leucovorin (5-FU/LV)

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Background: mGPS has been identified as a prognostic factor of OS in patients with pancreatic cancer. Here we report the association between mGPS and OS in a post-hoc analysis of the NAPOLI-1 study (NCT01495460), which demonstrated improved
survival for na-BLI-1 5-FU/LV vs 5-FU/LV in the treatment of patients with mPDAC previously treated with gemcitabine-based therapy.

**Methods:** All patients treated in the NAPOLI-1 study with available baseline plasma C-reactive protein (CRP) and albumin data (data cutoff: Nov 16, 2015) were included in this post-hoc analysis. Eligibility criteria were stratified by mGPS (mGPS-0: CRP ≤10 mg/L, CRP >10 mg/L, albumin >35 g/L, and mGPS-2: CRP >10 mg/L, albumin <35 g/L). OS was assessed in individual and pooled treatment arms. A stepwise Cox regression model of OS was used to evaluate the prognostic significance of mGPS.

**Results:** Baseline plasma C-reactive protein and albumin data was available for N = 184 patients: mGPS-0: n = 79; mGPS-1: n = 88; mGPS-2: n = 17. For patients in pooled treatment arms, median OS was worse for the mGPS-1 group than for the mGPS-0 group (4.0 vs 8.0 months, respectively), but was comparable between the mGPS-2 and mGPS-1 groups (3.2 vs 4.0 months, respectively). Multivariate analysis revealed both mGPS-1 and mGPS-2 were independent predictive factors of death (mGPS-1: HR, 3.34; 95% CI, 2.25–4.5, P < 0.001; mGPS-2: HR, 5.89; 95% CI, 3.21–10.80, P < 0.001). Similarly, analysis by treatment arm showed OS of patients treated with na-BLI-1 5-FU/LV was significantly worse in the mGPS-1 (N = 26) and mGPS-2 (N = 5) groups than in the mGPS-0 (N = 27) group (4.6, 3.3 vs 9.3 months, respectively).

**Conclusions:** Data from this post-hoc analyses of mGPS in patients with mPDAC previously treated with gemcitabine-based care consistent with the reports of the prognostic value of the mGPS in estimating OS. Median OS was significantly improved in pts with a mGPS-0 vs mGPS-1 or mGPS-2, including the treatment group of patients receiving na-BLI-1 5-FU/LV.

**Clinical trial identification:** NCT01494506.

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**Legal entity responsible for the study:** Ipsen Biopharmaceuticals, Inc.

**Funding:** Ipsen Biopharmaceuticals, Inc.

**Disclosure:** T. Chen: Consulting or advisory role: Bristol-Myers Squibb, Five Prime Therapeutics, Lilly, Merck Serono, Novartis, Polaris, TTY Biopharm; Patents, Royalties, Other intellectual property: Anti-alpha- enolase (ENO-1) monoclonal antibody to HumL billionaire. Taiwan. B. Belanger, B. Mirakhur: Employee stock, Other ownership interests: Ipsen Biopharmaceuticals, Inc. F.A. de Jong: Employee: Shire Stock, Other ownership interests: Amgen, Shire, J. Sovika: Consulting, Advisory role: Basilea, Celgene, Lilly, Merck, the Merrimack, Research funding: 45C; Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Novartis, Travel, accommodations, expenses: Celgene, Roche. All other authors have declared no conflicts of interest.

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**750P** Prognostic value of the neutrophil-lymphocyte ratio and CA 19-9 in predicting survival endpoints with metastatic pancreatic cancer

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**Background:** The predictive value of different prognostic biomarkers has been studied in various cancer types. The aim of our study is to determine the degree of risk and prognostic significance of the pre-treatment neutrophil-to-lymphocyte ratio (NLR) and CA19-9 level in patients with metastatic pancreatic cancer and establish its relation with survival.

**Methods:** In our study, clinical and laboratory data of 118 patients with metastatic pancreatic cancer at the time of diagnosis were retrospectively analyzed. Overall survival (OS) rates were calculated using the Kaplan–Meier method. The Cox regression analysis was used to determine the prognostic factors affecting pancreatic cancer.

**Results:** The mean age of the patients was 67 ± 9.57 years. The patients were analyzed during the follow-up, and the median OS was 12 months (95% CI: 9.73–14.26).

**Conclusions:** According to ROC curve analysis, the cut-off value was 5.54 (AUC:0.653,95%CI:0.56–0.73, P = 0.006) for NLR and 437 (AUC:0.670,95%CI:0.57–0.75, P = 0.002) for the CA19-9 level. Statistically significant differences were observed between the CA19-9 level (P < 0.001) and NLR (P < 0.001) and OS. As a result of the multivariate Cox regression analysis, NLR (≥3.54 vs < 3.54, HR = 2.17, 95% CI: 1.17–4.03, P = 0.013) and the CA19-9 level (≥437 vs < 437, HR = 1.81, 95% CI: 1.08–3.03, P = 0.022) were found to be significant prognostic factors in OS analysis.

**Disclosures:** In our study, the pre-treatment NLR and CA19-9 level were found to be reliable predictive markers for poor prognosis in patients with metastatic PC. According to the results of our study, the NLR and CA19-9 level can be used in predicting the survival of patients with pancreatic cancer. We believe that our findings will shed light on the management of treatment protocols for patients diagnosed with metastatic pancreatic cancer.

**Legal entity responsible for the study:** Isu Dede.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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### Table: 751P

<table>
<thead>
<tr>
<th>Patients</th>
<th>N (%)</th>
<th>N (%)</th>
<th>P value</th>
<th>N (%)</th>
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<tr>
<td>All</td>
<td>&lt;8 mmol/L</td>
<td>&gt;8 mmol/L</td>
<td>&lt;14 mmol/L</td>
<td>≥14 mmol/L</td>
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<tr>
<td>Stage 1-4</td>
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<td>360</td>
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<td>232</td>
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<tr>
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<td>274</td>
<td>7.6 (6.7-8.3)</td>
<td>201</td>
</tr>
<tr>
<td>Curative</td>
<td>115</td>
<td>83</td>
<td>27.4 (21.8-34.0)</td>
<td>29</td>
</tr>
</tbody>
</table>

According to ROC curve analysis, the cut-off value was 5.54 (AUC:0.653,95%CI:0.56–0.73, P = 0.006) for NLR and 437 (AUC:0.670,95%CI:0.57–0.75, P = 0.002) for the CA19-9 level. Statistically significant differences were observed between the CA19-9 level (P < 0.001) and NLR (P < 0.001) and OS. As a result of the multivariate Cox regression analysis, NLR (≥3.54 vs < 3.54, HR = 2.17, 95% CI: 1.17–4.03, P = 0.013) and the CA19-9 level (≥437 vs < 437, HR = 1.81, 95% CI: 1.08–3.03, P = 0.022) were found to be significant prognostic factors in OS analysis.

**Conclusions:** In our study, the pre-treatment NLR and CA19-9 level were found to be reliable predictive markers for poor prognosis in patients with metastatic PC. According to the results of our study, the NLR and CA19-9 level can be used in predicting the survival of patients with pancreatic cancer. We believe that our findings will shed light on the management of treatment protocols for patients diagnosed with metastatic pancreatic cancer.

**Legal entity responsible for the study:** Isu Dede.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Clinical utility of serum type III collagen in patients with pancreatic carcinoma

Background: Collagen III is highly expressed in pancreatic cancer (PC) stroma. Collagen accumulation compromises penetration of macromolecules into tumor tissues and is associated with poorer outcome and increased tumor invasion. The aim of this biomarker study was to investigate the clinical utility of serum pro-peptide of type III collagen (PRO-C3) in patients with PC, including 851 consecutive subjects with histologically confirmed PC, a cohort from the Danish BIOPAC study (ClinicalTrials.gov ID: NCT03311776) including 851 consecutive subjects with histologically confirmed PC, and increased with greater stage. Higher levels were associated with poorer outcome in univariate analyses, as was log2-transformed PRO-C3 (HR = 0.001). No statistically significant difference for serum PRO-C3 was observed in multivariate models, while CA19-9, CRP, YKL-40 along with higher PS and stage remained independently significant. PRO-C3 was positively correlated with smoking yes/no: 207/629; smoking yes/no: 50 vs. 50-69 vs. 70+ (P < 0.001). No statistically significant difference for serum PRO-C3 was observed in patients with pancreatic cancer who underwent palliative chemotherapy.

Methods: A cohort from the Danish BIOPAC study (ClinicalTrials.gov ID: NCT03311776) including 851 consecutive subjects with histologically confirmed PC, a cohort from the Danish BIOPAC study (ClinicalTrials.gov ID: NCT03311776) including 851 consecutive subjects with histologically confirmed PC, and increased with greater stage. Higher levels were associated with poorer outcome in univariate analyses, as was log2-transformed PRO-C3 (HR = 0.001). No statistically significant difference for serum PRO-C3 was observed in multivariate models, while CA19-9, CRP, YKL-40 along with higher PS and stage remained independently significant. PRO-C3 was positively correlated with smoking yes/no: 207/629; smoking yes/no: 50 vs. 50-69 vs. 70+ (P < 0.001). No statistically significant difference for serum PRO-C3 was observed in patients with pancreatic cancer who underwent palliative chemotherapy.

hazardous concentration: 752P Clinical utility of serum type III collagen in patients with pancreatic carcinoma

V. W-C. Chou, 1 J-S. Chen, 2 Y-Y. Chen, 3 C-H. Lu, 4 P-H. Chang 5

Background: Veno US thromboembolism (VTE) is a common complication in patients with pancreatic cancer. VTE in Asian patients with cancer is known to be less prevalent than in Western patients; however, few studies have reported the epidemiology and clinical outcomes of VTE in Asian patients with pancreatic cancer. This study investigated the incidence, risk factors, and clinical outcome of VTE in patients with pancreatic cancer who underwent palliative chemotherapy.

Methods: Medical records of VTE incidence in patients after initiation of chemotherapy were retrospectively reviewed. The clinical characteristics of 838 patients were analyzed to identify independent predictors of VTE and survival outcome.

Results: With a median follow-up period of 7.7 months (1.6–55.6), VTE occurred in 67 (8.0%) of the 838 patients. The 6-, 12-, 24-, and 36-month cumulative incidences of VTE were 5.6%, 8.9%, 19.4%, and 24.3%, respectively. Of the 67 patients who developed VTE, 26.9%, 53.8%, and 70.2% of VTE occurred within 2, 4, and 6 months of chemotherapy initiation, respectively. Predictors of VTE in patients with VTE were white blood cell count >11,000/µl of peripheral blood and presence of liver metastases. Khorana risk score was not a significant predictor of VTE. Patients with VTE were not significantly associated with a poorer survival outcome than those without VTE.

Conclusion: The incidence of VTE in Asian patients was found to be half that in Western patients. Only patients with early onset VTE had a poorer prognosis than those without VTE. Awareness of the clinical characteristics and survival outcome of patients with VTE may assist clinicians and patients in choosing the appropriate prophylaxis and management of VTE for Asian patients with pancreatic cancer.

Legal entity responsible for the study: Wen-Chi Chou.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

V. W-C. Chou, 1 J-S. Chen, 2 Y-Y. Chen, 3 C-H. Lu, 4 P-H. Chang 5

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Legal entity responsible for the study: Wen-Chi Chou.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

V. W-C. Chou, 1 J-S. Chen, 2 Y-Y. Chen, 3 C-H. Lu, 4 P-H. Chang 5

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Legal entity responsible for the study: Wen-Chi Chou.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Merck KGaA, Darmstadt, Germany.


Table: 758P

<table>
<thead>
<tr>
<th>ITT</th>
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<tr>
<td>625 mg/m²</td>
<td>725 mg/m²</td>
</tr>
<tr>
<td>(n = 8)</td>
<td>(n = 6)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (13)</td>
</tr>
<tr>
<td>PR</td>
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Conclusions: NUC-1031 + cisplatin demonstrated a very high ORR, with a favourable safety profile, and may provide an improved treatment option over cis/gem for advanced BTC. Further development of NUC-1031 in BTC is planned.

Clinical trial identification: NCT02351765.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: NuCana.

Disclosure: All authors have declared no conflicts of interest.

758P A new ProTide, NUC-1031, combined with cisplatin for the first-line treatment of advanced biliary tract cancer (ABC-08)

M.G. McNamara1, J. Bridgewater2, D. Palmer3, H. Wasan4, W.D. Ryder5, C. Gnanaranjan6, E. Ghazaly1, T.F. Evans7, I.W. Valle8

Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; 1Oncology, University College London Hospitals London, London, UK; 2Medical Oncology, Clatterbridge Cancer Centre, Liverpool, UK; 3Medical Oncology, Imperial College London - Hammersmith Hospital, London, UK; 4MAHIC-CTU, The Christie NHS Foundation Trust, Manchester, UK; 5Cancer Institute, Bart’s Cancer Institute-Queen Mary University of London, London, UK; 6Centre for Haemato-Oncology, Bart’s Cancer Centre, London, UK; 7Institute of Cancer Sciences, Beatson Institute for Cancer Research, Glasgow, UK

Background: Cisplatin + gemcitabine (cis/gem) is the standard global care of standard for 1st-line treatment of patients (pts) with locally advanced/metastatic biliary tract cancer (BTC). No agents have regulatory approval for this disease. Cis/gem achieves an objective response rate (ORR) of 26% and median overall survival (OS) of 11.7 months (ABC-02). Inherent/acquired resistance mechanisms limit gemcitabine efficacy. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome resistance mechanisms associated with poor gemcitabine response.

Methods: Pts with locally advanced/metastatic BTC, ECOG PS of 0 and 1 prior systemic therapy received NUC-1031 (625 or 725 mg/m²) combined with cisplatin (25 mg/m²) on days 1, 8 and 21 every 21 days. Primary endpoints: safety and determination of RP2D. Secondary endpoints: ORR, pharmacokinetics, progression-free and OS.

Results: 14 pts (median age 61 yrs, 8 male; 5 hilar, 4 distal bile duct, 2 intrahepatic, 2 ampullary and 1 gallbladder) were enrolled across cohorts 1 (625 mg/m², n = 8) and 2 (725 mg/m², n = 6). 11 pts completed ≥1 cycle and were efficacy evaluable, receiving a median of 6.5 cycles (range 3.5-12). ORR was 64% (1 CR, 6 PRs) and DCR: 73%. PFS/ OS data collection is ongoing. High, durable intracellular levels of the active anti-cancer metabolite (TH-302) were achieved.

Conclusions: NUC-1031 + cisplatin demonstrated a very high ORR, with a favourable safety profile, and may provide an improved treatment option over cis/gem for advanced BTC. Further development of NUC-1031 in BTC is planned.

760P Phase II study of evofosfamide (TH-302) monotherapy as a second-line treatment in advanced biliary tract cancer

L.J. Tseang1, I.H. Lee2, G.J. Cheon3, Y.J. Bang2, D.Y. Oh1

1Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 2Medical Oncology, Seoul National University Hospital, Seoul, Republic of Korea; 3Department of Nuclear Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Background: Evofosfamide (TH-302), a nitromidazole-linked produg of a brominated version of isophosphoramide mustard, is converted to an activated form and acts as a DNA crosslinking agent when exposed to a hypoxic environment. Biliary tract cancer (BTC) is well known to contain large hypoxic area, and there is no standard 2nd line chemotherapy in advanced BTC. This study is a prospective, open-label, single-arm phase II trial to evaluate the efficacy and safety of evofosfamide as 2nd line treatment in advanced BTC.

Methods: Patients (pts) with unresectable or recurrent BTC whose disease progressed after 1st line chemotherapy were enrolled. Pts received evofosfamide at a dose of 340 mg/m² via intravenous (IV) infusion over 30 minutes on Day 1, 8, 15 of every 28-day cycle. The primary end point was progression-free survival (PFS) rate at 4 months. Secondary end points included overall survival (OS), PFS, objective response rate (ORR), disease control rate (DCR), metabolic response by 18F-FDG PET, and safety profile. Response evaluation was done every 8 weeks using RECIST v1.1. Metabolic response was evaluated by PERCIST v1.1, and toxicity was assessed by CTC-AE v4.03.

Results: A total of 20 pts were treated with IP and 16 were response-evaluable. The median age was 58.7 years (range 34.90 - 62.9). The primary origin of tumor was intrahepatic cholangiocarcinoma in 9 pts, extrabiliary BTC 3, gallbladder cancer 6, and ampullary of vater 2. 16 pts had ECOG PS 0, and 4 had ECOG ≥1. There was no objective response, stable disease was observed in 9 pts, results in DCR 56.3%. The PFS rate at 4 months was 31.25%. The median PFS was 3.80 months (95% CI 1.03 - 5.37), and the median OS was 6.37 months (95% CI 3.94 - 8.99). Liver metastasis was associated with poor PFS. Reduction of tumor metabolic activity was observed in 8 pts out of 14 (57.1%). Majority of adverse events (AEs) were grade 1/2; neutropenia(30%), anemia (59%), thrombocytopenia (49%), nausea (13%), arthralgia (5%). Grade 3 anemia was observed in 15%, anorexia 5% and arthralgia 5%. There was no treatment-related death.

Conclusions: Evofosfamide monotherapy showed promising efficacy in terms of disease stabilization and PFS and OS, and acceptable AE profiles used as 2nd line treatment in advanced BTC.

Clinical trial identification: NCT02433639.

Legal entity responsible for the study: Do-Youn Oh, Seoul National University Hospital.

Funding: Merck Serono.

Disclosure: All authors have declared no conflicts of interest.
Results: A total of 16 patients were treated in four different dose cohorts. 11 patients completed the 8 cycles of combination therapy; 5 patients were early withdrawals. PCI of gemcitabine was well tolerated with no Dose Limiting Toxicities, and with a general safety profile characteristic of the patient population included. At 6 months, in the two highest dose cohorts independent reading showed that 7 out of 8 patients had radiologically evaluable tumours. Of these, 2 were complete and 2 partial responses, with one stable disease. In 17/19 target lesions before treatment, a > 20% reduction in tumour size was seen, with 12 lesions undetectable at 6 months. Median OS ended at 14.4 months. As of March 2018, 4 of the 16 patients are alive 24-3 to 38.8 months after treatment (overall study average 17.4 months).

Conclusions: In this dose escalation trial of PCI of gemcitabine in perihilar CCA patients, a safe and tolerable dose of light and Amphilene® was established. The overall safety profile and promising results, including a proportion of patients with highly durable objective tumor response, are encouraging. A larger, controlled and randomized study is underway.

Clinical trial identification: NCT01990158.

Legal entity responsible for the study: PCI Biotech AS.

Funding: PCI Biotech AS.

Disclosure: A. Høgest, L. Finnesand, H. Olsensva: Employee: PCI Biotech AS. All other authors have declared no conflicts of interest.

FOLFRINOX as a first-line chemotherapy for patients (pts) with advanced biliary cancer (BTC)

A. Riazi, 1 A. Kodama, 1 A. Karikari, 1 A. Kerecn, 1 J. Hopton, 1 M. Gerber, 1 S. Huma, 1 Y. Paik, 1 W. Almqvist, 2 J. Tjulandin, 3 J. Kjellman, 4 J. Gertz, 5 E. Kallberg, 6 H. Olson, 7 S. Sato, 8 T. Yamauchi, 9 K. Kajinami, 10 Y. Hasegawa, 11 T. Ioka, 12 T. Tohyama, 13 H. Yoda

Background: FOLFRINOX is a first-line regimen in the treatment of pancreatic cancer. Historically, BTC and pancreatic cancers were treated similarly with gemcitabine alone or combined with a platinum compound. A growing body of evidence supports the role of fluoropyrimidines in the treatment of BTC.

Methods: We retrospectively analyzed data of all our pts with locally advanced (LA) or metastatic (M) BTC who received FOLFRINOX as a first-line therapy from 2012/2013 to 2017/2017 at Paul Brousse University hospital. The main endpoints were OS, TTP, ORR, RFS, and toxicity.

Results: There were 42 pts: 17 male (40%) and 25 female (60%) pts aged 36 to 84 years (median: 70). Pts had PS of 0 (55%) and 1 (45%). They had intrahepatic cholangiocarcinoma (ICCA) (21 pts, 50%), gallbladder carcinoma (8 pts, 19%), perihilarCCA (7 pts, 17%), distalCCA (4 pts, 10%) and ampulloma (2 pts, 5%). No biopsy could be obtained in 2 pts. BTC was LA or M in 9 (21%) and 33 pts (79%) respectively. Biliary stent was placed in 14 pts (33%). A median (m) of 10 courses was given with m treatment duration of 6 months (m). At the cutoff on 01/01/2018, regimen was ongoing in 7 pts (18%). Dose intensity (m) was 74, 34 and 110 mg/m²w for inotecan, oxaliplatin and SFU respectively. The most common nonhematological toxicity was sensory neuropathy: grade 1/2 in 15 pts (36%), grade 3/4. We observed 15 PR (36%), 16 SD (38%), and 10 PD (24%); 1 pt had not been evaluated for efficacy. Fifteen pts (36%) were alive, 24 pts (57%) died, 3 pts (7%) lost to follow-up. Four out of 5 pts who underwent resection were alive without disease. At a median follow-up time of 12 mo (1 to 26), mTTP was 9 mo [95%CI, 5 – 12] and mOS was 15 mo [14 – 16]. mTTP was better for LA (not reached) than M-BTC (8 mo), p < 0.05; OS was statistically similar. mTTP was worse in pts with ICCA than other primaries (7 mo [4 – 10] vs 14 mo [9 – 19], p < 0.005); OS was not significantly different. ORR and DC were associated with both better TTP and OS. ORR: mTTP (16 vs 5 mo, p < 0.001), mOS (19 vs 11 mo, p = 0.01); DC: mTTP (10 vs 2 mo, p < 0.001), mOS (18 vs 7 mo, p < 0.002).

Conclusions: First-line FOLFRINOX offers promising results in patients with LA and M-BTC. It deserves prospective evaluation to further improve outcomes for advanced BTC.

Legal entity responsible for the study: Department of Oncology, Hôpital Paul Brousse.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Neoadjuvant vs. adjuvant chemotherapy for cholangiocarcinoma: A propensity score matched analysis

S. Yato, 1 H. Xie, 1 L. Riazi, 1 P. Sharma, 1 A. Mahipal, 1 R. McWilliams 1

1Department of Surgery, Mayo Clinic, Rochester, MN, USA, 2Department of Internal Medicine, Ridgeview Hospital, Yale New Haven Health System, Bridgeport, CT, USA

Background: The role of neoadjuvant-chemotherapy (NADJ) in cholangiocarcinoma is unknown. The purpose of this study is to evaluate whether NADJ improves overall survival (OS) in cholangiocarcinoma compared to adjuvant-chemotherapy (ADJ).

Methods: Using the National Cancer Database, we identified patients who underwent surgery and chemotherapy for stage I-III cholangiocarcinoma between 2008 and 2014. Patients with metastatic disease at diagnosis or unknown chemotherapy sequence with surgery were excluded. Propensity score for NADJ was calculated with multivariate logistic regression method. Matching with patients who received ADJ was then performed at the ratio of 1:3 using nearest neighbor method with a caliper width of 0.2. Covariates included in matching were: age at diagnosis, sex, race, insurance status, Charlson score, year of diagnosis, location of tumor, tumor grade, clinical stage, and use of radiation.

Results: 1450 patients met our inclusion criteria, 299 (20.6%) received NADJ while 1151 (79.3%) received ADJ. The median age at diagnosis was 63 years. Factors associated with higher (p < 0.05) use of NADJ compared to ADJ were: ages <54 (35% vs. 26%), white race (91% vs. 86%), year of diagnosis 2012-2014 (48% vs. 40%).
Advanced intrahepatic cholangiocarcinoma (iCCA) treated with arterial-directed therapies (ADT): Outcomes and safety from a multicenter Italian experience


Medical Oncology I, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto IRCCS, Padua, Italy; "Oncology Radiodiagnostico, Department, Istituto Oncologico Veneto IRCCS, Padua, Italy; "Oncologia 2 Università, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; "Medical Oncology I, Istituto Nazionale Tumori Regina Elena, Rome, Italy; "Oncologia, Policlinico S. Orsola-Malpighi, Bologna, Italy; "Medical Oncology, San Raffaele Scientific Institute, Milan, Italy; "Oncologia, Università University and General Hospital, Udine, Italy; "Medical Oncology, IRCCS Istituto di Candiolo, Candiolo, Italy; "Oncologia, Campus Bio-Medico di Roma, Rome, Italy

Background: Most of iCCA patients die because of hepatic progression, even in metastatic stage. Chemotherapy leads to modest increase in life expectancy; arterial-directed therapies (ADT), such as chemoembolization (TACE) or radioembolization (TARE), have been proposed to obtain local disease control, eventually leading to a survival benefit.

Methods: We conducted a multicenter retrospective study involving 8 Italian Cancer Centers to evaluate efficacy outcomes and safety of ADT in advanced iCCA. Primary endpoint was overall survival (OS) from the first ADT.

Results: 99 patients received at least one ADT from 2007 to 2017. TACE was performed in 74 patients, TARE in 25 patients. Median time from diagnosis of advanced disease to first ADT was 7.0 months. Median OS from first ADT was 11.9 months (95% CI: 9.9-16.1); progression-free survival was 3.4 months (95% CI: 3.2-4.8) with a disease control rate of 64% and an objective response rate of 20%. Adverse events (AE) after procedure were reported in 37 patients, more commonly low grade (G1-G2) abdominal pain (19%) and fever (18%); G3-G4 AE were reported in 11% of patients, while one fatal (G5) AE occurred due to brain hemorrhage one week after the procedure. No survival differences were observed in patients receiving more than one ADT (P=0.471) compared to those receiving only one procedure (n=52). OS according to procedure (TARE or TACE) was 19.1 and 10.5 months respectively (HR=0.53, 95% CI 0.32-0.88; P=0.031). Extraregional disease and CA19.9 levels >100 KU/L were significantly associated with worse OS at univariate analysis (HR=1.77 and 2.73 respectively).

Conclusions: Patients receiving ADT had good survival outcomes when compared with historical data of systemic chemotherapy, although authors acknowledge these data could also be driven by a selection bias. Procedures were feasible and tolerable, with limited serious AEs. Notably, patients receiving more than one procedure did not gain an OS benefit compared to those receiving only one ADT. According to these retrospective data, performing ADT in presence of extraregional disease may be questionable. Specific prospective studies should be designed in order to confirm ADT role in iCCA.

Legal entity responsible for the study: Istituto Oncologico Veneto IRCCS

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
765P Prognostic factors in patients with advanced biliary tract cancer (BTC) who showed durable disease control with first-line gemcitabine plus cisplatin (GemCis)

Y. Suzuki 1, M. Kan 1, K. Kimura 1, K. Umemoto 1, K. Watanabe 1, M. Sasaki 1, H. Takahashi 1, T. Hashimoto 1, H. Inoua 1, I. Ohara 3, S. Minatoya 1, M. Ikeda 1
1Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: GemCis is the standard first-line chemotherapy for patients with advanced BTC. In ABC-02 study, the BTC patients received up to 6-8 cycles of three-weekly GemCis. Currently, treatment strategy and prognostic factors of patients without progression to first-line GemCis is not well defined.

Methods: Advanced BTC patients treated with GemCis between April 2010 and February 2016 at Asan Medical Center, Seoul, Korea, were retrospectively analyzed. The patients without progression after 6-8 cycles were included in the study. Univariate and multivariate analyses were performed to identify prognostic factors for overall survival (OS).

Results: Among the 740 BTC patients in the initial screen, 231 cases (31.2%) were eligible for analysis. Median follow-up period was 23.8 months [IQR 18.1-36.3 months], the median OS from the initiation of treatment was 22.3 months [95% CI 19.0-25.7 months], and the median PFS was 12.5 months [95% CI 11.1-13.9 months]. Median age was 60-year-old (29-77) and 211 patients (91.3%) had ECOG performance status of 0 or 1 at the time of diagnosis. Objective response was achieved in 49 patients (21.2%). OS was significantly associated with number of metastatic site (>2 vs ≤2: Hazard ratio [HR] = 1.5, 95% CI 1.0-2.3, p = 0.04), best response to GemCis (stable disease vs partial response: HR = 1.9, 95% CI 1.3-2.7, p = 0.006). Maintenance therapy after durable disease control after at least 6 cycles of GemCis was not associated with OS (p = 0.47).

Conclusions: In patients who showed durable disease control to first-line GemCis, number of metastatic sites and objective response were significant poor prognostic factors. These results might help to design future clinical trials for this patient population.

Legal entity responsible for the study: Changhoon Yoo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

766P Nomograms predicting survival of patients with advanced or recurrent biliary tract cancer receiving a first-line chemotherapy

Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Background: Some clinical factors are known to be associated with the survival of patients with advanced biliary tract cancer (BTC). A comprehensive model based on these variables is necessary for prediction of an individual's survival and appropriate patient counseling.

Methods: A nomogram for predicting 1-year survival in patients with advanced BTC in the palliative chemotherapy setting was developed using clinical data from 222 patients with advanced or recurrent BTC who had received first-line systemic chemotherapy from 2006 to 2017 at The University of Tokyo Hospital (Baseline Nomogram). For 214 patients whose initial response to chemotherapy is known, another nomogram (Chemorresistance-based Nomogram) was constructed using the response to chemotherapy as additional variable. Nomogram performance in terms of discrimination and calibration ability was evaluated using the C-statistic.

Results: Two different nomograms were developed and subjected to internal validation. The baseline nomogram incorporated 8 baseline clinical variables (age, sex, performance status, tumor location, disease status, CEA, CA19-9, and modified Glasgow prognostic score), whereas the chemoresistance-based nomogram was composed of 9 variables including initial response to chemotherapy evaluated by RECIST ver 1.1. Internal validation revealed good performance of the two nomograms in discrimination: C statistics of 0.685 for the baseline and 0.734 for the chemoresistance-based nomogram, which showed better discrimination performance than the baseline nomogram.

Conclusions: This study suggests that individual 1-year survival probability of patients receiving first-line systemic chemotherapy for advanced or recurrent BTC can be reliably predicted by a nomogram-based method incorporating clinical variables and initial response to chemotherapy.

Legal entity responsible for the study: The ethical committee of The University of Tokyo.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

767P Stromal progesterone receptor expression and long-term survival in patients with resected periampullary adenocarcinoma

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Background: Early trials have reported a beneficial effect from tamoxifen treatment in patients with unresectable pancreatic cancer, in particular in women. However, the presence and prognostic significance of female hormone receptors in pancreatic or other periampullary cancers has not yet been described.

Methods: Immunohistochemical screening of normal and malignant pancreatic tissue revealed that the predominantly expressed female hormone receptor was the progesterone receptor (PgR), in particular in the cancer-associated stroma. The impact of PgR expression on overall survival (OS) was further examined on tissue microarrays with primary tumours from a consecutive retrospective cohort of 175 patients with resected periampullary adenocarcinoma.

Results: Median follow-up time was 29.7 (range 1.9-185.1) months. Stromal PgR positivity (PgR+), allowed denoted in 31% of the cases, was significantly higher in pancreaticobiliary-type than in intestinal-type tumours (58.7% vs 19.0%, p < 0.008), with an equal distribution between sexes. Stromal PgR+ was significantly associated with a prolonged OS in KRAS-mutated tumours, whereas the opposite was seen in KRAS wild-type tumours (p for interaction < 0.015). This association was particularly evident in women, with a median OS of 60.5 months for PgR+/KRAS mutated tumours and 9.9 months for PgR-/KRAS wild-type tumours (p for interaction <0.001). PgR expression was not prognostic in male patients.

Conclusions: The finding of stromal PgR expression, and its link to clinical outcome in a considerable proportion of pancreatic and other periampullary cancers is novel. The concept of tamoxifen treatment for patients with unresectable disease, in particular elderly women, should be pursued, and PgR and KRAS may be relevant biomarkers for improved patient stratification.

Legal entity responsible for the study: Karin Jirström.
A novel immune-inflammatory score to predict survival in patients (pts) with advanced biliary tract cancer (ABTC) receiving first-line chemotherapy (1-line cht)

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Medical Oncology, University Hospital of Modena, Modena, Italy

**Background:** Cht is the mainstream of treatment for ABTC with median overall survival (mOS) < 12 months. Given the palliative intent of treatment, its limited survival gain and not negligible toxicities it is of paramount importance to properly select pts.

**Determination of immune-inflammation are regarded as promising prognostic factors in ABTC.**

**Methods:** Clinical and laboratory data before starting 1-line cht were evaluated in 123 pts with unresectable locally advanced and metastatic ABTC (intrahepatic, perihilar and distal cholangiocarcinoma and gallbladder cancer) treated from 1st January 2010 to 31st July 2017 at Modena Cancer Centre. Potential prognostic factors were assessed by univariate (Cox proportional hazard univariate model) and multivariate analyses (multiple Cox proportional hazard regression with the likelihood ratio test).

**Results:** At univariate analysis ECOG PS ≤ 0, metastatic disease, gallbladder cancer, no previous surgery, monocht, LDH > upper limit of normal, albumin < 3.5 gr/dl, absolute neutrophil count (ANC) > 8000/μl, lymphocyte/monocyte ratio (LMR) < 2.1, neutrophil/lymphocyte ratio (NLR) > 3, platelet/lymphocyte ratio > 160, AST > 40 IU/L, gamma-glutamyl-transpeptidase > 40 IU/L, CEA > 9.5 ng/ml, CA19-9 > 700 U/l were significantly associated with shorter OS. At multivariate analysis, LMR < 2.1, NLR > 3, ANC > 8000/μl, albumin < 3.5 gr/dl retained statistical significance as poor prognostic factors. By combining these four variables, three different risk groups were identified: low-risk group (0 factors), intermediate-risk group (1-2 factors) and high-risk group (3-4 factors), with mOS of 22.12, and 5 months respectively (P < 0.001). The prognostic value of the score was independent from treatment procedures (doublet vs monocht) and primary tumour site (P < 0.001).

**Conclusions:** We developed a cost-effective and easily available scoring system that discriminates ABTC treated with 1-line cht into three, different, statistically significant prognostic groups. It could become a useful tool to add established factors for improving pts’ selection in daily practice.

**Legal entity responsible for the study:** Massimiliano Salati

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

The German-Registry of incidental gallbladder cancer and the GAIN- phase III trial: Transformation from a registry to treatment platform due to a trial in trial concept

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Institute of Clinical Cancer Research, Nordwest-Krankenhaus, Frankfurt am Main, Germany, 1Surgical Department, Retterer-Krankenhaus, Dillenheim, Germany

**Background:** The biggest biliary platform in Europe - the German-Registry (GR) shows significant survival benefit for radical resection (RR) in gallbladder carcinoma. But nevertheless results for T2-3 are still disappointing even after RR.

**Methods:** For data analysis the GR was used. Currently more than 1100 cases of incidental gallbladder carcinoma (IGBC) are registered. Based on the GR a new multicenter patient (pts) with the support of the DFG (grant) has been started in 20 centers in Germany and in addition a trial in trial concept, including GAIN and the GR is planned. GAIN is a randomized multicenter phase III trial for resectable and borderline resectable biliary tract cancers (BTC), evaluating the role of neoadjuvant CTX with Gem/Cis in a multimodal setting in front of and after surgery vs. upfront surgery alone. If screened pts. is not eligible for RR, wedge resection of the liver showed good data in T1b and T2. For T3 more radical techniques showed better results. Less than 50% of T2-3 tumors in the GR have had RR.

**Conclusions:** There is a significant benefit after RR in T1b–T3 IGBC but the results in T2-3 are directly linked in the whole entity of BTC. Data of current (PRODIGE 12, BILCAP) adjuvant trials are inconsistent. Therefore the multimodal concept based on a biliary network is needed. The gain RR is supported by the DFG and is also supported by the German AIO and the German CALG/ACO. Due to the trial in trial concept patients screened for GAIN but are candidates for 1st cht will be directly included in another 1st line trial without time delay so the project directly closes a healthcare gap. The data of the GR were already able to change the current treatment standards for GBIC in Germany, reflected by the current S3- Guidelines. So GR will now transform to treatment platform and potentially create a new way how to treat biliary pts.

**Clinical trial identification:** EudraCT: 2017-004444-38, DFG Projektnummer 316590476.

**Legal entity responsible for the study:** Krankenhaus Nordwest gGmbH Frankfurt

**Funding:** DFG (Deutsche Forschungsgemeinschaft/ German Research Foundation) DFG- Projektnummer 316590476.

**Disclosure:** T.O. Götze: COLI MSD, Lilly, BMS, Celgene, Shire, Bayer. All other authors have declared no conflicts of interest.
Conclusions: N- SBAs are associated with decreased nodal sampling compared to N+ SBAs. Low sampling is associated with decreased survival, possibly related to the presence of occult nodal disease. While further work is needed to determine what is considered adequate nodal sampling in N- SBAs, this analysis suggests that N- cases where less than 17 nodes have been examined have a poorer outcome.

Legal entity responsible for the study: Macede Thiessen.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 773P

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<td>12</td>
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<tr>
<td>Proportion of Cases by T Stage</td>
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<td>T2</td>
<td>11.5%</td>
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<td>T3</td>
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</tr>
<tr>
<td>T4</td>
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</table>

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy that accounts for 1–2% of gastrointestinal tumours. We evaluated the clinicopathological characteristics, outcomes and prognostic factors of patients who underwent surgery for SBA.

Methods: We retrospectively analysed the features and outcome parameters of 54 SBA patients from 6 Italian institutions between 2005 and 2017.

Results: The primary tumour was in the duodenum, jejunum and ileum in 30 (55.6%), 18 (33.3%) and 6 (11.1%) patients, respectively. Among the 54 patients studied, adjuvant chemotherapy were performed in 35.2% of patients with stage II and in 27.8% of patients with stage II. Resection margins were higher for chemonaive patients compared to treated patients (50% vs 25.9%). Median overall (OS) and progression-free survival (PFS) were 26.98 and 19.78 months, respectively. Duodenal adenocarcinoma (p = 0.022), lymph node metastases (p = 0.00269), long-term treatment with metformin (p = 0.00895), no adjuvant treatment (p = 0.0006) and PLR > 0.1766 (p = 0.0137) were associated with poorer overall survival outcomes. The factors associated with PFS were patients with older age (> 75 years) (p = 0.014) and 14 according to TNM system (p = 0.002).

Conclusions: The lack of well-defined guidelines for treatment of SBA justifies the heterogeneity of therapeutic choices resulting in negative impact on patient outcomes. Thus, there is an urgent need for prognostic and predictive biomarkers to guide therapy decisions and improve patient outcomes. Our results strongly suggest that the site, lymph node metastases, metformin and PLR > 0.1766 could be novel prognostic markers for SBA patients who undergo curative surgery. However, prospective studies are necessary to confirm the role of these factors and identify new potential biomarkers of treatment efficacy, that could improve the selection of the right treatment for the right patient.

Legal entity responsible for the study: Modena University Hospital.
minimize F, TR binding on macrophages that, based on preclinical evidence, is believed to minimize potentially negative interactions with other immune cells. A phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed preliminary evidence of activity in patients with advanced solid tumors, including RCC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 4 weeks (Q4W) has been established for tislelizumab.

Trial design: This global, phase 3, randomized, multicenter study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a potential first-line treatment of unresectable HCC. Adult patients, aged $\geq 18$ years, with unresectable, histologically confirmed HCC, an ECOG score $\leq 1$, Child-Pugh A classification, BCLC Stage C disease or BCLC Stage B disease that has relapsed after loco-regional therapy, and who have not received prior systemic therapy, are being enrolled. Approximately 640 patients from 100 international centers are planned to be randomized in a 1:1 ratio to receive tislelizumab 200 mg Q4W or sorafenib 400 mg orally BID. The primary outcome of this study is overall survival (OS) of patients treated with tislelizumab compared with OS of patients treated with sorafenib; secondary outcomes include objective response rate, progression-free survival, duration of response, time to progression, and quality-of-life outcomes. Safety/tolerability assessments include monitoring adverse events (AEs), including immune-related AEs, as well as physical examination, vital signs, and electrocardiograms. Exploratory endpoints include assessment of potential biomarkers, characterization of the tislelizumab pharmacokinetic profile in patients with HCC, and assessment of host immunogeneity to tislelizumab. As of April 11, 2018, 11 patients have been enrolled.

Clinical trial identification: NCT03412773.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Regina Switzer, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: Beigene, Ltd.

Funding: Beigene, Ltd.


Trial design: A phase III, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy

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Background: Gastric cancer is the fifth most common cancer, and is the third leading cause of cancer deaths worldwide. In patients with locally advanced or metastatic gastric cancer, fluoropyrimidine- and platinum-based combination chemotherapy is first-line standard of care. Despite refinement in chemotherapy regimens, outcomes are poor and median survival after first-line treatment remains low. A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD. Pamiparib [previously known as BGB-290] is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA-PARP trapping, and has demonstrated antitumor activity in preclinical models. In early phase clinical studies (NCT02361723; NCT03339151), pamiparib was generally well tolerated and showed preliminary antitumor activity. These studies also established 60 mg orally twice daily as the recommended pivotal dose.

Trial design: This double-blind, placebo-controlled, randomized, multicenter phase 3 study (NCT03427814) conducted in Asia, Australia, Europe, and North America is designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in ~540 patients with advanced gastric cancer who have responded to first-line, platinum-based chemotherapy. Patients who are $\geq$ 58 weeks after their last platinum-based dose of first-line chemotherapy will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo. Patient randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG status. Radiologic assessments will be centrally evaluated per RECIST every 8 weeks after first dose. The primary endpoint is progression-free survival, key secondary endpoints include safety/tolerability, overall survival, objective response rates, and duration of response.

Clinical trial identification: NCT03427814.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Aarati Rai, PhD (SuccinctChoice Medical Communications, Chicago, IL).

Legal entity responsible for the study: Beigene, Ltd.

Disclosure: Y. J. Bang: Consulting role, research funding: Samyang, Beigene, Astellas, Genentech, Roche; F. Chen, MedImmune, Novartis, MSD, Merck Serono, Bayer, GSK, BMS, Pfizer, Lilly, Boehringer Ingelheim, Macrogenics, Takeda, Boston Biomedical, Five Prime, HKD, Ono, Taiho, Beigene, Curis, GreenBay, C. Benn: Gilead, Genentech, BMS, Five Prime, Lilly, Merck, MedImmune, Genentech, MSD, Sorafenib, Taiho, H. Macrogenics, HKD, Novartis, OnoMed, Leap, TG Therapeutics, AstraZeneca, BI, Daiichi Sankyo, Bayer, Incyte, Apexigen, Roche, Kolan, SynDevRx, Forty Seven, Abbvie, StemCentra, Array, Onyx, Sanofi, Takeda, Abbott, Eisai, Celldex, Agios, Armo, CytoMs, Nektar, Armo, Boston Biomedical, Ipsen, Merrimack, Novartis, Tarveda, Tyrogenex, OncogeneX, Marshall Edwards, Pieris, Merusana, Calithera, Blueprint, Gristone, Evedo, Forma, Forty Seven, EMD Serono, Merus, R. Brachmann, K. Zhang, H. Farin: Employee: Beigene, M. Raki: Employee: Beigene, Ownership interest: Beigene, Clavis Oncology. All other authors have declared no conflicts of interest.

Trial design: The INTEGA trial will evaluate two trastuzumab and PD-1/PD-L1 based combinations to determine the best regimen to challenge the TOGA regimen in a phase 3 trial.

Trial design: INTEGA is a randomized exploratory phase II investigator initiated trial by the AIO esophagousphagogastrophic working group with two experimental arms. Patients (pts) with previously untreated (for metastatic disease) HER2 + or 2 (HER2 +) or 3 (HER2 +) EGA will be randomized to receive trastuzumab and nivolumab in combination with either mFOLFOX6 or ipilimumab (3mg/kg every 3 weeks). Treatment with nivolumab is limited to a maximum of 12 months, ipilimumab to 4 applications. Primary endpoint is 12month overall survival rate, which should be increased from 55% (TOGA regimen) to 70% in each arm. Based on a type I error of 5% and 80% power 41 pts per arm are required overall and with a 15% drop out rate 47 pts will be randomized. An early stopping rule will be applied in case of an increase in toxicity after the first 15 pts received at least two months of treatment. The trial is planned by a large translational program including immunophenotyping to determine and correlate the respective immune response signatures with clonal dynamics. Recruitment has started in March 2018. Overall 40 German sites are planned. Conclusion: The INTEGA trial will determine the feasibility and efficacy of trastuzumab and nivolumab in combination with either mFOLFOX6 or ipilimumab in 1st line HER2 + EGA. The translational research program will shed light on the potential mode of action of these novel combinations.

Clinical trial identification: NCT03499848.

Legal entity responsible for the study: AIO-Studien-gGmbH.

Funding: BMS.

Disclosure: E. Goek Kurt: Advisory board: Sanofi, Merck, BMS, MSD, Servier, Sirtex, Pfizer, Lilly; Speakers fees: Servier, MSD, BMS. M. Binder: Travel expenses: BMS, Hexal, Advisory board: Roche, BMS, MSD, Hexal, Takeda, Celgene, AbbVie; Speakers fees: Chugui, Roche, BMS, Janssen-Cilag, Gilead, Celgene, Acerogen; S. Lorenzen: Advisory board: Sanofi, Merck, BMS, MSD, Servier, Lilly, Roche; Speakers fees: Servier, Roche, BMS, Lilly, Roche; P. C. Thuss-Patience: Advisory board: Merck, Roche, Lilly, Pfizer, MSD, BMS, Nordis; S. E. Al-Batran: Advisory board, speakers fees: BMS. A. Hinke: Honoraria: Roche; S. Hegewisch-Becker: Advisory board: Lilly, BMS, Merck. C. Bokemeyer: Research funding: German Cancer Aid, Sanofi, Roche, Merck, GBA Innovationstiftung, BMS; Honoraria: Merck, Sanofi, Roche, Bayer, BMS, Servier, AstraZeneca; Advisory board: Lilly/ImClone, Novartis, Boehringer, Hexal, Bayer, Schering.
Background: Perioperative chemotherapy improves survival in locally advanced gastric and esophago-gastric adenocarcinoma (EGA), in comparison with surgery alone. The pathologic complete response rate (pCR) is a possible surrogate for survival and is influenced by the chemotherapy regimen given. We and others have previously described the efficacy of docetaxel/cisplatin/fluorouracil (DCF) in the perioperative management of this cancer. Research by other groups has shown equivalent efficacy and lesser toxicity of a modified DCF regimen. Given the promising activity of immune checkpoint inhibitors in these malignancies, we hypothesize that the addition of immuno-therapy with avelumab, an anti-PD-L1 agent, to mDCF chemotherapy (immuno- chemotherapy), will result in improved outcomes. Our trial is approved by Health Canada and our hospital Research Ethics Board. It is registered as NCT03288350 (www.clinicaltrials.gov).

Trial design: Eligible patients will receive neoadjuvant therapy consisting of 4 cycles of avelumab + mDCF, followed by surgery and assessment of pathologic response. Then they will receive 4 cycles of adjuvant mDCF therapy of mDCF + avelumab. Primary endpoint is pCR. Secondary endpoints are 2-year disease-free survival rate and incidence of non- hematological grade 3-4. Exploratory translational studies are planned. We hypothesize that immune chemotherapy will yield a pCR rate of 35% in patients treated with chemotherapy only (historical data). Main inclusion criteria are: diagnosis of gastric or EGA adenocarcinoma, locally advanced disease, adequate organ function, performance status 0-1, stages III-IV. Main exclusion criteria are: other histologies, metastatic disease, use of immunosuppressants, serious autoimmune disease, daily prednisone intake > 10 mg or equivalent. To validate the hypothesis with power of 0.80 and r = 0.50, 500 participants will be needed. Enrollment has started and is following a 2-stage Simon’s rule: accrual will stop if no more than 1 pCR is seen in the first 16 patients; if more than 6/50 patients show pCR, the trial will be considered successful in that the alternative hypothesis cannot be rejected.


Legal entity responsible for the study: Research Institute of the McGill University Health Centre.

Funding: EMD Serono.

Disclosure: T. Alcindor: Consultant: EMD Serono, BMS, Lilly. J. Asselah: Taiho, Ipsen, Pfizer. M. Vanhuyse: BMS. All other authors have declared no conflicts of interest.

**780TIP**
Phase II trial of perioperative PD-L1 inhibition with avelumab and mDCF chemotherapy for resectable locally advanced gastric and esophago-gastric adenocarcinoma

T. Alcindor1, A. Avan1, T. Opui2, J. Asselah2, M. Vanhuyse3, C. Mueller2, L. Fenn2

1Medicine & Oncology, McGill University Health Centre - Glen Site, Montreal, QC, Canada, 2Oncology, The McGill University Health Centre - Glen Site, Montreal, QC, Canada, 3Oncology, Cedars Cancer Center, Montreal, QC, Canada, 4Surgery, The McGill University Health Centre - Glen Site, Montreal, QC, Canada

Background: Perioperative chemotherapy improves survival in locally advanced gastric and esophago-gastric adenocarcinoma (EGA), in comparison with surgery alone. The pathologic complete response rate (pCR) is a possible surrogate for survival and is influenced by the chemotherapy regimen given. We and others have previously described the efficacy of docetaxel/cisplatin/fluorouracil (DCF) in the perioperative management of this cancer. Research by other groups has shown equivalent efficacy and lesser toxicity of a modified DCF regimen. Given the promising activity of immune checkpoint inhibitors in these malignancies, we hypothesize that the addition of immuno-therapy with avelumab, an anti-PD-L1 agent, to mDCF chemotherapy (immuno- chemotherapy), will result in improved outcomes. Our trial is approved by Health Canada and our hospital Research Ethics Board. It is registered as NCT03288350 (www.clinicaltrials.gov).

Trial design: Eligible patients will receive neoadjuvant therapy consisting of 4 cycles of avelumab + mDCF, followed by surgery and assessment of pathologic response. Then they will receive 4 cycles of adjuvant mDCF therapy of mDCF + avelumab. Primary endpoint is pCR. Secondary endpoints are 2-year disease-free survival rate and incidence of non- hematological grade 3-4. Exploratory translational studies are planned. We hypothesize that immune chemotherapy will yield a pCR rate of 35% in patients treated with chemotherapy only (historical data). Main inclusion criteria are: diagnosis of gastric or EGA adenocarcinoma, locally advanced disease, adequate organ function, performance status 0-1, stages III-IV. Main exclusion criteria are: other histologies, metastatic disease, use of immunosuppressants, serious autoimmune disease, daily prednisone intake > 10 mg or equivalent. To validate the hypothesis with power of 0.80 and r = 0.50, 500 participants will be needed. Enrollment has started and is following a 2-stage Simon’s rule: accrual will stop if no more than 1 pCR is seen in the first 16 patients; if more than 6/50 patients show pCR, the trial will be considered successful in that the alternate hypothesis cannot be rejected.


Legal entity responsible for the study: Research Institute of the McGill University Health Centre.

Funding: EMD Serono.

Disclosure: T. Alcindor: Consultant: EMD Serono, BMS, Lilly. J. Asselah: Taiho, Ipsen, Pfizer. M. Vanhuyse: BMS. All other authors have declared no conflicts of interest.
Annals of Oncology

Clinical trial identification: NCT03434379

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

Funding: F. Hoffmann-La Roche AG.

Disclosure: M.P. Ducreux: Employee: Sandoz. P. Follana: Advisory board, board of directors, consultant board: AstraZeneca, Novartis, Teasno, O. Bouche: Stock owner: Amgen, Bayer, Merck, Roche; Employment: Lilly, Pierre Fabre, Novartis. All other authors have declared no conflicts of interest.


Legal entity responsible for the study: UNICANCER.

Funding: French Program for Cancer Clinical Research (PHRC).

Disclosure: M.P. Ducreux: Wife employee: Sandoz. P. Follana: Advisory board, board of directors, consultant board: AstraZeneca, Novartis, Teasno, O. Bouche: Stock owner: Amgen, Bayer, Merck, Roche; Employment: Lilly, Pierre Fabre, Novartis. All other authors have declared no conflicts of interest.

Background:

Advanced hepatocellular carcinoma (HCC) is a disease of high unmet medical need. Despite considerable toxicities, sorafenib (sor) is the 1L standard of care. Single-agent inhibition of PD-L1/PD-1 or VEGF signaling has only modest activity in HCC, but in a Phase Ib study of atezolizumab (atezo; anti-PD-L1) + bevacizumab (bev; anti-VEGF) combination, a response rate of 61% with a manageable safety profile (Pishvian ESMO 2018, submitted) is observed. Clinical benefit with atezo + bev was also seen in 1L renal cell carcinoma and 1L non-small cell lung cancer (Motzer ASCO GU 2018, Rock ESMO IO 2017). The potential synergy between atezo and bev may stem from bev’s additional immunomodulatory effects in the tumour microenvironment (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and Tregs in tumours) that may potentiate the efficacy of atezo in re-activating the anti-tumour T-cell response.

Trial design: IMbrave150 is a global, multicentre, randomised, open-label, Phase III trial enrolling 1L patients (pts) with locally advanced or metastatic and/or unresectable HCC. Key inclusion/exclusion criteria are shown in the table. Pts will be randomised 2:1 to receive atezo (1200 mg) plus bev (15 mg/kg) IV Q3W or sor (400 mg) PO BID until loss of clinical benefit or unacceptable toxicity. Crossover is not allowed.

Stratification factors are ECOG PS (0 vs 1), baseline alpha-fetoprotein level (< 400 vs > 400 ng/ml), macrovascular invasion and/or extrapancreatic spread (presence vs absence) and region (Asia excluding Japan vs rest of world). Co-primary endpoints are investigator (INV)-assessed ORR (RECISt v1.1) and OS, which will be tested in parallel. Secondary endpoints are INV-assessed PFS, DOR and time to progression (TTP; RECISt v1.1), along with independent review facility (IRF)-assessed ORR, PFS, DOR and TTP (RECISt v1.1 and HCC mRECISt). Approximately 480 pts will be enrolled globally.

Table: 782TiP Eligibility criteria

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<th>Inclusion Criteria</th>
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<tr>
<td>- ≥ 1 measurable untreated lesion (per RECISt v1.1) - Naïve to prior systemic therapy for HCC - Child-Pugh class A liver function - ECOG PS 0/1 - Adequate hematologic and end-organ function</td>
<td>- Co-infection of HBV and HCV - Pts with untreated varices with bleeding or high risk for bleeding - History of autoimmune disease or immune deficiency - Inadequately controlled arterial hypertension</td>
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Clinical trial identification: NCT03383458

Background: Despite significant improvements in the treatment of early HCC, curative therapies remain associated with high recurrence rates (70% 5 y) (EASL). Hepatocellular carcinoma (HCC) at high risk of recurrence after curative resection or ablation

CA209-9Dx: phase III, randomized, double-blind study of adjuvant nivolumab vs placebo for patients with hepatocellular carcinoma (HCC) at high risk of recurrence after curative resection or ablation


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Background: Despite significant improvements in the treatment of early HCC, curative therapies remain associated with high recurrence rates (70% 5 y) (EASL). Hepatocellular carcinoma (HCC) at high risk of recurrence after curative resection or ablation.

The trial will include 530 pts aged ≥ 18 with a first diagnosis of HCC (any etiology) who are at high risk for HCC recurrence after curative resection or ablation, and who have well-preserved liver function (Child-Pugh score 6 or randomised: 1:1) or receive NIVO (480 mg intravenous Q4W) or placebo (PBO). Additional eligibility criteria include Eastern Cooperative Oncology Group performance status of 0 or 1, no evidence of tumor metastasis, no prior therapy for HCC (including loco-regional therapies), and no liver transplant. Pts will be treated until recurrence per blinded independent central review (BIRC) assessment, unacceptable toxicity, or withdrawal, or for up to 1 total duration. Survival follow-up will continue for up to 5 y. The primary endpoint is to compare recurrence-free survival, by BIRC assessment. Secondary endpoints include overall survival and time to recurrence (defined as time from randomization to first documented disease recurrence). The trial will be open for enrollment in 20 countries worldwide and is currently recruiting.
Section 1: Background

Background: Pembrolizumab is FDA-approved for the treatment of pts with recurrent locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after ≥2 prior therapies and whose tumors express PD-L1 (combined positive score ≥1). Combining pembrolizumab with chemotherapy in the neoadjuvant/adjuvant setting may benefit pts with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 (NCT03221426) is a phase 3, randomized, double-blind study of chemotheraphy + pembrolizumab to placebo as neoadjuvant treatment for locally advanced resectable G/GEJ cancer.

Phase 3 KEYNOTE-585 study of chemotherapy (Chem) + pembrolizumab (Pembro) vs chemio + placebo as neoadjuvant/adjuvant treatment for patients (Pts) with gastric or gastroesophageal junction (G/GEJ) cancer

Trial design: Eligibility criteria are age ≥18 years; previously untreated, resectable G/GEJ adenocarcinoma (pts with Siewert type 1 tumors are eligible if initial treatment is with chemotheraphy) and no metastatic disease; ECOG performance status 0/1; and no active autoimmune disease. Pts will be randomly assigned 1:1 to planned perioperative chemo and resection), with no evidence of metastatic disease; adequate organ function; ECOG performance status 0/1, and no active autoimmune disease. Pts will be followed up for survival status. Planned enrollment is 880 pts.

Clinical trial identification: NCT03221426. Study start date was October 9, 2017.

Section 2: Trial design

Trial design: Eligibility criteria are age ≥18 years; locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after ≥2 prior therapies and whose tumors express PD-L1 (combined positive score ≥1). Combining pembrolizumab with chemotherapy in the neoadjuvant/adjuvant setting may benefit pts with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 (NCT03221426) is a phase 3, randomized, double-blind study of chemotheraphy + pembrolizumab to placebo as neoadjuvant treatment for locally advanced resectable G/GEJ cancer.

Trial design: Eligibility criteria are age ≥18 years; previously untreated, resectable G/GEJ adenocarcinoma (pts with Siewert type 1 tumors are eligible if initial treatment is with chemotheraphy) and no metastatic disease; ECOG performance status 0/1; and no active autoimmune disease. Pts will be randomly assigned 1:1 to receive chemio + pembrol (arm 1) or chemo + placebo (arm 2). Pts will receive neoadjuvant (preoperative) chemio + pembrol every 3 weeks (Q3W) for 3 cycles followed by surgery, then adjuvant chemo + pembrol Q3W for 3 cycles, then monotherapy with pembrol or placebo Q3W for 12 cycles; overall treatment is up to 17 cycles. Chemio is cisplatin 80 mg/m2 IV on day 1 + 1–2 cycles of 1000 mg/m2 IV over 14 days or 5–fluorouracil (5-FU) 800 mg/m2 IV daily for 5–7 days (investigator’s choice). Pembrol 200 mg IV on day 1. Adjuvant monotherapy is pembrol (arm 1) or placebo (arm 2). In a separate safety cohort, 5-FU 6000 mg/m2 IV + docetaxel 50 mg/m2 IV or oxaliplatin 85 mg/m2 IV + Ixracim 200 mg/m2 IV (FLDTG) is being studied as a potential chemo option. Primary end points are overall survival, event-free survival per central review, and rate of pathologic complete response (no invasive disease and histologically negative nodes). Adverse events are graded and monitored for up to 90 days after treatment. Pts will be followed up for survival status. Planned enrollment is 880 pts.

Clinical trial identification: NCT03221426. Study start date was October 9, 2017.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Sarita Shevitz, PhD, of the ApolloCom pembrolizumab team (Yardley, PA, USA).

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

Funding: Merck & Co., Inc.


viis268 | Gastrointestinal tumours, non-colorectal

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Annals of Oncology
Background: Although standard radical gastrectomy is recommended after non-curative resection of endoscopic submucosal dissection for early gastric cancer, in most cases, no residual tumor and no lymph node metastasis was revealed after surgery. Lymph node metastasis can be evaluated using sentinel basin dissection, however, there was no evidence that sentinel lymph node concept can be applied after endoscopic resection.

Trial design: This trial is an investigator-initiated, multicenter prospective phase II trial. Patients who underwent endoscopic submucosal dissection for clinical stage T1N0M0 gastric cancer and the resections were proven as non-curative were eligible. Qualified investigators who completed the prior phase III trial (Senorita I) are exclusively allowed to participate in this study. Intraoperative endoscopic submucosal injection of a standardized dual tracer was administered to normal mucosa nearby the scar, and sentinel basins were detected using gamma-probe and dissected. Then, standard laparoscopic gastrectomy with lymphadenectomy was performed. Sample size was calculated based on inferior confidence interval of detection rate of 99%, and estimated accrual was 237. The primary and secondary end-points were detection rate and sensitivity of sentinel basin, respectively. This study is expected to evaluate the feasibility of laparoscopic sentinel node navigation surgery versus laparoscopic standard gastrectomy in gastric cancer patients. Clinical trial identification: NCT0332042; registered April 21st, 2017.

Legal entity responsible for the study: Sentinel Node Oriented Tailored Approach (SENORITA) Study Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**References**

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Background: In gastric cancer patients, treatment options after curative gastrectomy are limited. Adjuvant chemotherapy is recommended after R0 resection for stage III or IV(M0). However, there are several limitations in adjuvant chemotherapy, such as increased toxicity, impaired quality of life, and low overall survival. Therefore, novel, less toxic, and more effective treatments are needed. In this study, we aimed to evaluate the feasibility of adjuvant chemotherapy with a standardized dual tracer which can be used for sentinel node navigation surgery. The primary end-point was the detection rate of sentinel lymph node navigation surgery versus standard gastrectomy.

**Trial design:** A phase III study of adjuvant docetaxel, capecitabine, and oxaliplatin triplet vs capecitabine and oxaliplatin doublet in patients with surgically resected stage IIIb or IV(M0) AJCC 6th ed gastric adenocarcinoma (TRIUMPH, KCSG CT14-05).

**Participants:** Patients (pts) with surgically resected stage IIIb or IV(M0) (by AJCC 6th edition) gastric adenocarcinoma (GC) are eligible. The primary end-point is the detection rate of sentinel node navigation surgery versus standard gastrectomy. The secondary end-points include overall survival and safety. Translational research will explore the use of biomarkers for predictive benefit of NUC-1031 over gemcitabine.

**Clinical trial identification:** SCRISCTN16763535.

Legal entity responsible for the study: Clatterbridge Cancer Centre NHS Foundation Trust.

Funding: Nucana Biomed Ltd.

HALO 109-301: Phase III, randomized, double-blind, placebo-controlled study of pegylated-hyaluronidase alfa (PEGPH20) + nab-paclitaxel/gemcitabine (AG) 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 high stromal HA content (HA-high). In vitro, PEGPH20 degrades tumor HA and may increase access and efficacy of tumor therapies. In a Phase 2 study, PEGPH20 + standard-dose nab-paclitaxel/gemcitabine (PAG) improved PFS over chemotherapy alone (AG) in tumors retrospectively identified as HA-high. In this Phase 3 study, we investigate the efficacy and safety of PAG vs AG in patients with HA-high, previously untreated, Stage IV PDA. There are 2 primary endpoints: PFS and OS. Secondary endpoints are objective response rate, duration of response, and safety.

Trial design: Patients ≥18 years of age with untreated HA-high, Stage IV PDA and ECOG PS 0–1 are eligible. Exclusion criteria include a history of thromboembolic events (TEs) or parin prophylaxis is administered subcutaneously once daily at 1 mg/kg to minimize TEs. Tumor response is independently assessed per RECIST v1.1. Adverse events are graded per NCI CTCAE v4.03. An independent data monitoring committee is overseeing the safety data. The trial was initiated in 2016, is open at 200 study sites across 20 countries, and is expected to complete by 2020.

Clinical trial identification: EudraCT 2015-004068-13; NCT02713804

Editorial acknowledgement: Medical writing assistance was provided by Tamzin Williamson at Paragon, Knutsford, UK.

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

Funding: Halozyme Therapeutics, Inc.

GENITOURINARY TUMOURS, PROSTATE

**Updated results of GETUG-12, a phase III trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow-up**

K. Fizazi 1, A. Carmel 2, R. Delva 3, G. Gravis 4, F. Rolland 5, F. Priou 6, J-M. Ferrero 7, N. Houede 8, I. Krakowski 9, M. Baciuchka Palmaro 10, B. Laguerre 11, A. Flechon 12, A. Ravaud 13, M. Brihoum 14, S. Culine 15, G. Le Ten 16

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**A randomized phase II study of cabazitaxel (CAB) vs (ABI) abiraterone or (ENZ) enzalutamide in poor prognosis metastatic castration-resistant prostate cancer (mCRPC)**


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Preliminary results from TRITON2: A phase II study of rucaparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination repair (HRR) gene alterations


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Prospective comprehensive genomic profiling (CGP) of 3,343 primary and metastatic site prostate tumors

S.M. Ali 1, J. Chung 1, N. Deva 1, L.M. Gay 1, Y. He 2, E.S. Sokol 2, S.Z. Mills 2, J.K. Killian 2, A.B. Schrock 1, S.K. Pat 1, V.A. Miller 2, J.S. Ross 2, N. Agarwal 2

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Genomic profiling of circulating tumour DNA (ctDNA) and tumour tissue for the evaluation of rucaparib in metastatic castration-resistant prostate cancer (mCRPC)


1Medical Oncology, Guy’s Hospital and Sarah Cannon Research Institute, London, UK, 2Genito-Urinary Oncology, ANZCH Adelaide and Meath Hospital, Dublin, Ireland, 3Medical Oncology, Institut Català de la Oncologia, Barcelona, Spain, 4Medical Oncology, Cabrini Hospital, Malvern, Australia, 5Oncology, Veyle Sygehus, Veyle, Denmark, 6Oncology, Urology Associates Clinical Research, Nashville, TN, USA, 7Clinical Oncology, Mount Vernon Cancer Centre, Northwood, UK, 8Department of Medicine, University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA, 9Urology, The Urology Group, Cincinnati, OH, USA, 10Urology, Premier Medical Group of the Hudson Valley, Poughkeepsie, NY, USA, 11Medical Oncology, Firminy Health NVS Foundation Trust, Slough, UK, 12Medical Oncology, Centre Hospitalier Universitaire Dr-Georges-L-Dumont, Moncton, NB, Canada, 13Department of Medicine, University of Southern California, Los Angeles, CA, USA, 14Medical Oncology, Henry Ford Health System, Detroit, MI, USA, 15Gynaecological Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA, 16Medical Oncology, Hospital Universitario Germans Trias i Pujol, Badalona, Spain, 17Translational Medicine, Clovis Oncology, Inc., Boulder, CO, USA, 18Translational Medicine, Clovis Oncology, Boulder, CO, USA, 19Clinical Science, Clovis Oncology, Inc., Boulder, CO, USA, 20Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Detection of circulating tumor DNA in de novo metastatic castrate-sensitive prostate cancer

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LATITUDE study: PSA response characteristics and correlation with overall survival (OS) and radiological progression-free survival (rPFS) in patients with metastatic hormone-sensitive prostate cancer (mHSPC) receiving ADT + abiraterone acetate and prednisone (AAP) or placebo (PBO)


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In-depth assessment of metastatic prostate cancer with high tumour mutational burden


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PD Phase I dose-escalation study of fractionated dose 177Lu-PSMA-617 for progressive metastatic castration resistant prostate cancer (mCRPC)


1Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA, 2Radiology, Weill Cornell Medical College, New York, NY, USA, 3Department of Healthcare Policy & Research, Weill Cornell Medical College, New York, NY, USA, 4Urology, Weill Cornell Medical College, New York, NY, USA, 5Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA

The prognostic value of the proportion and subtype patterns of intraductal carcinoma of the prostate in patients with de novo metastatic prostate cancer: A propensity score matching study


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Background: Intraductal carcinoma of the prostate (IDC-P) is an adverse prognosticator of prostate cancer (PCa). However, the role of IDC-P proportion and architectural patterns in patient outcome remain unclear.

Methods: Data of 644 de novo metastatic PCa (mPCa) patients between 2010-2017 were retrospectively analyzed. IDC-P was identified from 12-core prostate biopsy. IDC-P proportion were calculated. IDC-P were classified into two architectural patterns according to the 2016 WHO classification: pattern-1 (loose cribriform or micro-papillary) and pattern-2 (solid or dense cribriform). Propensity-score matching (PSM) was conducted to balance the baseline characteristics between patients with and without IDC-P. Kaplan-Meier curves and COX regression were utilized in survival analysis. The endpoints were castration-resistant PCa free survival (CFS) and overall survival (OS).
Results: Totally, 180/644 (28.0%) patients harboured IDC-P. IDC-P proportions were significantly different in survival (Table 1). Patients in Group 0 (Without de novo IDC-P) and IDC-P-Group 1 (IDC-P ≤ 10%) had favorable mCFS (18.0- vs. 17.8-Mo, \( p = 0.066 \)) and mOS (68.8- vs. 63.8-Mo, \( p = 0.003 \)) were independently associated with worse prognosis in the post-PSM cohort. Based on these two risk factors, all men could be classified into five groups with significant differences in survival (Table 1). In Group 1 (Without de novo IDC-P) and IDC-P-Group 1 (IDC-P ≤ 10% AND IDC-P pattern-1) had favorable mCFS (18.0- vs. 17.8-Mo, \( p = 0.066 \)) and mOS (68.8- vs. 63.8-Mo, \( p = 0.003 \)). While men of IDC-P-Group 4 (IDC-P ≥ 10% AND IDC-P pattern-2) had worse outcomes (mCFS: 8.4-Mo; mOS: 29.9-Mo). IDC-P-Group 2 (IDC-P < 10% AND IDC-P pattern-2) harboured the worst outcomes (mCFS: 18.0-Mo; mOS: 29.9-Mo). IDC-P-Group 3 (IDC-P < 10% AND IDC-P pattern-1) had median OS and CFS 10% (CFS: HR: 2.63, \( p < 0.001 \) and IDC-P pattern-2) harboured the worst outcomes (mCFS: 8.4-Mo; mOS: 29.9-Mo). IDC-P-Group 2 (IDC-P < 10% AND IDC-P pattern-2; mCFS: 14.2-Mo; mOS: 45.9-Mo) and IDC-P-Group 3 (IDC-P ≥ 10% AND IDC-P pattern-1; mCFS: 11.9-Mo; mOS: 38.7-Mo) had intermediate prognosis. Conclusions: IDC-P proportion ≥ 10% and pattern-2 were two unfavorable prognosticators for PCa. Pathological reporting criterion based on IDC-P could further improve the prediction of patient outcome and optimize treatment decision. Legal entity responsible for the study: Department of Urology, Institute of Urology, West China Hospital, Sichuan University. Funding: This work was supported by the National Natural Science Foundation of China (NSFC 81672347, 81402110, and 81272820), Science and Technology Support Program of Sichuan Province (2015 SZ0142), The 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University. Disclosure: All authors have declared no conflicts of interest.

### Table: 800P The CFS for patients of different IDC-P groups and patients without IDC-P after propensity-score matching

#### A. The survival outcomes for de novo mPCa patients of different IDC-P groups

<table>
<thead>
<tr>
<th>IDC-P group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 0</td>
</tr>
<tr>
<td>Group 0</td>
<td>180</td>
<td>(50.0%)</td>
<td>17.8 (15.3-20.5) -</td>
</tr>
<tr>
<td>IDC-P-Group 1</td>
<td>41</td>
<td>(1.1%)</td>
<td>18.0 (12.7-23.2) -</td>
</tr>
<tr>
<td>IDC-P-Group 2</td>
<td>58</td>
<td>(16.1%)</td>
<td>14.2 (10.1-18.3)</td>
</tr>
<tr>
<td>IDC-P-Group 3</td>
<td>22</td>
<td>(6.1%)</td>
<td>11.9 (6.0-17.8)</td>
</tr>
<tr>
<td>IDC-P-Group 4</td>
<td>59</td>
<td>(16.4%)</td>
<td>8.4 (6.7-10.1)</td>
</tr>
</tbody>
</table>

#### B. The survival outcomes for de novo mPCa patients of different risk group

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 1 or 0</td>
</tr>
<tr>
<td>Favorable-risk: Group 1 or 0</td>
<td>221 (61.4%)</td>
<td>17.8 (15.5-20.1) -</td>
<td>0.009</td>
</tr>
<tr>
<td>Intermediate-risk: Group 2 or 3</td>
<td>80 (22.2%)</td>
<td>14.1 (10.3-17.9)</td>
<td>0.020</td>
</tr>
<tr>
<td>Poor-risk: Group 4</td>
<td>59 (16.4%)</td>
<td>8.4 (6.7-10.1)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 1 or 0</td>
</tr>
<tr>
<td>Favorable-risk: Group 1 or 0</td>
<td>221 (61.4%)</td>
<td>17.8 (63.8-72.6)</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate-risk: Group 2 or 3</td>
<td>80 (22.2%)</td>
<td>43.2 (35.2-51.1)</td>
<td>0.027</td>
</tr>
<tr>
<td>Poor-risk: Group 4</td>
<td>59 (16.4%)</td>
<td>29.9 (20.7-39.2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

CFS: CRPC-free survival; OS: Overall survival; IDC-P: Intraductal carcinoma of the prostate; CI: Confidence interval; mPCa: metastatic prostate cancer

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**Table: 800P The CFS for patients of different IDC-P groups and patients without IDC-P after propensity-score matching**

<table>
<thead>
<tr>
<th>IDC-P group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 0</td>
</tr>
<tr>
<td>Group 0</td>
<td>180</td>
<td>(50.0%)</td>
<td>17.8 (15.3-20.5) -</td>
</tr>
<tr>
<td>IDC-P-Group 1</td>
<td>41</td>
<td>(1.1%)</td>
<td>18.0 (12.7-23.2) -</td>
</tr>
<tr>
<td>IDC-P-Group 2</td>
<td>58</td>
<td>(16.1%)</td>
<td>14.2 (10.1-18.3)</td>
</tr>
<tr>
<td>IDC-P-Group 3</td>
<td>22</td>
<td>(6.1%)</td>
<td>11.9 (6.0-17.8)</td>
</tr>
<tr>
<td>IDC-P-Group 4</td>
<td>59</td>
<td>(16.4%)</td>
<td>8.4 (6.7-10.1)</td>
</tr>
</tbody>
</table>

### B. The survival outcomes for de novo mPCa patients of different risk group

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 1 or 0</td>
</tr>
<tr>
<td>Favorable-risk: Group 1 or 0</td>
<td>221 (61.4%)</td>
<td>17.8 (15.5-20.1) -</td>
<td>0.009</td>
</tr>
<tr>
<td>Intermediate-risk: Group 2 or 3</td>
<td>80 (22.2%)</td>
<td>14.1 (10.3-17.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Poor-risk: Group 4</td>
<td>59 (16.4%)</td>
<td>8.4 (6.7-10.1)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>CASE</th>
<th>Median CFS (95% CI)</th>
<th>Log-rank test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 1 or 0</td>
</tr>
<tr>
<td>Favorable-risk: Group 1 or 0</td>
<td>221 (61.4%)</td>
<td>17.8 (63.8-72.6)</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate-risk: Group 2 or 3</td>
<td>80 (22.2%)</td>
<td>43.2 (35.2-51.1)</td>
<td>0.027</td>
</tr>
<tr>
<td>Poor-risk: Group 4</td>
<td>59 (16.4%)</td>
<td>29.9 (20.7-39.2)</td>
<td>0.000</td>
</tr>
</tbody>
</table>
account for multiple comparisons, a p-value of < 0.001 was considered potentially significant.

Results: Of 1,313 men, 799 had baseline BMB. Pt characteristics ([median (range) or n (%)]: age 67y (19-92); PSA 29 ng/mL (2-6710); Gleason >7: n = 479 (46%); bone mets: 604 (76%); biopsy/denoussabm: 44 (5.3%); Zubrod PS 0: 547 (68%); & minimal disease extent: 389 (49%). Median BMB: CTX 0.46 ng/mL (0.03-12.2); PDT 1.68 mol/L (0.35-17.5); CICP 116 ng/mL (0.25-3360); BAP 1.66 u/L (1-1001). At least one BMB was > median in 83% vs in top quartile in 57%. In 84% vs bone mets, 540 had at least 1 BMB > median while distribution of BMB elevation >median differed significantly w/ in groups defined by PSA (p < 0.001), Gleason score (p < 0.001), PS (p < 0.001) & disease extent (p < 0.001). For example, in 292 with PSA >29, 30% had all 4 BMB ele-
vated; in those with PSA < 29, only 6 had all 4 BMB. Elevated BMB distribution in all men did not differ within race/ethnicity, age, & bisphos/denoussabm groups. Trends were similar when BMB upper quartile was used.

Conclusions: In men w/ HSPC initiating ADT, at least one BMB was elevated in 87%. Differences in BMB distribution were seen within pre-defined subsets, with BMB elevation tracking with higher tumor grade, disease burden & lower PS. Assessment of BMB associated with different strategies is planned.

Clinical trial identification: SWOG S1216; NCT01180691.

Legal entity responsible for the study: SWOG.

Funding: NIH/NCI grants CA108888, CA18019, and Millennium Pharmaceuticals (Takeda Oncology Company) NIH.

Disclosure: All authors have declared no conflicts of interest.

## 804P

**Health-related quality of life (HRQoL) after progressive disease (PD) in SPARTAN: A phase III trial of apalutamide (APA) versus placebo (PBO) in men with nonmetastatic castration-resistant prostate cancer (nmCRPC)**


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Background: Compared with PBO, APA prolongs the median metastasis-free survival (MFS) by > 2 y (HR = 0.30; 95% CI, 0.24-0.36), and provides a 55% reduction in the risk of symptomatic progression (SaPD) (HR = 0.45; 95% CI, 0.32-0.65) in patients (pts) with nmCRPC. SPARTAN study, Smith MR, et al. NEJM 2018, with no decline in HRQoL in either treatment group up to the time of developing distant metastases (Mts). Here, we report pt HRQoL following PD.

Methods: 1207 pts (median age, both arms: 74 y) with nmCRPC were randomized 2:1 to APA (240 mg QD) or PBO. ADT was continued in all pts. HRQoL was assessed using

**Annals of Oncology**

**803P**

**Randomized trial of androgen deprivation therapy (ADT) + enzalutamide (Arm A) versus ADT + bicalutamide (Arm B) in metastatic hormone sensitive prostate cancer (mHSPC)**


1Oncology, Kanaman Cancer Institute, Detroit, MI, USA; 2Oncology, Kanaman Cancer Center, Detroit, MI, USA; 3Oncology, Ohio State University, Columbus, OH, USA; 4Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA; 5Oncology, Henry Ford Hospital, Detroit, MI, USA; 6Oncology, Kanaman Cancer Center, Detroit, MI, USA

Background: The addition of abiraterone or docetaxel has shown overall survival (OS) benefit in mHSPC. There is adequate rationale for clinical efficacy of enzalutamide and ADT combination in mHSPC. We compared the combination of enzalutamide (Arm A) or bicalutamide (Arm B), each with ADT in mHSPC.

Methods: The primary endpoint was the seven month PSA remission (SMR), with PSA nadir of < 4 ng/mL as this is an accepted surrogate for overall survival (OS) outcomes. Secondary endpoints were toxicities, biochemical and radiologic progression free survival (PFS), and OS. Stratification was by presence of bone pain (yes/no) and race (AA or other). PSA was monitored monthly for first 7 months and then every 3 months. Metastatic site biopsies were mandatory pretherapy and optional post therapy.

Results: 71 men; 29 African American (AA), 41 Caucasian and 1 Asian were enrolled. The median age was 67 years (range 46-87 years) and median baseline PSA was 56.3 ng/ ml in Arm A (4.2-10.43 ng/ml) and 49.4 (12.0-32.00 ng/ml) in Arm B. 26 pts (39%) had bone pain and 37(52%) had extensive disease. Predominant grade 3+4 events on Arm A were: Hypertension (13%), infection (7%), and syncope (7%) and on Arm B were: Hypertension (21%), Fatigue (7%), and Hematruia (7%). No sezuors were noted. PSA nadir < 4ng/ml at month 7 was achieved in 29(31/34%) pts in arm A and 16/24 (67%) pts in arm B. 33% on arm A and 43% on Arm B continue to maintain PSA < 4 ng/ml. 4 (11%) deaths have occurred on enzalutamide arm as compared to 13 (37.1%) deaths on Arm B. Among AA patients, SMR was 100% on Arm A and 46% on Arm B. 53 (75%) biopsy samples had tumor tissue available. TMDPSS ERG fusion gene and CCGX4 expression and abiraterone biosynthetic enzyme levels were determined in metastatic biopsies. Patients with low copy number of ERG had an increased likelihood of SMR (19/20 or 95%) as compared to high copy number (14/20 or 70%).

Conclusions: Early enzalutamide use in mHSPC improved PSA remission rates and has the potential to subsequently improve OS outcomes High ERG copy number was associated with decreased SMR. This is the first randomized trial to report efficacy results of the combination of ADT and enzalutamide compared with ADT and bicalutami-
d in mHSPC.

Legal entity responsible for the study: Kanaman Cancer Center.

Funding: Astellas Inc.

Disclosure: U.N. Vaishampayan: Research support, consulting: Astellas Inc. P. Monk, G. Sonpavde, S. Chinni: Research support: Astellas Inc. All other authors have declared no conflicts of interest.
the pt-reported outcome (PRO) questionnaire Functional Assessment of Cancer Therapy-Prostate (FACT-P). Following development of Mets, pts in the 2 arms received similar treatments, and PROs were collected at 4, 8, and 12 mo. PSA was defined as 1) development of a skeletal-related event; 2) initiation of new systemic anti-cancer treatment due to pain progression or worsening of disease-related symptoms; or 3) development of clinically significant symptoms due to loco-regional tumor progression requiring surgery or radiation. Descriptive statistics were performed for all FACT-P subscales.

**Results:** Group mean PRO scores after PD were available from 341 pts and from 60 pts in the 2 arms at baseline. FACT-P scores up to 12 mo after Sx PD were available from FACT-P subscales up to 12 mo after Sx PD. While APA delayed time to Sx PD, once Sx PD was reached there were similar numeric decreases from baseline across FACT-P subscales up to 12 mo after Sx PD. Thus, in HRQoL through the time of Mets, and similar HRQoL after Mets. Sx PD was delayed relative to PBO, pts treated with APA had a longer MFS, with no decline in PRO group mean scores after PD. While APA delayed time to Sx PD, once Sx PD was reached there were similar numeric decreases from baseline across FACT-P subscales up to 12 mo after Sx PD. Therefore, HRQoL decline for pts treated with APA was delayed because of a longer time to Sx PD. Clinical trial identification: NCT01946204.

**Editorial acknowledgement:** This study was funded by Janssen Research & Development. Writing assistance was provided by Ann Tighe, PhD, of PAREXEL, and was funded by Janssen Global Services, LLC.

**Legal entity responsible for the study:** Janssen Research & Development.

**Funding:** Janssen Research & Development.


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### Table: 805P PRO group mean scores

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 1401)</th>
<th>Age &lt; 75 y (n = 756)</th>
<th>Age ≥ 75 y (n = 645)</th>
<th>Europe (n = 690)</th>
<th>Rest of world (n = 507)</th>
<th>North America (n = 204)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age category, no. (%)</td>
<td>&lt; 75 y ≥ 75 y</td>
<td>190 (14) 566 (40)</td>
<td>190 (25)</td>
<td>0.0 645 (100)</td>
<td>100 (15) 285 (41)</td>
<td>316 (16) 81 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>645 (46)</td>
<td>566 (75) 0</td>
<td>305 (44)</td>
<td>250 (49)</td>
<td>90 (44)</td>
</tr>
<tr>
<td>ECOG PS, no. (%)</td>
<td>0 1</td>
<td>1129 (81) 270 (19)</td>
<td>668 (88) 87 (12)</td>
<td>461 (72) 183 (28)</td>
<td>555 (80) 134 (19)</td>
<td>401 (79) 105 (21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>153 (11)</td>
<td>77 (10)</td>
<td>76 (12)</td>
<td>74 (11)</td>
<td>36 (7)</td>
</tr>
<tr>
<td>Use of bone-targeting agent, no. (%)</td>
<td>Yes</td>
<td>3.7 (0.7-71.8)</td>
<td>3.5 (0.6-28.9)</td>
<td>4.0 (0.4-71.8)</td>
<td>3.9 (0.4-71.8)</td>
<td>3.5 (0.4-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1076 (77)</td>
<td>596 (79)</td>
<td>480 (74)</td>
<td>510 (74)</td>
<td>411 (81)</td>
</tr>
<tr>
<td>PSA doubling time, median (range), mo</td>
<td>0.29 (0.24-0.35)</td>
<td>0.25 (0.20-0.33)</td>
<td>0.35 (0.26-0.47)</td>
<td>0.24 (0.18-0.32)</td>
<td>0.32 (0.23-0.43)</td>
<td>0.41 (0.25-0.66)</td>
</tr>
<tr>
<td>PSA doubling time &lt; 6 mo, no. (%)</td>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFS HR (95% CI) P value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**Abbreviation:** ECOG PS, Eastern Cooperative Oncology Group Performance Status.

### Background

Men with M0 CRPC are at high risk of developing metastatic (M1) CRPC. The goal of M0 CRPC treatment is to delay M1 disease progression, delay additional antineoplastic therapies, and ultimately prolong survival and maintain quality of life. In the primary analysis of PROSPER, ENZA improved metastasis-free survival (MFS) in men with M0 CRPC. Here we report results in subgroups of patients (pts) by age and region.

**Methods:** Eligible men with M0 CRPC, prostate-specific antigen (PSA) doubling time ≤ 10 mo and PSA ≥ 2 ng/mL at screening continued androgen deprivation therapy and were randomized 2:1 to ENZA 160 mg or PBO. The primary endpoint was MFS. Secondary endpoints included time to PSA progression, time to first use of new antineoplastic therapy, overall survival, and safety.

**Results:** 1401 men were enrolled with a median age of 74 y (standard deviation, 7.8 y). Baseline characteristics were generally similar across regions and age groups (Table). Baseline use of bone-targeting agents was higher in North America compared with the other 2 regions. A greater proportion of pts aged ≥ 75 y had and ECOG PS of ≥ 1 than pts aged ≤ 75 y. In all men, ENZA reduced the risk of metastasis or death by 71% (HR, 0.29).

### Table: 805P A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) in men with nonmetastatic (M0) castration-resistant prostate cancer (CRPC): Results of PROSPER by age and region

<table>
<thead>
<tr>
<th></th>
<th>APA (n = 597)</th>
<th>PBO (n = 805)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>190 (14)</td>
<td>316 (16)</td>
<td>0.32 (0.23-0.43)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age &lt; 75 y</td>
<td>190 (25)</td>
<td>316 (16)</td>
<td>0.32 (0.23-0.43)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
<td>645 (46)</td>
<td>90 (44)</td>
<td>0.32 (0.23-0.43)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Abbreviation:** APA, enzalutamide; PBO, placebo; CRPC, castration-resistant prostate cancer; HR, hazard ratio.
Results:

Inclusion of patients (pts) with nmCRPC and prostate-specific antigen doubling time <10% of those who required dose reductions/interruptions due to AEs. The MFS population (9% with ENZA vs 6% with PBO), and more pts in North America reported falls (15%) than in Europe (7%) or rest of world (10%).

Conclusions:

We assessed the impact of ENZ on prostate cancer symptoms (PCS) and health-related quality of life (HRQoL).

Methods:

Results: Complete rates were high for patients (pts) remaining on study (>85% for all visits). BL scores were similar between arms and showed low symptom burden (including urinary and bowel symptoms) and high HRQoL. The proportion of pts reporting either no change or improvement in HRQoL and PCS scores at week 49 was higher with ENZ (67–87%) than PBO (62–81%). Over the course of treatment, ENZ significantly delayed worsening of symptoms including urinary and bowel symptoms/function (Table). In contrast, ENZ significantly increased the risk of worsening of hormonal treatment related symptoms compared to PBO (Table).

Conclusions:

The phase 3 SPARTAN study evaluated the efficacy and safety of APA vs placebo (PBO) in men with high-risk nmCRPC. Because dose reductions/interruptions for the management of AEs that occur during treatment can affect drug efficacy, this analysis sought to understand the relationship of APA pharmacokinetic exposure and the primary end point of SPARTAN, MFS.

Methods:

Please note that this is a truncated version of the text, and the full text is too long to be accurately and comprehensively summarized in this response.
Random-effects or fixed-effects models were performed on the basis of the heterogeneity of the hazard-ratio (HR) for OS and MFS, with 95% CI. The safety profile was investigated in patients, but failed to demonstrate a statistically significant increase in overall survival with placebo.

Background: Androgen deprivation therapy (ADT) is the cornerstone treatment of prostate cancer. However, androgen independent status inevitably develops over time, leading to the castration resistant prostate cancer (CRPC) phenotype. Several treatments, including chemotherapy agents and novel hormonal agents, have been shown to improve outcome of patients with metastatic CRPC (mCRPC). Recently, two randomised controlled trials (RCT) demonstrated increased metastases free survival in mCRPC patients with apalutamide (SPARTAN Trial) and enzalutamide (PROSPER Trial) in nmCRPC patients, but failed to demonstrate a statistically significant increase in overall survival (OS).

Methods: A meta-analysis at trial level was performed including published data from SPARTAN and PROSPER trials. Efficacy data was investigated and retrieved to calculate hazard ratio (HR) for OS and MFS, with 95% CI. The safety profile was investigated for fatal adverse events (FEAEs) and the relative risk (RR) calculated with 95% CI. Random-effects or fixed-effects models were performed on the basis of the heterogeneity of included studies. A P-value <0.05 was considered statistically significant.

Results: A total of 2,602 patients were included for efficacy (intention-to-treat (ITT) population) and 2,596 for safety analysis (per-protocol population). 1,736 patients received novel hormonal agents (806 apalutamide and 930 enzalutamide) and 866 placebo. Efficacy analysis confirmed improved MFS (HR 0.29, 95% CI, 0.25 –0.33, P < 0.0001) and also demonstrated a significant increase in OS (HR 0.76, 95% CI, 0.59 –0.76, P = 0.03). Safety analysis showed an increased risk of FAEs (HR 5.24, 95% CI, 1.89 –14.55) with apalutamide and enzalutamide, however this should be interpreted with caution due to the much longer exposure time to the experimental arm compared to placebo.

Conclusions: This meta-analysis reinforces the benefit of MFS and demonstrated a significant increase in OS with novel hormonal agents apalutamide and enzalutamide in patients with nmCRPC. Further analysis will be necessary to determine the breakdown of treatment-related versus –unrelated deaths.

Legal entity responsible for the study: Daniel Vargas Privato de Almeida.

Funding: Has not received any funding.


S. Srinivas: Data and Safety Monitoring Committee: Pfizer, Advisory Board: Janssen.

T. Dorff: Advisory board: Janssen; Promotional speaker: Exelixis, Prometheus; Consulting: Bayer, EMD Serono.

E.Y. Yu: Honoraria: Janssen, F.A. Schutz: Site Principal investigator: Roche, BMS, MSD, Astra Zeneca; Speaker’s bureau: Sanofi, Astra Zeneca, Bayer, Janssen, Astellas, BMS, Pfizer, Roche; Advisory board: Bayer, Janssen, Astellas, Novartis, Roche, MSD. All other authors have declared no conflicts of interest.
Conclusions: Use of statins by pts treated in the TROPIC trial was associated with a longer OS, independent of treatment arm and other prognostic variables. Further analyses will elucidate the role of statins in mCRPC.

Clinical trial identification: EudraCT: 2006-003087-59; NCT00417079.

Legal entity responsible for the study: David Lorente / Prostate Targeted Therapy Group.

Funding: The TROPIC trial was funded by Sanofi. No specific funding was received for the development of the current abstract.

Disclosure: All authors have declared no conflicts of interest.

Table: 810P Multivariable Cox-Regression OS Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin Use</td>
<td>0.79 (0.62-0.99)</td>
<td>0.048</td>
</tr>
<tr>
<td>Treatment Arm</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline PSA</td>
<td>1 (1-1)</td>
<td>0.394</td>
</tr>
<tr>
<td>Baseline Hb</td>
<td>0.89 (0.85-0.93)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline ALP</td>
<td>1 (1-1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Visceral Metastases</td>
<td>1.36 (1.11-1.68)</td>
<td>0.003</td>
</tr>
<tr>
<td>EOCG PS</td>
<td>1.67 (1.43-1.96)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Background: The use of continuation of luteinizing hormone-releasing hormone (LHRH) therapy in castration-resistant prostate cancer (CRPC) remains controversial and clear evidence is lacking. Especially upon treatment with the life-prolonging cytochrome P450 17α-hydroxylase/c17,20-lyase (CYP17)-inhibitor, abiraterone, which in combination with prednisone, has the ability to further suppress testosterone serum levels over LHRH therapy alone, continuation of LHRH therapy seems to be negligible. The aim of the SPARE trial therefore was to explore the role of continuation of LHRH therapy when starting treatment with abiraterone acetate plus prednisone (AA + P) in patients with asymptomatic or mildly symptomatic, chemotherapy-naïve CRPC.

Methods: Patients were randomized to receive continuing LHRH therapy versus LHRH withdrawal at the time of starting abiraterone AA + P therapy (NCT02077634). The primary endpoint was time to PSAm at month 12. Secondary endpoints included PSA response rate, objective response rate, time to PSA progression and safety.

Results: Altogether, 68 patients were randomized. Median age was 75 (60-86) years with a median PSA at baseline of 23.9 (0.17-1680) ng/ml. Results of the secondary endpoints were evaluated.

Table: 810P

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline PSA (ng/ml)</th>
<th>Baseline PSA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>74 (60-86) years</td>
<td>76 (60-86) years</td>
</tr>
<tr>
<td>Median baseline PSA</td>
<td>31.9 (0.17-313.2)</td>
<td>20.59 (1.97-1680)</td>
</tr>
<tr>
<td>PSA-decline &gt;50%</td>
<td>23/34 (67.6%)</td>
<td>24/33 (72.7%)</td>
</tr>
<tr>
<td>Median treatment duration</td>
<td>266</td>
<td>420</td>
</tr>
<tr>
<td>Time to PSA</td>
<td>288</td>
<td>336</td>
</tr>
<tr>
<td>HR (p-value)</td>
<td>1.67 (1.97)</td>
<td>1.733 (1.188)</td>
</tr>
</tbody>
</table>

*study was not powered for these endpoints.

Conclusions: Treatment with abiraterone plus LHRH therapy when starting treatment with abiraterone acetate plus prednisone (AA + P) therapy for men with mCRPC. Prophylactic granulocyte colony-stimulating factor was given to patients with Grade 3 NP. OS and progression-free survival (PFS) were analyzed using Kaplan-Meier (K) estimates and Cox proportional hazard models. Nominal p values were determined by log-rank tests. Prostate-specific antigen response rate (PSAR) defined as proportion of patients with a > 50 % PSA decline from baseline) was analyzed in the eligible population using KM estimates with Chi² tests and odds ratios. OS, PFS and PSAR were correlated with Grade 3 NP occurrence and baseline neutrophilia (neutrophils >7000 G/l) by univariate analysis.

Background: Subset analysis of trials investigating taxanes in patients with mCRPC suggest an association between Grade 3 NP and disease outcomes. In the Phase 3 PROSELICA trial (NCT01308580), NP was more common in patients receiving cabazitaxel 25 mg/m² (C20) vs cabazitaxel 20 mg/m² (C20) - 79% vs 42%, respectively. Post hoc analyses of PROSELICA examined the relationship between incidence of NP, survival and response. Methods: PROSELICA assessed the non-inferiority of C20 (n = 598) vs C25 (n = 602) in terms of overall survival (OS) in men with mCRPC. Prophylactic granulocyte colony-stimulating factor was given to patients with Grade 3 NP. OS and progression-free survival (PFS) were analyzed using Kaplan-Meier (KM) estimates and Cox proportional hazard models. Nominal p values were determined by log-rank tests. Prostate-specific antigen response rate (PSAR) defined as proportion of patients with a > 50 % PSA decline from baseline) was analyzed in the eligible population using KM estimates with Chi² tests and odds ratios. OS, PFS and PSAR were correlated with Grade 3 NP occurrence and baseline neutrophilia (neutrophils >7000 G/l) by univariate analysis.

Results: In the intent-to-treat (ITT) population, development of Grade 3 NP was associated with better PSAR, PFS and OS (p < 0.001; Table). The positive association was observed in both treatment arms and in poor-risk patients with baseline neutrophilia.

Table: 811P

<table>
<thead>
<tr>
<th>Population</th>
<th>Outcome</th>
<th>Grade ≥1 NP</th>
<th>No Grade ≥1 NP</th>
<th>Hazard ratio/Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population</td>
<td>OS, months (mo)</td>
<td>15.1</td>
<td>12.4</td>
<td>0.78</td>
<td>0.0002</td>
</tr>
<tr>
<td>(n = 1200)</td>
<td>DFS, mo</td>
<td>3.7</td>
<td>2.8</td>
<td>0.79</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PSA, %</td>
<td>n = 1079</td>
<td>44.1</td>
<td>25.5</td>
<td>2.3</td>
<td>0.0037</td>
</tr>
<tr>
<td>C25 (n = 602)</td>
<td>OS, mo</td>
<td>15.3</td>
<td>12.2</td>
<td>0.77</td>
<td>0.0009</td>
</tr>
<tr>
<td>PSA, %</td>
<td>n = 538</td>
<td>46.2</td>
<td>34.5</td>
<td>1.6</td>
<td>0.015</td>
</tr>
<tr>
<td>C20 (n = 598)</td>
<td>OS, mo</td>
<td>14.6</td>
<td>12.6</td>
<td>0.78</td>
<td>0.0006</td>
</tr>
<tr>
<td>PSA, %</td>
<td>n = 541</td>
<td>40.7</td>
<td>21.3</td>
<td>2.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophilia</td>
<td>OS, mo</td>
<td>12.8</td>
<td>7.5</td>
<td>0.63</td>
<td>0.0004</td>
</tr>
<tr>
<td>(n = 174)</td>
<td>PSA, %</td>
<td>4.1</td>
<td>2.1</td>
<td>0.66</td>
<td>0.002</td>
</tr>
<tr>
<td>PSA, %</td>
<td>n = 156</td>
<td>43.8</td>
<td>16.9</td>
<td>3.8</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Conclusions: Post hoc assessment of Grade ≥3 NP in PROSELICA was associated with improved survival and response to cabazitaxel independent of dose. These results are consistent with data obtained in the Phase 3 TAX327 (docetaxel) and TROPIC (cabazitaxel) trials. Funded by Sanofi.

Clinical trial identification: NCT01308580.
Background: PROSELICA (NCT01308567) assessed the non-inferiority of cabazitaxel 20 mg/m² (C20) vs 25 mg/m² (C25) in patients (pts) with mCRPC post docetaxel, while FIRSTANA (NCT01308567) investigated whether C20 and C25 were superior to docetaxel 75 mg/m² (D75) in chemotherapy-naive mCRPC. This analysis evaluated the impact of cabazitaxel on HRQL in both trials.

Methods: Alongside pain and analgesic score, HRQL was assessed using the Functional Assessment of Cancer Therapy Prostate (FACT-P) questionnaire. The analysis focused on FACT-P (clinically meaningful improvement or deterioration of total score (TSI) among responders.

Results: Pt baseline characteristics are shown in the table. In PROSELICA, 57.2% and 59.4% of pts receiving C20 and C25 had FACT-P TS improvements in FIRSTANA, 63.5%, 62.9% and 57.7% of pts receiving C20, C25 and D75 had FACT-P TS improvements. FACT-P responders, FACT-P TS improvements occurred as early as Cycle 1 (C1) (mean change from baseline: PROSELICA C20 10.4, n = 63; C25 10.6, n = 61; FIRSTANA C20 10.4, n = 17; C25 10.5, n = 19; D75 11.5, n = 20) and maintained until C9 (C20 9.0, n = 27; C25 9.6, n = 28; D75 10.5, n = 38). These were largely maintained for pts with a pain response in PROSELICA, FACT-P TS improvements occurred as early as C1 (C20 6.8, n = 71; C25 11.1, n = 81) and maintained until C9 (C20 9.0, n = 27; C25 9.2, n = 26; D75 10.5, n = 26). In FIRSTANA, FACT-P TS improvements in pts with a pain response were seen as early as C1 (C20 15.5, n = 41; C25 12.9, n = 41; D75 14.5, n = 32) and maintained until C9 (C20 19.0, n = 27; C25 19.5, n = 26; D75 16.4, n = 20). In pts with a tumor or PSA response, HRQL was maintained for all treatment arms in both studies. Additional results for clinical responder subgroups and FACT-P subscales will be presented.

Table: 812P

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>FIRSTANA</th>
<th>PROSELICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>69.0 (41–87)</td>
<td>68.0 (44–90)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>68.5 (42–85)</td>
<td>68.0 (45–89)</td>
</tr>
<tr>
<td>0–1</td>
<td>62.0 (45–88)</td>
<td>62.0 (45–88)</td>
</tr>
<tr>
<td>2</td>
<td>59.9 (42–85)</td>
<td>59.9 (42–85)</td>
</tr>
<tr>
<td>Mean PSA, ng/mL (SD)</td>
<td>252.8 (625.2)</td>
<td>213.2 (434.2)</td>
</tr>
<tr>
<td>Median present pain intensity, score (range)</td>
<td>370 (95.1)</td>
<td>213.2 (434.2)</td>
</tr>
<tr>
<td>Median FACT-P TS (range)</td>
<td>1.0 (0.0–4.0)</td>
<td>1.0 (0.0–4.0)</td>
</tr>
<tr>
<td>D75</td>
<td>376 (96.9)</td>
<td>1.0 (0.0–4.0)</td>
</tr>
<tr>
<td>C20</td>
<td>539 (90.1)</td>
<td>1.0 (0.0–4.0)</td>
</tr>
<tr>
<td>C25</td>
<td>540 (89.7)</td>
<td>1.0 (0.0–4.0)</td>
</tr>
</tbody>
</table>

Conclusions: More than half of the pts experienced HRQL improvements, which were maintained. Pts with a pain response experienced HRQL improvements. Funding: Sanofi.


Disclosure: Editorial acknowledgement: Editorial assistance was provided by Mark Cockrell of MedTech Media Ltd, funded by Sanofi.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

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813P

Treatment of metastatic castration-resistant prostate cancer (mCRPC); Survival by type of progression at initiation of treatment

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Background: The usual sequence of progression events in mCRPC patients treated with new hormonal agents is known: PSA progression, followed by radiological progression and finally pain progression (Ryan, NEJM 2013; Beer, NEJM 2014). Although the impact of type of progression on outcomes is not well documented in phase III trials with chemotherapy. Here, we investigated the impact of type of progression on OS in mCRPC patients receiving docetaxel-based chemotherapy.

Methods: Data from the phase III study VENICE evaluating docetaxel 75mg/m² q3w ± abiraterone (Tannock, Lancet Oncol 2013) was used as a training dataset. At randomization, group 1 (G1) had PSA progression only (n = 231), G2 had radiological progression (± PSA) but no pain (n = 348), and G3 had pain (± PSA, ± radiological) (n = 447). The TAX327 definition for pain was used: Mean present pain intensity ≥ 2 and/or mean analgesic score ≥ 20. The impact of type of progression on OS was evaluated in a multivariate Cox regression analysis with backward elimination (5% level), stratified for ECOG performance status (0-1 vs 2) and treatment arm.

Results: In the VENICE trial median OS was 28.6 months for G1, 26.3 months for G2 and 16.9 months for G3. Hazard ratios [95% CI] for death were 1.14 [0.92-1.41] in G2
and 2.13 (1.75 - 2.59) in G3 compared to G1. In multivariate analysis, pain at randomization was the strongest predictor of poor OS: HR 1.71, 95% CI 1.39-2.11, vs PSA progression only. Other significant prognostic factors included older age, high alkaline phosphatase, short duration of androgen deprivation therapy, low hemoglobin level and high neutrophil-lymphocyte ratio. Cox test led to ≤ 50% decline in PSA in 67.3%, 80.5% and 77% in G1, G2 and G3 respectively.

Conclusions: The type of progression at initiation of first-line chemotherapy in mCRC is prognostic. Patients with pain at initiation of chemotherapy had a median OS of −1 year shorter than those having PSA progression only. Validation of these results by an independent dataset (TAX 327) is ongoing. Results will be presented at ESMO.

Legal entity responsible for the study: Sanofi.

Funding: Sanofi.


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Background: Platinum compounds have been tested in a large number of mostly small to medium sized clinical trials in molecularly unselected prostate cancer patients (pts). Advances in castration-resistant prostate cancer (CRPC) molecular profiling have shown that a significant proportion of pts harbor DNA repair defects, which may serve as predictive markers for sensitivity to platinum agents. Our aim was to evaluate the antitumour activity of platinum agents in a contemporaneous mCRPC cohort with or without DNA repair defects.

Methods: International, multicenter retrospective database project in 14 centers worldwide. Pts with mCRPC treated with a platinum agent were included. Pts with primary pure small cell carcinoma and/or insufficient outcome data were excluded. For antitumour activity PSA levels at baseline, after 4-, 8- and 12-weeks of therapy (tx) were analyzed as well as soft tissue response and duration of platinum-based chemotherapy. Overall survival (OS) was analyzed by Kaplan Meier method.

Results: A total of 167 pts have been included in this analysis, 33 (20%) received platinum monotherapy, 134 (80%) a platinum combination therapy. Carboplatin was used in 140 (84%), cisplatin in 26 (16%) of pts. Combination tx with etoposide was used in 45 (27%), paclitaxel in 35 (21%) and docetaxel in 28 (13%) of pts. At start of platinum tx median age was 68 years, median PSA 78 μg/l, median ALP 183 U/l, median hemoglobin 103 g/l. The metastatic sites at start of platinum therapy were: bone 84%, lymph node 39% and visceral 60%. Outcome data by DNA repair defect status are summarized in the table.

![Table 814P](https://via282.com/Genitourinary-tumours/prostate/Table_814P.png)

Conclusions: In this retrospective analysis of a contemporary cohort of men with mCRC and poor prognostic characteristics platinum-based treatment seems to have significant anti-tumor activity irrespective of DNA repair status. Comparison of subgroups is limited by small sample size. Updated analyses will be presented.

Legal entity responsible for the study: Ethical Committee St. Gallen.

Funding: Has not received any funding.


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Background: Bone metastases are common in CRPC patients and these patients (pts) are at risk for symptomatic skeletal related events (SSE). Bone directed therapy and early initiation of a life-prolonging drug (LPD) therapy can prevent or prolong time to SSEs. The objective is to evaluate whether delay in LPD has adverse outcome in CRPC pts and a shorter SSE-free interval.

Methods: CAPRI is an investigator-initiated, observational study in 20 hospitals in the Netherlands. All treated CRPC pts are retrospectively included in subgroups based on type of first line treatment: LPD (docetaxel, abiraterone, enzalutamide or radium-223) or non-LPD (other drugs as anti-androgens, prednisone). SSEs are defined as the occurrence of either radiotherapy (RT) to the bone, surgery to the bone, pathological fracture or spinal cord compression (SCC).

Results: 1,618 pts were included in this analysis. Median follow-up was 26 months (IQR 15-39). 466 (29%) were treated with LPD (mostly docetaxel 15%) and 1,152

![Table 815P](https://via282.com/Genitourinary-tumours/prostate/Table_815P.png)

Annals of Oncology
Androgen decline and outcome in castration resistant prostate cancer (mCRPC) patients treated with docetaxel (Doc), prednisone +/- bevacizumab (B)

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Background: Androgen levels are associated with overall survival (OS) in mCRPC. Doc impacts microtubules and has AR inhibitory effects. This analysis evaluates change in androgen levels (Testosterone (T), Androstenedione (A) and DHEA (D)) and outcome in Doc-treated mCRPC patients.

Methods: Data from 1,050 men treated on CALGB 90401 with Doc, prednisone and either B or placebo were used. Pre-treatment, 6 week and progression serum assays for T, A and D were performed via tandem Liquid Chromatography-Mass Spectrometry (LC-MS/MS). Ratio of change in androgen (6 week value / baseline value) was calculated. Decline was further evaluated as high or low (< or ≥ median decline for all patients). The logistic regression and proportional hazards models were used to assess the prognostic significance of changes in T, A and D in predicting PSA response, PPS and OS adjusting for known prognostic factors.

Results: Median values for baseline T, A, and D were 1.0, 13.5 and 8.1, ng/dl, respectively, while androgen levels at 6 weeks were 0.64, 7.0 and 6.8, ng/dl, respectively. At 6 weeks a decline in all three androgens was observed. The ratio of 6weeks/baseline in T, A and D were 0.95, 0.56 and 0.86, respectively. There was interaction between levels of T decline and treatment arm (p-value = 0.047). Among 291 patients with high levels of T decline, those who also received B were more likely to experience a ≥ 50% decline in PSA (87%) compared to those who did not receive B (67%). Associations between androgen decline and PFS were NS. In multivariable analysis adjusting for prognostic factors, the hazard ratio (HR) for OS demonstrated that decline in T at 6-weeks/base-line was associated with longer OS, HR 1.02 (95% CI 1.01 to 1.03 p = 0.001). Median OS for low T change (ratio > -0.93) was 20.9 mos vs 26.3 mos for high T change (p <0.93).

Conclusions: Patients treated with Doc who experience a greater drop in T on therapy experience a significantly longer OS and higher rate of PSA decline but not effect on PFS. B and androgen decline may confer interacting beneficial effects. Data are consistent with the favorable prognostic significance of higher serum androgens in the CRPC setting and reducing the potential effect of Doc on AR signalling.

Clinical trial identification: NCT00102124.

Legal entity responsible for the study: Alliance for Clinical Trials in Oncology.

Funding: National Cancer Institute: R21 CA195424-01, U01CA188082, U10CA180882.

Disclosure: C.J. Ryan. Consulting fees: Sanofi. All other authors have declared no conflicts of interest.
From a total of 3,616 pts in the CAPRI database, we identified 356 pts treated with CAB, of which 173 pts were treated directly post-DOC. Trial pts had less symptoms and visceral disease, lower LDH, higher hemoglobin, received more DOC cycles and had a longer treatment-free interval since last DOC (see Table). The median number of CAB cycles was higher in trials compared to SOC (5 vs 4, p = 0.031). Median OS was 13.6 vs 9.6 months for trial pts and SOC, respectively (HR 0.73, p = 0.07). PSA response (≥ 50% decline) was 27 vs 11%, respectively (p = 0.210). However, after correction for prognostic factors, trial participation did not retain statistical significance (HR 0.94, p = 0.73), but longer period on ADT, lower LSH and absence of visceral metastases were significant for better OS. In addition, lower PSA and absence of symptoms had a trend for better OS.

Conclusions: The OS in the trial subgroup is in agreement with the OS of the TROPIC trial in a contemporary real world setting. However, the SOC pts had a trend for worse OS which may be explained by worse prognostic factors at CAB initiation. Accordingly, pts whose disease has progressed post-DOC should be carefully selected for treatment to ensure optimal outcomes.

Clinical trial identification: The CAPRI study is registered in the Dutch Trial Registry as NTR3591.

Legal entity responsible for the study: Institute for Medical Technology Assessment, Erasmus University Rotterdam.

Funding: The CAPRI registry was funded by Sanofi-Aventis Netherlands B.V., Janssen-Cilag B.V., Astellas Pharma B.V., and Bayer B.V. The funding organizations had no role in the design and conduct of the study, collection, management, analysis, interpretation of the data, and preparation, review, or approval of the abstract.

Disclosure: A.J.M. van den Eertwegh: Study grant: Sanofi; Travel expenses, speaker fee, advisory board: Astellas. J. Van Moorleaken: Grants/research support: Astellas, Ferring, Ipsen; Honors/consultancy fees: Amgen, Astellas, AstraZeneca, Bayer, Janssen, Sanofi-Genzyme. I. van Oort: Sanofi; Travel expenses, speaker fee, advisory board: Sanofi R. de Wit: Sanofi, Merck, Roche. A. Bergman: PI of one IIS sponsored by Sanofi. W.R. Gerritsen: Speaker fees: Astellas, Bavarian Nordic, Bristol-Myers Squibb, MSD, Janssen-Cilag, Advisory boards: Amgen, Astellas, Bayer, Bristol-Myers Squibb, Curevac, Dengron, Janssen-Cilag, Merck (MSD); Morphsys, Sanofi; Ad hoc consultancy: Aglaia Biomedical Ventures, Psioxus Therapeutics. All other authors have declared no conflicts of interest.

Table: 818P

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>68.0 (42–89)</th>
<th>68.0 (43–89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, n (%) &lt;65 years 65–75 years ≥75 years</td>
<td>271 (29.7) 433 (47.4) 209 (22.9)</td>
<td>230 (32.5) 339 (47.9) 139 (19.6)</td>
</tr>
<tr>
<td>ECOG PS, n (%) 0–1 2*</td>
<td>N = 912 816 (89.5) 96 (10.5)</td>
<td>N = 708 665 (93.9) 43 (6.1)</td>
</tr>
<tr>
<td>Median cabazitaxel cycles, n (range)</td>
<td>4 (1–6)</td>
<td>10 (7–49)</td>
</tr>
<tr>
<td>Median duration of cabazitaxel exposure, months (range)</td>
<td>2.8 (1–6)</td>
<td>6.9 (5–33)</td>
</tr>
<tr>
<td>Median time from prostate cancer diagnosis, years (range)</td>
<td>4.5 (0–22)</td>
<td>4.7 (0–20)</td>
</tr>
<tr>
<td>Median time from mCRPC diagnosis, years (range)</td>
<td>1.7 (0–14)</td>
<td>1.8 (0–12)</td>
</tr>
<tr>
<td>Median docetaxel cycles at last administration, n (range)</td>
<td>7 (1–69)</td>
<td>8 (1–58)</td>
</tr>
<tr>
<td>Metastatic sites, n (%) Bone Visceral Regional lymph nodes</td>
<td>N = 912 829 (90.8) 47 (5.1) 282 (30.9)</td>
<td>N = 707 630 (89.0) 23 (3.2) 214 (30.2)</td>
</tr>
<tr>
<td>G-CSF during Cycle 1, n (%) Prophylactic Therapeutic Both</td>
<td>N = 499 385 (42.2) 69 (7.6) 45 (4.9)</td>
<td>N = 380 314 (44.4) 33 (4.7) 33 (4.7)</td>
</tr>
<tr>
<td>Pain at baseline (CAPRISTANA study only), n (%) None Moderate Severe</td>
<td>N = 86 15 (17.4) 63 (73.3) 8 (9.3)</td>
<td>N = 68 18 (26.5) 47 (69.1) 3 (4.4)</td>
</tr>
</tbody>
</table>

*Includes one patient with ECOG PS 3 receiving ≤ 6 cabazitaxel cycles.

818P Post hoc analysis of the effect of baseline characteristics on treatment duration in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel in the compassionate use (CUP)/expanded access programs (EAP) and CAPRISTANA registry

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Background: Cabazitaxel is approved for patients with mCRPC, post docetaxel. The CUP (CABAZ-C_05005) and EAP (NCT01254279) provided access to cabazitaxel before commercial availability and assessed real-world safety. CAPRISTANA (CABAZC 06092), a prospective, observational study, evaluated the routine clinical use of cabazitaxel. In this analysis we examined factors associated with cabazitaxel treatment duration in a real-life setting.

Methods: Patients ≥18 years of age with mCRPC previously treated with docetaxel, received cabazitaxel 25 mg/m² intravenously every 3 weeks until disease progression, death, unacceptable toxicity or physician/patient decision. Of note, treatment was capped at 10 cycles in some countries.

Results: The CUP/EAP/CAPRISTANA studies combined included 1,621 patients (CUP/EAP, N = 1,432; CAPRISTANA, N = 189). The median number of cabazitaxel cycles received was 6. Overall, 708 patients (43.7%) received > 6 cycles (Table). 211 (13.0%) received > 10 cycles. For patients receiving > 10 cycles, the median number of cabazitaxel cycles received was 14. Patients receiving more cabazitaxel cycles tended to have better ECOG performance status of 0–1 (Table, P = 0.0017 for ≤ 6 vs > 6 cycles). In total, 348 patients (21.5%) were ≥ 75 years of age, of which 40% (n = 139) received > 6 cycles. Further analysis into the patient subgroups and reasons for treatment discontinuation are ongoing.

Conclusions: Cabazitaxel was well tolerated by patients across these global studies, including elderly patients. Many patients derived benefit from cabazitaxel and went on to receive a greater number of cycles. Further analyses may identify prognostic factors that could indicate which patients are likely to receive > 6 cabazitaxel cycles and derive greater benefit. Funding: Sanofi.


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Legal entity responsible for the study: Sanofi.

Funding: Sanofi.

Prognostic associations of early prostate-specific antigen (PSA) changes in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate or enzalutamide


Background: The availability of multiple treatments for metastatic castration-resistant prostate cancer (mCRPC) mandates the need to identify prognostic factors applicable to clinical practice. Variations in (PSA) levels are widely used in the monitoring of response to treatment with abiraterone acetate (AA) or enzalutamide, but are not validated as an early biomarker for overall survival (OS). Objective: To evaluate the association between early PSA changes and OS following enzalutamide or AA treatments in mCRPC.

Methods: We retrospectively evaluated mCRPC patients treated with AA or enzalutamide, before or after docetaxel, in 11 reference hospitals between 2011 and 2017. A descriptive and multivariate analysis of the data was carried out in order to establish the association of PSA variations at 4 and 12 weeks (expressed as 30% and 50% percentage modifications, respectively, relative to baseline value at the start of AA or enzalutamide) with OS. Associations with OS was analyzed using multivariate Cox regression and log-rank analyses. Spearman’s rho correlation coefficient (r) was calculated to evaluate the association between PSA changes at 4 and 12 weeks.

Results: We analyzed 450 mCRPC patients with a median follow-up of 16 months (1-65). A 30% PSA decline at 4 weeks was associated with longer OS (30 vs 20 months; hazard ratio [HR] 0.55 (0.42-0.73), p < 0.001), as well as a 50% PSA decrease at 12 weeks (39 vs 19 months; HR 0.42 (0.31-0.56), p < 0.001). We found a detriment in survival in patients with a 30% PSA rise at 4 weeks, with shorter OS (22 vs 26 months; HR 1.5 (1.07-2.11), p = 0.023) and a 50% PSA increase at 12 weeks (41 vs 29 months; 2.66 (1.93-3.67) p < 0.001), in both univariate and multivariable models. The percentage PSA decline at 4 weeks was significantly correlated with the percentage PSA change at 12 weeks (r = 0.635, p < 0.001). Limitations include the retrospective design of this analysis.

Conclusions: PSA changes as early as 4 weeks after enzalutamide or AA initiation are highly associated with OS in mCRPC. Prospective multicentre validation studies are needed to confirm these findings.

Legal entity responsible for the study: Fernando López Campos.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Annals of Oncology

Cabazitaxel under routine conditions for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC): Interim results of the non-interventional SCOPE study

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Background: Several treatment options are currently available for patients with mCRPC who were treated with a docetaxel-containing regimen. As one therapeutic option, cabazitaxel (CABA) in combination with prednisolone (P) can be adminstered. SCOPE is the first multinational, non-interventional study to address this question prospectively.

Methods: Within the ongoing SCOPE study, data on medical history, therapeutic management and outcome of mCRPC patients starting treatment with CABA under routine conditions are assessed with a target recruitment of 900 patients. For the current interim analysis (cut-off: MAR 16, 2018) descriptive statistics were used to analyse preliminary data on treatment outcomes.

Results: Of 551 enrolled patients, 137 patients (median age: 73 [47 to 88] years, ECOG of ≤ 1, 81.8%, median duration of CRPC at study inclusion: 20.4 [0.8 to 199.1] months) have completed CABA therapy. For 27 patients, first line therapy with an androgen-receptor targeted agent (ARTA) was documented (ARTA 1st line), of which 10 patients received an ARTA in a 2nd line (ARTA post ARTA). None (0.0%) of the 10 ARTA post-ARTA patients had reductions in PSA levels ≥50% (PSA50 response) compared to baseline. Median progression-free survival (PFS) after the start of the respective therapy was longer for 1st line ARTA than for ARTA post-ARTA therapy (10.8 vs 3.5 months, p = 0.0116). Fifty patients received docetaxel as 1st line therapy directly followed by CABA (CABA 2nd line) and for 24 patients ARTA therapy was documented after docetaxel and prior to CABA (CABA 3rd line). PSA50 response to CABA was 38.0% (CABA 2nd line) and 37.5% (CABA 3rd line), respectively. Median PFS after start of CABA therapy showed no significant differences between the CABA 2nd line and CABA 3rd line group (4.2 vs 5.1 months, p = 0.5663).

Conclusions: The current results indicate that the outcome of ARTA post-ARTA is unfavourable compared to 1st line ARTA therapy and that CABA is effective in both ARTA and docetaxel refractory patients. However, interpretation of results is challenging due to the highly diverse treatment sequences administered in patients with mCRPC under routine conditions.

Clinical trial identification: BfArM data base No: 6658.

Legal entity responsible for the study: Sanofi Aventis Deutschland GmbH.

Funding: Sanofi Aventis Deutschland GmbH.

Disclosure: J. Gschwend: Lectures: Amgen, Astellas, Bayer, Jansen, MSD, Novartis, Roche; Sanofi; Advisor role: Bayer, BMS, jansen, MSD, Novartis, Pfizer, Roche, C. Bokemeyer: Honorary: Merck KGaA, Sanofi, Roche, Bayer, Brystol-Meyer Squibb, Servier/Pfizer, AstraZeneca; Consulting: Lilly/ImmTone, Merck Serono, Sanofi, Mundipharma, Bayer Schering Pharma, Hexal. All other authors have declared no conflicts of interest.

Kinetiks of prostate-specific antigen (PSA) as a marker of abiraterone acetate (AA) efficacy in patients (p) with metastatic castration-resistant prostate cancer (mCRPC)

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Background: Studies have suggested an association between PSA kinetics and outcome to AA. In order to identify p with resistance to AA, we assessed potential factors associated with overall survival (OS) in p with mCRPC treated with AA after progression to docetaxel.

Methods: We included 104 p with mCRPC treated with AA plus prednisone after progression to docetaxel at three centers of the Catalan Institute of Oncology from August 2011 to October 2014. All p were assessed every 4 weeks by PSA level and hematological parameters. We used a multivariable Cox proportional hazards model to explore the association of baseline characteristics and PSA parameters with OS.

Results: Median OS was 16.4 months (m) and the median of duration of treatment was 7.54 m. In the univariate analysis, 14 factors were significantly associated with OS: ECOG PS, metastatic site, hemoglobin, alkaline phosphatase, lactate dehydrogenase (LDH), baseline PSA levels (classified by terciles), neutrophil-lymphocyte ratio (NLR), interval between end of docetaxel and start of AA, early PSA response (decrease >30%, at week 4), PSA nadir, time to PSA nadir, PSA decrease >50%, end-of-treatment (EOT) PSA levels, and EOT PSA doubling time (PSADT). The multivariate analysis identified lymph node metastases (P = 0.016), NLR < 4 (P = 0.038), baseline PSA levels < 45 ng/ml (P = 0.026), normal LDH (P = 0.035), early PSA response (P = 0.001), and EOT PSADT > 1.5 m (P = 0.001) as independent markers of longer OS.

Conclusions: Our results suggest an association between PSA kinetics, primarily early PSA response, with outcome to AA after progression to docetaxel. Taken together with other factors, lack of an early PSA response could identify patients that will probably not obtain a benefit from AA and who might be considered for alternative therapies.

Legal entity responsible for the study: Catalan Institute of Oncology, Hospital University Germans Trias i Pujol.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Abiraterone acetate (AA) improves OS and PFS in asymptomatic/mildly symptomatic mCRPC patients (pts) who are chemotherapy (CT) naïve. Upon progression with CT strategy, docetaxel (D) is currently recommended. However, the value of maintaining AA along with D despite progression to the former has not been tested yet. ABIDO is a randomized-phase II trial that evaluates efficacy and safety of D + AA vs. D after disease progression to first line AA in mCRPC.

Methods: mCRPC control naïve pts with no visceral metastases, ECOG PS 0-1, testosteone < 50 ng/dl, and adequate, hematologic, hepatic, and renal function were included. The study has two stages. In stage I pts receive AA at the approved regime (AA 1000mg/day prednisone (P) 5 mg/dl) until progressive disease determined by PSWG/2 criteria. Upon progression, in stage II pts are randomized to receive either three-weekly D+ AA (Arm A) or three-weekly D alone (Arm B).

Results: So far 148 pts have been included and 88 were randomized already. Of those 77 have completed D and have been analyzed (39 in Arm A and 38 in Arm B). Median age was 72 yr (64% had ECOG 0 and 88% had bone metastasis and 16% visceral metastases. Patients received 235 and 274 cycles of D in Arm A and B respectively with a median number of cycles of 7 and 8. Docetaxel median dose intensity was 90% and 92% for each arm and 94% for AA. Nine pts discontinued treatment due to toxicity, 5 in Arm A and 4 in Arm B. Most frequent G-3 toxicities per arm (AA/ D) were: neutropenia (56%/29%), febrile neutropenia (21%/8%), diarrhea (10%/8%), and asthenia (13%/11%). Most common toxicities all grades per arm were: asthenia (74%/66%), neutropenia (59%/34%), alopecia (44%/45%), nail toxicity (49%/34%), diarrhea (46%/42%), neurotoxicity (39%/46%), nausea (28%/26%), mucositis (28%/29%) and anemia (23%/11%).

Conclusions: In the AA maintenance cohort, more frequent and severe hematological treatment related adverse events (neutropenia, febrile neutropenia and anemia) were observed. No other differences were relevant. Prophylactic G-CSF use is encouraged in all patients. These preliminary data require confirmation once the study is completed.

Clinical trial identification: NCT02056060; EudraCT: 2013-00811-23.

Editorial acknowledgement: Juan Luis Sanz, APICES.

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

Funding: Janssen-Cilag, S.A.

Disclosure: J. Puente: Honoraria: Astellas, Bayer, Janssen, Roche, Ipsen, Consulting or advisory role: Astellas, Roche, Ipsen, Pfizer, Bristol-Myers Squibb, Merck & Co., BMS; Research funding: Astellas, BMS; M.I. Mendez: Consulting: Janssen, Sanofi, Pfizer, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Pfizer- Fabre, Bristol-Myers Squibb, MSD; Consulting: Sanofi, Astellas, Bayer, Roche, Boehringer Ingelheim, Pfizer-Fabre, Bristol-Myers Squibb, MSD; T. Alonso: Consulting: Sanofi, Astellas, Bayer, Roche, Boehringer Ingelheim, Pfizer-Fabre, Bristol-Myers Squibb, MSD.

M.A. Gonzalez del Alba Page 12: Honoraria: Astellas, Sanofi, Bayer, Janssen, Roche, Ipsen, Pfizer, Bristol-Myers Squibb, Merck & Co., BMS; Research funding: Astellas, BMS; M.I. Mendez: Consulting: Janssen, Sanofi, Pfizer, Bristol-Myers Squibb, Roche, Boehringer Ingelheim, Pfizer-Fabre, Bristol-Myers Squibb, MSD; Consulting: Sanofi, Astellas, Bayer, Roche, Boehringer Ingelheim, Pfizer-Fabre, Bristol-Myers Squibb, MSD.


Legal entity responsible for the study: Pablo Gaete Bonas.

Funding: Has not received any disclosure.

Disclosures: All authors have declared no conflicts of interest.

Table: 823P PFS at first-line treatment of mCRPC

<table>
<thead>
<tr>
<th>H (m)</th>
<th>CT (m)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSAADT &lt; 3</td>
<td>PSAADT &gt; 3</td>
<td>m</td>
</tr>
<tr>
<td>4.46 9.39</td>
<td>627.39 559.34</td>
<td>0.06 0.07</td>
</tr>
<tr>
<td>4.33 9.55</td>
<td>559.34 559.12</td>
<td>0.59 0.12</td>
</tr>
<tr>
<td>4.34 12.0</td>
<td>559.81 559.3</td>
<td>0.29 0.3</td>
</tr>
<tr>
<td>3.81 11.99</td>
<td>693.52 559.3</td>
<td>0.03 0.63</td>
</tr>
<tr>
<td>3.81 8.54</td>
<td>552.58 552.38</td>
<td>0.35 0.14</td>
</tr>
</tbody>
</table>

Conclusions: Baseline characteristics at CRPC disease could help us to identify the best therapy option for pt pretreated with D + ADT in mHSPC. Our analyses suggest that CT could benefit pt with more aggressive clinical features.

Legal entity responsible for the study: Pablo Gaete Bonas.

Funding: Has not received any disclosure.

Disclosures: All authors have declared no conflicts of interest.

Table: 823P PFS at first-line treatment of mCRPC
### Table: 825P

<table>
<thead>
<tr>
<th>Marker</th>
<th>Ratio of RA+EZ to EZ</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Specific Alk Phos</td>
<td>0.38</td>
<td>0.270–0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C Telopeptide</td>
<td>0.66</td>
<td>0.441–1.00</td>
<td>0.060</td>
</tr>
<tr>
<td>N Telopeptide</td>
<td>0.61</td>
<td>0.480–0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Procollagen 1 N-Terminal</td>
<td>0.52</td>
<td>0.350–0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pyridinoline</td>
<td>1.02</td>
<td>0.801–1.30</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Table: 824P**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior Abi (n = 223)</th>
<th>Abi naive (n = 321)</th>
<th>Overall population (n = 708)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG: 0 and 1, n (%)</strong></td>
<td>195 (87)</td>
<td>273 (85)</td>
<td>618 (87)</td>
</tr>
<tr>
<td><strong>PSA, median (ng/ml)</strong></td>
<td>290</td>
<td>100</td>
<td>143</td>
</tr>
<tr>
<td><strong>ALP median (U/l)</strong></td>
<td>169</td>
<td>148</td>
<td>150</td>
</tr>
<tr>
<td><strong>Time since diagnosis of prostate cancer, median (months)</strong></td>
<td>81</td>
<td>53</td>
<td>64</td>
</tr>
<tr>
<td><strong>Time between diagnosis of prostate cancer and bone metastases, median (months)</strong></td>
<td>26</td>
<td>11</td>
<td>19</td>
</tr>
<tr>
<td><strong>Time from diagnosis of bone metastases to Ra-223 treatment, median (months)</strong></td>
<td>37</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td><strong>Prior docetaxel, n (%)</strong></td>
<td>189 (85)</td>
<td>117 (36)</td>
<td>423 (60)</td>
</tr>
<tr>
<td><strong>Prior bisphosphonate, n (%)</strong></td>
<td>19 (9)</td>
<td>13 (4)</td>
<td>48 (7)</td>
</tr>
<tr>
<td><strong>Prior denosumab, n (%)</strong></td>
<td>6 (3)</td>
<td>6 (2)</td>
<td>14 (2)</td>
</tr>
<tr>
<td><strong>Concomitant bisphosphonates, n (%)</strong></td>
<td>30 (14)</td>
<td>56 (17)</td>
<td>122 (17)</td>
</tr>
<tr>
<td><strong>Concomitant denosumab, n (%)</strong></td>
<td>44 (20)</td>
<td>53 (17)</td>
<td>129 (18)</td>
</tr>
<tr>
<td><strong>Total Ra-223 injections, median (range)</strong></td>
<td>5.0 (1–6)</td>
<td>6.0 (1–6)</td>
<td>6.0 (1–6)</td>
</tr>
<tr>
<td><strong>OS, median (95% CI) (months)</strong></td>
<td>11.2 (9.7–13.5)</td>
<td>17.1 (12.7, Not available)</td>
<td>15.9 (13.4, Not available)</td>
</tr>
<tr>
<td><strong>Any SSE, n (%)</strong></td>
<td>58 (26)</td>
<td>45 (14)</td>
<td>145 (21)</td>
</tr>
<tr>
<td><strong>Treatment-emergent fracture, n (%)</strong></td>
<td>8 (4)</td>
<td>11 (3)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>** Experienced pathological bone fracture, n (%)**</td>
<td>12 (5)</td>
<td>15 (5)</td>
<td>39 (6)</td>
</tr>
</tbody>
</table>
Use of bone health agents (BHAs) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 (Ra-223) after abiraterone (Abi): An interim review of REASURE


1Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy; 2Dept. of Urology, University Hospital Magdeburg, Magdeburg, Germany; 3Medical Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; 4Dept. of Imaging and Oncology, Leeds, UK; 5Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy; 6Dept. of Oncology, Clinicum Universitatis St-Luc, Brussels, Belgium; 7Medical Oncology, Charité Berlin, Berlin, Germany; 8Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; 9Medical Oncology, Charité Berlin, Berlin, Germany; 10Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy; 11Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy.

Abstract:

Background: When the Ra-223 phase 3 clinical trial (ALSTOMPICA) was conducted, Abi was not available; REASURE is a prospective, observational clinical study of Ra-223 in pts with mCRPC, with a 7-year follow-up (NCT02141438). Pts could have had anti-hormonal agents, such as Abi, prior to receiving Ra-223. The objective of this interim review was to evaluate the fractures and skeletal-related events (SREs) based on prior Abi and the use of BHAs, denosumab and ibandronate.

Methods: Descriptive statistics were generated for baseline characteristics, fractures, SREs and overall survival (OS) by BHA use in pts who had completed Abi treatment prior to receiving Ra-223 (prior Abi) or who had no prior Abi (Abi-naïve). An SRE was defined as any skeletal-related adverse event or any radiotherapy to bone.

Results: As of Nov 2017, 1439 pts were enrolled, with a median follow-up time of 9.1 months. 708 (49%) pts had received BHAs at baseline, and BHAs were given concomitantly with Ra-223 in 533 (38%) pts. 430 (30%) pts received prior Abi, and Ra-223 was given as second line in 37% (157/430) of those pts; 705 (49%) pts were considered Abi-naïve. For the prior Abi group, median time of exposure to Abi was 11 months. In the prior Abi group, SREs occurred in 17% and 22% of pts, with and without BHAs, respectively. In the Abi-naïve group, 16% of pts had SREs regardless of BHA use. Fractures were reported in 743 pts (10.6%) in the prior Abi group. In the Abi-naïve group fractures were reported in 2/311 (0.6%) and 8/494 (2%) pts with and without BHAs, respectively (Table).

Conclusions: BHAs were under-utilised in this study despite several guidelines and recommendations. The rate of fracture was the same in those who were Abi-naïve compared with those who received Abi prior to Ra-223. Pts with prior Abi had a shorter OS; these pts received Ra-223 at a later time during their disease course, as reflected by a longer time from CRPC to Ra-223 initiation.

Clinical trial identification: NCT02141438.

Editorial acknowledgement: Medical writing support was provided by Michael Sheldon of Scion, London UK, funded by Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.


### Table: 826P

<table>
<thead>
<tr>
<th>Patient outcomes</th>
<th>With BHAs (n = 511)</th>
<th>Without BHAs (n = 394)</th>
<th>With BHAs (n = 216)</th>
<th>Without BHAs (n = 214)</th>
<th>Overall cohort (n = 1439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 SRE, n (%)</td>
<td>6 (0–134)</td>
<td>8</td>
<td>10 (0–109)</td>
<td>23 (0–80)</td>
<td>12 (0–147)</td>
</tr>
<tr>
<td>≥1 fracture, n (%)</td>
<td>4 (11, 160)</td>
<td>46 (15, 161)</td>
<td>114 (31, 331)</td>
<td>121 (30, 311)</td>
<td>13 (0–117)</td>
</tr>
<tr>
<td>S-6 Ra-223 injections, n (%)</td>
<td>199 (64)</td>
<td>252 (64)</td>
<td>128 (59)</td>
<td>128 (60)</td>
<td>116 (16)</td>
</tr>
<tr>
<td>OS from initation of Ra-223, median months (95% CI)</td>
<td>15 (13.1, 16.6)</td>
<td>14.8 (13.5, 16.0)</td>
<td>14.8 (13.5, 16.0)</td>
<td>14.8 (13.5, 16.0)</td>
<td>14.8 (13.5, 16.0)</td>
</tr>
</tbody>
</table>

827P Clinical outcome with radium-223 (Ra-223) in patients (pts) previously treated with abiraterone (Abi) or enzalutamide (Enza): A retrospective study of real-world (RW) data from pts with metastatic castration-resistant prostate cancer (mCRPC)


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Abstract:

Background: Ra-223 pivotal phase 3 trial was conducted prior to Abi and Enza becoming available. Here, we analysed registry data to determine clinical outcomes with Ra-223 therapy in pts previously treated with Abi or Enza in a RW setting.

Conclusions: The time from CRPC to Ra-223 initiation, median months (range), PSA, median ng/mL (Q1, Q3), Prior doctetaxel, n (%) and Patient outcomes were similar for pts treated with Ra-223, median months (95% CI) in this study.

Table 827P

<table>
<thead>
<tr>
<th>Patient outcomes</th>
<th>With BHAs (n = 708)</th>
<th>Without BHAs (n = 731)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 SRE, n (%)</td>
<td>60 (14, 212)</td>
<td>59 (19, 201)</td>
</tr>
<tr>
<td>≥1 fracture, n (%)</td>
<td>60 (14, 212)</td>
<td>59 (19, 201)</td>
</tr>
<tr>
<td>S-6 Ra-223 injections, n (%)</td>
<td>480 (68)</td>
<td>465 (64)</td>
</tr>
</tbody>
</table>
Table: 827P

<table>
<thead>
<tr>
<th></th>
<th>Ra-223 pts with prior Abi (n = 187)</th>
<th>Ra-223 pts with prior Enza (n = 164)</th>
<th>All Ra-223 pts (n = 625)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (years)</td>
<td>75</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>ECOG 0–1, n (%)</td>
<td>84 (45.0)</td>
<td>73 (44.5)</td>
<td>260 (41.6)</td>
</tr>
<tr>
<td>ALP (U/L), median</td>
<td>111</td>
<td>113</td>
<td>108</td>
</tr>
<tr>
<td>PSA (µg/L), median</td>
<td>67</td>
<td>53</td>
<td>38</td>
</tr>
<tr>
<td>LDH (U/L), median</td>
<td>204</td>
<td>207</td>
<td>196</td>
</tr>
<tr>
<td>Time from castration resistance to baseline, median (months)</td>
<td>18</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Pts with prior SREs, n (%)</td>
<td>89 (47.6)</td>
<td>87 (53.0)</td>
<td>314 (50.2)</td>
</tr>
<tr>
<td><strong>Duration of prior therapy (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ab, median (range)</td>
<td>5.8 (0.0–46.9)</td>
<td>Not applicable</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Enza, median (range)</td>
<td>Not applicable</td>
<td>4.8 (0.0–49.0)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Clinical outcomes with Ra-223 therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time, median (months)</td>
<td>7</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Ra-223 doses, median (range)</td>
<td>4 (1–6)</td>
<td>4 (1–6)</td>
<td>4 (1–6)</td>
</tr>
<tr>
<td>Pts with SREs, n (%)</td>
<td>39 (21)</td>
<td>33 (20)</td>
<td>168 (27)</td>
</tr>
<tr>
<td>Pts with pathological fractures, n (%)</td>
<td>13 (7)</td>
<td>10 (6)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Median time from castration resistance to death (months)</td>
<td>29</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>OS, median (95% CI) (months)</td>
<td>10.5 (8.6, 12.3)</td>
<td>9.8 (7.8, 13.2)</td>
<td>15.2 (13.2, 16.3)</td>
</tr>
</tbody>
</table>

Methods: This was a retrospective study of data from the Flatiron prostate cancer registry, providing electronic health records from >245 US cancer clinics. Data were collected from 01/01/2013–30/06/2017. Ra-223-treated mCRPC pts were included; prior to receiving Ra-223, pts completed Abi/Enza/both. Prior Abi and prior Enza groups excluded pts with concomitant/concurrent Abi or Enza. Baseline was defined as the index date at start of Ra-223 therapy. Pts were followed until death or study end. Descriptive analysis was performed for baseline characteristics, prior Abi or Enza therapy, skeletal-related events (SREs) and OS (Kaplan–Meier method).

Results: Among 625 Ra-223-treated pts, 29.9% (n = 187) and 26.2% (n = 164) completed prior Abi or Enza treatment, respectively (Table). At baseline, SREs were documented in 50% (314/625) of pts (48% [189/390] in prior Abi and 53% [87/164] in prior Enza pts). During/demanding Ra-223 therapy, SREs were reported at a similar rate in prior Abi (21% [39/185]) and prior Enza pts (20% [30/163]). Pathological fractures were reported in 10% (61/623) of pts (7% [13/185] and 6% [10/163] in prior Abi and prior Enza pts, respectively). Median (95% CI): OS was 15.2 (13.2–16.3) months in all pts (10.5 [8.6–12.3] for prior Abi and 9.8 [7.8–13.2] for prior Enza pts).

Conclusions: In this retrospective RW study of 4 yr clinical practice, a high proportion of pts had SREs prior to start of Ra-223. Sequential use of Ra-223 after Abi or Enza does not negatively affect bone-related safety outcomes when compared with the overall cohort. Ra-223 is a feasible treatment option after Abi or Enza.

Editorial acknowledgement: Medical writing support was provided by Samantha Kew, BSc, of Scion, London UK, funded by Bayer.

Legal entity responsible for the study: Bayer.

Funding: Bayer.

During Ra-223 treatment, an average of 4.8 (CI 4.6-5.1) cycles were administered and 51 (50%) were treated with a PAIW of 7.1 (CI 6.1-8.2) and a mean score of 56.1 (CI 35.5-67.7).

Conclusions: QoL and pain remained stable during Ra-223 treatment. The lack of pain response might be related to opiate use, which will be analyzed.

Clinical trial identification: NCT02327327

Legal entity responsible for the study: Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital.

Funding: Bayer.

Disclosure: A. Bergman: Grants: Bayer BV. All other authors have declared no conflicts of interest.

Table: 828P

<table>
<thead>
<tr>
<th>S5E, n (%)</th>
<th>All patients</th>
<th>Prior Abi</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 533</td>
<td>n = 67</td>
<td>EOD 0–2</td>
</tr>
</tbody>
</table>
|           |             | (>20 meta-
|           |             | static lesions) |
| n = 149   |             | EOD 3–4  |
| n = 165   |             | (>20 meta-
|           |             | static lesions) |

During Ra-223 treatment

Follow-up after end of Ra-223 treatment

During long-term follow-up

Over the course of the study ERTB

Fractures Spinal

cord compression intervention

Percentages calculated based on number of pts for whom documentation was available within the specified time period. ≥30 days after treatment completion.

Disclosure: T. Neuffer: Employee: Bayer Healthcare; Holds stocks: Bayer. J. Kalinovsky: Employee: Bayer Healthcare. All other authors have declared no conflicts of interest.

828P

Pain and quality of life in metastasized Castration Resistant Prostate Cancer patients treated with Radium-223 (ROTOR registry): A prospective observational registry in a non-study population


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Background: In the ALSTIMPCA study a survival benefit of Radium-223 (Ra-223) treated metastasized Castration Resistant Prostate Cancer (mCRPC) patients with bone disease was established. However, the effect of Ra-223 treatment on pain and Quality of Life (Qol) was not explored. 200 mCRPC patients treated with Ra-223 in 20 Dutch hospitals were included in the prospective ROTOR registry.

Methods: Qol (FACT-P) and pain (BPI-S) were recorded at Base-Line (BL) and at every Ra-223 cycle. Patients with complete questionnaires at BL and at least one on treatment were included in the analysis. Patients with a BPI-S Pain At Its Worst (PWI) of ≥4 were considered symptomatic. A decrease of FACT-P and BPI-S PAIW of ≥6 points and ≥2 points, respectively, were considered clinically meaningful.

Results: Currently, data is collected from 244 patients. In 101 (41%) patients Qol and pain could be evaluated. Mean age was 72.9 (range 47-89.9) years. 85 (83%) had ≥6 bone meta-
s, an average of 4.8 (4.1-5.5) cycles were administered and 51 (50%) were treated with 6 cycles. The mean total FACT-P was in 70.6 (CI 68.4-72.8). The lowest FACT-P score was at cycle 3 (67.6: CI 65.0-70.1) and was 67.0 (CI 66.3-73.6) at cycle 6, which were 3.0 and 3.6 points lower than BL, respectively. The mean total BPI-S score was 43.5 (CI 38.9-48.0) at baseline. Asymptomatic patients (57; 96%) had a PAIW score of 2.1 (CI 1.8-2.5) and a mean total score of 31.0 (CI 25.9-36.0) at base line. The lowest PAIW score was at cycle 1 (1.7 Ci 1.1-2.2) and mean total score of 24.3 (CI 16.2-32.9). Symptomatic patients (34; 53%) had a PAIW of 6.9 (CI 6.5-7.2) and a mean total score of 56.0 (CI 45.0-66.6). The lowest PAIW score was at cycle 2 (6.1CI 5.6-6.6) and mean total score of 51.2 (CI 44.9-59.9) which were 0.8 and 2.8 points lower than base line, respectively. Patients treated with cycles of Ra-223 had a PAIW of 7.1 (CI 6.1-8.2) and a mean score of 56.1 (CI 35.5-67.7).

Conclusions: QoL and pain remained stable during Ra-223 treatment. The lack of pain response might be related to opiate use, which will be analyzed.

Clinical trial identification: NCT02327327

Legal entity responsible for the study: Netherlands Cancer Institute-Antoni van Leeuwenhoek hospital.

Funding: Bayer.

Disclosure: A. Bergman: Grants: Bayer BV. All other authors have declared no conflicts of interest.

830P

Synthetic DNA immunotherapy in biochemically relapsed prostate cancer


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Background: INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12), a synthetic DNA immunotherapy, was assessed for safety, immunogenicity and efficacy in biochemically recurrent prostate cancer patients (pts).

Methods: Phase I, open-label, multi-center study in the US included pts with rising PSA after surgery and/or RT, PSA doubling time (PSADT) >3 months (mos), testosterone one >150 ng/dL and no concurrent ADT. Safety, immunogenicity and efficacy (PSA kinetics, PFS) were evaluated in 4 treatment arms of 15 pts each. Arms A: 2mg INO-5150, B: 8.5 mg INO-5150, C: 2mg INO-5150 + 1mg INO-9012 and D: 8.5mg INO-5150 + 1mg INO-9012. Pts received 4 IM doses of vaccine followed by electroporation on day 0, 13, 26 and 24 and were followed for 72 wks.

Results: 50/61 (82%) pts completed all visits and treatments were well tolerated with no safety concerns. Median PFS for overall population (N=61), had a PAIW of (D0) PSADT range (mos) 1.5-217.1, median 9.8 and for a subset of pts with D0 PSADT <12mos (N=36) had not yet been reached (FU 3-19 mos). 86% of pts with D0 PSADT ≥12 mos were progression free through 19mos FU. 27 of 36 (75%) pts with D0 PSADT <12 mos had disease stabilization at wk 27 evidenced by significant improvement in log PSA change over time (slope) and PSADT from D0 (Slope=0.19 declined to 0.1, PSADT=5.3 improved to 10.1 mos, p <0.0001). This effect was maintained at wk 72 (Slope=-0.09, PSADT=18.6, p <0.0001). Immunogenicity was observed in 27% (47/162) of pts by multiple immunologic assessments. Patient immunogenicity to INO-5150 as determined by CD38 and Perforin + C reaction was reactive with attenuated % PSA rise compared to pts without reactivity (p =0.05, n = 50).

Conclusions: INO-5150 +/- INO-9012 was safe, well tolerated and immunogenic. Clinical efficacy was observed in the patients with D0 PSADT ≥12 mos as evidenced by a significant drop in log PSA change over time and increased PSADT up to 72 weeks FU. Additional genomic analyses are ongoing to further elucidate the correlation of immunologic efficacy and clinical benefit. (NCT02541213)

Clinical trial identification: FDA IND number 15870.

Legal entity responsible for the study: Inovio Pharmaceuticals, Inc.

Funding: Inovio Pharmaceuticals, Inc.

Disclosure: N. Shne: Consulting or advisory role for multiple pharmaceutical companies. E.I. Heath: Consulting or advisory role and honoraria or funding received for multiple pharmaceutical companies. H. Cheng, Y. Whang: Funding received from multiple pharmaceutical companies. K. Bharad, M. Morrow, T. McMullan, K. Kraynak, J. Lee, B. Sacchetta, L. Liu, S. Rosenzweig, I. Cuki, M.L. Bagarazzi: Employee of the pharmaceutical company sponsoring this research trial. S.T. Tagawa, R. Tutrone, J. Garcia, W. Kelly: Consulting or advisory role and funding received from multiple pharmaceutical companies. All other authors have declared no conflicts of interest.
Table: 832P Association between 3-month FACT-P and OS (worst 25% and best 25% of patients)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR (worst 25% vs best 25%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT + D</td>
<td>0.70</td>
<td>0.37-1.34</td>
</tr>
<tr>
<td>ADT</td>
<td>3.91</td>
<td>1.37-4.58</td>
</tr>
</tbody>
</table>

1. Adjusted for treatment arm, disease volume, ECOG PS, Gleason, prior local therapy and BMI, and stratification factors at randomization.

Conclusions: In men with mHSPC, baseline and 3 month poor QOL are associated with OS in ADT patients but not ADT + D. The latter may be due to positive treatment effect from docetaxel in pts with poor baseline QOL. There was no association between chemotherapy induced poor QOL and OS.

Clinical trial identification: NCT03099985.

Legal entity responsible for the study: ECOG - ACRIN.

Funding: Has not received any funding.


832P

Association between patient reported quality of life (QOL) and survival: Analysis of EB0805 chemohormonal androgen ablation randomized trial in prostate cancer

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Background: Chemohormonal therapy (docetaxel and androgen deprivation (ADT + D)) for metastatic hormone sensitive prostate cancer (mHSPC) prolongs overall survival (OS) versus ADT alone. We assessed the association between QOL and OS in men with mHSPC treated with ADT + D vs ADT.

Methods: Men were randomized to ADT + D (6 cycles) or ADT. QOL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), FACT-G, Fatigue, and Brief Pain Inventory (BPI). Logrank test and Cox proportional hazards models were used to evaluate the association between QOL and OS in men with mHSPC treated with ADT + D vs ADT.

Results: 790 men were randomized (ADT + D, N = 397; and ADT, N = 393). OS was significantly poorer for ADT patients with baseline FACT-P < median than median patients (p = 0.03), but not for ADT + D patients (p = 0.34). FACT-P at 3 months was associated with OS for ADT patients (median OS lowest vs highest quartile 26.5 vs 44.1 mo, p = 0.003) but not ADT + D (median OS lowest vs highest quartile 46.1 vs 84.4 mo, p = 0.98 and Table). Change in QOL from baseline to 12 months in the patients with most improvement and most decline was associated with OS (median OS in best vs worst 25% in ADT: 61 vs 23.7 mo, p = 0.048; median OS in best vs worst 25% in ADT + D: NR vs 37.1 mo, p = 0.006). Baseline fatigue, but not baseline pain, was associated with OS after adjusting for multiple prognostic factors (BPI (p = 0.86); FACT-G: Fatigue 3-unit increase HR = 0.95, p = 0.016).

Conclusions: The PJK3 pathway plays an important role in cell growth and survival of PTEN-null tumours. An ongoing phase 1/2 study (NCT01884285) previously reported that AZD8186, a potent and selective inhibitor of PJK3 (minimal PJK3 activity), can be well tolerated in pts with solid tumours; here we present preliminary data in heavily pretreated mCRPC.

Methods: Pts with mCRPC received escalating doses of AZD8186 (5 days on, 2 days off; 2 days on, 5 days off; or continuous schedules) as monotherapy (study Part A) or in combination with AAP (1000 mg qd + prednisone 10 mg qd, study Part B) until progressive disease (PD) or dose-limiting toxicities. Analyses included tolerability, RECIST tumour response, prostate-specific antigen response, circulating tumour cell counts and cell-free DNA.

Results: Fifty-two pts with mCRPC were treated with AZD8186 as monotherapy (n = 39) or in combination with AAP (n = 13). Prior treatment status: AAP (n = 14), enzalutamide (enza, n = 10), both (n = 21) or AA/enza-naive (n = 7). Diarrhoea (39%) and nausea (27%) were the most frequently reported adverse events (AEs, all grades) related to AZD8186. Grade 3 AEs of interest included diarrhoea/colicis (10%), which was fully reversible with dose interruption/SoC treatment, and rash (7%). Two (4%) pts had grade 4 AEs (thrombocytopenia, hypokalaemia); no grade 5 AEs. AZD8186 did not appear to alter tolerability of AAP. Among pts with RECIST measurable disease, one had a confirmed partial response (Part C1), 10 had stable disease, nine had PD. Nine (17%) pts had reduction in PSA >50%. Twelve pts completed >16 weeks of treatment, five pts >24 weeks (PTEN proficient (n = 0), PTEN-deficient (n = 3). PTEN-unknown (n = 2). Recruitment of pts with PTEN-deficient mCRPC into an expansion phase in combination with AAP is ongoing.

Conclusions: Data from this phase 1/2 study indicates that the tolerability of AZD8186 supports combination treatment with AAP in pts with metastatic prostate cancer. Preliminary evidence of antitumour activity has been observed. Updated results will be presented.

Clinical trial identification: NCT01884285.

Editorial acknowledgement: Medical writing and editorial assistance was provided by Tyrone Daniel from Bioscript Medical (Macclesfield, UK) and funded by AstraZeneca.

Legal entity responsible for the study: AstraZeneca.

832P

ADZ8186, a potent and selective inhibitor of PJK3/6, as monotherapy and in combination with abiraterone acetate plus prednisone (AAP), in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC)

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Background: The PJK3 pathway plays an important role in cell growth and survival of PTEN-null tumours. An ongoing phase 1/2 study (NCT01884285) previously reported that AZD8186, a potent and selective inhibitor of PJK3 (minimal PJK3 activity), can be well tolerated in pts with solid tumours; here we present preliminary data in heavily pretreated mCRPC.

Methods: Pts with mCRPC received escalating doses of AZD8186 (5 days on, 2 days off; 2 days on, 5 days off; or continuous schedules) as monotherapy (study Part A) or in combination with AAP (1000 mg qd + prednisone 10 mg qd, study Part C1) until progressive disease (PD) or dose-limiting toxicities. Analyses included tolerability, RECIST tumour response, prostate-specific antigen response, circulating tumour cell counts and cell-free DNA.

Results: Fifty-two pts with mCRPC were treated with AZD8186 as monotherapy (n = 39) or in combination with AAP (n = 13). Prior treatment status: AAP (n = 14), enzalutamide (enza, n = 10), both (n = 21) or AA/enza-naive (n = 7). Diarrhoea (39%) and nausea (27%) were the most frequently reported adverse events (AEs, all grades) related to AZD8186. Grade 3 AEs of interest included diarrhoea/colicis (10%), which was fully reversible with dose interruption/SoC treatment, and rash (7%). Two (4%) pts had grade 4 AEs (thrombocytopenia, hypokalaemia); no grade 5 AEs. AZD8186 did not appear to alter tolerability of AAP. Among pts with RECIST measurable disease, one had a confirmed partial response (Part C1), 10 had stable disease, nine had PD. Nine (17%) pts had reduction in PSA >50%. Twelve pts completed >16 weeks of treatment, five pts >24 weeks (PTEN proficient (n = 0), PTEN-deficient (n = 3). PTEN-unknown (n = 2). Recruitment of pts with PTEN-deficient mCRPC into an expansion phase in combination with AAP is ongoing.

Conclusions: Data from this phase 1/2 study indicates that the tolerability of AZD8186 supports combination treatment with AAP in pts with metastatic prostate cancer. Preliminary evidence of antitumour activity has been observed. Updated results will be presented.
At data cutoff, 16 pts were treated; 12 at 200 mg and 4 at 300 mg niraparib

Results:


Background: Prostate cancer is a major global challenge due to the increasing number of aging population and frequency of diagnosis. During the past decade new treatments have been targeted to the androgen signaling axis either by inhibiting the binding of androgens to androgen receptor (AR) and AR nuclear translocation, or by inhibiting androgen production via CYP1A1 enzyme. Despite the significant progress on the research and new therapies, CRPC is still prevalent and there is urgent need for better, more effective treatments. OMD-208 is an oral, non-steroidal and selective inhibitor of CYP1A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential AR ligands.

Methods: The inhibition of CYP1A1 was measured in vitro by the formation of radio-labeled isocaproic acid in a human adrenal cortex cell line (I2993R). The tumor growth inhibition of OMD-208 was studied in VCaP CRPC xenograft model. Full length AR (AR-FL) and AR-V7 were analysed from the tumors by western blot and also key enzymes of androgen biosynthesis, CYP1A1, AKR1C3, SRD5A1 were quantified by PCR. At the end of the xenograft study, plasma ACTH and LH, and key steroid hormone concentrations were analysed from plasma and target tissues.

Results: OMD-208 potently inhibits CYP1A1 enzyme in vitro. In addition, in vivo in the VCaP CRPC xenograft model OMD-208 significantly inhibited tumor growth. Importantly, the amount of AR-FL and AR-V7 levels remained unchanged in the tumors after OMD-208 treatment. Slight increase of CYP1A1 and SRD5A1 enzyme levels was observed, indicating the activation of steriodogenesis in VCaP tumors in vivo. Treatment had no effect on plasma LH, whereas ACTH was significantly increased demonstrating reduction in glucocorticoid levels by negative feedback. In line with ACTH, all measured steroid hormones were significantly reduced both in plasma and target tissues.

Conclusions: OMD-208 shows promising antitumor activity in preclinical CRPC models and has favorable toxicological profile. Thus, OMD-208 might have potential for treating patients with CRPC. Based on the nonclinical results, a phase 1/2 clinical trial (NCT03436485) has been initiated.

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

Funding: Orion Corporation, Orion Pharma.


Background: In prostate cancer, AR-V7 plays a critical role in the development of castration-resistant prostate cancer (mCRPC) with 25% of metastatic prostate cancer patients later developing AR-V7 positive clones. AR-V7 is an alternative splice variant of AR, which is involved in the maintenance of castration-resistant prostate cancer and is detected in 20%–30% of castration-resistant prostate cancer patients. AR-V7 is associated with resistance to conventional therapies and poor patient outcomes. In the last decades, AR-V7 has been targeted to the androgen signaling axis either by inhibiting the binding of androgens to androgen receptor (AR) and AR nuclear translocation, or by inhibiting androgen production via CYP1A1 enzyme. Despite the significant progress on the research and new therapies, CRPC is still prevalent and there is urgent need for better, more effective treatments. OMD-208 is an oral, non-steroidal and selective inhibitor of CYP1A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential AR ligands. OMD-208 is an oral, non-steroidal and selective inhibitor of CYP1A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential AR ligands.

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Results: OMD-208 potently inhibits CYP1A1 enzyme in vitro. In addition, in vivo in the VCaP CRPC xenograft model OMD-208 significantly inhibited tumor growth. Importantly, the amount of AR-FL and AR-V7 levels remained unchanged in the tumors after OMD-208 treatment. Slight increase of CYP1A1 and SRD5A1 enzyme levels was observed, indicating the activation of steriodogenesis in VCaP tumors in vivo. Treatment had no effect on plasma LH, whereas ACTH was significantly increased demonstrating reduction in glucocorticoid levels by negative feedback. In line with ACTH, all measured steroid hormones were significantly reduced both in plasma and target tissues.

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

Funding: Orion Corporation, Orion Pharma.

these combined cohorts were analyzed (n = 148): those who had failed an ARsi, and were about to go onto a second ARsi (n = 73) or taxane (n = 75). A risk score was used to adjust for underlying patient imbalances and therapy choice propensity.

**Results:** 75 of 148 (51%) received A-T and 73 of 148 (49%) received A-A. Adjusting for patient risk, a discernable difference in OS was not detected (HR = 1.16, CI 0.73 – 1.85, p = 0.52). Incorporating AR-V7, there was a significant interaction between positivity for AR-V7 and OS on taxanes (HR = 0.16, CI 0.052 – 0.52, p = 0.0020). In risk-matched analysis, there was a significant difference in OS between AR-V7+ patients on taxanes vs. ARsi (11.6mo vs. 5.5mo, p = 0.0029).

**Conclusions:** Sequential ARsi use in the US is common. Adjusting for patient risk and physician therapy choice, AR-V7 use after ARsi failure identifies patients who would live longer on taxanes vs. ARsi. Physician intuition alone was not sufficient to achieve predictive effect of AR-V7.

**Legal entity responsible for the study:** MSKCC.

**Funding:** NIH/NCI P01-CA92679, SPORE in Prostate Cancer, NIH/NCI Cancer Center Support Grant P30-CA08748, NIH grant RO1-CA207250, Department of Defense Prostate Cancer Research Program (PC121111 and PC131984), Prostate Cancer Foundation Challenge Award, and David H. Koch Fund for Prostate Cancer Research.

**Disclosure:** H.I. Scher: Consultant: Sanofi, Clovis, Janssen, Pfizer; Grant/research support to MSK, Janssen, Janssen; Board of directors: Asteras Biotherapeutics; Advisory board: WCG Oncology. R.P. Graf: Employee of Epic Sciences, Inc. R. Dittamore: Employee: Epic Sciences. All other authors have declared no conflicts of interest.

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**Table 837P**

<table>
<thead>
<tr>
<th>BxG vs pGS</th>
<th>OR/95% CI of OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GS Downgrade</td>
<td>1.00</td>
<td>0.58</td>
</tr>
<tr>
<td>Any GS upgrade</td>
<td>1.77</td>
<td>1.20</td>
</tr>
<tr>
<td>bG56 to pGS3 + 4</td>
<td>1.61</td>
<td>1.06</td>
</tr>
<tr>
<td>bG56 to pGS4 + 3</td>
<td>2.46</td>
<td>0.90</td>
</tr>
<tr>
<td>bG57 to pGS 8-9</td>
<td>4.49</td>
<td>1.32</td>
</tr>
</tbody>
</table>

Referent in all models is no change in GS.

**Conclusions:** GPS is a significant predictor of the likelihood of Gleason score upgrading from biopsy to RP. Incorporation of GPS results into treatment decision making can improve risk assessment for newly diagnosed patients with clinically low-risk prostate cancer.

**Legal entity responsible for the study:** GHG & CPDR.

**Funding:** Genomic Health, Inc.

**Disclosure:** H.I. Lawrence: Consultant, stock owner: GHG. All other authors have declared no conflicts of interest.

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**838P**

**PIK3/AKT pathway deleterious mutations in lethal prostate cancer**


**Prostate Cancer Targeted Therapy Group, The Royal Marsden Hospital and Institute of Cancer Research, London, UK, **Prostate Cancer Targeted Therapy Group, The Institute of Cancer Research, London, UK

**Background:** PIK3/AKT signaling is commonly hijacked in prostate cancer (PC), associated with poorer prognosis and worse response to next generation hormonal treatment (NGHT) including abiraterone and enzalutamide. We studied deleterious pathway mutations in metastatic castration resistant PC (mCRPC) patients correlating these to prognosis and response to NGHT in a case-control study.

**Methods:** Patients with mCRPC and available treatment-naive and/or CRPC tumor samples were evaluated. Mutation analyses involved MiSeq,[9] based targeted next generation sequencing (NGS); PTEN was assessed by immunohistochemistry (IHC) with the control cohort having no PTEN IHC loss. Correlations between pathway mutations and outcomes and response to NGHT utilized Cox and Kaplan-Meier analyses.

**Results:** Overall 418 samples (from Feb/15 to Dec/17) were sequenced by targeted NGS; 46 (11%) had mutated pathway genes of which 26 (6%) PTENCA, n = 18; AKT1, n = 6; PIK3R1, n = 2) were pathogenic pathway activating mutations. Among these 25 were previously described, while an undescribed PIK3R1 mutation (R343*), located in the SH2 in domain, was also identified. We then randomly selected 56 tumour samples with normal PTEN expression by IHC as a control group without detected pathway aberrations. Overall, 45% (102/225) of patients with mutated cancers had NGHT in pre- and 57% (13/23) in post-chemotherapy settings, while 3 were NGHT naive. In the control group, 14 patients (25%) were pre-chemotherapy while 42 (75%) post-chemotherapy.

**Conclusions:** PIK3/AKT pathway deleterious mutations impart a poor prognosis from mCRPC and are associated with shorter responses to NGHT. We envision that these data can impact treatment selection in a targeted treatment approach for mCRPC.

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

**Funding:** CRUK, Movember, PCF, PCUK.

**Disclosure:** All authors have declared no conflicts of interest.

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**839P**

**Clinico-genomic profiling and outcome prediction of neuroendocrine prostate cancer (NEPC)**


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**Background:** NEPC is a variant of prostate cancer that may present “de novo” or after androgen receptor (AR)-targeted therapies (“treatment related”) with a spectrum spanning both small cell prostate cancer (SCPC) and adenocarcinoma with neuroendocrine differentiation (adeno-NE). The comprehensive clinical and molecular landscape of different NEPC subtypes and its potential impact on outcome is poorly understood.

**Methods:** 274 prostate cancer patients (pts) with metastatic biopsy tumor morphology confirming NEPC (n = 97); 56 with SCPC, and 51 with adeno-NE) or castration resistant adenocarcinoma (CRPC) (n = 187) between 2004 and 2017 in a single academic center were evaluated. Baseline, treatment and outcomes data along with tumor whole-exome and RNA-seq data were retrospectively reviewed. Statistical comparisons utilized Cox regression analysis and Kaplan-Meier method for association with NEPC, CRPC and overall progression-free survival (OS/PFS).

**Results:** In NEPC, PSA at time of biopsy was lower compared with CRPC (median 1.18 vs 38.0, p = 0.001) and liver metastases were more common (32.2% vs 52.1%, p = 0.027). OS from time of prostate cancer diagnosis differed by subtype, with SCPC having shortest survival (median 2.98 years), followed by adeno-NE (median 5.98 years) then CRPC (median 12.14 years) (log rank p < 0.0001). For arthritis resistant adenocarcinoma (CRPC) (n = 187) between 2004 and 2017 in a single academic center were evaluated. Baseline, treatment and outcomes data along with tumor whole-exome and RNA-seq data were retrospectively reviewed. Statistical comparisons utilized Cox regression analysis and Kaplan-Meier method for association with NEPC, CRPC and overall progression-free survival (OS/PFS).

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**Results:** In NEPC, PSA at time of biopsy was lower compared with CRPC (median 1.18 vs 38.0, p = 0.001) and liver metastases were more common (32.2% vs 52.1%, p = 0.027). OS from time of prostate cancer diagnosis differed by subtype, with SCPC having shortest survival (median 2.98 years), followed by adeno-NE (median 5.98 years) then CRPC (median 12.14 years) (log rank p < 0.0001). For arthritis resistant adenocarcinoma (CRPC) (n = 187) between 2004 and 2017 in a single academic center were evaluated. Baseline, treatment and outcomes data along with tumor whole-exome and RNA-seq data were retrospectively reviewed. Statistical comparisons utilized Cox regression analysis and Kaplan-Meier method for association with NEPC, CRPC and overall progression-free survival (OS/PFS).
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Clinical data and germline DNA samples from 352 consecutive aPC patients were sequenced on an Illumina HiSeq2500. GATK best practices were followed for alignment and variant calling. 35 genes deemed clinically actionable and/or included in the Pritchard publication were evaluated. Free testosterone levels were measured before (n = 82) and during carboplatin/docetaxel chemotherapy (n = 76).

Results: Of the 106 pts. treated since February 2005, 96.2% had bone and 63.2% soft tissue metastases (45% lymph node, 27% liver and 21% lung involvement). At the time of the current analysis, the median follow-up time was 13.5 months. 101 pts. died and 102 had progressive disease. The objective response rate was 43.2% and the disease control rate 64.2% in the 76 pts. with measurable disease. Response of prostate-specific antigen (≥ 50%) was observed in 50 patients (47.1%). Median progression-free survival (PFS) for all 96 pts. was 6.9 months (CI 95% 5.7, 8.0) and median OS was 14.1 months (CI 95% 10.9, 17.3). The most common reversible grade 3/4 toxicity was leukopenia/neutropenia (40/35.2%). Median free and total testosterone levels were reduced below the detection limit during DC treatment (from 0.55 pg/ml to < 0.18 pg/ml and 0.08 to < 0.05 ng/ml, respectively). Testosterone nadir values < 0.18 pg/ml during DC treatment were associated with longer PFS, OS and post-ohc (p < 0.05).

Conclusions: These data suggest that carboplatin plus weekly docetaxel may be an important second-line treatment option for DRPC patients by inhibiting the testosterone biosynthesis.

Legal entity responsible for the study: Christoph Reuter.

Funding: Has not received any funding.

Disclosures: C.W.M. Reuter: Advisory board: Eisai, Bayer, Tesaro, Sanofi, Astellas, Janssen. All other authors have declared no conflicts of interest.

841P

Prevalence of clinically actionable germline pathogenic variants (PVs) in advanced prostate cancer (aPC)

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Background: Recent data suggest that carboplatin plus weekly docetaxel (DC) may be effective in mDRPC. Platinum- (II)-complexes have been shown to interfere with steroid biosynthesis lowering testosterone levels by inhibiting the cholesterol side chain cleavage enzyme. This study compared androgen dehydrogenase (HSD3B1,2) and 17α hydroxylase/C17,20-lyase (CYP17A1).

Methods: Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least two cycles of carboplatin (AUC3) on day 1 every 4 weeks (q4w), docetaxel at a dose of 55 mg/m2 iv for one course on days 1, 8, 15) plus prednisone 2Xmg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done using PCWG2 recommendation. Free testosterone levels were measured before (n = 82) and during carboplatin/docetaxel chemotherapy (n = 76).

Results: Of the 106 pts. treated since February 2005, 96.2% had bone and 63.2% soft tissue metastases (45% lymph node, 27% liver and 21% lung involvement). At the time of the current analysis, the median follow-up time was 13.5 months. 101 pts. died and 102 had progressive disease. The objective response rate was 43.2% and the disease control rate 64.2% in the 76 pts. with measurable disease. Response of prostate-specific antigen (≥ 50%) was observed in 50 patients (47.1%). Median progression-free survival (PFS) for all 96 pts. was 6.9 months (CI 95% 5.7, 8.0) and median OS was 14.1 months (CI 95% 10.9, 17.3). The most common reversible grade 3/4 toxicity was leukopenia/neutropenia (40/35.2%). Median free and total testosterone levels were reduced below the detection limit during DC treatment (from 0.55 pg/ml to < 0.18 pg/ml and 0.08 to < 0.05 ng/ml, respectively). Testosterone nadir values < 0.18 pg/ml during DC treatment were associated with longer PFS, OS and post-ohc (p < 0.05).

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Legal entity responsible for the study: Christoph Reuter.

Funding: Has not received any funding.

Disclosures: C.W.M. Reuter: Advisory board: Eisai, Bayer, Tesaro, Sanofi, Astellas, Janssen. All other authors have declared no conflicts of interest.

842P

CTC-based biomarkers & PSMA-targeted imaging in patients with metastatic castrate-resistant prostate cancer (mCRPC)


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Background: Prostate-specific membrane antigen (PSMA) is highly expressed in prostate cancers, making it an imaging & therapeutic target of interest. The utility of the PSMA-targeted imaging agent 99mTc-EC0652 is being evaluated, along with biomarker analysis of circulating tumor cells (CTCs), in pts with mCRPC in a completed PSMA-targeted chemotherapeutic study. We now report the PSMA heterogeneity via CTCs vs. imaging in the pt population treated to date.

Methods: A total of 51 pts evaluated at the time of the data cut had baseline CT & bone scans performed in addition to a 99mTc-EC0652 SPECT/CT as a measure of imaging-based PSA response. 41 of 51 pts provided pre-treatment blood samples evaluable for CTC biomarker analysis, which included PSA expression & predicted genomic instability status (pGI). Images collected from pts were analyzed for both their PSMA+ status as well as sensitivity relative to conventional imaging.

Results: 41 of 51 pts (80.4%) had detectable CTCs in their samples prior to therapy while 32 of 38 (84.2%) of the analyzed paired on-therapy samples had CTCs after treatment. At baseline PSA CTCs were found in 19 of 51 (37.2%) pts and overall was expressed on 33% (FDR 11.3% - 40.1%) of CTCs within each pt sample. 15 of 17 (88%) PSMA+ pts samples were also pGI+. 51 of the 51 pts (60.7%) of the pts had bone scan (BS) data available to analyze. 27 of the 51 pts had CT scan data available to analyze for nodal lesions. Concordance between Conventional Imaging & 99mTc-EC0652.

Conclusions: In this cohort, most pts had CTCs for assessment. The majority of pts with CTCs had PSMA CTCs. The pts CTCs expressing PSA accounted for a small percentage of the total CTCs observed. These PSMA+ CTCs had high pGI. Pts with CTCs had PSAImagable disease, especially in bone. The discordance between CTCs & imaging illustrate the disease heterogeneity in regards to PSMA expression. These data should be considered in designing future PSMA-directed regimens.

Clinical trial identification: NCT02202447.

Legal entity responsible for the study: Endocyte Inc.

Funding: Endocyte Inc.

Disclosure: M.J. Morris, O. Sarto: Consultant: Endocyte. A. Armour, R. Messmann, M. Groaning: Employee: Endocyte. All other authors have declared no conflicts of interest.

Table: 842P

<table>
<thead>
<tr>
<th>Bone Lesion (770)</th>
<th>770 (100%)</th>
<th>0</th>
<th>587</th>
<th>183</th>
<th>N/A</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodes &gt;1.5cm (54)</td>
<td>48 (88.9%)</td>
<td>N/A</td>
<td>6</td>
<td>1 (11.1%)</td>
<td>N/A</td>
<td>54</td>
</tr>
<tr>
<td>Nodes &lt;1.5cm (69)</td>
<td>69</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

843P

The neurotrophin–lymphocyte ratio (NLR) as a predictive marker of response to abiraterone acetate: A retrospective analysis of the COU302 study

T. Loubergé 1, S. Chakak 1, M. Ngule-Makoa 1, V. Fradet 1, P. Toren 1

1Urology, CHU de Nantes, Nantes, France, 2Uro-oncology, CHU Hôtel dieu quebec, Quebec, QC, Canada

Background: The neurotrophin–lymphocyte ratio (NLR) is recognized as a prognostic marker in many cancers, including metastatic castration-resistant prostate cancer (mCRPC). In this study, we perform a retrospective analysis of the pivotal COU302 study of abiraterone acetate (AA) as first-line therapy for mCRPC.
844P The clinical impact of targeted next generation sequencing (tNGS) in the treatment of metastatic prostate cancer


Medical Oncology, Taussig Cancer Institute Cleveland Clinic, Cleveland, OH, USA

Background: Tumor profiling by tNGS is increasingly common in patients (pts) with metastatic solid tumors. It is unclear if this strategy leads to changes in treatment decision for mPCa pts.

Methods: A retrospective analysis of mPCa pts treated at Cleveland Clinic with available comprehensive genomic profiling using tumor tissue (FoundationOne, F1) or cell-free circulating tumor DNA (FoundationAssay, Guardant360) was conducted. Targatable genomic alterations (tGA) were defined as a change in the copy number (amplification/duplication) or a mutation (deletion/rearrangement/truncation/fusion) in AR, DNA repair genes, mismatch repair (MMR) genes, cyclin-dependent kinases (CDK), ERBB2, RAF, TSC and PIK3-mTOR pathway.

Results: Within 2013-2017, 66 pts, median age 68y (49-85), 86% castration-resistant (CRPC), received a median of 3 (0-7) systemic treatments for CRPC before tNGS panel. The most common tNGS platform used was F1 (91%) based on archival tumor tissue (45% primary, 55% metastatic). Overall, frequent alterations included TP53 (42%), PTEN (35%), AR (30%), DNA repair genes, mismatch repair (MMR) genes, cyclin-dependent kinases (CDK), ERBB2, RAF, TSC and PIK3-mTOR pathway.

Conclusions: Among the 1088 patients in the COU302 study, baseline NLR values showed significantly better PSA PFS compared to baseline NLR ≥2.5 (p = 0.003); no significant differences were seen in men in the placebo arm. Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: V. Fradet: Speaker Abbvie, Bayer, Ferring, Janssen, Sanofi; Consultant: Amgen, AstraZeneca, Astellas, Bayer, Ferring, Janssen, Sanofi; Adviser: Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi; Research grant: Amgen, AstraZeneca, Janssen, Sanofi; Clinical trial: AstraZeneca, Bayer, Janssen; Meeting sponsor: Bayer, Janssen, Lilly; Educational grant: Janssen, P. Toren: Scientific study or trial: Innocrin Pharma, Roche, Consultant, Adviser: Sanofi Canada, Ferring, Abbvie, Aller. Disclosure: All other authors have declared no conflicts of interest.

845P Phase III double-blind study evaluating lens opacifications (LO) in patients with nonmetastatic prostate cancer (PCa) receiving denosumab (Dmab) for bone loss due to androgen deprivation therapy (ADT)

S.T. Tagawa1, T. Dai2, D. Jandial1

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Background: Men with PCa undergoing ADT experience bone loss that may be associated with fracture risk and reduced survival. Therapy with Dmab (Prolia®), Amgen, Inc significantly increased bone mass and reduced vertebral fracture risk in men with nonmetastatic PCa receiving ADT. However, in that study (unlike other Dmab randomized trials), cataracts were reported more often in the Dmab group (4.7% vs 1.2% for placebo [PBO]). This trial (NCT00925600) assessed the effect of Dmab (at doses of 120 mg) on the development of LO (cataract) or progression in men with nonmetastatic PCa receiving ADT.

Methods: Men aged ≥30 years with nonmetastatic PCa with bilateral orchectomy or initiated ADT were randomized 1:1 to receive Dmab 60 mg or PBO subcutaneously every 6 months, stratified by Lesions Opacity Classification System III (LOCS-III) score (<3.0 at all sites, ≥3.0 at any site), age (<75, ≥75 years), and prior cataract history. The primary endpoint was LO development or progression by month 12 based on a change of ≥1.0 in posterior subcapsular cataract, ≥2.0 in cortical cataract, or ≥0.7 in nuclear opalescence per LOCS III score. Noninferiority was demonstrated if the upper bound of the 95% 2-sided CI was <10%. Results: 769 men with median age 71 were randomized to receive Dmab (n = 383) or PBO (n = 386). Baseline demographics were balanced. Development or progression of LO by month 12 was similar in the Dmab and PBO groups (33.5% vs 33.2%); the absolute risk difference was 0.4% (95% CI -6.3 to 7.2; noninferiority P = 0.0026), indicating that Dmab was noninferior to PBO for the primary endpoint. Results for other LO endpoints also showed no increased risk of cataracts with Dmab (Table). Rates of AEs, serious AEs, AEs leading to treatment discontinuation, AEs of interest, and death were similar in the 2 groups.


Disclosure: S.T. Tagawa: Consulting fees, research grants (paid to Weill Cornell Medicine): Lilly, Sanofi, Janssen, Astellas, Progenics, Millennium, Amgen, BMS, Dendreon, Rexahn, Bayer, Genentech, Newlink, Inovio, AstraZeneca, Immunomedics, travel, accommodations and expenses: Pfizer. D. Solah: Consultant, advisor: Perthera, Foundation Medicine; Research funding: Novartis, Celgene, OncoMed, Bayer, Genentech/Roche. J.A. Garcia: Consultant, advisor: Sanofi, Pfizer, Bayer, Eisai, Elyionx, MindMed (Astellas), Research funding: Pfizer, Astellas Pharma, Ono Pharma GmbH, Bayer, Janssen Oncology, Genentech/Roche, Lilly. All other authors have declared no conflicts of interest.

Table 845P

<table>
<thead>
<tr>
<th>Endpoint (Parameters)</th>
<th>Dmab, n/N* (%)</th>
<th>PBO, n/N* (%)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development or progres-</td>
<td>127/379 (33.5)</td>
<td>124/374 (33.2)</td>
<td>0.4 (~6.3 to 7.2)</td>
</tr>
<tr>
<td>sion of LO by month 12</td>
<td></td>
<td></td>
<td>Noninferiority P = 0.0026</td>
</tr>
<tr>
<td>Incident of LO develop-</td>
<td>32/379 (8.4)</td>
<td>40/374 (10.7)</td>
<td>–2.2 (~6.4 to 2.0)</td>
</tr>
<tr>
<td>ment or progression by</td>
<td></td>
<td></td>
<td>month 12†</td>
</tr>
<tr>
<td>Incident of LO develop-</td>
<td>72/379 (19.0)</td>
<td>72/374 (19.3)</td>
<td>–0.3 (~5.9 to 5.3)</td>
</tr>
<tr>
<td>ment or progression by</td>
<td></td>
<td></td>
<td>month 6†</td>
</tr>
<tr>
<td>Incident of confirmed LO</td>
<td>59/367 (16.1)</td>
<td>66/361 (18.3)</td>
<td>–2.7 (~7.6 to 2.3)</td>
</tr>
<tr>
<td>development or progres-</td>
<td></td>
<td></td>
<td>sion by month 12†</td>
</tr>
</tbody>
</table>

*N is the number of patients with at least one post-baseline LOCS III measurement by month 12. †A confirmed LO development or progression was defined as two directly subsequent events per protocol assessments at the same location; for this endpoint, N is the number of patients with at least two post-baseline LOCS II measurements by month 12.
846P Patterns of therapy in pelvic lymph node positive prostate cancer in Europe and Asia: A real-world data analysis

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Background: Treatment for node positive prostate cancer can vary from palliation to radical therapy. Guidance for N1 prostate cancer is unclear but evidence supports a multimodal approach including radical radiotherapy, hormonal manipulation and possible surgery while a survival benefit for metastatic disease has been demonstrated. Recent improvements in diagnostic techniques and technical advances in radiation therapy including intensity modulated radiotherapy (IMRT) which is capable of delivering a radical dose of radiation to pelvic nodes within acceptable toxicity profiles are anticipated to result in an increased use of radiation in this patient population. This study assesses changes in treatment modality for N1 prostate cancer over time to reflect real world practice.

Methods: Patient data from 17,695 prostate cancer cases taken from a cross-sectional survey of physicians in France, Germany, Italy, Spain, UK, China, Japan and S. Korea between Jan 1997 – Dec 2016 was reviewed. Patients with non-metastatic, node positive prostate cancer were included for analysis. Any exposure to any of three therapy types (systemic, radiotherapy, surgery) prior to recurrence.

Results: 2542 patients were included in the analysis. Over the time studied, the use of surgery has decreased (from 36% in pre 2009 to 16% in 2016) and initially, this decline was matched by a rise in the use of systemic therapy alone (37% to 51%). Since 2011 systemic therapy alone has reduced to 40%. In the same time period, there has been an increase in the use of radiation (with or without systemic therapy) to treat node positive prostate cancer (15% to 29%). The average increase in radiotherapy use across European countries was 11% (range Italy 2% - Spain 19%). A group of patients receiving combined surgery, radiotherapy and systemic therapy comprised 11% of all cases, a figure that does not vary over time.

Conclusions: These data have demonstrated an international change in the management of node positive prostate cancer with decreasing use of surgery and increasing use of radiation. Although initially rising, the recent decline in the use of local systemic therapy is likely to represent an increasing view that N1 prostate cancer is no longer a definitively palliative diagnosis.

Legal entity responsible for the study: IQVIA.

Disclosure: I. Wong: Honorary: Janssen, Sanofi Aventis. H. Payne: Honoraria, advisory boards, travel expenses, consultant: AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferrer, Sandog and Novartis, Work support: UCLH/UCL Comprehensive Biomedical Research Centre. All other authors have declared no conflicts of interest.

847P The prognostic significance of the 2014 International Society of Urological Pathology (ISUP) grading system in patients with high-risk prostate cancer

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Background: Since the new 2014 grading system was recommended by international society of urological pathology (ISUP), it has been validated in patients with localized prostate cancer (PCa) with excellent prognostic value. However, its predictive power in high-risk PCa has not been verified.

Methods: A total of 420 patients with high-risk PCa underwent radical prostatectomy (RP) were included. The predictive accuracy of the 2005 and 2014 grading systems were validated and compared. Biochemical-recurrence free survival (BRFS) was set as the endpoint.

Results: Compared to the 2005 system, the 2014 system could fairly well distinguish BRFS of patients into five groups with higher predictive accuracy (C-index: 0.999 vs 0.646). In multivariate analyses, together with baseline prostate specific antigen, extraprostatic extension and perineural invasion status, the new system was independent predictor for BRFS in these population. The relatively higher proportion of tertiary Gleason pattern 5 (TCP5) among patients with Gleason grade group 3 (GGG3) could be considered as an important interfering factor leading to the overlap of survival between GGG4 and GGG3.

Conclusions: This is the first study to validate the new 2014 ISUP grading system in patients with high-risk PCa underwent RP. The new system could better separate patients into five groups with higher predictive accuracy over the old one. It should be paid attention that, the existence of TCP5 need to be routinely reported in clinical practice, which could help retaining the predictive ability of the new grading system. Due to miscellaneous factors among these patients, the prognostic prediction need to be comprehensively evaluated.

Legal entity responsible for the study: None.

Disclosure: All authors have declared no conflicts of interest.

848P Overall survival (OS) implications for patients with mCRPC through coverage and adoption of nuclear AR-V7 testing by healthcare systems

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1Clinical Economics and Outcomes Research, Genomic Health, Redwood City, CA, USA; 2Translational Research, Epic Sciences, Inc., San Diego, CA, USA

Background: Nuclear-localized AR-V7 testing of circulating tumor cells (CTCs) has been validated as a predictive biomarker of chemotherapy response and ARSI non-response in 2nd+ line therapy for metastatic castration-resistant prostate cancer (mCRPC). A validation study showed that AR-V7+ pts have improved OS with taxane chemotherapy, and AR-V7- pts have improved OS with ARSIs. We assessed the effect of AR-V7 testing on OS when generalized to non-trial clinical settings, as found in third-party US healthcare systems.

Methods: The causal effect of treatment and nuclear AR-V7 status on OS was estimated from risk-adjusted hazard rates of the MSK, ICR, LHS validation study. Therapeutic strategies assessed were (1) taxanes only, (2) ARSIs only, (3) current US utilization rate of ARSIs, and (4) nuclear AR-V7-guided treatment. Quality of life adjustments were extracted from meta-analysis of large cohort studies. We applied US utilization rate of consecutive ARSIs administration (abiraterone after enzalutamide, or enzalutamide after abiraterone) and compared to switching with taxane-based chemotherapy (docetaxel after abiraterone, or docetaxel after enzalutamide).

Results: The following table shows OS, adjusted and unadjusted for quality of life, and treatment by strategy. The net effects on OS were robust to variation on the clinical effects, and on systems covariates, e.g., demographic, patient, and payer case-mix.

<table>
<thead>
<tr>
<th>Table: 848P</th>
<th>2nd line mCRPC therapy strategy</th>
<th>% ARSI</th>
<th>OS (months) QALY (Unadj / Adj)</th>
<th>Net OS gain (months) QALY (Unadj / Adj)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only use taxanes 0%</td>
<td>19.2 / 12.2</td>
<td>-3.7 / -2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only use ARSi/s 100%</td>
<td>25.4 / 15.6</td>
<td>2.5 / 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use of ARSi (US) 60%</td>
<td>22.9 / 14.2</td>
<td>2.7 / 2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR-V7-guided treatment 77%</td>
<td>27.3 / 16.7</td>
<td>4.4 / 2.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Health outcome modeling of the validation data support that current use and access to 2nd ARSIs can improve OS of patients over strict use of taxane chemotherapy (+ 7.0mo OS). 2nd+ line nuclear-localized AR-V7 guided treatment for men with progressive mCRPC provides higher OS than non-guided, almost doubling the gain (+ 4.4 mo OS) observed with current US utilization rate of ARSIs versus taxanes only. Cost effectiveness analyses of the adoption/coverage of nuclear AR-V7 testing in healthcare systems is ongoing.

Legal entity responsible for the study: MSKCC.

Funding: NIH/NCI P50-CA92629 SPORE in Prostate Cancer, NIH/NCI Cancer Center Support Grant P30-CA008748, NIH grant R01-CA207220, Department of Defense Prostate Cancer Research Program (PC11111111 and PC131984), Prostate Cancer Foundation Challenge Award, and David H. Koch Fund for Prostate Cancer Research were used to support the design and conduct of the study at Memorial Sloan Kettering Cancer Center. Funds from the London Regional Cancer Program Catalyst Grant and TELUS Rfs For Dad/Prostate Cancer Fight Foundation were used to support the study at London Health Sciences Centre. A Medical Council Clinical Research Fellowship (AJ) and NHS funding to the Royal Marsden and Institute of Cancer Research Biomedical Research Centre.

Quality of docetaxel toxicity reporting for castration resistant prostate cancer (CRPC): A systematic review

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Medical Oncology, Sunnybrook Odette Cancer Center, Toronto, ON, Canada

Background: Prostate cancer trial design is structured following the Prostate Cancer Clinical Trials Working Group (PCWG) guidelines which focus on harmonization of inclusion criteria and outcome data. The PCWG, however, does not provide clear outlines for reporting of safety data. In fact, there is a perceived lack of widely accepted guidelines for safety reporting.

Methods: A PubMed search of phase II and III clinical trials published until 2015 (included) was conducted using keywords “prostate cancer” and “docetaxel.” Docetaxel-naive CRPC patients who received 75 mg/m² docetaxel monotherapy every three weeks were included. To assess quality of toxicity reporting, the Consolidated Standards of Reporting Trials (CONSORT) harms checklist was adapted and each trial scored by two independent reviewers. CONSORT scores as well as PSA and radiological survival in advanced prostate cancer patient and being tested in a phase III clinical trials were associated with a significantly higher CONSORT score coefficients were not significant for all comparisons of CONSORT scores and response rates versus years of accrual or year of publication. In univariable linear regression, phase III clinical trials were associated with a significantly higher CONSORT score (p = 0.03) as was a journal impact factor greater than 15 (p = 0.02). In exploratory analyses, none of the examined factors were significant in multivariable linear regression.

Conclusions: CONSORT scores and thus toxicity reporting quality in CRPC trials studying docetaxel show need for improvement and should be subject to further discussion. There has been no significant improvement in toxicity reporting quality over time. It remains to be studied if our findings also apply to other agents used for the treatment of CRPC. Legal entity responsible for the study: Sunnybrook Research Institute.

Disclosure: All authors have declared no conflicts of interest.

Intermittent short course enzalutamide in biochemically recurrent prostate cancer: Analysis of PSA recovery, testosterone levels and tolerability

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Background: Androgen deprivation therapy (ADT) and surveillance are standard options for patients (pts) with biochemical recurrence (non-metastatic, castration sensitive) prostate cancer (BCRPC) after localized therapy. Enzalutamide (enza) extends survival in advanced prostate cancer patients and is approved for the treatment of metastatic Castration-Resistant Prostate Cancer (mCRPC). ENZA and NDE could lead to early identification of patients who will not benefit from ENZA as well as to optimize their treatment choice.

Methods: Eligible pts had a PSA between 2.0-20.0 ng/ml, no metastatic disease, normal testosterone (T), and a PSA doubling time of less than 12 months. Treatment for all pts included enz 160 mg daily for 84 days (D) without/with PROSTVAC (recombinant poxvirus PSA vaccine), but no ADT. After an amendment, pts were eligible for a 2nd course of enz after PSA returned to baseline and confirmation of non-metastatic disease. This analysis evaluated all pts for the impact of enz on PSA and T regardless of randomized arms and was powered in earlier stages of disease.

Results: Median age for all pts (n = 36) was 64 years (range: 54-85) with a median baseline PSA of 5.02 (range: 2.02–19.43). The median PSA decline during the first course of enz was >99% (range: 84 – >99%). After enz was discontinued, the median time to first PSA rise was 28 D (range:13–182) and median recovery to baseline PSA was 224 D (range:84–924). The median time to first PSA rise was 29 D (range:6–83) with a median time to 2nd PSA recovery of 189 D (range:78–400). Enz was well tolerated with no grade 4 or 5 adverse events (AEs). Grade 3 AEs included increased ALT (5%) and decreased ANC (3%). The most common grade 2 AEs included fatigue (18%), dizziness (8%), decreased WBC (8%), and a decreased ALB (8%). T increased above normal limits in 20/36 pts (median Tmax = 834 ng/dl).

Conclusions: Intermittent, short course (84 D) enz without ADT leads to deep and prolonged PSA suppression below baseline in pts with BCRCp, a median of more than 7.5 months beyond treatment period. Pts who received a 2nd 84 D course of enz had similar depth and duration of PSA suppression below baseline (more than 6 months after enz treatment). Intermittent enz was well tolerated and warrants further study in BCRCp.

Legal entity responsible for the study: National Institutes of Health

Disclosure: P. Arlen: Stock, Salary: Precision Biologics. All other authors have declared no conflicts of interest.
Methods: 259 eligible men from the BT/RT cohort (2004-2011) and 123 patients (2009-2010) from a RT cohort assessed their AEs and QoL by questionnaires a minimum of 5 years after treatment. Hormonal therapy was given for 1-2 years. EPIC-26 covered urinary, sexual and bowel function and bother. The hormone domain was excluded. The SF-12 questionnaire covered QoL. The scores ranged from 0 (worst) to 100 (best). Clinical significance was set to a score difference ≥ 10 points. Statistical significance was evaluated by Student t-test with significance level p < 0.05. Chronic fatigue was reported as percentage.

Results: Median age at survey was 74 years for both cohorts. The EPIC-26 and SF12 scores for the above domains were similar in the two cohorts with no clinical or statistically significant difference. (Table). Chronic fatigue was higher after treatment with RT compared BT/RT, although not significantly.

Conclusions: Dose escalation by means of BT/RT does not increase the AEs reported for the urinary, bowel and sexual domains of EPIC-26 or health-related QoL. Hence, BT/RT is a good treatment option for eligible patients.

Legal entity responsible for the study: Wolfgang Lileyte.

Funding: Raagholt Foundation, Bergersen Foundation, Eckbo Foundation.

Disclosure: All authors have declared no conflicts of interest.

Table: 853P

<table>
<thead>
<tr>
<th>Measure</th>
<th>BT/RT Mean (SD)</th>
<th>RT Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual function</td>
<td>27.9 (29.5)</td>
<td>255</td>
<td>20.8 (24.3) n = 120</td>
</tr>
<tr>
<td>Sexual bother</td>
<td>48.2 (37.5)</td>
<td>n = 254</td>
<td>45.9 (34.7) n = 121</td>
</tr>
<tr>
<td>Urinary function</td>
<td>83.6 (18.0) n = 258</td>
<td>80.1 (20.5) n = 123</td>
<td>0.10</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>88.7 (18.1) n = 258</td>
<td>85.0 (22.5) n = 123</td>
<td>0.11</td>
</tr>
<tr>
<td>Urinary bother</td>
<td>79.9 (26.3) n = 257</td>
<td>77.6 (30.0) n = 123</td>
<td>0.47</td>
</tr>
<tr>
<td>Bowel function</td>
<td>86.7 (20.0) n = 254</td>
<td>83.1 (21.7) n = 121</td>
<td>0.12</td>
</tr>
<tr>
<td>Bowel bother</td>
<td>83.0 (25.1) n = 258</td>
<td>80.4 (26.7) n = 121</td>
<td>0.34</td>
</tr>
<tr>
<td>PCS12 (SF12)</td>
<td>46.4 (10.5) n = 224</td>
<td>45.1 (10.1) n = 101</td>
<td>0.30</td>
</tr>
<tr>
<td>MCS12 (SF12)</td>
<td>53.6 (8.0) n = 224</td>
<td>52.7 (9.2) n = 101</td>
<td>0.58</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>22.0% n = 199</td>
<td>27.1% n = 86</td>
<td>0.28</td>
</tr>
</tbody>
</table>

References:

1. Apostolidis C, NierniedL, E. Winkler A, Burger A, Kratochvil C, Kaiser A, Jaeger T, Hoelderferen C, Thunberg H, Siemers F, Ditsler F, Gruhich D. Department of Medical Oncology, National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany. Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany. Institute of Pathology, Klinikum Nürnberg, Paracelsus Medical University, Nürnberg, Germany. Department of Urology, Klinikum Nürnberg, Paracelsus Medical University, Nürnberg, Germany.

Background: Neuroendocrine Carcinomas of the prostate (NEPC) are rare tumors with poor prognosis. While platinum and etoposide based chemotherapy regimens (PE) are commonly applied in first-line for advanced disease, clinical-grade evidence for treatment options in second-line and beyond is very limited. The aim of this study was to analyze the treatment outcomes of NEPC patients.

Methods: Retrospective analysis of all patients NEPC including mixed differentiation with adrenocortical component and well differentiated neuroendocrine tumors (NECs, carcinoids) at two high volume oncological centers between 12/2000 and 11/2017.

Results: Of 43 identified patients 18 (41.9%) had a prior diagnosis of prostatic adenocarcinoma only, 19 (44.2%) had a mixed differentiation at NEPC diagnosis, 29 (67.4%) developed visceral metastases, 5 (15.4%) showed paraneoplastic syndromes. Overall survival from diagnosis of any prostatic malignancy was 69.2 months, from NEPC diagnosis 15.3 months. 31 patients received palliative first line chemotherapy, mostly PE. Overall response rate (ORR) for PE was 50%, median progression-free survival (PFS) was 6.6 months. 15 patients received second line therapy, mostly with poor response rates. Regimens with notable activity were topotecan (1 PR, 3 PD), enzalutamide (1 SD), FOHER (2 SD), and platinum + nivolumab (1 PR). A single patient with prostate carcinoid was sequentially treated with octreotide, peptide receptor radionuclide therapy (PRRT) and everolimus and survived for more than 10 years.

Conclusions: Visceral metastases and paraneoplastic syndromes are frequent in NEPC. EP in first-line shows notable ORR, however limited PFS. For patients with progression after first line therapy, topotecan, FOLFIRI, enzalutamide, abiraterone and immune checkpoint blockade are possible treatment options. Prostatic carcinoids can be treated in analogy to well differentiated NETs of the gastrointestinal tract.
Effect of prednisone on docetaxel pharmacokinetics in metastatic prostate cancer: A randomized drug-drug interaction study

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1Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands, 2Department of Medical Oncology, St. Francisca Gasthuis, Rotterdam, Netherlands

Background: In metastatic hormone-naive prostate cancer it is currently unclear whether docetaxel chemotherapy should be administered with or without prednisone. Furthermore, the role of corticosteroids in metastatic castration-resistant prostate cancer is controversial, concerning its limited effect on chemotherapy-induced toxicities, small biological anti-tumor effect on PSA-response, and potential toxicity of long-term use. Prednisone is known to induce CYP3A4, which metabolizes taxanes, resulting in a possible drug-drug interaction (DDI). Therefore, we investigated the pharmacological aspects of the addition of prednisone to docetaxel chemotherapy in men with metastatic prostate cancer.

Methods: We conducted a prospective randomized pharmacokinetic (PK) cross-over study in metastatic prostate cancer patients, who received 6 cycles of docetaxel (Q3W, 75mg/m2), in which prednisone was added to 3 consecutive chemotherapy cycles. These were followed or preceded (determined by randomization) by 3 consecutive cycles of docetaxel monotherapy. Blood sampling for PK purposes occurred during cycle 3 and cycle 6. Primary endpoint was the difference in docetaxel exposure (AUC(0-∞), geomean) with and without prednisone, compared to exposure of docetaxel monotherapy by means of a linear mixed model analysis on log-transformed data.

Results: Eighteen patients were evaluable for the primary endpoint. Docetaxel exposure with concomitant prednisone (geomean AUC(0-∞) 2784 ng*h/mL, CV 27%) was slightly higher (1.8%; 95% CI -9.9% till 15.2%, p = 0.75) as compared to docetaxel monotherapy (geomean AUC(0-∞) 2647 ng*h/mL, CV 22%). Toxicity rates were similar for docetaxel cycles with and without prednisone.

Conclusions: No difference in docetaxel pharmacokinetics in cycles with or without prednisone was observed. Moreover, we found similar toxicity profiles in the docetaxel cycles with concomitant prednisone as in the docetaxel monotherapy cycles. This suggests that docetaxel for metastatic prostate cancer can be administered safely without prednisone from a pharmacological perspective.

Clinical trial identification: EudraCT: 2016-001269-10; Dutch trial register: NTR6037.

Table 856P

<table>
<thead>
<tr>
<th>Question</th>
<th>Europe</th>
<th>North America</th>
<th>Other</th>
<th>Urology</th>
<th>Medical Oncology</th>
<th>Radiation Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you recommend docetaxel plus ADT in de novo low-volume mCNPC?</td>
<td>15</td>
<td>26</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In majority</td>
<td>53%</td>
<td>13%</td>
<td>22%</td>
<td>27%</td>
<td>23%</td>
<td>45%</td>
</tr>
<tr>
<td>In selected minority</td>
<td>47%</td>
<td>79%</td>
<td>67%</td>
<td>67%</td>
<td>69%</td>
<td>55%</td>
</tr>
<tr>
<td>No</td>
<td>0%</td>
<td>8%</td>
<td>11%</td>
<td>7%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>In mCRPC pats on abi/enza with progress only in the bone, do you recommend the addition of radium-223?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In majority</td>
<td>28%</td>
<td>52%</td>
<td>50%</td>
<td>50%</td>
<td>29%</td>
<td>64%</td>
</tr>
<tr>
<td>In selected minority</td>
<td>39%</td>
<td>39%</td>
<td>38%</td>
<td>36%</td>
<td>46%</td>
<td>27%</td>
</tr>
<tr>
<td>No (inc stop abi/enza)</td>
<td>33%</td>
<td>9%</td>
<td>13%</td>
<td>14%</td>
<td>25%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Preferred first-line mCRPC treatment in symptomatic men with PD within 6 m after chemo-hormonal therapy for CNPC?

| Abi/Enza                                                               | 37%    | 70%           | 71%   | 62%     | 56%              | 55%               |
| Caba/taxel                                                             | 42%    | 13%           | 29%   | 38%     | 28%              | 9%                |
| Docetaxel                                                              | 0%     | 0%            | 0%    | 0%      | 0%               | 0%                |
| Radium-223                                                            | 16%    | 4%            | 0%    | 0%      | 4%               | 27%               |
| Other or no pref.                                                      | 5%     | 13%           | 0%    | 0%      | 12%              | 9%                |

Legal entity responsible for the study: Erasmus MC Cancer Institute.
Funding: Dutch Uro-Oncology Studygroup.
Disclosure: R.J. van Soest: Honoraria: Astellas, Sanofi, Janssen. R. de Wit: Consultancy role, speakers fee: Sanofi, R.H.J. Mathijssen: Research support: Astellas, Bayer, Boehringer Ingelheim, Cristal Therapeutics, Novartis, Ferring, Pfizer, Roche en Sanofi; Consultation fees: Novartis, Servier; Travel support: Astellas, Pfizer. All other authors have declared no conflicts of interest.
Background: The way in which prostate cancer (PC) is diagnosed and treated is fragmented across some Asian countries. We have established a PC registry (UFO) with the aim of providing a comprehensive picture of PC diagnosis, prognosis, treatment and outcome. The registry will collect patient-reported treatment outcomes and underlying reasons for clinical decision-making.

Methods: This is a large multi-national, prospective, observational registry of PC patients presenting to tertiary care hospitals in China, India, Japan, Malaysia, Singapore, South Korea, Taiwan and Thailand. Patients with existing or newly diagnosed high-risk localized PC (HRL), non-metastatic biochemically recurrent PC (mHSPC) and 290 had castration-resistant PC (mCRPC). Mean age at first diagnosis was similar in each group (Table). At enrollment, 62% of patients had at least one co-morbidity; mainly cardiovascular disease or diabetes and 14.3% of M0 patients were castration-resistant. A total of 84.5% of patients had mHSPC and 75.9% with mCRPC had de novo metastases. Decisions to start therapy were mainly driven by PSA or clinical progression. Decision to discontinue therapy was most often due to disease progression (hormonal therapy) or completion of therapy (chemotherapy).

Conclusions: The UFO registry will provide descriptive data on current disease characteristics and treatment landscape among patients with PC in Asia.

Table: 857P Baseline characteristics of patients with prostate cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HRL N = 357</th>
<th>M0 N = 378</th>
<th>mHSPC N = 1038</th>
<th>mCRPC N = 290</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years from diagnosis until enrolment, median (IQR)</td>
<td>2.7 (0.3-4.0)</td>
<td>6.7 (3.7-9.7)</td>
<td>2.5 (0.2-3.5)</td>
<td>4.3 (1.8-5.5)</td>
</tr>
<tr>
<td>Age at first diagnosis (years) mean (SD)</td>
<td>68.3 (8.10)</td>
<td>65.7 (6.83)</td>
<td>69.1 (7.91)</td>
<td>67.6 (8.38)</td>
</tr>
<tr>
<td>PSA at diagnosis (ng/mL), median (IQR)</td>
<td>29.1 (14.7-59.5)</td>
<td>13.2 (7.7-25.1)</td>
<td>105 (40.8-498)</td>
<td>100 (3.5-9883)</td>
</tr>
<tr>
<td>Reasons that triggered suspicion of PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom driven</td>
<td>56.9%</td>
<td>42.1%</td>
<td>68.6%</td>
<td>77.5%</td>
</tr>
<tr>
<td>During regular health screening</td>
<td>31.4%</td>
<td>46.1%</td>
<td>14.5%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>11.7%</td>
<td>11.8%</td>
<td>16.9%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Had undergone radiologic imaging at enrollment</td>
<td>29.1%</td>
<td>16.7%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>% castrated at enrollment</td>
<td>79.3%</td>
<td>70.4%</td>
<td>85.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>37.4%</td>
<td>52.4%</td>
<td>11.8%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>56.9%</td>
<td>58.7%</td>
<td>55.2%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.0%</td>
<td>0.0%</td>
<td>8.8%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td>2.3%</td>
<td>2.6%</td>
<td>11.0%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>37.7%</td>
<td>65.3%</td>
<td>7.8%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Reason for initiating hormonal therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA progression</td>
<td>17%</td>
<td>52%</td>
<td>24.6%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>10%</td>
<td>8.3%</td>
<td>11.4%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td>2%</td>
<td>0.5%</td>
<td>3.7%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Following treatment guidelines (international, national or site)</td>
<td>40.6%</td>
<td>23.2%</td>
<td>36.3%</td>
<td>55.8%</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td>7.4%</td>
<td>11.2%</td>
<td>13.6%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Reason for initiating chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA progression</td>
<td>-</td>
<td>-</td>
<td>30.4%</td>
<td>48.3%</td>
</tr>
<tr>
<td>Clinical progression</td>
<td>-</td>
<td>-</td>
<td>12.5%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Radiographic progression</td>
<td>-</td>
<td>-</td>
<td>8.3%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Following treatment guidelines (international, national or site)</td>
<td>-</td>
<td>-</td>
<td>29.2%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td>-</td>
<td>-</td>
<td>7.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Reason for stopping hormonal therapy</td>
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<tr>
<td>Treatment-related side-effects</td>
<td>2.3%</td>
<td>2.6%</td>
<td>2.8%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5.8%</td>
<td>9.2%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Disease progression</td>
<td>26.7%</td>
<td>39.5%</td>
<td>42.0%</td>
<td>62.3%</td>
</tr>
<tr>
<td>Reason for stopping chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related side-effects</td>
<td>-</td>
<td>-</td>
<td>8.0%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Completed therapy</td>
<td>-</td>
<td>-</td>
<td>54.5%</td>
<td>50.0%</td>
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<tr>
<td>Disease progression</td>
<td>-</td>
<td>-</td>
<td>20.5%</td>
<td>34.1%</td>
</tr>
<tr>
<td>New or deterioration of existing comorbidities</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4.5%</td>
</tr>
<tr>
<td>Patient’s decision</td>
<td>-</td>
<td>-</td>
<td>1.1%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

SD = standard deviation, IQR = interquartile range

Funding: Janssen.

Legal entity responsible for the study: Johnson & Johnson.
**Annals of Oncology**

**Deployment of advanced real-world data (RWD) analytics for the accelerated recruitment of patients into an ongoing metastatic castrate-resistant prostate cancer (mCRPC) trial, together with the development of a sophisticated patient referral network**

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**Background:** Proprietary advanced analytics were applied within US RWD, e.g. medical prescription claims and physician reference data, to identify high potential sites and physicians treating eligible mCRPC patients, with the aim of accelerating recruitment into an ongoing mCRPC clinical trial. Furthermore, a bespoke methodology to identify physician-to-investigator relationships was used to implement an advanced data driven patient referral network.

**Methods:** Relevant standard diagnosis, drug, and procedure codes were applied to medical and prescription claims datasets and crossed with physician reference data, to identify medical oncologists treating the target population. Physicians were also referenced to their affiliated sites. Stored patient counts between investigators and local physicians were also quantified, providing valuable insights into physician-to-investigator relationships to prioritise and leverage into a patient referral network.

**Results:** Selected results summarised below: ~20k eligible patients were identified - 270 sites each with ≥20 eligible patients were identified -2k oncologists treating eligible patients and with trial experience in the past year were identified - ~4k shared patients between targeted physicians and trial investigators were identified.

**Conclusions:** To facilitate faster patient access to effective medicines, novel methods such as those outlined above are required to optimise clinical trial operations and increase efficiency. Together with the innovative use of RWD to find eligible mCRPC patients and the physicians and sites treating these, we implemented sophisticated techniques to quantify shared patient counts between identified physicians and investigators. This created a foundation for a referral network that has been successfully implemented, as an alternative to the lengthy and costly initiation of a new site(s).

**Legal entity responsible for the study:** IQVIA.

**Funding:** IQVIA.

**Disclosure:** The author has declared no conflicts of interest.

**859TIP**

TALAPRO1-1: An open-label, response rate phase II study of talazoparib (TALA) in men with DNA damage repair defects (DDR) and metastatic castration-resistant prostate cancer (mCRPC) who previously received taxane-based chemotherapy (CT) and progressed on > 1 novel hormonal therapy (NHT)

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**Background:** No therapies are currently approved for men with mCRPC who have progressed on taxane and NHT. Preclinical evidence has shown that DDR + prostate tumours may be sensitised to PARP inhibition. TALA inhibits PARP activity and traps PARP on DNA, preventing DNA damage repair and causing cell death in BRCA1/2-mutated cells.

**Trial design:** Approximately 100 patients (pts) will be enrolled. Eligible pts are ≥18 yrs with measurable soft tissue disease per RECIST v1.1 and have progressive mCRPC, DDR likely to sensitize to PARP inhibition, ECOG PS ≤ 2, no brain metastases, and received 1-2 CT regimens (including ≥1 taxane-based regimen) and progressed on ≥ 1 NHT (enzalutamide or abiraterone acetate). Pts who received a prior PARP inhibitor, cyclophosphamide, mitoxantrone, or a platinum-based CT within 6 mos of study entry or progressed on a platinum-based CT at any time are excluded. Pts will receive TALA 1 mg orally on alternate days (75 mg for those with moderate renal impairment) until radiographic progression, unacceptable toxicity, or withdrawal of consent. Study drug should not be discontinued based on increased PSA or circulating tumour cell (CTC) count alone. Primary endpoint is best objective response (OR) rate (exact 2-sided 95% CI), defined as a complete or partial soft tissue response per RECIST v1.1. Responses must be confirmed ≥ 4 wks later by CT/MRI with no evidence of confirmed bone progression per PCWG3 criteria on repeat bone scan ≥ 6 wks later. Secondary endpoints include time to OR, duration of response, PSA decrease ≥ 50%, CTC count conversion (to CTC<0 and CTC<5 per 7.5 ml of blood), time to PSA progression, radiographic progression-free survival, overall survival, safety, patient-reported outcomes, and pharmacokinetics of TALA. Efficacy will be assessed every 8 wks during the first 24 wks, then every 12 wks thereafter. An initial safety and efficacy analysis will be performed on 20 pts after receiving study drug ≥ 8 wks. An interim efficacy analysis is planned when 60 pts have completed ≥ 6 mos of treatment.

**Clinical trial identification:** NCT03148795.

**Editorial acknowledgement:** Editorial and medical writing support funded by Pfizer Inc.


**860TIP**

Phase II trial evaluating olaparib maintenance in patients with mCRPC after docetaxel treatment reaching partial or stable response

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**Background:** Durable and complete responses following docetaxel chemotherapy in patients with advanced prostate cancer (PC) are uncommon. Most patients will ultimately experience disease progression within 6 months after initial response. Optimal second line therapy in metastatic castration resistant PC (mCRPC) is not well established and several options are possible. Maintenance treatment in tumours as non-small cell lung cancer or ovarian cancer has become a standard improving overall survival (OS), and a phase II study in bladder cancer has demonstrated longer progression-free survival (PFS) after first-line platinum with vinflunine maintenance. Recently PARP-inhibitors have demonstrated improvement in response and PFS in mCRPC with somatic or germline DNA-repair defects [1-4].

**Trial design:** ID: NCT03434158 is a phase II trial of olaparib (300 mg tablet bid) maintenance in patients with mCRPC and a complete or partial response to docetaxel treatment and germline or somatic mutation studied by a next-generation sequencing panel of homologous recombination gene repair. Primary endpoint to assess the effect of olaparib maintenance on radiologic PFS in these patients (RECIST v1.1). Secondary endpoints are: effect of maintenance treatment on PSA-PFS and clinical PFS, PSA response rate, safety and tolerability. Exploratory objectives are: to determine the frequency of BRCA and other genes mutations and to establish a correlation between tumour and germline mutation presence. Previous studies showed that one year PFS was about 10%. To accept treatment efficacy we will assume that the 12-months PFS with olaparib maintenance will be at least 39%. An overall simple size of 27 patients achieves 80% power at a 0.05 significance level (alpha) to accept the efficacy of this treatment after completion 6-8 cycles of docetaxel. An accrual time of 12 months in 8 SOGUG centres in Spain is planned.

**Clinical trial identification:** NCT03434158.

**Legal entity responsible for the study:** SOGUG.

**Funding:** AstraZeneca.

**Disclosure:** All authors have declared no conflicts of interest.
Multimodality treatment for pN1 prostate cancer: Adding elective para-aortic radiation in the PART trial

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Disclosure: All authors have declared no conflicts of interest.

Funding: Legal entity responsible for the study: University Hospitals Leuven, Belgium. Trial design: This is a multicenter, non-randomized phase 2 trial (NCT03079323) conducted in 5 sites in Belgium. Men are eligible for the study when (1) age >18 years, (2) histological proven adenocarcinoma of the prostate at biopsy (cT1-4) and referred for primary high-dose radiotherapy or after radical prostatectomy (pT2-4), and (3) presence of pN1 disease after extended pelvic lymph node dissection. If pN1 disease is present, patients are eligible if one of the following criteria is fulfilled: ≥ 2 positive lymph nodes, a ratio positive / removed lymph nodes > 7% or presence of extracapsular metastatic extension at the level of any lymph node. Patients will receive radiotherapy on the prostate (bed), pelvic lymph nodes and the para-aortic lymph nodes combined with 24 months of ADT. We aim to include 137 patients to detect an improvement in clinical relapse free survival (cRFS) by 15% at 5 years (power of 80%). The primary endpoint is 5 year-clinical relapse-free survival (cRFS) defined as the absence of any clinical relapse that would be visible at top of the line imaging. Secondary endpoints are Quality of life (QoL), treatment-related acute and late toxicity, time to palliative ADT, time to castration refractory prostate cancer (CRPC), cause-specific survival (CSS) and in field pelvic and para-aortic disease control. Recruitment is ongoing, with the first patient included in the trial on 06/02/2017.

Clinical trial identification: NCT03079323.

Legal entity responsible for the study: University Hospitals Leuven, Belgium.

Funding: "Kom op tegen kanker (Stand up to Cancer), the Flemish Cancer Society" (ref. 0010048).

Disclosure: All authors have declared no conflicts of interest.

ReCab II: A phase II trial of Cabazitaxel +/- Rhenium-188-HEDP in patients with metastatic castration resistant prostate cancer who progressed on or after a docetaxel-containing treatment

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Disclosure: All authors have declared no conflicts of interest.
Axitinib vs placebo in patients at high risk of recurrent renal cell carcinoma (RCC): ATLAS trial results


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Pembrolizumab for high-risk (HR) non–muscle invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guérin (BCG): Phase II KEYNOTE-057 trial


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RANGE, a phase III, randomized, placebo-controlled, double-blind trial of ramucirumab (RAM) and docetaxel (DOC) in platinum-refractory urothelial carcinoma (UC): Overall survival results


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Comprehensive biomarker analyses and updated results of PURE-01 study: Neoadjuvant pembrolizumab (pembro) in muscle-invasive urothelial bladder carcinoma (MIBC)

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Comprehensive genomic profiling (CGP) of chemotherapy-resistant, primary mediastinal nonseminomatous germ cell tumors (PMNSGCT)


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Brain metastases response to nivolumab in patients with renal cell carcinoma (RCC): Prospective analysis from the GETUG-AFU 26 (NIVOREN) trial

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Tumor molecular characteristics in patients (pts) with international metastatic renal cell carcinoma database consortium (IMDC) good (G) and intermediate/poor (I/P) risk

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KEYNOTE-427 (NCT02853344) is a single-arm, open-label, 2-cohort, postbaseline phase 2 study to evaluate efficacy and safety of the PD-1 inhibitor pembrolizumab (pembrolizumab) as first-line monotherapy in advanced ccRCC and non-ccRCC. Results from the ccRCC cohort (cohort A) are presented.

Methods: Pts with histologically confirmed advanced ccRCC who had received no prior systemic therapy were eligible. Additional key eligibility criteria: measurable disease (RECIST v1.1), independent central review (ICR) and Karnofsky performance status ≥70%. Pts had ECOG ≤1; adequate organ function; ≥18 years old (≥25 years old in Japan); pretreated with prior RCC therapy; adequate recovery from previous therapy; no prior anti-PD-1/PD-L1 therapy; at least 1 prior tyrosine kinase inhibitor (TKI) allowed if <24 weeks from enrollment; no prior immunotherapy. Additional key exclusion criteria: ≥2 prior systemic treatments; ≥2 prior TKIs; ≥3 prior targeted agents; synchronous metastatic disease; unacceptable disease burden; active infection; uncontrolled comorbidity; ≥2 active malignancies; ≥2 prior malignancies; pregnancy or breastfeeding; radiotherapy or local therapy ≤4 weeks; <2 weeks from prior radiation therapy; <2 weeks from prior local therapy.

Results: 110 pts enrolled; 107 were included in efficacy analysis (opportunity for follow-up data and outcomes by PDL-1 status and other relevant subgroups). Median age (range) was 64 (29-87) years; 78% were male. 37.3%, 47.3%, and 15.5% had IMDC risk categories poor risk, favorable risk, and intermediate-risk, respectively. Median DOR was not reached (range 1.4+ to 8.2+ mo); 86.1% of responders had response ≥6 months. Median PFS was 6.9 (95% CI 5.1-11.3) mo; PFS rate at 6 mo was 53.6%. OS rates at 3 and 6 mo were 97.2% and 92.4%, respectively. 73.6% of pts had a treatment-related adverse event (AE); most common (≥10%) were fatigue (23.6%), pruritus (21.8%), diarrhea (16.4%), rash (12.7%), and arthralgia (11.8%); 18.2% experienced a grade 3-5 treatment-related AE; 1 pt had grade 5 pneumonitis.

Conclusions: Pembrolizumab monotherapy showed encouraging efficacy and acceptable tolerability in pts with advanced ccRCC. Updated analyses will be presented using additional follow-up data and outcomes by PD-L1 status and other relevant subgroups.


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Funding: Merck & Co., Inc.

**Abstracts**

872P Phase Ib study (COSMIC-021) of caborozumab in combination with atezolizumab: Results of the dose escalation stage in patients (pts) with treatment-naive advanced renal cell carcinoma (RCC)

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Background: Caborozumab (C) is an inhibitor of multiple receptor tyrosine kinases involved in tumor cell proliferation, neoangiogenesis, and immune cell regulation, including MET, VEGFRs, and TAM family of kinases (TYRO3, MER, and AXL). Preclinical/clinical studies suggest that C promotes an immune-permissive environment that may facilitate synergistic effects with checkpoint inhibitors. This Phase Ib study evaluates C in combination with the programmed death ligand (PD-L1) targeting antibody atezolizumab (A) in pts with solid tumors (NCT03179060).

Methods: Safety and clinical activity of C (2 dose levels: 40 mg, 60 mg QD) administered in 3-week cycles were evaluated in a 3+3 dose escalation design. Safety data of all pts and criteria for dose limiting toxicity (DLT) determined the recommended dose (RD) for a subsequent expansion stage. Tumor response was assessed by CT/MRI and bone scan (RECIST v1.1).

Results: 12 pts with treatment-naive advanced RCC (mostly clear-cell subtype) were treated in the dose escalation stage (6 at each dose level). At data cutoff, all pts were actively receiving study treatment (range, 3–12 cycles). There were no DLTs or serious adverse events (SAEs) in either C+1-A dose cohort. Most AEs were Grade 1/2 including immune-related AEs. Grade 3 AEs included 3 events of hypertension, 2 events each of diarrhea and hypophosphatemia, and 1 pulmonary embolism. There were no Grade 4/5 AEs. Among 10 pts investigator-assessed confirmed ORR was 50% (1 CR, 4 PRs); 2 additional pts had unconfirmed Pts with only 1 tumor assessment at data cut-off.

Conclusions: C+1-A is well tolerated and shows encouraging anti-tumor activity in advanced RCC. C 40 mg QD þ A 1200 mg Q3W was selected as the RD for expansion into multiple solid tumor cohorts including RCC.

Clinical trial identification: NCT03179060.

Legal entity responsible for the study: Evelinx, Inc.

Funding: Evelinx, Inc.

Disclosure: N. Agarwal: Consulting or advisory role: Pfizer, Novartis, Merck, Genentech, Eisai, Evelinx, Clovis, EMD Serono, IMS, AstraZeneca, Astellas, U. Vashishapantam: Honoraria: Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, Genentech, Jansen, Novartis, Pfizer, Sanofi; Consulting or advisory role: Astellas Pharma, Bayer, Bristol-Myers Squibb, Evelinx, Genentech/Roche, Novartis, Pfizer; Speakers’ bureau: Astellas Pharma, Bayer, Bristol-Myers Squibb, Exelixis, Genentech/Roche, Novartis, Pfizer, Sanofi; Research funding: Astellas Pharma, Astellas Pharma, Bristol-Myers Squibb, Evelinx, Novartis, Pfizer, Sanofi; Funding: Research funding: BMS, Genentech. D. Tayama: Honoraria: Genentech, Pfizer, Novartis, Roche, Bristol-Myers Squibb, Nektar, Merck, Evelinx, Acceleron Pharma, Peleton, Eisai, Cellnex, Alexion Pharmaceuticals, AstraZeneca/MedImmune, GlaxoPharma, Agener, Idera, Argus Therapeutics, Roche Pharma, Boehringer Ingelheim, Aduro Biotech; Honoraria: Bristol-Myers Squibb. T. B. Powles: Consulting or advisory role: Roche/Genentech, Bristol-Myers Squibb, Novartis, Merck, AstraZeneca; Honoraria: Bristol-Myers Squibb, Roche/Genentech, Merck; Research funding: AstraZeneca/ MedImmune, Roche/Genentech. B. I. Rini: Consulting or advisory role: Corus Pharmaceuticals, Pfizer, Merck, Honoraria: Bristol-Myers Squibb, Roche/Genentech, Merck; Travel, accommodations, expenses: Pfizer; Research funding: Pfizer, Bristol-Myers Squibb, Merck, Roche/Genentech. R. J. Motzer: Consulting or advisory role: Pfizer, Novartis, Eisai, Exelixis, Roche/Genentech, Merck; Travel, accommodations, expenses: Bristol-Myers Squibb, Research funding: Pfizer, Bristol-Myers Squibb, GlaxoSmithKline; Novartis, Eisai, Roche, Genentech. S. K. Pal: Consulting role: Pfizer, Novartis, Acreo, Myriad, Genentech, Exelixis, IMS, Astellas, Pfizer, Eisai; Honoraria: Novartis, Medivation, Astellas; Research funding: Medication. L. Fong: Research funding to institution: Roche/Genentech. U. De Giorgi: Personal fees: Astellas, Bristol-Myers Squibb, Jansen, Pfizer, Pierre-Fabre, Sanofi; Non-financial support: Astellas, Bristol-Myers Squibb. Y. Wang, F. di Nucci, C. Kaiser, D. Tayama: Employee of Roche/Genentech. T. Khaznadar: Employee of Roche. F. Donskov: Research funding: Novartis, Pfizer, Ipsen. All other authors have declared no conflicts of interest.

873P Safety and tolerability of atezolizumab (atezo) plus bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC): Pooled analysis of IMmotion150 and IMmotion151


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Background: Atezo (anti-PD-L1) þ bev (anti-VEGF) demonstrated improved PFS and favourable safety vs sun in Ph II and III trials in patients (pts) with untreated mRCC (McDermott 2018; Motzer ASCO GU 2018). To further explore the improved tolerability with this regimen, we performed additional safety analyses using pooled data from the atezo þ bev and sun arms of these studies.

Methods: Safety data were assessed from the primary analyses of the Ph II IMmotion150 and Ph III IMmotion151 trials, which enrolled treatment-naive pts with mRCC with clear-cell and/or sarcomatoid histology. Pts were randomised 1:1 to receive atezo 1200 mg IV q3w þ bev 15 mg/kg IV q3w or sun 50 mg PO QD 4 wk on/2 wk off until progression (RECIST v1.1) or loss of clinical benefit.

Results: Pooled cohorts included 552 atezo þ bev–treated pts and 546 sun–treated pts. Mean duration of treatment for atezo þ bev was 11.4 mo for atezo and 10.8 mo for bev vs 10.0 mo for sun. Treatment-related AEs (TRAEs) occurred in 91% of pts with atezo þ bev and 96% with sun. Grade 3–4 TRAEs were reported in 40% and 54% of pts with atezo þ bev and sun, respectively, with hypertension (14%, 16%), proteinuria (4%, 1%), and fatigue (1%, 6%) as the most common reported events. Grade 5 TRAEs occurred in 1% of pts in each cohort. TRAEs leading to treatment regimen (atezo þ bev or sun) and discontinuation occurred in 5% of pts with atezo þ bev and 8% with sun. AEs of special interest (AESIs), commonly reported with atezo treatment regardless of investigator attribution, were Grade 2–3 in 79% of pts receiving atezo þ bev and 78% receiving sun. Corticosteroid use for AESIs (mostly Grade 1–2) occurred in 16% of pts with atezo þ bev and 5% with sun. The safety profile in pts with components of sarcomatoid histology or with PD-L1 þ tumours was similar to that in pts with clear-cell mRCC. Additional safety data will be reported.

Conclusions: Atezo þ bev had a tolerable safety profile in mRCC, with fewer high–grade TRAEs and TRAEs leading to regimen discontinuation vs sun. Corticosteroid use for atezo AESIs was low. Toxicities were consistent with each agent alone, and no new toxicities were identified.

Clinical trial identification: NCT01984242, NCT02420821.

Editorial acknowledgement: Medical writing assistance for this abstract was provided by Page S. Davies, PhD, of Health Interactions.

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

Funding: F. Hoffmann-La Roche AG.

Disclosure: T.K. Choueiri: Personal fees: Roche; Personal fees: Pfizer; Grants and personal fees: BMS; Personal fees: Merck; Personal fees: Eisai; Personal fees: Novartis; during the conduct of the study. D.F. McDermott: Consulting or advisory role: Bristol-Myers Squibb, Novartis, Pfizer, Novartis, Exelixis, Ipsen, EUSA Pharma; Travel, accommodations, expenses: funding; Novartis, Pfizer, Bristol-Myers Squibb, Honoraria: Bristol-Myers Squibb, Pfizer, Novartis, Ipsen, Exelixis, Roche/Genentech. M. Green, F. di Nucci: Employee: Genentech. P-Y. Chang: Employee of Exelixis Inc. C. Scheffold: Employee of and owns stock in Exelixis, Inc. S. Pal: Honoraria: Astellas Pharma, Medivation, Novartis; Consulting or advisory role: Aveo, Bristol-Myers Squibb, Exelixis, Genentech, Myriad Pharmaceuticals, Novartis, Pfizer; Research funding: Medivation. F. Donskov: Research funding: Novartis, Pfizer, Ipsen. All other authors have declared no conflicts of interest.
Background: Pts with metastatic melanoma who discontinue N-I may experience sustained clinical benefit and a delayed need for subsequent systemic therapy. In this analysis, TFI was retrospectively analyzed using data from the phase 3 CheckMate 214 trial, in which N-I demonstrated superior efficacy vs S in pts with IMDC intermediate/poor-risk aRCC.

Methods: In CheckMate 214, pts with previously untreated clear cell aRCC were randomized 1:1 to N-I mg/kg + ipilimumab (N-I) or sunitinib (S) in patients (Pts) with advanced renal cell carcinoma (aRCC): CheckMate 214 analysis.

Conclusions: The use of N-I was associated with a significant longer TFI beyond treatment discontinuation in pts with IMDC intermediate/poor-risk aRCC and irrespective of whether pts achieved response or disease control. TFI should be considered along with traditional efficacy measures when evaluating treatment options for aRCC.

Clinical trial identification: NCT02331749.

Editorial acknowledgement: Professional medical writing and editorial assistance were provided by Richard Daniel, PhD, and Lawrence Hargett of PPSI (a PAREXEL company), funded by Bristol-Myers Squibb.

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

Table: 875P

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N-I int/poor-risk pts</th>
<th>S int/poor-risk pts</th>
</tr>
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<tbody>
<tr>
<td>Total n = 425</td>
<td>CR n = 40</td>
<td>PR n = 137</td>
</tr>
<tr>
<td>BOR (95% CI), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42 (37–47)</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Median (range) time to response, months</td>
<td></td>
<td></td>
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<tr>
<td>2.8 (0.9–11.3)</td>
<td>2.8 (0.9–11.0)</td>
<td>2.8 (1.4–11.3)</td>
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<tr>
<td>Median (95% CI) duration of response, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR (21.8–NE)</td>
<td>NR (18.8–NE)</td>
<td>18.2 (14.8–NE)</td>
</tr>
<tr>
<td>Pts with ongoing response in responders, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-month PFS rate (95% CI), %</td>
<td>50 (44–55)</td>
<td>97 (83–100)</td>
</tr>
<tr>
<td>18-month OAS rate (95% CI), %</td>
<td>78 (74–81)</td>
<td>100 (100–100)</td>
</tr>
</tbody>
</table>

BOR, best overall response; NE, not estimable; NR, not reached; PR, partial response.
A new prognostic model for overall survival (OS) in second line (2L) for metastatic renal cell carcinoma (mRCC): Development and external validation

L. Derosa 1, M.A. Bayar 2, L. Albiges 1, G. Le Teuff 2, B. Escudier 1

Background: The IMDC classification scheme for OS has been validated in 2L mRCC. Recently, we showed that two new prognostic factors, Time from first to second line (< 1 year) and tumor burden (≥ 100 mm), are independently associated with OS in the same setting. Here, we present a new classification scheme.

Methods: mRCC patients treated in 2L between January 2005 and December 2014 after initial first line clinical trials at Gustave Roussy Cancer Campus (GRCC) formed the discovery set. Patients from 2 phase III clinical trials from Pfizer database (PZEREDB), AXIS (NCT00678392) and INTORSECT (NCT00474786), formed the external validation set. In addition to the IMDC predictors, the 2 new prognostic factors were tested using a multivariable Cox model with a backward selection procedure. The performance of the new GRCC model and the classification scheme derived from it, measuring R², c-index and calibration, was evaluated on the validation set and compared to MSKC and IMDC.

Results: Two-hundred and twenty-one patients were included in GRCC cohort and 855 patients in PZEREDB. Median OS was similar in the two datasets (16.8 [95% CI 12.9-21.7] vs 15.3 [13.6-17.2] months, respectively). Time from first to second line and tumor burden confirmed their significant effect on OS with HR = 1.68 [1.23-2.31] and 1.43 [1.03-1.99]. The new classification, derived by counting the number of factors, allows categorizing patients into 4 risk groups: median OS from the start of 2L in the validation cohort was not reached (NE) [95% CI 29.4-NE] in the favorable risk group (n = 20, 4 deaths, 0 risk factor), 21.8 months (11.6-15.8) in the intermediate risk group (n = 367, 135 deaths, 1-2 risk factors), 12.7 months (11.0-13.8) in the low-risk poor group (n = 347, 211 deaths, 3-4 risk factors), and 5.5 months (4.7-6.4) in the high-risk poor group (n = 121, 105 deaths, ≥ 5 risk factors). Not surprisingly, the incorporation of factors that characterize post first line features and the new stratification allowed a better performance compared to previous models.

Conclusions: The GRCC classification derived from the model is a new reliable prognostic tool that can be applied to better predict OS in previously treated mRCC patients. Legal entity responsible for the study: L. Derosa.

Funding: No new funding.

Disclosure: All authors have declared no conflicts of interest.

Full text: https://doi.org/10.1016/j.annonc.2018.05.031

Table: 877P

<table>
<thead>
<tr>
<th>1L (n = 62)</th>
<th>2L (n = 20)</th>
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<tr>
<td>Response ORR (95% CI), %</td>
<td>Duration of response, median (95% CI), mo</td>
</tr>
<tr>
<td>16.1 (8.0-27.7)</td>
<td>10.4 (2.8-10.4)</td>
</tr>
<tr>
<td>10.0 (1-23.1)</td>
<td>NE (6.9-NE)</td>
</tr>
<tr>
<td>PFS Median (95% CI), mo</td>
<td>12-mo rate (95% CI), %</td>
</tr>
<tr>
<td>8.3 (5.5-9.7)</td>
<td>55.7 (41.9-76.4)</td>
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<tr>
<td>5.6 (2.3-8.2)</td>
<td>44.9 (21.9-65.6)</td>
</tr>
<tr>
<td>OS Median (95% CI), mo</td>
<td>12-mo rate (95% CI), %</td>
</tr>
<tr>
<td>NE (85.9) [73.4-92.8]</td>
<td>16.9 (8.3-NE)</td>
</tr>
<tr>
<td>65.0 (40.3-81.5)</td>
<td>NE, not estimable</td>
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Conclusions: Avelumab, administered either as 1L or 2L monotherapy, showed durable responses, promising survival outcomes, and an acceptable safety profile in pts with aRCC. These data, as well as those recently reported from phase IIIb trial JAVELIN Renal 101 (NCT02684006) comparing avelumab + axitinib with sunitinib as 1L treatment for pts with aRCC.

Clinical trial identification: NCT01772004

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

References:

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Background: Avelumab is a human anti-PD-L1 IgG1 monoclonal antibody approved for the treatment of metastatic Merkel cell carcinoma and, in the US/Canada, advanced urothelial carcinoma programmed on platinum therapy. Here, we report phase Ib data from the multicohort JAVELIN Solid Tumor trial (NCT01772004) in pts with aRCC treated with avelumab monotherapy in either the 1L or 2L setting.

Methods: Eligible pts in the 1L subgroup had measurable aRCC with a clear cell component and ECOG ≤ 1. The phase I portion of the study was conducted in 1L with pts assigned 1:1 to N 3 mg/kg Q3W for 4 doses then N 3 mg/kg Q2W or S 50 mg QD for 4 weeks on, 2 weeks off. Efficacy, safety, and quality of life (QoL) were explored in pts with measurable disease by RECIST v1.1 and by investigator-defined response criteria. Efficacy assessments included objective response rate (ORR; according to RECIST v1.1 pur investigator), progression-free survival (PFS), overall survival (OS), and safety.

Results: As of 27 April 2017, 82 pts received avelumab: 62 pts as 1L (median follow-up, 14.2 mo [range, 2.5-17+ mo] and 20 pts as 2L (median follow-up, 22.1 mo [range, 16-23 mo]; 2 pts remained on treatment). Efficacy data are summarized below. The rates of treatment-related adverse events (TRAEs) were 75.8% (grade ≥ 3, 12.9%) and 70.0% (grade ≥ 3, 5.0%) in the 1L and 2L subgroups, respectively. The only grade ≥ 3 TRAE that occurred in > 1 pt was elevated lipase (n = 4); no TR deaths or unexpected immune-related TRAEs occurred. Updated data will be presented.

Table: 877P

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Conclusions: Avelumab, administered either as 1L or 2L monotherapy, showed durable responses, promising survival outcomes, and an acceptable safety profile in pts with aRCC. These data, as well as those recently reported from phase IIIb trial JAVELIN Renal 101 (NCT02684006) comparing avelumab + axitinib with sunitinib as 1L treatment for pts with aRCC.
878P

Tivozanib combined with nivolumab: Safety and efficacy in patients with metastatic renal cell carcinoma (mRCC)


Background: Recently approved in the EU, tivozanib is a VEGFR-TKI with high specificity and low incidence of class effect adverse events. We reported earlier that tivozanib can be combined with nivolumab at full dose of each drug. We report herein safety and efficacy data from a phase Ib/II combination of tivozanib and nivolumab.

Methods: In the phase Ib portion of the study, tivozanib was administered orally at 1 mg and 1.5 mg, once daily for 21 days every 28 day cycle using a standard 3 + 3 dose escalation design in combination with nivolumab 240 mg every 14 days intravenously. As there were no DLTs in phase I, in the phase II portion of the study tivozanib was administered orally at 1.5 mg in combination with nivolumab.

Results: 28 patients have been enrolled, 6 in phase Ib and 22 in phase II. 25 were treated with full dose tivozanib, 1.5 mg daily for 21 days with nivolumab. The median age was 63; 8 patients were IMDC favorable; 19 IMDC intermediate; 1 IMDC poor. 18 patients were ECOG 0, 10 ECOG 1 and there were 20 male. 14 had clear cell histology. All patients experienced at least one AE and 52% experienced a grade 3/4 AE. 44% experienced a grade 3/4 AE and efficacy data from a phase Ib/II combination of tivozanib and nivolumab.

Conclusions: The combination of tivozanib with nivolumab is safe and manageable at full dose of both drugs. The safety profile and the activity is favorable for a combination of a TKI with a checkpoint inhibitor as would be expected for a highly selective and well tolerated TKI.

Clinical trial identification: NCT03136627.

Legal entity responsible for the study: Aveo Oncology.

Funding: Aveo Oncology; Bristol Myers Squibb.

Disclosure: P. Barthelemy: Consulting: research support, honoraria: Novartis, Pfizer, Roche, MSD; Honoraria: Janssen Cilag, Sanofi, Astellas. B. Escudier: Honoraria: Pfizer, Novartis, BMS, Roche, Ipsen, EUSA. R. A. Davud: Member of advisory boards in RCC; Pfizer, Novartis, BMS, Ipsen, Roche; Travel support for meetings or speeches: Pfizer, Novartis, BMS, Roche, Ipsen, Astellas. S. Negrier: Honoraria: Pfizer, Ipsen, BMS, EUSA Pharma, Novartis; Research grant: Pfizer; Travel expenses: BMS, Pfizer, Ipsen. M. N. Needle: Full time employee, officer and shareholder: Aveo Oncology. L. Albiges: Financial interest: Merck, BMS, AstraZeneca, Pfizer; Payment for services provided: AstraZeneca, EUSA Pharma, Novartis; Research grant: Pfizer, Novartis, BMS; Travel expenses: BMS, Pfizer, Ipsen. M. N. Needle: Full time employee, officer and shareholder: Aveo Oncology. L. Albiges: Financial interest: Merck, BMS, AstraZeneca, Pfizer; Payment for services provided: AstraZeneca, EUSA Pharma, Novartis; Research grant: Pfizer, Novartis, BMS; Travel expenses: BMS, Pfizer, Ipsen.

880P

Subgroups analysis and circulating biomarkers evaluation of RESORT trial: A randomized phase II study in metastatic renal cell carcinoma patients (mRCC) after metastasisectomy

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Background: RESORT trial (NCT01444887) was the largest prospective study whose aim was to assess the role of VEGF inhibition in mRCC pts after radical metastasectomy. It showed that sorafenib (SO) was safe and feasible but did not affect Relapse-Free Survival (RFS) compared to observation (OB) in this population. Early identification of dynamic predictors of outcome such as circulating Tumor cells (CTCs) may be helpful to move up clinical tumor relapse.

Methods: We included 69 patients with mRCC who received cabo after progression on ICB alone or in combination with VEGF or other therapies. Baseline characteristics, best response (BR, investigator-assessed), time to treatment failure (TTF) and overall survival (OS) were analyzed.

Results: Median age was 62 years (range 37-78). Median number of prior therapies was 2 (range 1-10). Median time on prior ICB was 3.9 months (range 0.5-38). Type of prior therapy was ICB single agent (54%) or in combination with a VEGF inhibitor (35%) or other therapies (12%). At time of cabo initiation, IMDC risk groups were 6% good, 67% intermediate and 27% poor. BR was 33% PR, 46% SD, 17% PD, 3% un evaluable. Median follow up after cabo initiation was 12 months. At time of analysis, 35% (n = 24) remained on cabo and median TTF was 6.6 (95%CI: 5.3-8.5) months. Of those discontinued cabo, 58% (n = 26) received additional therapy. At time of analysis, 62% (n = 43) were alive with 1-year OS rate of 53% (95%CI: 37%-66%).

Table: 879P

<table>
<thead>
<tr>
<th>N</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Unevaluable</th>
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<tbody>
<tr>
<td>All patients</td>
<td>69</td>
<td>23(33%)</td>
<td>32(46%)</td>
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<tr>
<td>By prior ICB type</td>
<td></td>
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<tr>
<td>ICB alone</td>
<td>37</td>
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<td>15(41%)</td>
<td>5(14%)</td>
</tr>
<tr>
<td>ICB+VEGF</td>
<td>24</td>
<td>6(25%)</td>
<td>12(50%)</td>
<td>5(21%)</td>
</tr>
<tr>
<td>ICB+Other</td>
<td>8</td>
<td>1(13%)</td>
<td>6(75%)</td>
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</tr>
<tr>
<td>By prior ICB duration</td>
<td></td>
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<tr>
<td>&lt;6mos</td>
<td>42</td>
<td>12(29%)</td>
<td>22(52%)</td>
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<td>&gt;6mos</td>
<td>27</td>
<td>11(41%)</td>
<td>10(37%)</td>
<td>4(15%)</td>
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</table>
Correlations between disease-free survival (DFS) and overall survival (OS) in patients (pts) with renal cell carcinoma (RCC) at high risk for recurrence: Results from S-TRAC trial

D.J. George1, A.J. Pantuck2, R. Fidrig1, B. Erciyes1, S. Hablas3, M. Casey4, X. Lin5, T. Phillips1, D. J. George5, M.J. Lechuga Fean5, A. Ravid6

1Division of Oncology, Duke University Medical Center, Durham, NC, USA; 2Department of Urology, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; 3Department of Urology, Hospital Clinico Universitario de Valencia, Valencia, Spain; 4Division of Medical Oncology, Gustave Roussy Institut de Cance ´rologie, Villejuif, France; 5Department of Medical Oncology, Duke University, Durham, NC, USA; 6Department of Oncology, Pfizer Inc, Collegeville, PA, USA; 7Pfizer Oncology, Pfizer Inc, La Jolla, CA, USA; 8Medical, Pfizer, Paris, France; 9Oncology, Pfizer, Milan, Italy; 10Department of Medical Oncology, CHU Bordeaux Hospita Centre St. Andre, Bordeaux, France

Background: S-TRAC, a prospective phase 3 randomized trial in pts with resected RCC at high risk for recurrence, demonstrated a statistically significant improvement in DFS with sunitinib vs placebo. HR 0.76, 95% CI 0.59-0.98; P = 0.03. We hypothesized that DFS is a surrogate for OS and evaluated the association of DFS events with OS.

Methods: DFS (by blinded independent review) was defined from randomization to first evidence of recurrence, second primary malignancy, or death, whichever occurred first. Pts were categorized as having DFS or censored ≤2 years vs DFS >2 years, and as having OS or censored ≤5 years or OS >5 years. The odds ratio (OR), positive predictive values (PPV) and negative PV (NPV) were reported. To determine if DFS can be a surrogate for OS, 2 conditions need to be tested: 1) DFS and OS are strongly correlated, and the correlation coefficient between DFS and OS is tested at the level. Similar results were observed with investigator assessed DFS. Analyses of trial level Clayton, and Plackett copula, suggesting a moderate correlation at the individual pt level. Correlations between DFS and OS were explored considering dichotomizing blood innate and adaptive immunity in mRCC pts.

Conclusions: A significant reduction of myeloid immunosuppressive cell subsets in favor of protective antitumor adaptive and innate immunity was detected in most post vs pre PBRM. Specifically, granulocytic myeloid-derived suppressor cells (MDSCs) (CD11b+ CD14+HLA-DRneg), monocytes (CD11b+ CD14+HLA-DRneg) and TIM3+ myeloid cells (CD11b+TIM3+ and CD14+TIM3+) were remarkably reduced. Total CD11b+ CD14+ cells were also decreased, while classical protective (CD14+ CD68+HLA-DRneg) and patrolling (CD14+ CD68negHLA-DR+) monocytes showed a clear boost. Concomitantly, higher frequency of cytolytic and activated NK cells (CD3+ CD16+ CD56+CD3nega n d TIM3-), detected in post-Cabos samples. Activated CD8+ and CD4+ T cells (CD3+ CD8+CD4+ CD49d+) were also raised by treatment along with a specific increase of ADCP-prone CD3+ CD16+CD56+ T cells. These latter data indicate that Cabo could intensively direct and Ab-mediated enhancing tumor killing potential in NK and T cells, either as direct effect or through the reduced immunosuppressive pressure exerted by myeloid populations.

Conclusions: Cabo mediates a rapid remodeling of myeloid cells from an immunosuppressive to an antitumor phenotype, with a priming of circulating cytotoxic NK and T cells. Even in advanced disease, Cabo can still contribute to reset systemic immune conditions by creating more favorable conditions for immunotherapy.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori di Milan.

Funding: Has not received any funding.

Disclosure: E. Verzoni: Honoraria: Ipsen, Novartis, Pfizer. G. Procopio: Honoraria: BMS, Ipsen, Novartis, Pfizer. All other authors have declared no conflicts of interest.

Methods: Pts were randomized (1:1) within 12 weeks from surgery to receive SO or OBS for a maximum of 52 weeks or until disease recurrence, with stratification according to time from nephrectomy to metastases (more or less than 12 months), site of disease (lung, liver, single or multiple lesions). For pts who had an impaired DFS at the time of CABO, a trial level. Similar results were observed with investigator assessed DFS. Analyses of trial level Clayton, and Plackett copula, suggesting a moderate correlation at the individual pt level. Correlations between DFS and OS were explored considering dichotomizing blood innate and adaptive immunity in mRCC pts.

Conclusions: A significant reduction of myeloid immunosuppressive cell subsets in favor of protective antitumor adaptive and innate immunity was detected in most post vs pre PBRM. Specifically, granulocytic myeloid-derived suppressor cells (MDSCs) (CD11b+ CD14+HLA-DRneg), monocytes (CD11b+ CD14+HLA-DRneg) and TIM3+ myeloid cells (CD11b+TIM3+ and CD14+TIM3+) were remarkably reduced. Total CD11b+ CD14+ cells were also decreased, while classical protective (CD14+ CD68+HLA-DRneg) and patrolling (CD14+ CD68negHLA-DR+) monocytes showed a clear boost. Concomitantly, higher frequency of cytolytic and activated NK cells (CD3+ CD16+ CD56+CD3nega n d TIM3-), detected in post-Cabos samples. Activated CD8+ and CD4+ T cells (CD3+ CD8+CD4+ CD49d+) were also raised by treatment along with a specific increase of ADCP-prone CD3+ CD16+CD56+ T cells. These latter data indicate that Cabo could intensively direct and Ab-mediated enhancing tumor killing potential in NK and T cells, either as direct effect or through the reduced immunosuppressive pressure exerted by myeloid populations.

Conclusions: Cabo mediates a rapid remodeling of myeloid cells from an immunosuppressive to an antitumor phenotype, with a priming of circulating cytotoxic NK and T cells. Even in advanced disease, Cabo can still contribute to reset systemic immune conditions by creating more favorable conditions for immunotherapy.

Legal entity responsible for the study: Fondazione IRCCS Istituto Nazionale Tumori di Milan.

Funding: Has not received any funding.

Disclosure: E. Verzoni: Honoraria: Ipsen, Novartis, Pfizer. G. Procopio: Honoraria: BMS, Ipsen, Novartis, Pfizer. All other authors have declared no conflicts of interest.

Methods: Pts were randomized (1:1) within 12 weeks from surgery to receive SO or OBS for a maximum of 52 weeks or until disease recurrence, with stratification according to time from nephrectomy to metastases (more or less than 12 months), site of disease (lung, liver, single or multiple lesions). For pts who had an impaired DFS at the time of CABO, a
mRCC patients with ECOG PS2. The Bryant and Day design allows for joint evaluation of two primary outcomes. Tolerability was defined as the proportion of patients at 6 months who were free from drug-related grade 3-4 toxicities resulting in SAE reporting or drug discontinuation. >3 weeks. Efficacy was assessed by patients' response rate (RECIST 1.1) and alive at 6 months. Secondary endpoints included response, drug safety, progression-free survival (PFS) and overall survival (OS).

Methods: Patients with mRCC and ECOG PS 2 without prior systemic treatment were registered. Unfavorable tolerability was defined at 30%, with 40% being desirable. Patients with 1 missing risk factor were excluded. Treatment comprised pazopanib 800mg PO once daily (OD). Dose modifications using 600mg PO, OD and 400mg PO, OD were permitted. Treatment continued until progression or unacceptable toxicity.

Results: A total of 75 patients were registered into the trial from 26 UK sites between 2013-2016. All patients were ECOG PS 2; median age 68 years (IQR 64, 76), 72% were male, HENG poor prognosis 59% and intermediate prognosis 41%. 47 patients met the tolerability criteria (vs 34 required). Further analysis showed that 18 (24%) patients stopped treatment due to toxicity within the same period. 23 patients were required to be progression free and alive at 6 months with 38 being observed. Kaplan Meier 6 month PFS was 66% (95% CI 54, 76), with a median PFS of 9 months (95% CI 7.6, 13.5). Overall survival data is not yet mature.

Conclusions: Our results suggest that treatment with pazopanib is tolerable and shows similar efficacy in ECOG PS 2 patients as compared to previously reported data with ECOG PS 0-1. This suggests that excluding patients from trials based solely on their performance status may not appropriate.


Legal entity responsible for the study: The University of Birmingham.

Funding: Novartis.

Disclosure: E. Porfiri: Grants: Novartis, during the conduct of the study; Personal (speaker and advisory board) fees: Novartis, Pfizer, BMS, Ipsen, outside the submitted work. K. Fife: Non-financial support: BMS; Personal fees: BMS, Ipsen, Pfizer, Roche, Eisa, Novartis, outside the submitted work. C. McDonald-Smith: Personal fees: Pfizer, BMS, outside the submitted work. N.S. Vasudev: Non-financial support: Ipsen; Grants and non-financial support: Bristol Meyers Squibb, outside the submitted work. All other authors have declared no conflicts of interest.

Annals of Oncology

Real-world effectiveness of pazopanib in patients with intermediate prognostic risk advanced renal cell carcinoma (PRINCIPAL study)


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Background: Stratification by prognostic risk informs efficacy for various treatments in patients with advanced renal cell carcinoma (RCC). Whether further stratification beyond prognostic risk aids in predicting treatment outcomes is unknown. We conducted a post-hoc analysis of the real-world PRINCIPAL study (NCT01649778) to assess the effectiveness of pazopanib (PAZ) in pts with intermediate risk advanced RCC.

Methods: In this prospective, observational study, pts with advanced and/or metastatic clear cell RCC were enrolled within 30 days of initiating PAZ. Data on progression, survival, and safety were collected approximately every 3 months (mos) until death, consent withdrawal, or loss to follow-up, for up to 30 mos. Primary efficacy endpoints included overall survival (OS), progression-free survival (PFS), and overall response rate (ORR). A post-hoc analysis of pts with intermediate risk per Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria was conducted to evaluate effectiveness by number of risk factors (1 vs 2), age (<65 vs >65 years), and Eastern Cooperative Oncology Group performance status (ECOG PS).

Results: Of the 657 enrolled pts who received ≥1 dose of PAZ, 363 (55.3%) and 343 (52.3%) had intermediate risk per MSKCC and IMDC criteria, respectively. Within the subgroup of pts with intermediate risk MSKCC and IMDC, median PFS (but not OS) was numerically longer in pts with 1 (vs 2) risk factors, and outcomes were poorer in pts with ECOG PS ≥ 2 (vs < 2) (Table). Median OS within each MSKCC and IMDC risk group was longer than anticipated based on previous clinical trial and real-world data.

*Patients with 1 missing risk factor were excluded.

Table: B84P Median progression-free survival

<table>
<thead>
<tr>
<th>Disease progression or death/N (%)</th>
<th>Median (95% CI) months</th>
<th>Disease progression or death/N (%)</th>
<th>Median (95% CI) months</th>
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</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
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<tr>
<td>&lt;2</td>
<td>8/193 (33.6) 11.2 (9.5-14.1)</td>
<td>2/81 (10.00) 5.6 (1.3-12.8)</td>
<td>8/193 (33.6) 11.2 (9.5-14.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>2/86 (11.8) 34.3 (13.7-75.8)</td>
<td>1/7 (14.3) 38.3 (12.0-83.0)</td>
<td>2/86 (11.8) 34.3 (13.7-75.8)</td>
</tr>
</tbody>
</table>

Conclusions: The results of the PRINCIPAL study suggest pts with advanced RCC of intermediate prognostic risk can be further stratified to predict treatment outcomes.

Clinical trial identification: NCT01649778.

Editorial acknowledgement: Editorial support was provided by Chris Ontiveros, PhD (ApotoCom, New York).

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

**Abstracts**

**885P**

**Are adverse events (AEs) predictive of nivolumab activity? Data from the Italian expanded access program in metastatic renal cell carcinoma (mRCC)**

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**Background:** The Italian Renal Cell Cancer Early Access Program was an expanded access program that allowed access to nivolumab, for patients (pts) with mRCC prior to regulatory approval.

**Methods:** Pts with mRCC previously treated with agents targeting the vascular endothelial growth factor pathway were eligible to receive nivolumab 3 mg/kg every 2 weeks. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using CTCAE v. 4.0. Association between sex, age, BMI, metastatic sites, number and kind of previous therapies, ECOG PS and related toxicity were evaluated with a logistic regression model that identified only age ≥ 65 years (Odds Ratio = 1.54 [1.00-2.38], P = 0.05).

**Results:** A total of 389 pts were enrolled between July 2015 and April 2016, 79% after 2 or more lines of therapy. The most common any-grade treatment-related AEs were fatigue (13%) and rash (9%). Twenty-two (5.7%) pts discontinued treatment due to AEs. There were no treatment-related deaths. Treatment-related AEs (grade 1-4) were reported in 32% of pts. Median time to appearance of AEs was 1.4 months (range 9-11). Grade 3-4 AEs occurred in 27 (7%) pts. Of the 22 serious AEs who induced treatment discontinuation, 11 (50%) were considered AEs including: grade 4 hyperglycemia (n = 1), grade 3 diarrhea (n = 1), grade 3 hypothyroidism (n = 1), grade 3 bronchitis obstructum organizing (BOOP) (n = 1), grade 3 asthenia (n = 1), grade 3 hypertension (n = 1), grade 3 skin toxicity (n = 1), grade 3 tremor (n = 1), grade 2 eye-lid ptosis (n = 1), grade 2 liver toxicity (n = 1), grade 2 hydropsyphosism (n = 1). AEs were generally manageable with treatment as per protocol-specific guidelines. At a median follow-up of 12 months, the median progression-free survival was 4.5 months (95% CI 3.3 - 6.2), the 12-months overall survival rate was 63%. Pts with toxicity (124 pts) had a significantly longer survival (1 year OS 69%) in comparison to pts who did not experience AEs (1 year OS 59%).

**Conclusions:** The appearance of AEs strongly correlates with survival benefit in a real-life population of mRCC pts treated with Nivolumab.

**Legal entity responsible for the study:** Italian Renal Cell Cancer Early Access Program Group.

**Funding:** BMS.

**Disclosure:** E. Verzoni: Honoraria/Consultancy: Novartis, Pfizer, Ipsen, BMS. C.N. Sternberg: Honoraria/Consultancy: Novartis, Pfizer, Ipsen, Eisa, BMS. G. Procopio: Honoraria/Consultancy: Ipsen, BMS, Pfizer, Novartis. All other authors have declared no conflicts of interest.

**886P**

**Adiponectin-AdipoR1 axis in renal cell carcinoma plays a pivotal role in tumor progression and drug resistance**

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**Background:** It is well established that renal cell carcinoma (RCC) is an obesity-associated cancer. Adiponectin, a major adipocyte-secreted adipokine, plays anti-tumor properties in many malignancies, but exerted paradoxical actions on RCC. Herein, we investigated the effects of adiponectin on RCC progression and resistance to sunitinib, and to exploit this molecular mechanism.

**Methods:** Tissues were collected from 126 patients with metastatic renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitor (TKI) therapy. Tumor Adiponectin receptor 1 (AdipoR1) and Adiponectine receptor 2 (AdipoR2) were detected by immunohistochemistry. Assays with RCC cell lines were used to examine the signal transduction pathway of adiponectin in RCC.

**Results:** AdipoR2 was generally lower expressed than AdipoR1 in mRCC tumor (15.6% vs 89.1%, p < 0.001). AdipoR1 expression, but not AdipoR2, was a significant independent predictor of favorable responding to TKI and good survival outcomes. In cultured RCC cells adiponectin inhibited migration and invasion of RCC cells and sensitized cells to killing by sunitinib. Mechanistic investigations of ligand–receptor interactions revealed that AdipoR1 could hinder migration and invasion of RCC cells by blocking GSK3β and β-Catenin pathway and increase cells sensitivity to sunitinib through inhibiting AKT and NF-κB pathway. However, AdipoR2 was not associated with the tumor-limiting properties of adiponectin.

**Conclusions:** These results show that AdipoR1 is a potential prognostic marker for favorable outcomes of mRCC patients. Adiponectin-AdipoR1 axis could be a plausible target to impede tumor progression and sensitize tumors to TKI therapy.

**Legal entity responsible for the study:** Guangji Sun.

**Funding:** National Natural Science Foundation of China (NSFC 81672547, 81402110), the Science and Technology Support Program of Sichuan Province (2015SZ0230-3) and 1:3:5 project for disciplines of excellence, West China Hospital, Sichuan University.

**Disclosure:** All authors have declared no conflicts of interest.

**887P**

**Identification of IMDC intermediate-risk subgroups in patients with metastatic clear-cell renal cell carcinoma (cRCC)**

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**Background:** Majority of patients (pts) with cRCC at first line (1L) treatment are classified in the IR subgroup according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model. IR represents a heterogeneous class of pts while frontline strategies will be chosen on prognostic selection. The aim of this study is to better characterize IR pts.

**Methods:** Retrospective analysis was performed from IGReCC (Institut Gustave Roussy Renal Cell Carcinoma) database. Overall survival (OS) was defined from start of 1L therapy to death or last follow-up. A multivariable Cox model with backward selection procedure (alpha level = 0.01) and a Classification and Regression Tree (CART) analysis were performed to identify which prognostic factors of IMDC score (time from diagnosis to treatment [DDT] < 1 year, Karnofsky Performance Status [KPS] < 80%, Hemoglobin < lower limit of normal [LNL], neutrophils > upper normal level [UNL], platelet > UNL, calcium > UNL) were associated to OS in IR pts.

**Results:** From 2005 to 2016, 777 pts with cRCC were treated with an anti-VEGF first line therapy. Among 571 evaluable pts for IMDC score, 199 (34%) pts were classified as good risk, 82 (14%) as poor risk and 298 (51%) as IR. Median OS for IR pts was 24 months (mo). Within the IR population, only platelet (PLT) count was significantly associated to OS with a hazard ratio 1.88 (95%CI 1.27-2.88) = 0.0017. Median OS for pts with PLT > UNL was 18 months (mo) [95%CI 12.23 versus 29 mo [95%CI 21.4-35.7] for pts with normal PLT count. Therefore, the selection of PLT count was confirmed on bootstrap samples and was also selected for the first split of the CART-tree analysis.

**Conclusions:** Pts in the IR group have a heterogeneous prognosis. Elevated PLT count seems identifies a subgroup of pts with poor outcome in the IMDC intermediate-risk population with cRCC.

**Legal entity responsible for the study:** Laurence Albiges.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Anhydrase IX antibody 89Zr-girentuximab and 18F-fluorodeoxyglucose (FDG) PET/CT (PET). Here, we report preliminary analyses of a secondary endpoint: comparison of baseline contrast-enhanced (ce)CT, 89Zr-girentuximab and FDG PET to detect metastases.

Methods: mcrCC pts with good or intermediate prognosis (according to IMDC) and eligible for watchful waiting were included. Patients underwent 3 scans, i.e. ceCT, 89Zr-girentuximab and 18F-FDG PET. So far, baseline scans of 29 of the 40 pts to be accrued were independently reviewed by 3 experienced readers. Lesions by ceCT were defined positive according to RECIST1.1. For lesions with prominent uptake of 89Zr-girentuximab or 18F-FDG, maximum Standardized Uptake Values (SUVmax) were calculated. Analyses were performed on a lesion level, taking clustering of data within patients and lesions into account.

Results: In total 325 lesions were detected by at least one modality (mean 11 (2–33) per pt). ceCT detected 52% (95%CI:45;58), 18F-FDG PET 61% (95%CI:55;67) and 89Zr-girentuximab PET 69% (95%CI:63;74). Differences in lesion detection varied across organ sites (p < 0.001). Lesions were visualized by ceCT and 18F-FDG PET in all pts, whereas 89Zr-girentuximab PET detected lesions in 27 of 29 pts. Compared to ceCT, 89Zr-girentuximab PET visualized additional lesions in all organ sites. Location was strongly related with 89Zr-girentuximab uptake; highest uptake in kidney and adrenal gland tumor (mean SUVmax 63.2 and 70.3, resp) and lowest uptake in lung and lymph nodes (mean SUVmax 10.9 and 15.0, resp). After correction for location, no relation was observed between 89Zr-girentuximab SUVmax and tumor size, as measured by ceCT, and 18F-FDG SUVmax.

Conclusions: 89Zr-girentuximab and 18F-FDG PET visualize additional lesions compared to ceCT, however correlation was poor. The addition of 89Zr-girentuximab or 18F-FDG PET might aid in deciding to either delay or start systemic treatment.

Clinical trial identification: NCT02289554.

Legal entity responsible for the study: Radboud University Medical Center (Radboudumc).

Funding: Supported by the Dutch Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

**889P**

**Clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin inhibitors (mTORI) after immuno-oncology (IO) checkpoint inhibitors**


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**Background:** In an era of increasing treatment options for mRCC, optimal treatment sequence after IO therapy has not been well established. This study compares the effect of targeted therapy (TT) (VEGFR TKI [axitinib, sunitinib, cabozantinib, pazopanib, bevacizumab, and sorafenib] vs mTORI [everolimus and temsirolimus]) after progression on IO therapy.

**Methods:** Data were obtained from 7 international mRCC Database Consortium (IMDC) centers were used to examine time to first treatment discontinuation (TTD) time from TT initiation to discontinuation for any reason) and objective response rate (ORR: complete or partial tumor response) among mRCC patients (pts) treated with TT after IO between 2010-2018. Kaplan Meier analysis and Cox proportional hazards model adjusting for age, sex, IMDC risk score, and line of therapy were conducted. Overall survival will be reported when data is more mature.

**Results:** pts treated with VEGFR TKI (N = 156 [85%]) and mTORI (N = 28 [15%]) post IO had similar age and IMDC risk scores (mean age 61 vs 63 years; IMDC favorable: 5% vs 8%; IMDC intermediate: 62% vs 48%). Most common TT post IO were axitinib (35%), sunitinib (18%), and cabozantinib (15%). Unadjusted median TTD was significantly longer for VEGFR TKI vs mTORI (5.3 vs 2.5 months, p = 0.002). ORR was numerically higher in VEGFR TKI vs mTORI. Reported results are across all lines of therapy. The table has descriptive statistics.

| Table: 889P Descriptive statistics of clinical outcomes among patients treated with targeted therapy (i.e., VEGFR TKI, mTORI) subsequent to IO treatment |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Total N         | Number of treatment dis- | Median TTD, (95% CI) months | Objective response rate¹ |
|                                |                 | continuation (%)         |                               | N (%)                   |
| All                            | 156             | 118 (64)               | 4.9 (4.0, 5.6)                | 20 (17)                |
| By class                       |                 |                 |                               |                        |
| VEGFR TKI                      |                 |                 |                               |                        |
| All lines                      | 156             | 93 (60)              | 5.3 (4.3, 6.9)               | 19 (20)                |
| 2nd line                       | 44              | 28 (64)              | 3.8 (2.5, 5.4)               | 7 (23)                 |
| 3rd line                       | 72              | 43 (60)              | 5.7 (4.9, 9.9)               | 10 (22)                |
| ≥ 4th line                     | 40              | 22 (55)              | 6.1 (4.2, 10.9)              | 2 (10)                 |
| mTORI                          |                 |                 |                               |                        |
| All lines                      | 28              | 25 (89)              | 2.5 (1.4, 3.4)               | 1 (5)                  |
| 2nd line                       | 0               | -                   | -                             | -                      |
| 3rd line                       | 20              | 19 (95)              | 2.3 (1.0, 4.9)               | 1 (6)                  |
| ≥ 4th line                     | 8               | 6 (75)               | 3.2 (1.3, 4.9)               | 0 (0)                  |

**Conclusion:** Subsequent to IO therapy, VEGFR TKI pts had significantly longer adjusted TTD than mTORI pts. When larger sample sizes are available for TT, further examination of sequences is warranted.

**Legal entity responsible for the study:** Pfizer, Inc.

**Funding:** Pfizer, Inc.

**Disclosure:** R. McKay: Research funding: Pfizer and Bayer; Ad board: Janssen, Novartis. U.N. Vaishampayan: Research funding, Honoraria, and Consulting: Pfizer. A. Hansen: Research funding: Genentech/Roche, Merck, GlaxoSmithKline, Bristol Myers Squibb, Novartis; Advisory board: Pfizer, Roche, Merck, AstraZeneca, Ipsen, Bristol Myers Squibb. F. Donskov: Research funding: Pfizer, Novartis, Ipsen. G.A. Bjarnason: Research funding: Pfizer, Merck, Honoraria; Pfizer, Novartis, Bristol-Myers Squibb, Eisai, Ipsen; Travel funding: Pfizer, Novartis. B. Bruselinck: Research funding: Pfizer; Speaker’s fee: Ipsen, AstraZeneca, Roche. G. De Velasco: Research funding: Ipsen; Consulting or advisory role: Janssen, Pfizer, Novartis, Bayer, Astellas Medivation, Bristol-Myers-Squibb, Pierre Fabre. M.S. Duh, L. Huynh: M. Duh R. Chang: Employer of Analysis Group, which received funding from Pfizer for this project. J. Graham, K. Ramaaswamy: Employee of Pfizer. T.K. Choueiri: Research funding: AstraZeneca, BMS, Exelixis, Genentech, GSK, Merck, Novartis, Peloton, Pfizer, Roche, Tracon, Eisai; Consulting and Advisory Role: AstraZeneca, Bayer, BMS, Celgene, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, GlassmunkLine, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Ipsen. D.Y.C. Heng: Consultancies and Honoraria: Pfizer, Novartis, BMS, Ipsen. All other authors have declared no conflicts of interest.
Background: Novel therapies are needed as an initial or salvage treatment for patients with metastatic or locally advanced RCC. This study aimed to assess the safety and efficacy of everolimus in patients with metastatic RCC and/or unresectable clear cell RCC.

Methods: EVERYMORE is an open-label, multicenter, single-arm, phase 2 study (NCT01206764) that enrolled patients aged ≥18 yrs with advanced and histologically confirmed clear or non-clear cell RCC. Everolimus 10 mg/d was administered orally, as a first line or after cytokine therapy, until disease progression (PD), unacceptable toxicity, or study discontinuation for any other reason. The primary endpoint was progression-free survival (PFS) rate over time. The secondary endpoints were disease control rate (DCR; stable disease + partial response [PR] + complete response [CR]), objective response rate (ORR), duration of response (DOR), overall survival (OS), and safety.

Results: From 2009 to 2017, 142 patients with a mean age of 55.5 years from 10 countries were enrolled. Most of the patients (38.2%) had a clear cell adenocarcinoma as histology/cytology and 53.1% had stage IV disease at initial diagnosis. Of 142 patients, everolimus was received in 117 as first-line and in 25 as second-line treatment. The most common reason for early discontinuation of treatment was PD (n = 88, 62.0%). The median PFS for all assessed patients was 7.0 months (95% CI: 22.0, 37.29). The ORR was 12.6% (95% CI: 7.1, 19.9%). The median DOR in patients who had either CR or PR was 39.0 months (n = 17). The DCR was 74.6% (n = 106; 95% CI: 66.7, 81.6). The median OS was not evaluable. The most commonly reported adverse events (AEs) of all grades were anaemia (45.3%), stomatitis (29.6%), hyperglycaemia (26.1%), and decreased appetite (22.3%). The most commonly reported serious AEs were pneumonia (n = 6), dyspepsia (n = 4), urinary tract infection, decreased appetite, dehydration and diarrhoea (n = 3 each). In the study, 33 deaths were reported, of which, 19 deaths were due to study indication.

Conclusions: The PFS and safety results of everolimus when administered in patients as first-line or after cytokine therapy are consistent with the previously published data (RECORD-3).

Clinical trial identification: NCT01206764.

Legal entity responsible for the study: Novartis Pharma AG.

Funding: Novartis Pharma AG.

Disclosure: D. Amokrane: Advisory board, Speaker or Grants for Clinical research: Novartis, Sanofi, Bayer, Ipen, Agena, Roche, Janssen, Pfizer MSD, Pierre Fabre. M. Ghoun: Grants-research support: Pfizer, Novartis. K. Slimane, V. Pilipovic: Employee and shareholder of Novartis. All other authors have declared no conflicts of interest.
sequences in mRCC, while adjusting for differences in patient characteristics using inverse propensity score weighting method (IPWS).

Methods: Data of mRCC patients treated using most common treatment sequences were collected in REMIS between 06/2007 and 02/2018. Overall survival (OS) and progression-free survival (PFS) were evaluated. Baseline characteristics were balanced using IPWS. The propensity score was evaluated with nominal logistic model to balance Eastern Cooperative Oncology Group (ECOG) performance status, time from diagnosis to first treatment, nephrectomy, Memorial Sloan-Kettering Cancer Center (MSKCC) score, and age. Median and confidence intervals (CI) were derived from IPWS weighted Kaplan-Meier curves that were compared using log-rank test.

Results: Overall, 745 patients in five treatment sequences were included and analysed. Differences in OS were significant (p < 0.001) with sunitinib—axitinib—everolimus and sunitinib—axitinib—everolimus associated with improved survival over other sequences. These differences could be also linked to time when these drugs were introduced. PFS did not differ between sunitinib and pazopanib used as first line treatments (p = 0.44) but the PFS in the second line differed significantly (p = 0.035) (Table). Table: Results of OS and PFS for examined sequences computed using inverse propensity score weighting. Sunitinib—Axitinib—Everolimus sequence should be assessed with caution due to immortal time bias.

Conclusions: Improved outcomes were associated with sequences using second-line axitinib over those using second-line sunitinib or everolimus in a cohort of patients from a national registry.

Legal entity responsible for the study: Jindrich Finek.
Funding: Value Outcomes.

Disclosure: J. Finek: Honoraria: Amgen, BMS, Roche, Bayer, Teva, MSD, Merck, Sanofi, Pierre Fabre. R. Demlova: Honoraria for lectures: K. Kopeckova: Honoraria for lectures: Novartis; Travel grants: Pfizer, Bayer. T. Buchler: Honoraria for advisory boards and/or lectures: Novartis, Pfizer, Roche, B. Melichar: Honoraria for advisory boards and/or lectures: Novartis, Pfizer, Glaxo Smith Kline, Roche, Bayer. A. Poprach: Honoraria for lectures: Novartis, Bristol-Myers Squibb, Roche, Bayer. T. Hrıciarova, T. Milcoch, T. Doležal: Employee of Value Outcomes. All other authors have declared no conflicts of interest.

Table: 892P

<table>
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<tr>
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<th>n</th>
<th>Median</th>
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<tr>
<td></td>
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<td>Lower limit</td>
<td>Upper limit</td>
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<tr>
<td>OS (months)</td>
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<td>312  26.3</td>
<td>23.8</td>
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<td>Everolimus†</td>
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<td>Everolimus†</td>
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<td>PFS 1st line (months)</td>
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<td>10.8</td>
<td>0.440</td>
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<td>Pazopanib</td>
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Table: 893P

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<tr>
<td>Age</td>
<td>Median (range)</td>
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<tr>
<td>Histology</td>
<td>Clear Cell Papillary Other</td>
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<tr>
<td>IMDC Risc Category</td>
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<tr>
<td>Nephrectomy</td>
<td>Yes No</td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td>1.2 ≥17 (13) 66 (50) 14 (11) 19 (15) 47 (37)</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td>Lung Lymph node Bone Liver Brain Pleura/Peritoneal Other</td>
</tr>
<tr>
<td>Visceral and bone M1 spread</td>
<td>All patients with visceral M1 Both Visceral + bone M1 Visceral M1 without bone M1</td>
</tr>
<tr>
<td>Previous lines of therapy</td>
<td>1 2 ≥3</td>
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<tr>
<td>Duration of 1st VEGFR TKI</td>
<td>≤6 months &gt;6 months</td>
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<tr>
<td>1st subsequent treatment (N = 21)</td>
<td>Nivolumab Axitinib Everolimus Others</td>
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<td>PD-1/PDL1 inhibitors prior to Cabo</td>
<td>Nivolumab PD1/PDL1-VEGFR combo</td>
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</table>

Background: Cabozantinib demonstrated increased efficacy over everolimus in patients with mRCC progressing on VEGF targeted therapy in the randomised phase III METEOR trial. We report real world experience with Cabozantinib in 7 centres across the UK.

Methods: In this retrospective study, patients who started Cabozantinib from September 2016 to September 2017 within the UK EAP were included. Patients had mRCC progressing after at least 1 prior systemic treatment, PS 0-2 and adequate organ function. The goal was to analyse toxicities, efficacy and access to other drugs after progression.

Results: 128 patients were included. Median follow-up was 10.5 months. Median age was 62 years. 84% had clear cell histology, and 49% were classified as intermediate risk by IMDC score. 87% had visceral M1 and 52% bone M1. Patients received a median of 2 previous lines of therapy (1-6). Cabozantinib was used as 2nd line, 3rd line and 4th line or beyond in 56 (44%), 38 (30%) and 34 (26%) patients respectively. Baseline characteristics are summarized in the table. 48 (37%) of the patients developed G3/4 AEs, mainly fatigue (N = 14, 11%), diarrhoea (N = 12, 9%), mucositis (N = 7, 5%) and hand-foot syndrome (N = 6, 5%). No treatment-related deaths were seen. 71 patients (55%) required dose reductions. 12 (15%) discontinued Cabozantinib due to toxicity. Median OS was 9.1 months (95% CI 6.1-11.6), being 14.3 vs 9.3 vs 6.0 months for good, intermediate and poor prognostic patients, respectively (p = 0.01). Median PFS was 7.7 months (95% CI 5.3-10.1). Partial response to Cabozantinib was 26%, stable disease 24%, Progressive disease 30% and was not evaluated in 20%. Only 21/81 patients (26%) stopping Cabozantinib started on subsequent treatment.

Conclusions: Cabozantinib was safe and active in pretreated patients with mRCC.

Legal entity responsible for the study: Alfonso Gomez de Liano.
Funding: Has not received any funding.

Disclosure: S. Symeonides: Research funding: Merck Sharp & Dohme. T. Powles: Advisory role and research funding: Roche, AstraZeneca. All other authors have declared no conflicts of interest.
Disclosure: All authors have declared no conflicts of interest.

Legal entity responsible for the study: City of Hope.

End on treatment (range 5-16 m). Most pts (72%, n = 263) are alive, with median OS not reached (95% CI: 18.7-31.2) in patients with high BMI (P = 0.33).

Conclusions: High BMI was associated with improved OS in patients with mRCC treated with VEGF-TKI or VEGF/IO, but the inverse trend was observed among patients receiving IO. In addition to validating previous findings associating VEGF-TKI, BMI and clinical outcome, our data highlight the need to reassess this phenomenon in the context of IO-based regimens.

Legal entity responsible for the study: City of Hope.

Disclosure: Has not received any funding.

All authors have declared no conflicts of interest.

Background: VEGFR inhibition is a mainstay in the treatment of mRCC. In recent years third generation TKIs offer advantages in treatment efficacy while combinations further improve antitumor activity. To date, a LEN + EVE is approved based on a randomized phase 2 study in the second line setting. Data on activity and efficacy of this combination as ATL beyond second line is limited. We aimed to report the activity of LEN + EVE in mRCC patients (pts) treated per a national EAP.

Methods: Records from consecutive mRCC (pts) treated with LEN + EVE in ATL per a national EAP in 7 centers, were retrospectively reviewed. We report the clinical benefit, progression free survival (PFS), overall survival (OS), and toxicity.

Results: Between 11/2016 – 12/2017, 39 mRCC pts were treated with LEN + EVE. Median age 60 (39-82), male 72%. Majority of the pts (82%) underwent nephrectomy. Heng risk was high/intermediate in 13% (n = 5) (41%) (n = 16) (46%) (n = 18). According to the treating physician, 69% (n = 263) are alive, with median OS not reached (95% CI: 18.7-31.2) in patients with high BMI (P = 0.33).

Conclusions: LEN + EVE is an effective and manageable treatment option in metastatic renal cell carcinoma treated with systemic therapy.
**VOTRAGE study pazopanib in a population of “frail” elderly patients after geriatric assessment: A phase I study with geriatric criterion for DLT (2 points drop in Activity of Daily Living Score (ADL)).**

**Background:** Efficacy and toxicity of targeted therapies don’t seem to vary with age, but the impact of side effects in frail elderly patients (≥ 75 years-old) (EP) is a major concern for clinicians. Our study aims to explore an original method to find the maximum tolerated dose of pazopanib (P), in a population of EP, classified as “frail” after comprehensive geriatric assessment (CGA), using a phase I methodology, integrating a geriatric criterion for DLT (2 points drop in Activity of Daily Living Score (ADL)).

**Pharmacokinetic and pharmacodynamic studies were planned.**

**Methods:** Open-label, multicenter (2), non-randomized, first phase escalation clinical trial (standard 3 + 3 design) to determine MTD and DLT of P in a population of EP, selected after CGA. Tested dose levels of P were 200, 400, 600 and 800 mg/day. Toxicity was assessed during the first cycle (21days). Maximum tolerated dose (MTD) was defined as the highest dose level for which 6 patients are treated with a maximum of one patient (≤20%) presenting a DLT. Main inclusion criterion - Age ≥ 75 years-old. Metastatic solid cancers (kidney, lung, pancreatic endocrine, sarcoma, ovary, thyroid, bladder or breast). - Frail by CGA.

**Results:** From 11/2012 to 09/2017, 18 pts were included. Median age was 82.5 (range 75-91). No DLT was reported at 400mg/day. There was 1 DLT (asthenia Grade 3) at 600 mg/day. 5/6 patients experienced a DLT. Two patients had treatment interruption longer than two weeks due to side effects and one experienced a grade 3 hypertension. Diarrhea, fatigue and hypertension were the most frequently treatment related toxicity.

**Conclusions:** Our study used an original way to assess feasibility of an approved treatment in population of frail EP (≥ 75 years-old). The results demonstrate that it is probably deleterious to initiate a treatment with P in this vulnerable population at the approved dose level of 800mg/day. The treatment should be initiated at a lower dose (600mg/day). Our results reinforce the need to proceed to geriatric assessment in EP before initiation of cancer treatment to individualize their management.

**Clinical trial identification:** EudraCT. 2011-00112-29.

**Legal entity responsible for the study:** Institut Claudius Regaud.

**Funding:** None.

**Disclosure:** L. Mourey: Honoraria, travel expenses and research funding: Novartis. All other authors have declared no conflicts of interest.

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**A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABCASUR).**

**Background:** Atezolizumab is a PD-L1 inhibitor, which is licensed in metastatic urothelial cancer. This study investigates the efficacy and safety of neoadjuvant atezolizumab given prior to cystectomy in operable muscle invasive transitional cell carcinoma of the bladder.

**Methods:** This single arm phase 2 study investigated 2 cycles of atezolizumab (1200mg Q3W) pre- to cystectomy in muscle invasive transitional cell carcinoma (T2-IVM0).

**Pathological complete response (pCR) occurring in ≥ 20% of patients was the primary endpoint. Biomarker analysis on sequential tissue was a co-primary endpoint. Cross sectional imaging was performed at baseline and prior to cystectomy which occurred 4 - 8 weeks after starting atezolizumab. Radiological response was assessed.**

**Results:** At baseline PT2, T3, T4 disease occurred in 73%, 29% and 7% of patients respectively. 16 (21%) patients had only 1 cycle (9 due to AE). 7 patients did not have cystectomy (1 disease progression, 2 treatment related AE). There was 1 potential treatment related death during treatment/perioperative period (cardiovascular disease). Treatment related grade 3/4 toxicity occurred in 12% of patients. Grade 3 or 4 surgical complications occurred in 31% of pt. The pCR rate was 20/68 (29%) [95%CI: 19% to 42%] (GT0-4/4, Tis 6/6, T1N 0/24 T2 23% T3 15% T4 15% stage at surgery). 39% of patients were down staged to non-muscle invasive disease. 3/10 (15%) of the pCR patients had pT3N4 disease at baseline. 47% patients were positive for PD-L1 (≥5% IC SP142); pCR rates were 38% and 27% in PD-L1 positive and negative tumour respectively (n = 62). 47 patients had sequential imaging and radiologically measurable disease at baseline. 28% [95%CI: 16% to 43%] and 17% [95%CI: 8% to 31%] of these patients radiologically responded and progressively responded respectively.

**Conclusions:** Neoadjuvant atezolizumab is safe and associated with a meaningful pathological CR rate at this interim stage. Further exploration is justified.

**Clinical trial identification:** NCT02626309.

**Legal entity responsible for the study:** Queen Mary University of London.

**Funding:** I. Hoffmann - La Roche Ltd.

**Disclosure:** I. Duran: Consulting or advisory role: roche/Genentech, MSD Oncology, Bristol-Myers Squibb, Travel, accommodation, expenses: Roche/Genentech; Honoraria: Bristol-Myers Squibb, Ipsen, Roche/Genentech; Research funding: Roche/ Genentech (institutional). S.J. Grubb: Consulting or advisory role: Roche, Clovis Oncology, Bayer, Janssen-Cilag; Travel, accommodation, expenses: Bayer, Merck, Ipsen, Bristol-Myers Squibb, Roche, Janssen-Cilag. Honoraria: Novartis, Roche, Janssen-Cilag. Research funding: AstaZeneca, AstraZeneca Pharmaceuticals, Plexxikon, Clovis Oncology, M.S. van der Heijden: Consulting or advisory role (institution): Roche/Genentech, Astellas Pharma, AstraZeneca/MedImmune, Bristol-Myers Squibb; Travel, accommodation, expenses: Novartis, Astellas Pharma, MSD Oncology, Roche; Travel, accommodation, expenses: Novartis, Ipsen, Honoraria: Astellas Scientific and Medical Affairs Inc, Ipsen. C.N. Sternberg: Consulting or advisory role: Bristol-Myers Squibb, Novartis, Janssen, Bayer, Eisai, MSD, Lilly, Clovis Oncology, Ferring; Honoraria: Pfizer, Astellas Pharma, Sanofi, Ipsen, AstraZeneca. T.R. Powles: Consulting or advisory role: Roche/Genentech, Bristol-Myers Squibb, Merck, Novartis, AstraZeneca, Honoraria: Roche/Genentech, Bristol-Myers Squibb, Merck, Research funding: AstaZeneca/MedImmune, Roche/Genentech, Other relationship: Ipsen, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

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**Interim results of fight-201, a phase II, open-label, multicenter study of INCBO54828 in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) harboring fibroblast growth factor receptor (FGF)/FGF receptor (FGFR) genetic alterations (GA).**

**Background:** FGFR3 GA are implicated in the pathogenesis of UC; ≥ 15% of pts with advanced UC have mutations and ≥ 6% have translocations. INCBO54828, a selective, potent, oral inhibitor of FGFR2, 3, and 1, has shown efficacy in pts with FGF/FGFR GA tumors.

**Methods:** This study (NCT02872714) is enrolling pts with metastatic or unresectable UC who failed ≥ 1 therapy or are platinum ineligible and have FGFR3 mutations/fusions (cohort A, n = 100) or other FGF/FGFR GAs (cohort B, n = 40). Pts receive oral INCBO54828 13.5 mg once daily on a 21-day cycle (2 wk on, 1 wk off) until disease progression/untreatability or unacceptable toxicity. This interim analysis is based on first 20 pts (9 A, 11 B).

**Funding:** Astellas Pharma Worldwide Oncology R&D, F. Hoffmann-La Roche, Ltd., MSD, Roche, Bristol-Myers Squibb, Clovis Oncology, AstraZeneca, Merck, Sanofi, Lilly, F. Hoffmann-La Roche Ltd.


**Notes:** For additional information please visit www.fight201.com.
Abstracts of Annals of Oncology Volume 29 | Supplement 8 | October 2018

Impact of prognostic factors and risk groups on overall survival (OS) in patients treated with pembrolizumab vs investigator’s choice chemotherapy for advanced urothelial cancer (UC): Post hoc analysis of KEYNOTE-045


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Background: Well-defined prognostic factors (PF) and risk groups have been shown to impact OS in first- and second-line chemotherapy (chemo) for UC. Post hoc analysis of survival outcome per level of risk was conducted using data from the phase 3 KEYNOTE-045 trial (NCT02256436).

Methods: Data from the Oct 26, 2017 data cut were included. The presence or absence of 4 predefined criteria applied at study randomization was noted for each patient: ECOG PS (0 vs 1 or 2), hemoglobin level (<10 g/dL vs ≥10 g/dL), liver metastases (yes vs no), and time from prior chemotherapy (<3 months vs ≥3 months). Patients were grouped by the number of PFs they had (0, 1, 2, 3/4), and OS was estimated for each risk group receiving pembrolizumab (pembro) or chemo, using Kaplan-Meier (K-M) statistics.

Results: Data from 529/542 patients were included. Stratified randomization ensured that the distribution of risk levels was similar between the 2 treatment arms. Overall, OS decreased with increasing numbers of PFs for pembro (from 19 to 5 months) and chemo (from 18 to 3 months) (Table). Within the chemo arm, the results of the K-M survival profiles were consistent with previously published data, in which each risk group had different outcomes. Within the pembro arm, outcomes of pts with 0 and 1 PF were distinct from those with 2 and 3/4 PF groups. OS was longer with pembro than with chemo across all PF subgroups.

Conclusions: OS within the pembro and chemo arms decreased with increasing numbers of PFs. OS of patients treated with pembro was longer than those receiving chemo across the risk groups. Patients treated with pembro who had 2 or 3/4 PFs had overall similar outcomes. Additional analyses are needed to characterize novel risk models for patients treated with immunotherapies.

Clinical trial identification: NCT02256436, trial initiation date: October 3, 2014.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Grywacz, PhD, of the ApolloCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

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

Funding: Merck & Co., Inc.

Background: mUC arising from UTUC vs LTUC may involve distinct biology resulting in different treatment responses & outcomes. However, this hypothesis has not been studied in different settings. In the French GETUG consortium (Clinical trial identification: NCT02108652, NCT02302807), we explored the relationships between UTUC/LTUC primary tumor site, objective response rate (ORR)/overall survival (OS) & biomarker status.

Methods: From 1992 to 2017, we reviewed 234 NCUB cases (84% male, age 31–93 mo). Clinical characteristics, disease staging, treatments, progression, progression-free survival (PFS), and OS were obtained from medical records. Tissue samples were pooled for further biological analyses.

Results: Of 234 NCUB cases, 220 IMvigor210 & 339 IMvigor211 pts were efficacy evaluable (Table), of whom 35% had UTUC. Median OS (mo) 10.3 versus 11.7 for IMvigor210 & IMvigor211, respectively. ORR was numerically higher in IMvigor210 compared to IMvigor211 (13% vs 18%). For UTUC vs LTUC, ORR was numerically higher in UTUC (13% vs 10.9%). No differences were observed in terms of OS between UTUC vs LTUC. UTUC pts were older and had more frequent lower urinary symptoms (hematuria, pain) at diagnosis than LTUC pts. UTUC pts were more commonly diagnosed with diploid tumors, whereas higher proportions of IGT and elevated expression of activation receptor 1 (CD137) were observed in LTUC pts. Oligonucleotide microsatellite instability (OSI) was more frequent in UTUC vs LTUC.

Conclusions: Our data suggest pts with UTUC may have improved outcomes with atezolizumab compared to pts with LTUC, although benefit was observed in both groups. Numerically higher ORR/OS in pts with platinum-treated UTUC may be partly related to non-overlapping underlying biology & warrants further study in different settings.

Table: 902P

<table>
<thead>
<tr>
<th>UTUC</th>
<th>LTUC</th>
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<tbody>
<tr>
<td>IMvigor210 (n = 220)*</td>
<td>IMvigor211 (n = 339)*</td>
</tr>
<tr>
<td>n</td>
<td>52</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>13</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*Biomarker-evaluable pts from overall cohorts of 310 pts (IMvigor210 cohort 2) & 467 pts (IMvigor211). P values in the abstract are shown for descriptive purposes only based on this post hoc analysis.

Clinical trial identification: NCT02108652, NCT02302807.

Editorial acknowledgement: Medical writing support provided by Paige S. Davies, PhD, of Health Interactions.

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

Funding: F. Hoffmann-La Roche AG.


903P Neuroendocrine carcinoma of the urinary bladder: A large analysis of the French GETUG consortium

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Background: Neuroendocrine carcinoma of the urinary bladder (NCUB) is a rare malignancy, accounting for <1% of bladder cancers. Despite high sensitivity to platinum-based chemotherapy (CT), prognosis remains poor.

Methods: We retrospectively reviewed patients treated for NCUB in 18 French institutions to determine clinical/biological characteristics, treatment efficacy and outcomes. Patient characteristics, treatment, follow-up and histological data were obtained from medical records. Tissue samples were pooled for further biological analyses.

Results: From 1992 to 2017, we reviewed 234 NCUB cases (84% male, age 31–93 mo; median 67 years), ECOG PS 0–3 (median 1). Small cell carcinoma was found in 47% of patients, and large cell carcinoma in 9% of urothelial carcinoma. In our series, 51% of patients had one or more metastases. The most frequent sites of metastatic disease were lymph nodes (76%), liver (42%), bone (42%), pelvic recurrence (33%), lung (19%) or brain (12%). Of 230 patients evaluable for staging at diagnosis, 168 had stage I-II disease; stage I (3%), IIB (20%), III (34%), not evaluable (16%). They were treated with neoadjuvant CT (49%), mainly based on a
platinum-based agent + etoposide (85%), surgery (74%), radiotherapy (24%), and/or adjuvant CT (24%). Ninety-nine patients (99%) had metastatic recurrence. Median time to relapse was 4 months, disease-free survival was 14 months (99% confidence interval (CI) 12−16), and median overall survival (mOS) was 28 months (99% CI 20−32). COX2 patients (27%) with metastases at diagnosis, first-line CT was based on platinum + etoposide (81%), platinum + other drug (15%), or taxanes (4%). For these patients, median progression-free survival (mPFS) was 7 months (95% CI 3−9). Only 28 patients had second-line CT with mPFS of 5.2 months and mOS of 11 months (95% CI 8−15).

Conclusions: This is, to our knowledge, the largest cohort of NCUB patients studied to date. Data emphasize the heterogeneity and aggressiveness of this disease. Future studies should investigate disease biology and the activity of targeted therapies in NCUB. Molecular characteristics based on tumor tissue analysis are underway.

Legal entity responsible for the study: HEKP (European Georges Pompidou Hospital).

Funding: Pierre Fabre.

Disclosure: All authors have declared no conflicts of interest.

Impact of different programmed cell death ligand-1 (PD-L1) expression algorithms on patient selection and durvalumab efficacy in urothelial carcinoma (UC)

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Background: Antibodies targeting programmed cell death 1/PD-L1 (PD-L1) have shown clinical activity in advanced UC. The ability of PD-L1 to predict response has been investigated using different antibody clones and scoring algorithms. It is important to understand if these assays/algorithms identify the same patients and how they compare in predicting response.

Methods: Archival UC tumour samples from 335 patients from a commercial source were stained with VENTANA SP263, VENTANA SP142, PD-L1 IHC pharmDX 28-8 and PD-L1 IHC pharmDX 26C3 Assays; classified according to their respective algorithms: tumour cell (TC) or immune cell (IC) staining (≥25%) and PD-L1 staining IC area (≥5% of tumour (IC ≥ 5%), TC staining ≥1% or combined positive score (CPS >10)). Overlap between populations was assessed by overall percent agreement (OPA), negative percent agreement (NPA) and positive percent agreement (PPA). UC samples from study 1108 (NCT01693562) were stained using VENTANA SP263 and TC/IC ≥ 25%, IC ≥ 5% and CPS >10 algorithms were applied. (Objective response rate (ORR), data cutoff Oct 2017) in patients classified as PD-L1 high or low by these algorithms were investigated.

Results: There was moderate overlap between populations identified by VENTANA SP263 (TC/CIC ≥ 25%) and PD-L1 IHC pharmDX 28-8 (TC ≥ 16%) or PD-L1 IHC pharmDX 26C3 (CPS ≥ 10) and minimal overlap between VENTANA SP263 (TC/CIC ≥ 25%) and VENTANA SP142 (IC ≥ 5%) (Table). Applying different algorithms to data from study 1108 also gave differences in patient classification. ORR in patients determined as PD-L1 high vs low-negative were as follows: TC/CIC ≥ 25%: 28% vs 6%, IC ≥ 5%: 15% vs 2%, CPS >10% vs 14%.

Conclusions: The TC/IC ≥ 25% algorithm identifies a different population to IC ≥ 5% or CPS. In CD-ON MEDI4736-1108, highest response rates were seen in PD-L1 high patients determined by IC ≥ 5%, whereas TC/CIC ≥ 25% was optimal in predicting non-responders to durvalumab.

Table: 904P Overall (OPA), negative (NPA) and positive percent agreement (PPA) between PD-L1 assays

<table>
<thead>
<tr>
<th>Clinical Algorithm (assay)</th>
<th>VENTANA SP263 (TC/CIC ≥ 25%)</th>
<th>OPA</th>
<th>PPA</th>
<th>NPA</th>
</tr>
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<tbody>
<tr>
<td>PD-L1 IHC pharmDX22C3</td>
<td>77.0% (72.9%) 90.7% (85.0%)</td>
<td>69.6% (64.0%)</td>
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<tr>
<td>PD-L1 IHC pharmDX26C3</td>
<td>81.5% (77.6%) 67.2% (54.8%)</td>
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<tr>
<td>TC/IC ≥ 1% PD-L1 IHC</td>
<td>75.5% (71.3%) 66.9% (59.1%)</td>
<td>80.2% (75.2%)</td>
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<tr>
<td>IC ≥ 5% VENTANA SP142</td>
<td>69.9% (65.5%) 65.3% (59.1%)</td>
<td>96.6% (97.8%)</td>
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</tr>
</tbody>
</table>

*For each metric, lower boundary of 95% confidence interval (CI) was calculated with no upper bound using the Clopper-Pearson method.

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Clinical trial identification: CD-ON MEDI4736-1108 NCT01693562.

Legal entity responsible for the study: AstraZeneca.


905P CD103+ tissue-resident CD8+ T Cells correlate with protective anti-tumoral immune responses in muscle-invasive bladder cancer patients

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Background: CD103+ Tissue-resident CD8+ T cells are previously reported as memory CD8+ T cells and thus could promote adaptive immune response. While immune-therapy shows a great potential in muscle-invasive bladder cancer (MBIC) treatment, it is urgent to discover which subgroup MBIC patients could benefit most from immune-therapy. We here tried to explore the prognostic and predictive value of CD103+ tissue-resident CD8+ T cells, and provide possible molecular explanations.

Methods: We selected 259 MBIC patients who underwent radical cystectomy between 2002 and 2014. CD103+ tissue-resident CD8+ T cells were evaluated via immuno-fluorescence of CD103 and CD8 and performed in our constructed tissue microarrays. Prognostic value of CD103+ CD8+ T cells in MBIC was assessed, and was further validated in TCGA-BLCA cohort using tissue-resident CD8+ T cell core signatures. 10 fresh MBIC specimens were analyzed by flow cytometry to explore the anti-tumoral immune response and immune check-point expression of tissue-resident CD8+ T cell.

Results: Patients with higher CD103+ tissue-resident CD8+ T cells infiltration had a significant better overall survival in both our study population and TCGA-BLCA cohort (HR = 0.504, 95%CI: 0.312−0.816, P = 0.005 and HR = 0.637, 95%CI: 0.444−0.913, P = 0.014). Further Cox regression indicated that CD103+ tissue-resident CD8+ T cells was an independent prognosticator in MBIC patients. Flow cytometry results revealed that CD103+ CD8+ T cells tended to express more IFN-γ and granzyme B than CD103− CD8+ T cells (P < 0.001 and P = 0.007, respectively) (n = 10). However, expression of perforin did not show significant differences between CD103+ CD8+ T cells and CD103− CD8+ T cells. We then analyzed PD-L1 and TIM3 expression in CD103+ tissue-resident CD8+ T cells. Surprisingly, there was no significant differences of PD-L1 expression between CD103+ CD8+ T cells and CD103− CD8+ T cells. Nonetheless, CD103+ CD8+ T cells had more TIM-3+ phenotypes than CD103− CD8+ T cells (P = 0.034).

Conclusions: High CD103+ tissue-resident CD8+ T cells could predict better prognosis in MBIC patients. Patients with high infiltration of CD103+ tissue-resident CD8+ T cells might benefit most from anti-TIM3 immunotherapy.

Legal entity responsible for the study: Dai, Bo.

Funding: National Natural Science Foundation of China; Shanghai Municipal Natural Science Foundation; Shanghai Municipal Commission of Health and Family Planning Program; Guide Project of Science and Technology Commission of Shanghai Municipality; Shanghai Cancer Research Charity Center.

Disclosure: All authors have declared no conflicts of interest.

906P Immune-checkpoint inhibitors in previously treated patients with urachal carcinoma: A systematic review and meta-analysis

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Background: Very few therapeutic options are available in patients with advanced or metastatic urachal carcinoma progressed or unfit to platinum based therapy. After decades of failures, a new classes of agents: the immune-checkpoint inhibitors seem to be a new promising hope for these patients. However, to date of the two randomized studies comparing these compounds to standard chemotherapy only one trial showed a clear survival advantage in this setting.

Methods: We performed a systematic review and meta-analysis to assess the efficacy, in terms of overall survival, of single agent immune-checkpoint inhibitors vs. single agent chemotherapy as second-line treatment. Moreover, we evaluated the assessed ORR of single-agent immune-checkpoint inhibitors in patients with advanced urachal cancer exploring the predictive value of patients’ selection according to PD-L1 expression. To do this, we reviewed clinical trials published on PubMed/Medline, Cochrane library and clinical abstracts presented on main International meeting between 2014 and 2018.
**Results:** Systematic review included randomized (n = 2) and non-randomized (n = 4) clinical trials. We restricted meta-analysis to trials exploring immune-checkpoint inhibitors in previously platinum-treated patients. In randomized trials, immune-checkpoint inhibitors were associated with a significant improvement of overall survival compared to chemotherapy in unselected patients, with pooled Hazard Ratio 0.80 (95% confidence interval 0.69 – 0.93, p = 0.003), while the difference was not statistically significant in the subgroup of patients selected for the best PD-L1 expression (Hazard Ratio 0.72, 95% confidence interval 0.48 – 1.09, p = 0.12). Pooled probability of objective response was 0.18 (95% confidence interval 0.16 – 0.20) in unselected patients and 0.27% (95% confidence interval 0.25 – 0.32) in patients selected for the best expression of PD-L1.

**Conclusions:** Immunotherapy showed a significant survival advantage in patients not selected for PD-L1 expression while both OS and ORR analysis suggested that the predictive value of PD-L1 expression is far from being optimal.

**Legal entity responsible for the study:** Francesco Massari.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**907P** Match-adjusted indirect comparison of durvalumab and chemotherapy for locally advanced or metastatic urothelial carcinoma (UC) following failure of platinum-based therapy

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**Background:** Durvalumab gained FDA approval for locally advanced or metastatic UC following failure of platinum-based chemotherapy (CTx) based on the open-label, single-arm study 1108. Real-world evidence can be used to enable comparative analyses by matching patients’ baseline characteristics from independent datasets. Overall survival (OS) of patients on durvalumab vs CTx was evaluated by comparing patients in the phase I/II study 1108 (NCT01693562) with a real-world dataset.

**Methods:** Data from patients on durvalumab were compared with data from patients in the Flatiron oncology electronic medical record database treated with physician’s choice of 2nd line CTx. All patients had progressed following platinum-based CTx. Patients were matched on propensity score to adjust for differences in baseline demographics and disease characteristics. Treatment effect for OS was estimated using Cox proportional hazards models. Prognostic impact of expression of programmed cell death ligand-1 (PD-L1) (>25% tumour cells [TC]/immune cells [IC]) [high] < or = 25% TC/IC [low/negative]) on OS was also evaluated. As PD-L1 expression was only available for patients in study 1108, PD-L1 subgroups were compared to otherwise-matched CTx patients.

**Results:** After adjustment for baseline differences between the 2 groups, durvalumab demonstrated a statistically significant improvement in OS vs CTx (n = 158/arm; HR = 0.634, 95% CI 0.479–0.839; median OS 11.2 vs 8.19 months). Treatment effect of OS for durvalumab was 41.5 months for patients with PD-L1 high (n = 91/arm; HR = 0.434, 95% CI 0.292–0.645; median OS 19.9 vs 7.84 months) vs matched CTx patients. There was no significant difference in OS for the PD-L1 low/negative subgroup for durvalumab vs CTx (n = 74/arm; HR = 0.989, 95% CI 0.679–1.440; median OS 4.86 vs 7.20 months).

**Conclusions:** This indirect, match-adjusted comparison of durvalumab vs CTx suggests that durvalumab provides a statistically significant improvement in OS vs CTx for patients with locally advanced or metastatic UC who progressed after platinum-based CTx. Treatment effect was more pronounced in the PD-L1 high subgroup vs the PD-L1 low/negative subgroup.

**Clinical trial identification:** CD-ON-MED4736-1108 (NCT01693562).

**Editorial acknowledgement:** Editorial support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Anne-Marie Manwaring of Parexel, and was funded by AstraZeneca.

**Legal entity responsible for the study:** AstraZeneca.

**Funding:** AstraZeneca.


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**908P** Comparative effectiveness of neoadjuvant chemotherapy followed by cystectomy versus cystectomy followed by adjuvant chemotherapy versus palliative chemotherapy for cystectomy for node-positive bladder cancer: A retrospective comparative effectiveness study

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**Background:** In the AJCC 7th edition, bladder cancer with lymph node metastasis is classified into stage IV regardless of the extent or number of lymph node metastases. T1a-T4a, N1, and M0 were changed to stage IIIB, and T1a-T4a, N2-N3, and M0 were changed to stage IIIB in the AJCC 8th edition revised in 2018. Therefore, it is necessary to think about treatment strategy for clinically node positive bladder cancer. The aim of this study was to compare the treatment outcomes of chemotherapy and surgery, and combination therapy in patients with lymph node-positive bladder cancer.

**Methods:** From January 01, 2010 to December 31, 2015, patients with bladder cancer with clinically local lymph node metastasis at the time of diagnosis and were treated with neoadjuvant chemotherapy followed by cystectomy or cystectomy followed by adjuvant chemotherapy or palliative chemotherapy or cystectomy were retrospectively analyzed based on the clinical indices and survival time based on the medical record review.

**Results:** Of 230 patients with bladder cancer, 44 (19.1%) were treated with palliative chemotherapy, 103 (43.6%) with neoadjuvant chemotherapy followed by cystectomy, 129 (39.6%) with cystectomy followed by adjuvant chemotherapy, and 27 (11.7%) with chemotherapy alone. Median survival was 4.3 months in the neoadjuvant chemotherapy group, median OS was 19.3 months. Median OS for neoadjuvant chemotherapy followed by cystectomy was 49.1 months and for cystectomy followed by adjuvant chemotherapy was 42.6 months. Cystectomy show 11.2 months of median OS. The prognosis was different according to stage of lymph node in each groups (42.6 months for N1 vs 21.3 months for N2-N3), especially survival rate of cystectomy followed by adjuvant chemotherapy was good in T4a, N2-A1 stage.

**Conclusions:** This study is meaningful in understanding the actual clinical treatment patterns of lymph node - positive bladder cancer and comparing the results according to each group.

**Legal entity responsible for the study:** KCSC.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**909P** Plasma miR-371a-3p for detection of non-teratomatous viable germ cell tumor in testicular cancer

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**Background:** Active surveillance for CSI testicular cancer is currently based on serial radiological imaging and classic tumor markers (b-HCG, AFP, LDH). The management of borderline suspicious tumor markers negative enlaming nodes and non-neopteroplastic lymphadencentomy (RPLND). A blood-based approach to reliably identify patients with non teratoma viable GCT (NTVGC) would be valuable.

**Methods:** Plasma miR-371a-3p (miR371) of pts with GCT was analyzed by RT-PCR. Spike-in cel-mir-39-3p and miR-30b-3p as internal controls. miR-451a and miR-22a-3p
Increased risk of non-germ cell second cancer (SC) after cisplatin-based chemotherapy (CBCT) in 1-year testicular cancer (TC) survivors (TCS)


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Background: Previous studies have documented that TCS have a 1.7 to 3.5-fold increased risk of developing SC compared with an age-matched general population after chemotherapy (CT) and/or radiotherapy (RT), but no increased risk after surgery only. Previous studies lack treatment details, and/or include patients treated before the introduction of cisplatin.

Methods: All Norwegian 1-year TCS diagnosed with their first TC 1980-2009 and with no prior history of cancer (n = 5625), were identified through the Cancer Registry of Norway (CRN). Clinical parameters, including detailed information on all cancer treatment given initially and in case of a relapse, were extracted from medical records and linked with data from CRN. The TCS were categorized into treatment groups: Surgery only (24.8%), CT (43.9%), RT (27.4%) and CT and RT combined (CT + RT) (3.9%). Age-adjusted Cox regression models were performed to evaluate the impact of cancer treatment on the risk of SC, stratified according to decade of diagnosis.

Results: Median observation time was 16 years (IQR 10.9-23.8), during which 572 TCS (10.2%) were diagnosed with a non-germ cell SC. Median time to SC was 18.1 years (IQR 11.1-24.2). Overall, compared with surgery only, there was an elevated risk of SC after RT (Hazard Ratio (HR) 1.36, 95% CI 1.07-1.73) and RT + CT (HR 1.64, 95% CI 1.10-2.46). When excluding TCS with <10 years observation time, all treatment groups had increased risks for SC (CT: HR 1.57, 95% CI 1.14-2.16; RT: HR 1.77, 95% CI 1.31-2.35; RT + CT: HR 1.85, 95% CI 1.14-2.96). There was an increased risk for SC with increasing number of cisplatin-based CT (CBCT), significant for 4 cycles (HR 1.35, 95% CI 1.01-1.81) and ≥5 cycles (HR 1.69, 95% CI 1.06-2.70). The risk for bladder cancer increased after CBCT (HR 3.81, 95% CI 1.29-11.21) and RT (HR 2.93, 95% CI 1.00-8.60). RT + CT was associated with elevated risks for leukemia (HR 13.82, 95% CI 2.0-159.67) and cancers of the stomach (HR 6.79, 95% CI 1.60-28.70) and thyroid (HR 8.71, 95% CI 1.56-52.08).

Conclusion: Cytotoxic treatment increases the risk of SC in TCS. After CBCT, the risk significantly increases after ≥4 cycles. Long-term follow-up of TCS focusing on prevention and early detection of SC seem to be important.

Legal entity responsible for the study: Translational Cancer Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway

Funding: Helse Nord RHF

Disclosure: All authors have declared no conflicts of interest.
Germ cell tumors (GCTs) are extraordinarily sensitive to cisplatin (CDDP)-based chemotherapy. DNA damage represents one of the most important factors contributing to the toxic effects of CDDP-based chemotherapy. Previously, in a pilot study, we observed prognostic value of the DNA damage level in peripheral blood lymphocytes (PBLs) from chemo-naive GCT patients. This study was aimed to validate the prognostic value of the DNA damage level in PBL in chemo-naive, as well as chemotherapy pre-treated GCT patients.

Methods: PBLs isolated from 123 GCT patients (101 chemotherapy-naive and 22 chemotherapy pre-treated) baseline and before 2nd cycle of chemotherapy were included into this prospective study. The DNA damage levels in PBLs were evaluated by the Comet assay and scored as percentage of DNA in tail by the Metafer-MetaCyte analyzing software. The DNA damage level in PBL was categorized as ‘low’ or ‘high’ according to the cut-off level of 64%.

Results: The mean ± SEM (standard error of the mean) of the endogenous DNA damage level was 5.25 ± 0.64. Chemotherapy-naive patients with ‘low’ DNA damage levels at baseline had significantly better progression-free survival (PFS) (hazard ratio (HR) = 0.05 99%CI (0.02 – 0.17), P = 0.0001) and overall survival (OS) (HR = 0.00, P = 0.0002, no death occurred in patients with ‘low’ DNA damage level) compared to patients with ‘high’ DNA damage levels. In multivariate analysis, prognostic value of the DNA damage level in PBL was significantly associated with PFS and OS. Furthermore, there was significant correlation between the DNA damage level and response to treatment, non-pulmonary visceral metastases, number of metastatic sites, presence of mediastinal lymph node metastases and serum tumor markers level. There was no prognostic value of DNA damage level in PBL before 2nd cycle of chemotherapy and/or in pre-treated GCTs.

Conclusions: These data suggest that the DNA damage levels in PBLs of GCT patients are a novel prognostic marker timely identifying patients with poor outcome. We hypothesize that altered DNA damage level in PBLs could be induced by GCT’s similarly to cancer-related immunosuppression and is abolished by administration of chemotherapy.

Legal entity responsible for the study: Michal Mego.

Disclosure: All authors have declared no conflicts of interest.

914P Intermediate prognosis in metastatic germ cell tumors (IPGCT): Outcome and prognostic stratification


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Background: Germ cell tumor patients with intermediate prognosis (IPGCT) according to the IGCCCG classification represent a heterogeneous group exhibiting a variety of clinical features. We established a registry to identify prognostic markers to further characterize IPGCT.

Methods: A retrospective observational study was performed. Eligibility criteria were intermediate prognosis according to IGCCCG criteria, male age, ≥16 years. Patients were diagnosed from 1979 to 2014. Clinical characteristics were evaluated with uni- and multivariate analyses to detect new prognosticators. AFP and HCG were available in 83% and LDH levels in 72% of the cases, respectively. Overall survival (OS) was the primary endpoint.

Results: The database included n = 707 IPGCT with a median follow-up of 8.6 years (IQR: 14.4). First line cisplatin-based chemotherapy was administered to 701 patients (99%) and the 5-year OS rate was 87%. First diagnosis in the 1980s (n = 115), the 1990s (n = 118), and after 2000 (n = 434) were associated with 5-year OS rates of 81%, 85%, and 89%, respectively. Statistical analyses revealed AFP and LDH, but not HCG levels prior chemotherapy as prognosticators. A patient stratification according to AFP levels <1000 IU/ml (n = 360), 1000 to 2000 IU/ml (n = 77), >2000 to 5000 IU/ml (n = 93) >5000 IU/ml (n = 74) prior first course of chemotherapy, revealed a significant correlation between AFP levels and OS, associated with 5-year OS rates of 89%, 87%, 86% and 82%, respectively (p = 0.037). LDH levels prior chemotherapy also correlated with outcome, associated with five-year OS rates of 92% for <2 ULN (n = 289), 86% for ≥2 to 3 ULN (n = 91), 80% for >3 to 4 ULN (n = 37), and 78% for >4 ULN (n = 89), respectively (p = 0.011). In multivariate analysis cut-off values of AFP levels >6000 IU/ml (p = 0.036; HR 2.966) and LDH levels >2 ULN (p = 0.02; HR 2.121) or ≥3 ULN (p < 0.001; HR 2.505) were independent prognosticators for OS.

Conclusions: Prognostication according to LDH and AFP levels prior chemotherapy could offer a new approach to stratify IPGCT. The largest fraction of patients had AFP levels ≤2000 IU/ml and LDH ≤2 ULN associated with an outcome similar to the good prognosis category. These results need to be confirmed in the upcoming IGCCCG reclassification.

Legal entity responsible for the study: Christoph Seidel.

Disclosure: Has not received any funding.

915P Long term follow-up of the MRC TE23 randomized phase II trial of intensive induction chemotherapy (CBOP/BEP) in poor prognosis germ cell tumours (GCT) (CRUK/05/014; ISRCTN53643604)

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Background: Up to 50% of men with poor prognosis non-seminoma GCT die with standard BEP chemotherapy. An intensive regimen, CBOP/BEP (carboplatin, bleomycin, vinorelbine, cisplatin/BEP), met response targets in a phase II, multicentre, open-label, randomized trial (74% with complete response or partial response marker negative, 90% CI 61% to 85%; primary outcome). Here, we report long term outcomes and prognostic factors.

Methods: Patients with extrarenal GCT and IGCCCG poor prognosis features were randomised to 4xBEP or CBOP/BEP (2xCBOP, 2xBO, 3xBEP with bleomycin dose 15,000IU). Low-dose, stabilising chemotherapy prior to entry was permitted. This analysis focuses on progression-free survival (PFS), overall survival (OS) and toxicity (all secondary outcomes), and exploratory analysis of prognostic factors and the impact of marker decline (as defined in GETUG13).

Results: 89 patients (43 CBOP/BEP) were randomised. After median 63 months follow-up, 3-year PFS is 53.7% (95% CI 39.7% to 67.9%) for CBOP/BEP arm, 38.7% (24.7%, 52.4%) for BEP (HR 0.59 (0.33, 1.06), p = 0.079). 3-year OS is 65.9% (48.8%, 77.2%) and 58.5% (43.0%, 71.2%) respectively (HR 0.79 (0.41, 1.52), p = 0.49). 12-month toxicity was affected by subsequent treatments, with no clear differences between arms. There was no grade ≥3 toxicity in the CBOP/BEP arm. In multivariate models, use of pre-protocol chemotherapy was the only factor associated with poorer PFS (HR 0.99 (1.14, 3.81), p = 0.017). Mediastinal primary (HR 2.13 (1.02, 4.46), p = 0.045) and use of pre-protocol chemotherapy (HR 3.40 (1.74, 6.63), p < 0.001) were associated with poorer OS. Unfavourable marker decline, in 60 (70%) patients, was not associated with other prognostic factors, nor with long term outcomes (HR 0.82 (0.44, 1.53), p = 0.54 for PFS).

Conclusions: The trial was not powered to compare PFS and OS, but PFS results for CBOP/BEP are promising, and similar to the intensive arm of GETUG13. Impact on OS was less clear (and will be affected by subsequent therapy). Use of pre-protocol chemotherapy was associated with poorer outcomes. Future study in an international phase III trial is warranted.

Clinical trial identification: ISRCTN53643604.

Legal entity responsible for the study: Medical Research Council, UK.

Disclosure: Cancer Research UK (grant no CRUK/05/014).

Disclosure: R.A. Huddart: Stock or other ownership interests: Cancer Centre London LLP; Consulting or advisory role: MSD, Roche, Bristol-Myers Squibb; Speaker’s bureau: Roche, Elekta, Research funding: MSD, Elekta; Travel expenses: Roche, MSD. All other authors have declared no conflicts of interest.
**Table: 916P Summary results: EORTC QLQ-C30: Scores between treatment comparison intent-to-treat population (cycles 3-9)**

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<td>-1.17</td>
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<tr>
<td>Cognitive functioning</td>
<td>85.59</td>
<td>86.35</td>
<td>-0.76</td>
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<tr>
<td>Social functioning</td>
<td>83.10</td>
<td>85.31</td>
<td>-2.22*</td>
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<tr>
<td>Symptoms</td>
<td>(large values worse)</td>
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<tr>
<td>Fatigue</td>
<td>27.40</td>
<td>24.55</td>
<td>2.85</td>
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<tr>
<td>Nausea and vomiting</td>
<td>6.50</td>
<td>5.30</td>
<td>1.21</td>
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<tr>
<td>Pain</td>
<td>20.78</td>
<td>18.68</td>
<td>2.10</td>
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<tr>
<td>Dyspnea</td>
<td>14.36</td>
<td>14.04</td>
<td>0.32</td>
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<tr>
<td>Insomnia</td>
<td>20.71</td>
<td>20.89</td>
<td>-0.18</td>
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<tr>
<td>Appetite loss</td>
<td>12.21</td>
<td>7.74</td>
<td>4.47 *</td>
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<tr>
<td>Constipation</td>
<td>10.46</td>
<td>10.63</td>
<td>-0.17</td>
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<tr>
<td>Diarrhea</td>
<td>18.67</td>
<td>10.67</td>
<td>8.00 *</td>
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<tr>
<td>Financial difficulties</td>
<td>14.10</td>
<td>13.53</td>
<td>0.58</td>
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A repeated measures longitudinal analysis with an intercept term, and treatment, time, treatment by time, and baseline as covariate over all cycles. *P < 0.05

**Conclusions:** These analyses suggest that for pts who are able to tolerate SU for > 2 cycles (3 months), PRO profiles for SU are similar to PBO pts with similar discontinuation rates. Some pts do not tolerate SU early on, with higher discontinuation and dose reduction rates for SU than PBO, we describe a baseline reset analysis to assess the longitudinal PRO profile of pts who were able to tolerate and stay on treatment beyond the first 2 cycles (C).

**Methods:** After censoring the data from C1 and 2, and setting a new baseline at C3, the baseline reset analysis described here used the same statistical analysis done for PRO data in S-TRAC. For each scale, comparison of the two treatment arms was carried out using longitudinal repeated measures mixed effect model.

**Results:** Of the 615 pts enrolled in S-TRAC, 580 were included in the PRO analyses. Of these, 506 pts had PRO data at C3 and were included in this analysis. The longitudinal between treatment comparison resulted in statistically significant differences favoring PBO in 6 of the 13 scales with no clinically meaningful differences (> 10 points) (see Table). The discontinuation rates of the 2 treatment groups were comparable from C3 onward.
until 40 patients are enrolled. All patients will at baseline and weekly during treatment complete four e-questionnaires: EORTC QLQ-C30 & QLQ-BLM13, HADS, selected PRO-CTCAE™ questions and finally three general health questions. Reminders to complete the questionnaires are sent electronically to participants. The database will be monitored to ensure that all patients have an overview of the patients’ answers categorized into groups of severity. The overview is automatically incorporated into the electronic medical charts. The study will evaluate the feasibility of electronic reporting and describe toxicities, QoL, rate of completion and hospital admissions. The results of this study will contribute to the content of a randomized patient-reported outcomes study in the UC population initiated this autumn (2018).

Legal entity responsible for the study: Helle Pappot.

Funding: Danish Cancer Society.

Disclosure: All authors have declared no conflicts of interest.

Trial design: This open-label Phase 2 study will evaluate the efficacy and safety of PT2977, a highly selective small molecule inhibitor of HIF-2α, in patients with VHL disease who have at least 1 measurable ccRCC (as defined by RECIST 1.1). PT2977 will be administered orally at a dosage of 120 mg once daily. Key inclusion criteria include a genotypic HIF-2α alteration and at least 1 measurable solid ccRCC but no tumor > 3.0 cm that requires immediate surgical intervention. Patients may have VHL disease-associated tumors in other organ systems. Key exclusion criteria include prior systemic therapy for VHL disease and the history of metastatic disease, and history of a non-VHL disease-associated invasive malignancy in the past 2 years. The primary endpoint is objective response rate (ORR) of ccRCC tumors per RECIST 1.1. Secondary efficacy endpoints include duration of response (DOR), time to response (TTR), progression-free survival (PFS), and time to surgery (TTS) for ccRCC tumors as well as efficacy evaluations for non-ccRCC VHL disease-associated tumors. Safety/tolerability and pharmacokinetics of PT2977 will be evaluated. Patient recruitment is ongoing.


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

Background: In VHL disease, renal cell carcinomas (RCC) are known to be of clear cell histology (cCRC). HIF-2α has been established as an oncogenic driver in cCRC, where VHL deficiency is the underlying genomic alteration. In this setting of VHL gene inactivation, HIF-2α accumulates under normoxic conditions, driving the expression of genes associated with progression of cCRC, including vascular endothelial growth factor A (VEGFA), cyclin D1 and other factors that contribute to tumor growth and proliferation. Clinical management of VHL disease-associated renal tumors involves active surveillance until surgery is required for tumors larger than 3 cm to prevent metastasis. Repeated surgical procedures for tumors larger than 3 cm can carry significant morbidity. Systemic therapy options that can delay or obviate the need for surgery by reducing tumor size are needed.

Trial design: An open-label phase II study to evaluate the safety, efficacy, and antitumor activity of INCB054828 in patients with metastatic urothelial carcinoma (mUC) who have previously treated locally advanced or metastatic urothelial cancer (la/mUC).

Trial design: This is an open-label, single-arm, phase 2 study. Subjects will receive enfortumab vedotin at a dosage of 1.25 mg/kg twice weekly (Q2W) for 2 cycles, followed by once every 3 weeks (Q3W) for up to 1 year or until disease progression, intolerability, or other discontinuation criteria are met. The primary endpoint is overall survival (OS) of patients with mUC who respond to therapy, and overall response rate, as well as assessment of safety/tolerability, duration of response, and overall response rate, as well as assessment of safety/tolerability, duration of response, and overall response rate, as well as assessment of safety/tolerability, duration of response, and overall response rate, as well as assessment of safety/tolerability, duration of response, and overall response rate, as well as assessment of safety/tolerability, duration of response, and overall response rate, as well as assessment of safety/tolerability.


Legal entity responsible for the study: European Association of Urology Research Foundation.

Funding: Incyte Inc.

Disclosure: A. Necchi: Consultant role for Incyte Inc. W. Witjes: Employee of EAU-RF. All other authors have declared no conflicts of interest.

References:
- Background for ENL: Standard first-line treatment for patients (pts) with mUC is cisplatin-based chemotherapy or carboplatin-based chemotherapy for pts unfit for cisplatin. Recently, immune checkpoint inhibitors (ICIs) have become standard treatment options for pts who progressed during/after platinum-based chemotherapy or are ineligible for cisplatin. While some pts with mUC achieve durable responses with ICIs, only a minority respond. Following failure with CPI, no therapies are approved. Enfortumab vedotin (EV) is a fully humanized monoclonal antibody that delivers the microtubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, which is highly expressed in 90% of mUC patient samples (Pelton ASO 2017). In a phase 1 study (EV-101, NCT02919999), single-agent EV at the established recommended phase 2 dose of 1.25 mg/kg was generally well tolerated and demonstrated a confirmed objective response rate of 41% (n = 46/112) across the overall population, with overall survival (OS) of patients with mUC in pts with prior CPI therapy, confirmed ORR of 40% (n = 36/89) was observed.
- Trial design: EV-301 is a global, multicenter, open-label phase 3 trial (NCT03474107) enrolling adult pts with mUC and an ECOG score ≤1 who have received one prior platinum-containing chemotherapy, and have experienced disease progression during or following treatment with a CPI. Approximately 550 pts will be randomized 1:1 to receive EV 1.25 mg/kg (Arm A) or chemotherapy (Arm B); randomization will be stratified by ECOG score, regions of the world, and liver metastases at baseline. Patients in Arm A will receive ev on Days 1, 8, and 15 of each 28-day cycle; pts in Arm B will receive either docetaxel, paclitaxel, or vinflunine (determined by investigator) on Day 1 of every 21-day cycle. Patients will continue to receive study treatment until disease progression, intolerance, or other discontinuation criterion is met. The primary endpoint is overall survival; secondary endpoints include progression-free survival, duration of response, and overall response rate, as well as assessment of safety/tolerability, and quality-of-life parameters.
A phase I study of HERV-E TCR transduced autologous T Cells (HERV-E TCR T Cells) in patients (pts) with metastatic clear cell renal cell carcinoma (mccRCC)

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Background: Our team isolated cytotoxic T lymphocytes (CTLs) from a patient who had sustained mciRCC regression after an allogeneic transplant that showed specific killing of cRCC. Utilizing these CTL and cDNA expression cloning, we discovered: transcripts encoding antigens targeted by these CTL were derived from a novel human endogenous retrovirus (HERV-E); selective HERV-E expression was present in most cRCC tumors but not in normal tissues and VHL inactivation lead to transcription of HERV-E in cRCC. Using HERV-E reactive CTL, we cloned a TCR that recognizes a HERV-E HLA-A11 restricted peptide (CT-RC511) into a retroviral vector containing a truncated CD34 cassette for enrichment of transduced cells. Transduced T cells acquired selective killing of HLA-A11+ cRCC cells. A GMP method to manufacture enriched HERV-E TCR T cells was developed that incorporated cytokine stimulation of PBMCs followed by CD4+ depletion, T cell transduction, CD34 enrichment & ex vivo expansion. A scale up of this manufacturing process in 3 healthy donors showed transduced T cells: > 90% CD34+ and had > 90% CT-RC511 tetramer specificity. When co-cultured with HERV-E+ cRCC tumors, T cells secreted high levels of IFN-γ and killed cRCC cells (Table).

Trial design: Phase 1 (3 + 3 design) cell dose-escalation study (1 x 10^5, 3 x 10^5, 1 x 10^6 and 5 x 10^6 cells/kg) to determine the MTD of HERV-E TCR T cells in mccRCC. Pts first receive cyclophosphamide and fludarabine conditioning, followed by single infusion of HERV-E TCR T cells at moderate-dose level II. Eligibility criteria: histologically-confirmed cRCC, progressive disease and 2 prior lines of therapy. Primary endpoint: safety by day 21. Adverse events assessed using CTCAEv5. Biomarker objectives: persistence of HERV-E TCR T cells in blood, T cell lineage/functionality of these cells over time; cytokine profiles & HERV-E expression and presence of HERV-E TCR T cells in tumor tissue.

Table: 924TiP

<table>
<thead>
<tr>
<th>HERV-E TCR T cells</th>
<th>Method</th>
</tr>
</thead>
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<td>(n = 3 donors)</td>
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</tr>
</tbody>
</table>

Cell number after ex vivo expansion (range) 7.55 x 10^9 (1.34 x 10^9 - 6.34 x 10^9) Cellometer-based
CT-RC511 + % (range) 96.4 (96.1-96.8) Flow
Tumor Specific lysis, % (SD) 46 ± 8.5 LDH assay
IFN-γ secretion, pg/ml (range) 1635 (1555-1750) ELISA

Clinical trial identification: NCT03354940.
Legal entity responsible for the study: National Heart, Lung, and Blood Institute.
Funding: National Institutes of Health.
Disclosure: All authors have declared no conflicts of interest.

Phase I/II study to evaluate the safety, tolerability and pharmacokinetics of rogaratinib in combination with atezolizumab in cisplatin-eligible patients with locally advanced or metastatic urothelial cancer and FFGR mRNA overexpression

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Background: PD-L1 inhibitors have been shown to be effective in patients with metastatic urothelial cancer (UC) who are ineligible to receive cisplatin-based chemotherapy; with the PD-L1 inhibitor atezolizumab being FDA approved. Dysregulation of fibroblast growth factor receptors (FGFRs) has been shown to play a role in UC development and progression, and FGFR3 overexpression/molecular alterations are associated with a non-T-cell infiltrated tumor microenvironment. Ragaratinib, an oral pan-FGFR 1-4 inhibitor, has shown promising efficacy in a phase I study in UC patients selected based on FGFR1-3 overexpression, including patients who rapidly progressed on immunotherapy. The aim of this study is to explore the clinical safety and benefit of combining rogaratinib with atezolizumab.

Trial design: This is a multicenter, phase I/II study of rogaratinib in combination with atezolizumab in patients with FGFR3-positive locally advanced or metastatic UC. The primary objectives of the single-arm phase 1b portion are to determine the safety, tolerability, recommended phase-2 dose (RP2D) and pharmacokinetics of rogaratinib in combination with atezolizumab. The primary objective of the randomized phase 2 portion is to compare progression-free survival (PFS) of rogaratinib plus atezolizumab versus placebo plus atezolizumab in chemotherapy-unintreated patients with FGFR-positive locally advanced or metastatic UC. Patients will be tested for FGFR1/3 mRNA expression levels in archival tumor samples (RNAseq@6) and patients with FGFR-positive UC will enter into screening, regardless of the presence of FGFR mutations or translocations. Eligible patients will be treated with a starting dose of daily rogaratinib 800 mg po bid together with a fixed dose of 1200 mg atezolizumab on day 1 of a 21-day cycle. Following determination of the RP2D, patients will be randomized 1:1 to rogaratinib plus atezolizumab versus placebo plus atezolizumab. The primary efficacy variable is PFS based on assessment of blinded independent central review. Approximately 160 patients will be enrolled.

Clinical trial identification: NCT03473756.
Legal entity responsible for the study: Bayer AG.
Funding: Bayer AG.
Disclosure: K. Nakajima, C. Li, H. Nagai: Employee: Bayer. All other authors have declared no conflicts of interest.

Neo-adjuvant ipilimumab and nivolumab in high risk resectable bladder urothelial cancer (NABUCCO)

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1Medical Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, 2Molecular Oncology and Immunology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, 3Pathology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, 4Biometrics, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands, 5Surgical oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands, 6Medical Oncology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek (NKI-AVL), Amsterdam, Netherlands

Background: Although muscle-invasive urothelial cancer (UC) can be cured by surgery, recurrence rates are high. Despite impressive response rates to neo-adjuvant cisplatin-based chemotherapy, the absolute overall survival benefit is only 3%. Immunotherapy targeting the PD-1/PD-1L axis has shown promising activity in UC, particularly when combined with anti-CTLA-4, and patients with lymph node only disease treated with frontline immunotherapy appear to benefit most. Since responses to immunotherapy often appear to be durable, neo-adjuvant immunotherapy may improve prognosis, particularly for high risk N+ disease. Preliminary data on neo-adjuvant pembrolizumab showed remarkable pCR rates (38.9%) and a manageable toxicity profile after 3 cycles of pembrolizumab in resectable T2–N0 UC, underpinning the potential of neo-adjuvant combination trials for high risk UC.

Trial design: This is a single-arm phase 1B trial to establish whether sequenced pre-operative ipilimumab and nivolumab is safe and effective in high risk UC, defined as upper/lower tract T3–4aN0 M0 or T1, cN+ or T1, any N, resectable retroperitoneal lymph node metastasis. Patients are eligible if they are ≥ 18 years with WHO performance status 0–1. Patients must be cisplatin ineligible or refuse cisplatin-based chemo with no previous treatment with PD-1L1 and CTLA-4 immunotherapy. To mitigate the risk of immune-related toxicity, patients are treated with a mitigated schedule (based on Meerdink-Egink et al, Ann Oncol 2017): ipi 3 mg/kg (day 1), ipi 3 mg/kg + nivo 1 mg/kg (day 22) and nivo 3 mg/kg (day 43) followed by radical cystectomy or nephroureterectomy (day 57–71) with appropriate LN dissection. Six patients will undergo a re-TUR for in-depth analysis of T cell infiltrates. The primary endpoint of this trial is the percentage of patients having surgery < 12 weeks after study enrollment. Secondary endpoints are efficacy (pCR) and translational. In total 24 patients will be included. At the time of abstract submission, 5 patients were included.

Clinical trial identification: NCT03387761.
Legal entity responsible for the study: The Netherlands Cancer Institute.
Funding: BMS.
Disclosure: All authors have declared no conflicts of interest.
A phase III, randomized, placebo-controlled trial of adjuvant nivolumab plus ipilimumab in patients with localized renal cell carcinoma (RCC) who have at high risk of relapse after radical or partial nephrectomy

A. Bex1, V. Gunewardena2, P. Russo3, T. Tomita4, E. Berghorn5, M.B. McHenry6, R. Mazzoleni7

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Background: Surgery is the standard treatment for non-metastatic RCC. Unfortunately, pts with stage II or III RCC have high risk of relapse with 5-year survival rates of 20% to 33%. Prevention of recurrence is an unmet need. In CheckMate 214, the nivolumab + ipilimumab treatment combination demonstrated significant improvement in overall survival (OS) in first-line treatment of pts with advanced or metastatic RCC, with a manageable safety profile. This phase III multinational study will evaluate adjuvant nivolumab + ipilimumab vs placebo in pts with high risk of relapse after nephrectomy (NCT03138512).

Trial design: Key inclusion criteria: Radical or partial nephrectomy with negative surgical margins > 4 weeks and < 12 weeks before randomization; predominantly clear primary tumor histology; pathologic TNM staging T2a (grade 1) or 4, T2b (any G), T3 (any G), or T4 (any G) N0M0, or any T (any G) N1M0; Eastern Cooperative Oncology Group performance status < 1; no clinical/radiological evidence of macroscopic residual disease or distant metastases post-nephrectomy, and tumor tissue obtained ≤ 3 months pre-enrollment. Key exclusion criteria: Pts with conditions requiring corticosteroid or immunosuppressive systemic treatment, autoimmune disease, prior treatment with drugs specifically targeting T-cell co-stimulation or checkpoint pathways, and prior systemic treatment for RCC. Pts are randomized 1:1 to receive nivolumab and ipilimumab at the specified dose on specified days for 24 weeks, or placebo infusions on the same schedule for 24 weeks or until recurrence, unacceptable toxicity, or withdrawal of consent. Stratification factors: Tumor staging and type of nephrectomy procedure. Primary endpoint: Disease-free survival per blinded independent central review. Secondary endpoints: OS, safety, and tolerability. Tertiary exploratory endpoints include disease-related symptoms based on the Functional Assessment of Cancer Therapy-Kidney Symptom Index, and changes in global health status based on EuroQol’s EQ-5D-3L. Enrollment began July 2017 with a target of 800 pts.

Clinical trial identification: NCT03138512.

Editorial acknowledgement: Professional medical writing and editorial assistance were provided by Juan Sanchez-Cortes, PhD, and Lawrence Hargett of PSI (a PAREXEL Company), funded by Bristol-Myers Squibb.

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

Funding: Bristol-Myers Squibb and Ono Pharmaceutical Company Limited.

Disclosure: A. Bex: Honoraria: Bristol-Myers Squibb, Pfizer, Roche, Eisai, Ipsen; Consulting or Advisory role: Bristol-Myers Squibb, Pfizer, Roche, Eisai, Ipsen; Research funding: Pfizer. V. Gunewardena: Honoraria: Bristol-Myers Squibb, Consulting or Advisory role: Bristol-Myers Squibb, Novartis, Pfizer, Bayer; Speakers’ bureaus: Bristol-Myers Squibb, Novartis, Pfizer. Y. Tomita: Honoraria: Pfizer, Novartis, Ono Pharmaceutical Co., Ltd.; Consulting or Advisory role: Ono Pharmaceutical Co., Ltd., Novartis, Taiho; Research funding (Inst): Takeda, Pfizer. E. Berghorn, M.B. McHenry: Employment: Bristol-Myers Squibb Stock or Other ownership: Bristol-Myers Squibb. R. Mazzoleni: Consulting or Advisory role: Eisai, Exelixis, Genentech/Roche, Merck, Novartis, Pfizer, Research funding (Inst): Genentech/Roche, Bristol-Myers Squibb, Eisai, Exelixis, Novartis, Pfizer. All other authors have declared no conflicts of interest.
**929TiP**  
**BAYOU: Phase II study of efficacy and safety of durvalumab plus olaparib as first-line therapy in cisplatin-ineligible patients (pts) with stage IV urothelial cancer (UC)**  
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**Background:** UC is platinum-responsive and hypothesized to be sensitive to targeted DNA-damaging agents such as PARP inhibitors (PARPi). Cisplatin (cis)-ineligible pts with metastatic/untreatable primary UC have limited effective treatment options. Immune checkpoint blockade may increase the proportion of pts that respond to PARPi. Durvalumab is a selective, high-affinity, engineered, human IgG1 monoclonal Ab that blocks PD-L1 binding to PD-1 and CD80. In UC, the combination of olaparib (a PARPi) + durvalumab may broaden the therapeutic effect of monotherapy given their different mechanisms of action, with potentially enhanced benefit for pts with metastatic/untreatable UC and DNA repair deficiencies (mutations in homologous recombination repair genes [HRRm]).  
**Trial design:** BAYOU is a double-blind, randomized, placebo-controlled, multicenter phase 2 study designed to assess the efficacy and safety of durvalumab + olaparib vs durvalumab + placebo in cis-ineligible pts with stage IV UC. Adult pts (>18 years) who are cis-ineligible with histologically/cytologically confirmed unresectable stage IV UC, WHO performance status 0–2, and with known HRm will be randomized (1:1) to durvalumab (1500 mg intravenous, every 4 weeks) + placebo vs durvalumab (1500 mg intravenous, every 4 weeks) + olaparib (tablet) until disease progression. Olaparib dose will be 300 mg twice daily in pts with CrCl ≥ 50 mL/min and 200 mg twice daily in pts with CrCl > 50 mL/min. The primary endpoint is progression-free survival in HRmR pts (investigator assessed, RECIST v1.1). Secondary endpoints are overall survival (OS), duration of response, objective response rate, proportion of pts alive and progression-free survival (PFS) at 6 months, and OS at 18 months. Safety, pharmacokinetics, and immunogenicity will also be assessed. The trial is currently enrolling pts.  
**Editorial acknowledgement:** Editorial assistance, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Ingrid Monteiro of Cactus Communications (Mumbai, India).  
**Legal entity responsible for the study:** AstraZeneca.  
**Funding:** AstraZeneca.  

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**930TiP**  
**Phase II/III study of rogaratinib versus chemotherapy in patients with locally advanced or metastatic urothelial carcinoma selected on FGFR1/3 mRNA expression**  
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**Background:** Long-term survival is poor for patients with locally advanced or metastatic urothelial carcinoma (UC) receiving chemotherapy and/or immunotherapy following progression with platinum-containing chemotherapy. Genetic alterations of fibroblast growth factor receptor (FGFR) genes have been shown to play a role in disease development and progression. Non-genetic and epigenetic activation of FGFR gene expression have also been described. Rogaratinib, an oral pan-FGFR 1–3 inhibitor, has shown promising activity and a manageable safety profile in a phase I study in patients with UC who were selected based on FGFR1-3 mRNA overexpression and/or activating mutations in the FGFR3 gene.  
**Trial design:** This is a randomized, open-label, phase 2/3 study to evaluate the efficacy and safety of rogaratinib compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic UC who have received prior platinum-containing chemotherapy. The primary objective is to show superiority of rogaratinib over chemotherapy in prolonging overall survival (OS) of UC patients with FGFR-positive tumors. Secondary objectives include: objective response rate (ORR), progression-free survival, and overall survival (OS). Safety: Testing for FGFR1 and 3 mRNA over expression will be conducted centrally using an RNA in situ hybridization (RNAISH) in archival samples. Eligible patients will be randomized 1:1 to rogaratinib (800 mg po bid) or chemotherapy (GEM: docetaxel 75 mg/m²; paclitaxel 175 mg/m²; or docetaxel 20 mg/m² vinflunine). Randomization will be stratified according to PIK3CA and/or ARAS activating mutations, prior immunotherapy, and modified 4-factor Bellmunt risk score. The objective for the phase 2 part of the study is ORR. A total of 116 patients in PIK3CA and RAS WT patients will be enrolled to the phase 2 part of the study to rule out a low difference in ORR between rogaratinib and chemotherapy as futility. The phase 3 portion of the study is powered to detect an increase in median OS in PIK3CA and RAS WT patients. Total patient enrollment expected to be approximately 400 patients.  
**Clinical trial identification:** NCT03410693.  
**Legal entity responsible for the study:** Bayer AG.  
**Funding:** Bayer AG.  
**Disclosure:** K. Nakajima, C. Lu, A. Holynskyj. Bayer employment. All other authors have declared no conflicts of interest.
**GYNAECOLOGICAL CANCERS**

**9320**

Phase III trial of lurbinectin versus PLD or topotecan in platinum-resistant ovarian cancer patients: Results of CORAIL trial

S. Pautier1, A. Oaknin2, J. Rau1, J.B. Vergote3, G. Scambia4, N. Colombo5, S.A. Ghamande6, A. Soto-Matoso7, C.M. Fernandez1, C. Kahat1, J. Giome7, A. Neta8, N. Torres9, B. Pardo-Burdalo10, Z. Papai11, R.S. Kirstenini11, D.M. O’Malley12, J. Benjamin13, P. Pautier1, D. Lorussi1

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**9330**

Carboplatin/pegylated liposomal doxorubicin/bevacizumab (CD-BEV) vs. carboplatin/gemcitabine/bevacizumab (CG-BEV) in patients with recurrent ovarian cancer: A prospective randomized phase III ENGOT/GCIG-Intergroup study (AGO study group, ANZOG, GINECO, SGCG)

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934O Alienor/ENGOT-ov7 randomized trial exploring weekly paclitaxel (wP) + bevacizumab (bev) vs wP alone for patients with ovarian sex cord tumors (SCT) in relapse


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940O OVPSYCH2: A randomised study of psychological support versus standard of care following chemotherapy for ovarian cancer


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935PD Preliminary safety, efficacy, and PK/PD characterization from GARNET, a phase I clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-H endometrial cancer


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936PD A phase II study of durvalumab, a PD-L1 inhibitor and olaparib in recurrent ovarian cancer (OvCa)

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937PD A phase II trial of combination nivolumab and bevacizumab in recurrent ovarian cancer


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Quality of life and symptoms in longterm survivors with ovarian cancer: It's still an issue. Expression VI – Carolin meets HANNA – holistic analysis of long-term survival with ovarian cancer: The international NOGGO, ENGOT and GCIG survey

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Need for a stratified analysis in stage I malignant ovarian germ cell tumors (MOGCT): Prospective survival analysis of cases collection from the French rare malignant ovarian tumors (TMRO) network & GINECO group

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A prospective evaluation of tolerability of niraparib dosing based upon baseline body weight (wt) and platelet (blplt) count: Blinded pooled interim safety data from the PRIMA Study

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Response to neoadjuvant chemotherapy in ICON8: A GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/ fallopian tube/ primary peritoneal carcinoma (EOD) treatment

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Eligible pts received treatment with single agent niraparib in 4th or later line PARPi trials and derived modest benefit from treatment (ORR 25%).

Methods: Eligible pts received treatment with single agent niraparib in 4th or later line of therapy. Pts were evaluated for RR and HB status (MyChoice HRD Test). Pts received niraparib 300 mg once daily until progressive disease or unacceptable toxicity. Adverse events (AEs) were managed with dose reduction to 200 or 100 mg. The primary endpoint was ORR per RECIST v1.1. Results: 463 pts were treated. Median age was 65 years (range 29-91). 162 pts were platinum naïve (defined as progression within 28 days of the last dose of plat); 197 pts (42.5%) experienced a serious AE (SAE) and 91 pts (19.7%) a treatment-related AE. Twelve pts were progression-free at 6 months; PFS6 increased, and anemia. As of the cutoff date, 33 pts reached the timepoint for PFS6 and translational endpoints are pending additional data.

Conclusions: Niraparib demonstrated meaningful and durable responses among the difficult-to-treat patient population, including platinum resistant and refractory disease. The combination of durva and PLD in women with PROC appears to have a tolerable safety profile and promising efficacy. PFS6 and translational endpoints are pending additional data.

Disclosure: Programmed cell death ligand 1 (PD-L1) expression and preliminary evidence of antitumor activity with anti-PD-1 therapy have been reported in ovarian cancer. PLD, a pegylated, liposomal form of doxorubicin, is a standard option for this population; durva is an anti-PD-L1 antibody. The primary objectives of this study are to determine the safety of the combination and to evaluate clinical efficacy by progression-free survival rate at 6 months (PF66) using RECIST 1.1.

Methods: This is a phase 1/2, multicenter, open-label study (NCT02431559) of durva in patients (pts) with PROC, scheduled to receive PLD. The study includes a dose escalation (phase 1: 3+3 design; DLT evaluation over one 28-day cycle; n = 6-18) and a dose expansion (phase 2: n = 41). PLD has been reported to have a 25% PF66. A sample size of 41 evaluable pts yields 80% power to test the null hypothesis of a PF66 rate of ≤ 25% against the alternative hypothesis of a PF66 rate of ≥ 50% at an alpha level of 0.05 (one-sided). Blood and tumor samples were also collected for assessment of correlative immunologic responses.

Results: First pt dosed: 09Aug2016. As of 05Mar2018, 40 female pts (median age: 65 [52-83] years) were enrolled in phase 2 of the study; each received at least 1 dose of study therapy (PLD 40 mg/m2 + durva 1500 mg (Q4W)) and are included in the safety analyses. Most frequent (≥ 25%) treatment-emergent adverse events (AEs; all causality) were palmar-plantar erythrodysesthesia syndrome (PPES)/rash, stomatitis, fatigue, abdominal pain, nausea, pyrexia, and vomiting. Grade 3 treatment-related AEs in ≥ 2 pts included PPES/rash, stomatitis, lymphocyte count decreased, lipase increased, and anemia. As of the cutoff date, 33 pts reached the timepoint for PF66 assessment. Twelve pts were progression-free at 12 months; PF66 = 38% (12/40 pts). The remaining data will mature by July 2018, and further improvement in PF66 may be observed. Updated PF66 and preliminarycorrelative results will be presented at the meeting.

Conclusions: The combination of durva and PLD in women with PROC appears to have a tolerable safety profile and promising efficacy. PF66 and translational endpoints are pending additional data.

Disclosure: All authors have declared no conflicts of interest.
Brain metastases in primary ovarian cancer: Real-world data

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Background: Brain metastases (BM) is infrequently reported in patients (pts) with ovarian cancer (OC), with past studies reporting a rate of approximately 1%. This study estimated real-world incidence of BM in OC and assessed whether BRCA mutation (BRCAmut) increased risk of BM in OC pts.

Methods: This retrospective study included 4515 pts diagnosed with OC between Jan 1, 2011 and Jan 31, 2018 from the Flatiron Health database. This is a longitudinal, demographically and geographically diverse database derived from electronic health record data from over 265 cancer clinics and over 2 million active US cancer pts. A time-to-event analysis was conducted to assess whether pts with a known BRCAmut were more likely to develop BM compared with BRCA wild type (BRCAwt) pts.

Results: Of 4515 OC pts, 473 were BRCAmut, 1679 were BRCAwt, and 2363 had unknown BRCA status. A total of 46 pts (1%) had a diagnosis of BM subsequent to OC diagnosis. Of those with BRCAmut, 3% (14/473) developed BM; the BRM rate was 0.6% (10/1679) for BRCAwt. The K-M estimate for the proportion of pts with BM within 5 years of diagnosis was 5.7% in the BRCAmut population compared with 1.4% in BRCAwt. BRCAmut pts had a significantly higher risk of developing BM compared with BRCAwt (HR 4.44 [95% CI 1.97, 10.00], P < 0.0001). A total of 281 OC pts also had a breast cancer (BC) (186 developed BC prior to OC, 95 developed BC after OC diagnosis). After excluding these pts from the analysis, the HR for developing BM among BRCAmut pts vs. BRCAwt pts was 3.84 (95% CI 1.60, 9.22), P = 0.001. Multivariate models adjusting for other pt characteristics yielded similar HRs. Among pts who developed BM, median time from OC diagnosis to BM diagnosis was 27 months in BRCAmut pts and 35 months in BRCAwt. Median survival after diagnosis of BM was 7.16 months (95% CI 3.48, 16.49). Overall survival after BM did not differ significantly by BRCA status.

Conclusions: OC pts with BRCAmut seem to have a higher risk of developing BM. Further research is needed to confirm these findings and better understand potential mechanisms and implications for management, given the poor prognosis in pts who develop BM.

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Legal entity responsible for the study: Tesaro, Inc.

Disclosure: E. Ratner, Advisory board: Tesaro Inc. M. Bala, M. Louie-Gao, S. Hazard: Employment and stock and other ownership interests in Tesaro Inc. All other authors have declared no conflicts of interest.

Table: 947P

<table>
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<th>Cohort</th>
<th>Rucaparib, n</th>
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<tr>
<td></td>
<td>Median PFS, mo</td>
<td>P value†</td>
<td>Median PFS, mo</td>
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<td></td>
<td>HR† (95% CI)</td>
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<td>Patients with 2 prior chemotherapy regimens</td>
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<tr>
<td>BRCA mutant</td>
<td>73</td>
<td>40</td>
<td>0.24 (0.14–0.40)</td>
<td>21.9 vs 5.4, P &lt; 0.0001</td>
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<td>75</td>
<td>0.34 (0.23–0.49)</td>
<td>14.1 vs 5.5, P &lt; 0.0001</td>
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<td>ITT</td>
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<td>Patients with ≥ 3 prior chemotherapy regimens</td>
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<td>BRCA mutant</td>
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<td>0.21 (0.11–0.40)</td>
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<tr>
<td>ITT</td>
<td>144</td>
<td>65</td>
<td>0.28 (0.19–0.41)</td>
<td>11.1 vs 5.3, P &lt; 0.0001</td>
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*HRStratified log-rank P value, CI, confidence interval; HR, hazard ratio.

Subgroup analysis of rucaparib in platinum-sensitive recurrent ovarian carcinoma: Effect of prior chemotherapy regimens in ARIEL3


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Background: In the randomised, placebo-controlled, phase 3 study ARIEL3, patients were randomised 2:1 to oral rucaparib (600 mg BID) or placebo as maintenance treatment following response to platinum-based chemotherapy. Rucaparib significantly improved progression-free survival (PFS) vs placebo in all patient populations regardless of biomarker status (Coleman et al. Lancet. 2017;390:1499-61). This post hoc exploratory analysis investigated the effect of the number of prior chemotherapy regimens on the primary and secondary endpoints of investigation-assessed and blinded independent central review (BICR)-assessed PFS in ARIEL3.

Methods: In ARIEL3, all patients received ≥2 prior platinum-based regimens in accordance with the protocol. PFS was explored in subgroups of patients who received 2 or ≥ 3 prior chemotherapy regimens. These subgroup analyses were presented for the following predefined cohorts: BRCA mutant; BRCA mutant or BRCA wild type/high loss of heterozygosity (LOH); and intent-to-treat (ITT) population (ie, all randomised patients).

Results: The visit cutoff dates for efficacy and safety were 15 April 2017 and 15 August 2017, respectively. In each predefined cohort, rucaparib significantly improved PFS compared to placebo irrespective of the number of prior chemotherapy regimens (ie, 2 or ≥ 3) (Table). Rucaparib’s safety profile was consistent between patients who received 2 or ≥ 3 prior chemotherapy regimens as assessed by the rate of all grade (100%) and grade ≥ 3 (59% and 59%) treatment-emergent adverse events (TEAEs) and dose modifications (ie, treatment interruptions and/or dose reductions due to ≥1 TEAE) (79% and 74%) in each respective subgroup.
Intrapleural chemotherapy (IP CT) after cytoreductive surgery benefits survival in epithelial ovarian cancer (EOC): Results of a pooled meta-analysis including 9 randomized clinical trials (RCT)

M. Aranda 4, A. Cervantes 2 and B were analysed separately. IP CT showed a survival benefit over IV CT with CT) were included. In 8 RCTs IPCT was given after upfront surgery and in 1 (OV21/ were disease-free survival (DFS) and overall survival (OS).

Results:
Initially 92 papers were identified. After exclusion criteria only nine RCT were included. In 8 RCTs IPCT was given after upfront surgery and in 1 (OV21/ was to perform a meta-analysis of the survival benefit of IP vs IV CT after cytoreductive surgery including recent evidence.

Methods: A literature search in order to identify most relevant RCT comparing IV vs IP CT after cytoreductive surgery in EOC was performed. Non comparative studies or trials with no hazard or risk ratios were excluded. Statistical analyses were done using SPSS STATISTICS V.21. Fixed-effect meta-analysis for combining data was made. Degree of heterogeneity using the I² statistic was calculated. Endpoints meta-analysed were disease-free survival (DFS) and overall survival (OS).

Results: Initially 92 papers were identified. After exclusion criteria only nine RCT including pooled data from 3686 pts (2068 treated with IP CT and 1620 treated with IV CT) were included. In 8 RCTs IPCT was given after upfront surgery and in 1 (OV21/ PETRO) after neoadjuvant CT. In all RCTs CT cycles were foreseen in the IP arm. Seven RCTs including 3006 pts had DFS as endpoint. Among these, GOG252 cohorts A and B were analysed separately. IP CT showed a survival benefit over IV CT with HR = 0.86; (95% confidence interval (CI): 0.80 to 0.93). Heterogeneity was moderate (I² = 37.5). Eight RCTs including 2289 pts had OS as endpoint. IP CT showed a significant impact on OS with HR = 0.81; (95% CI: 0.73 to 0.90). Heterogeneity was low (I² = 9.01). Benefit of IP CT remained unchanged in the sensitivity analysis performed for both DFS and OS by eliminating the latest RCT of the meta-analysis.

Conclusions: IP CT benefits DFS and OS in this meta-analysis of pooled data from 9 RCTs and 3668 pts including latest negative results.

Legal entity responsible for the study:
Hospital Clinico Universitario de Valencia. INCLIVA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: The PARP inhibitor olaparib (Lynparza®) is approved as maintenance therapy in pts with PSR OC who are in complete or partial response to platinum-based chemotherapy. Currently, pts with SD on scans at the end of chemotherapy and the efficacy of maintenance olaparib vs observation.

Methods: In this open-label, multicentre trial, pts with PSR OC following platinum-based chemotherapy alone (Oza et al. Lancet Oncol 2017). Olaparib capsules have shown long-term benefit, with pts staying alive for 5 years (yrs; Gourley et al ASCO 2017). We analysed the long-term outcomes of 16 pts who have been evaluated; drug exposure was impacted in 1 pt. The efficacy data in these heavily pretreated platinum resistant ovarian cancer pts are encouraging & enrollment is ongoing. The safety profile appears to be manageable with hypertension being the most common adverse event related to navicixizumab.


Legal entity responsible for the study: OncoMed Pharmaceuticals.

Disclosure: All authors have declared no conflicts of interest.

Olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed (PSR) ovarian cancer (OC) and stable disease (SD) following platinum-based chemotherapy

Annals of Oncology
Methods: In SOL02, pts with BRCA-mutated PSR OC in response to platinum received maintenance olaparib tablets (300 mg bid) or placebo until disease progression. Adverse events (AEs) were graded by CTCAE v4.0.

Results: At the primary data cut-off (DCO; 19 Sep 2016), of 195 pts treated with olaparib, 62 (32%) had received olaparib for ≥1–2 yrs (Group 1) and 59 (30%) for ≥2 yrs (Group 2), vs 12/99 (12%) and 9/99 (9%), respectively, who received placebo. Most AEs that began after ≥1 yr (Group 1) or ≥2 yrs (Group 2) were grade 1–2, with few serious AEs (Table). The most common AEs with onset during the second yr of olaparib treatment were anaemia (19%), nausea (18%), and vomiting (15%). The most common AEs with onset after ≥2 yrs were diarrhoea (8%), abdominal pain (5%), and upper abdominal pain (5%). Four pts in Group 1 discontinued olaparib because of AEs of acute myeloid leukaemia, decreased neutrophil count, muscular weakness, disturbance in attention and depression; all n = 1) vs no pts in Group 2.

<table>
<thead>
<tr>
<th>AE (any grade), n (%)</th>
<th>Group 1 (n = 62)</th>
<th>Group 2 (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE (grade ≥3), n (%)</td>
<td>11 (18)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Serious AE, n (%)</td>
<td>7 (11)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dose interruption caused by AE, n (%)</td>
<td>14 (23)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Dose reduction caused by AE, n (%)</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment discontinuation caused by AE, n (%)</td>
<td>4 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table: 952P Long-term AE data for olaparib tablets as maintenance therapy

Conclusions: AEs reported during long-term olaparib maintenance therapy were mostly low grade, non-serious and associated with a low rate of treatment discontinuation. Common AEs were consistent with the known safety profile. Olaparib tablets are suitable for long-term maintenance therapy for PSR OC pts, without cumulative toxicity and with few late-onset AEs.


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Prevalence and clinical implications of mismatch repair (MMR) deficiency in unselected endometrial cancer (EC) patients

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Background: Endometrial cancer (EC) is the most common gynaecological malignancy worldwide. The TCGA data suggested up to 30% of EC pts have a MMR deficient (MMRd) tumours, however the exact concordance of this with the presence of a germ-line mutation (Lynch syndrome) in an unselected population is unclear. Lynch-associated tumours appear to have a better prognosis, however the implications for prognosis and survival in all MMRd tumours are less known.

Methods: 396 pts with primary endometrial cancer, treated at RMH were evaluated for MMR proteins by immunohistochemistry (IHC). Tumours with loss of at least one protein were considered MMRd, those with intact expression were MMR proficient (MMRp). Clinical-pathological characteristics and survival data was collected from electronic records. Progression free survival (PFS) and overall survival (OS) were assessed using Kaplan Meier and log-rank tests.

Results: Of 396 samples tested to date, 29% (114 pts) were MMRd. Frequencies of IHC MMR loss of expression were: MLH1/PMS2 loss: 10/12 pts, 65% MLH1 loss: 12, 10% MLH1/PMS2 loss: 5/63 pts, 26% MLH1 loss. Other patterns: 3. Germline testing has been completed in 37% (42 pts) thus far; 14pts had a concordant germline mutation: MLH1 (2/25), MSH2 (3/7), MSH6 (10/37); 12, PMS2 (12/25) respectively. Mean age varied significantly, 66 yrs (MMRD), 62 yrs (MMRP) and 58 yrs (Lynch mutation carriers, LS) p<0.02. Stage at diagnosis did not differ significantly between the groups but MMRd and LS pts were significantly more likely to have LVSI than MMRp (p=0.01), and to be high EORTC risk (p=0.086). OS for the entire cohort was 160mths (75-244.9) and PFS was 51mths (32.4-70.1). MMRd pts had a shorter OS, 96 mths, 99% (CI 65.7 – 127) than MMRp (160mths, 54.9 – 265) and a shorter PFS median 41.5mths (IC 15.9-68 – 64) vs 51.6mths (IC 95% 30- 72), p<0.01.

Conclusion: Almost one in three EC tumours are MMRd, with concordance between IHC and loss of expression. Those with somatically derived MLH1/PMS2 loss may have a poorer prognosis, and as a group may potentially benefit from checkpoint inhibitors. Further exploration of the clinical correlations and outcome with MMRd status is warranted.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

A phase 1b and randomised phase II trial of pazopanib with or without FOLFIRI in advanced recurrent ovarian cancer

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Background: Prospective trials have validated angiogenesis as a treatment target in ovarian cancer although improvements in PFS have been modest. One potential strategy to improve efficacy is to combine anti-vascular agents. Fosfotubulin (F) is an intravenous vascular disrupting agent and pazopanib (P) is an oral VEGFR tyrosine kinase inhibitor.

Methods: A multi-centre Phase 1b(P) /randomised phase 2 (RP2) trial that recruited women with recurrent epithelial ovarian cancer and a platinum-free interval of 1-12 months. Any Bevacizumab had been received ≥6 months prior to recruitment. Phase 1b dose levels ranged from F = 5mg/m2 d1,14,28d (P = 60mg/day) up to F = 60mg/m2 d1,14,28d (P = 800mg/day). In RP2 participants received either RP2D or P = 800mg/day (P800). Primary outcome in PB4 was safety plus RP2D and in RP2 was RP2D + F PFS.

Results: 12 and 21 patients were recruited to PB4 & RP2 respectively. The RP2D was F54-+P600. In the RP2D median PFS was 7 months (95% CI 4.1- not estimated) in F54-+P600 group vs 3.7 months (95%CI 1.0-8.4) in P800 group (HR 0.80, 95%CI 0.80- 1.03, P = 0.09). Of the 21 patients who received F+P (2 in PB4 and 2 in RP2) developed acute hypertension plus reversible secondary cardiac toxicity. The occurrence of cardiac toxicity resulted in premature discontinuation of the trial. Data on circulating biomarkers of angiogenesis collected in PB4 & RP2 will also be presented.

Conclusions: F54-+P600 appeared effective but was associated with reversible secondary cardiac toxicity that with better hypertension control might have been avoided.


Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Novartis & Mateus Therapeutics.

Disclosure: G.L. Rustin. Advisory board: Mateus, Roche, AstraZeneca in past 3 years, only Roche in past year. All other authors have declared no conflicts of interest.

Genomic profiling of the residual disease of advanced high-grade serous ovarian cancer after neoadjuvant chemotherapy

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Background: Tumor response to NAC predicts survival and can be considered a surrogate prognostic marker. Three tiered chemotherapy response score (CRS) of omental tissue sections showed a significant association with survival. In patients with CRS 1 or 2, NAC selects a subgroup of chemotherapy resistant tumor cells. Residual tumors remaining after neoadjuvant chemotherapy contain cell population intrinsically resistant to chemotherapy. However, the standard of care for patients with residual disease after NAC is the same regimen, as therapies that would be effective in reducing recurrences are unknown. We hypothesized that comprehensive molecular analyses of residual disease after NAC measured by targeted sequencing and Immunohistochemistry would be helpful to find out innovative new therapeutic targets.

Methods: During the study period between 2006 and 2017, Pre- and post NAC tumor tissue samples were collected from patients with advanced HGSC. Combined NGS and IHC was performed to identify actionable target and pathway activation in chemoresistant tumor cells. We examined whether profiling residual HGSC after NAC identifies targetable molecular lesions in the chemoresistant component of tumor.

Results: Alteration in TP53 were identified in 76 of 104 post-NAC samples (72.1%). HRR gene alteration were found in 30 of 104 post-NAC samples (28.8%). Patients with DNA repair alterations (BRCAl, BRCA2, ATM mutations) were found in 30% of HGSC and they had better chemotherapy sensitivity and survival outcomes than those with intact DNA repair system. Otherwise, rare individual actionable targets (less than 5%) were found in most of patients.

Conclusions: We showed the genomic landscape of drug-resistant tumor cells remaining in advanced HGSC after NAC.

Clinical trial identification: NCT03491033.

Legal entity responsible for the study: Jung-Yun Lee.

Funding: NRF.

Disclosure: All authors have declared no conflicts of interest.

Cemiplimab, a human PD-1 monoclonal antibody, in patients (pts) with recurrent or metastatic cervical cancer: Interim data from phase I cohorts

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Background: For pts who progress after first-line platinum based therapy for recurrent/metastatic cervical cancer, there are no therapies available that have been demonstrated to improve survival or quality of life. Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, exhibited encouraging efficacy and acceptable tolerability in a phase 1 dose escalation study. The present report focuses on interim data from the phase 1 cervical cancer expansion cohorts (ECs) of cemiplimab as a monotherapy.
Molecular profiles as a function of treatment response/progression free survival in a prospective cervical cancer study (RAIDs)

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Background: BioRAIDS is a supervised longitudinal collection of tumor and blood together with clinical outcome data in 419 primary cervical cancer patients from 7 European countries (NCT02488442).

Methods: Molecular analysis (Next Generation Sequencing (NGS) at SequOmics (Hungary)) and Reverse Phase Protein array (RPPA) at Institut Curie) was performed on quality-controlled primary tumor samples in 295 patients (70%) who subsequently had received primary radiotherapy (RCT). Integrative bioinformatics analyses were performed to identify pathway activations suggesting the need for additional different therapies.

Results: NGS demonstrated driver Tyrosine Kinase Receptor (TKR) pathway mutations in 27%, TKR/PI3K pathway alterations in 32%, and epigenetic alterations alone in 13% of patients. At a median follow up of 19 months (2-38), tumors for which no mutations in relevant genes from the TKR/PI3K pathway nor alterations in genes involved in epigenetic signaling appeared to be associated with a significantly better prognostic feature H= 2.45 [95% CI 1.1 - 5.2]. RPPA analysis was carried out separating patients in 3 subgroups according to signaling pathway activation (DMS, epithelial mesenchymal transition), DNA damage and MAPK/PI3K pathway), none of which was associated with bad prognosis.

Conclusions: The high frequency of epigenetic alterations with or without TKR/PI3K pathway mutations, suggests that epigenetically acting drugs (Vorinostat) may be relevant for patients whose tumors have genetic mutations of significance in epigenetically acting enzymes. Relevance of copy number alterations and of other frequently mutated genes (CMMRD, SYNE1), needs to be integrated and cross validated in a larger complementary dataset.

Clinical trial identification: NCT02488442.

Legal entity responsible for the study: Institut Curie.

Disclosure: All authors have declared no conflicts of interest.

Phase 1 study of BVAC-C in HPV type 16 or 18 positive recurrent cervical carcinoma: Safety, clinical activity and immunologic correlates

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Background: BVAC-C is a B-cell and monocytobased immunotherapeutic vaccine transfected with recombinant HPV E6/E7 gene and loaded with alpha-galactosyl ceramide, a natural killer T cell ligand. It may have activity against HPV positive cancer. This phase I study was performed to determine the safety and tolerability of BVAC-C in patients with HPV type 16 or 18 positive recurrent cervical carcinoma and to preliminarily assess tumor activity and immunologic correlates.

Methods: Ten patients who had experienced recurrence after at least one prior platinum-based combination chemotherapy, received three intravenous infusion of BVAC-C every 4 weeks in dose escalating three-patient cohorts at 1x10^7, 4x10^7, or 1x10^8 cells/ dose. Results: BVAC-C was well tolerated: grade 1 fever or myalgia were the most frequently observed without any grade 3 or 4 toxicity. One patient expired 3 weeks following 3rd dose for clinical disease progression. Of the 8 evaluable cases, one partial responses (12.5%), and four stable diseases (50%) were seen. Three patients are surviving more than one year. Adenocarcinoma and bulky tumor burden were associated with poor response to the therapy. Immunologic response analysis showed that BVAC-C induced activation of natural killer T cells, natural killer cells, and HPV 16/18 specific CD4 and CD8 T cells upon vaccinations in all patients evaluated. More follow-up results will be presented.

Conclusions: BVAC-C is well tolerated and associated with evidence of antitumor activity in HPV 16 or 18 positive cervical carcinoma. We are now planning further phase 2 efficacy trial.

Classical trial identification: NCT02866016.

Legal entity responsible for the study: Cellid Inc.

Funding: Cellid Inc.

Disclosure: All authors have declared no conflicts of interest.
Results: Three phase III RCTs with 1401 patients were eligible. The study arms used olaparib or niraparib or rucaparib while the control arms utilized placebo. The I statis-
tic for heterogeneity was 16.86, and the heterogeneity X² (Cochran’s Q) was 2 (P = 0.30), suggesting homogeneity. The SHDI incidence was 12 (1.28%) in PARP inhibitors group vs 3 (1.07%) in control group. The RR for SHDI was 1.14 (95% CI: 0.42 – 3.08, P = 0.79) and RD was 0.002 (95% CI: 0.001 – 0.014, P = 0.72). The RR of all-grade side effects were as follows: anaemia, 6.57 (95% CI: 4.44 – 9.90, P < 0.001); thrombocytopenia, 9.00 (95% CI: 6.19 – 15.06, P < 0.001); and neutropenia, 4.15 (95% CI: 2.79 – 6.12, P < 0.001). The RR of high-grade adverse effects were as follows: ane-
ma, 28.85 (95% CI: 10.06 – 82.72, P < 0.001); thrombocytopenia, 28.74 (95% CI: 8.24 – 100.24, P < 0.001); and neutropenia, 5.90 (95% CI: 3.01 – 11.57, P < 0.001).

Conclusions: Patients on PARP inhibitors experienced a notable increase in the risk of secondary hematological malignancies in PARP inhibitors group. Long-term follow-up of these patients is required to determine the actual relation.

Legal entity responsible for the study: Kuyz Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

References: 1. The Cochrane Collaboration. 2. RTOG/ECOG 0121. 3. The Mayo Clinic Cancer Center. 4. The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Abstract: A phase IIa study of tisotum vedotin in patients with previously
treated recurrent or metastatic cervical cancer: Updated analysis of full
carcinoma expansion cohort


Background: Tisotum vedotin (TV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody specific for tissue factor (TF) conjugated to the mitotubule-disrupting agent monomethyl auristatin E (MMAE) via a protease cleavable linker. TV is being evaluated in GEN0701 (innovaTV 201), a Phase I/IIa dose-escalation and expansion study in patients (pts) with previously treated recurrent locally advanced or meta-
static solid tumors. A previous report of the preliminary expansion cohort for cervical cancer (n = 34) showed an investigator (INV)-assessed response rate of 32% (26% con-
firmed) (Vergote et al., ESMO 2017 abstract #9310). INV response for the full cervical expansion cohort (n = 55) and response by independent imaging review (IR) (n = 34) are presented here.

Methods: Key eligibility criteria included recurrent or metastatic cervical cancer that
had progressed on standard therapy, adequate organ function and ECOG 0-1. TV 2 mg/kg QW was given until progression, toxicity or withdrawal. Activity and safety were assessed by RECIST 1.1 and CTCAE 4.03, respectively. Enrollment started in
November 2015 and continued through May 2018.

Results: The full cohort has 55 pts (median age was 67 [21-74]). Updated efficacy by INV review, safety data, and reported by TV TF expression will be presented. Median age in the first 34 pts was 44 [21-74] and pts received a median of 2 prior lines for recurrent or metastatic disease. ORR by IR of 41% (95% CI: 25%-59%), including 1 CR and 13 PR. (8 [6 CR, 7 PRs] were confirmed (24%, 95% CI: 15%-44%). Confirmed response rate was concordant between INV and IR (26% and 24%). Median duration of response was 4.9 months and median PFS was 4.2 months by IR.

Conclusions: These data demonstrate that TV has encouraging activity in previously
treated recurrent or metastatic cervical cancer, an underserved population with a high
unmet need, and that responses observed with TV are numerically higher than those
achieved by historical controls. These data support the continued investigation of TV
in this population.

Clinical trial identification: NCT02001623.

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Funding: Genmab A/S and Seattle Genetics, Inc.


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Background: This phase III RCT with 1401 patients was eligible. The study arms used olaparib or niraparib or rucaparib while the control arms utilized placebo. The I statis-
tic for heterogeneity was 16.86, and the heterogeneity X² (Cochran’s Q) was 2 (P = 0.30), suggesting homogeneity. The SHDI incidence was 12 (1.28%) in PARP inhibitors group vs 3 (1.07%) in control group. The RR for SHDI was 1.14 (95% CI: 0.42 – 3.08, P = 0.79) and RD was 0.002 (95% CI: 0.001 – 0.014, P = 0.72). The RR of all-grade side effects were as follows: anaemia, 6.57 (95% CI: 4.44 – 9.90, P < 0.001); thrombocytopenia, 9.00 (95% CI: 6.19 – 15.06, P < 0.001); and neutropenia, 4.15 (95% CI: 2.79 – 6.12, P < 0.001). The RR of high-grade adverse effects were as follows: ane-
ma, 28.85 (95% CI: 10.06 – 82.72, P < 0.001); thrombocytopenia, 28.74 (95% CI: 8.24 – 100.24, P < 0.001); and neutropenia, 5.90 (95% CI: 3.01 – 11.57, P < 0.001).

Conclusions: Patients on PARP inhibitors experienced a notable increase in the risk of secondary hematological malignancies in PARP inhibitors group. Long-term follow-up of these patients is required to determine the actual relation.

Legal entity responsible for the study: Kuyz Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
965P Prognostic factors in patients with uterine leiomyosarcoma: A multi-institutional retrospective study from the Japanese gynecologic oncology group

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Background: Uterine leiomyosarcomas (uLMS) are rare and aggressive tumours. Despite complete tumour resection, uLMSs are destined to relapse, and its prognosis is poor. The prognostic factors are not sufficiently known.

Methods: We performed a multi-institutional, retrospective study of women with stage I–IV uLMS, who were diagnosed between 2000 and 2012. For all cases, the histopathological slides of primary lesions were submitted to the central pathological review. Data obtained from medical records included clinicopathological features, treatment and outcome information.

Results: In total of 259 patients (median age 54 years) were confirmed to have uLMS of which 159 (61%) were stage I, 19 (7%) were stage II, 21 (8%) were stage III, 58 (22%) were stage IV and 2 (1%) were unknown. The median disease-free survival (DFS) period was 10.2 months (95% confidence interval (CI) 13.6–24.1), and the median overall survival (OS) period was 4.42 months (95% CI 3.27–6.62). Overall, 162 (62%) patients received adjuvant treatment; 135 (60%) received chemotherapy and 8 received radiotherapy. With regard to chemotherapy regimens, 65 (42%) were given docetaxel and gemcitabine; 32 (21%) were given ifosfamide, doxorubicin and cisplatin; 10 (6%) were administered taxane and carboplatin; 39 (25%) were given other regimens and 9 (6%) were unknown. In a multivariate analysis, stage III–IV disease, high serum lactate dehydrogenase (LDH) level and no adjuvant treatment were significantly associated with shorter median DFS and OS periods. Even in stage I of the disease, high LDH level and no adjuvant treatment were significantly associated with shorter median DFS and OS.

Conclusions: Advanced stage, high LDH level and no adjuvant treatment were associated with poor prognoses. In stage I of the disease, when the tumour was confined to the corpus uteri, postoperative adjuvant chemotherapy was associated with improved survival.

Editorial acknowledgement: Enago for English language review.

Legal entity responsible for the study: Japanese Gynecologic Oncology Group.


Disclosure: All authors have declared no conflicts of interest.

966P Screening for inherited cancer syndromes in Chinese patients with endometrial cancer

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Background: Endometrial cancer (EC) is a component of several cancer syndromes especially the Lynch syndrome, caused by the germline mutations in corresponding cancer predisposition genes. This study aims to outline the mutation prevalence, clinical and biological characteristics of the cancer susceptibility genes in Chinese EC patients, and to establish a screening criterion for identifying affected individuals.

Methods: The pathologic diagnosed EC patients meeting at least one of the following criteria were involved: (1) diagnosed before 50 years, (2) personal or (3) family history of Lynch related cancers, (4) loss of any MMR protein expression by immunohistochemistry (IHC). Next generation sequencing (NGS) was used for the germline mutations detection, of which, 41 located in LS associated genes (10 MLH1, 17 MSH2, 11 MSH6 and 3 PMS2) and 2 located in non-LS genes (1 BRCA1 and 1 PALB2). 58 uncertain significance variations were also identified in 53 patients (26.6%) while 20 (34.5%) of them were located in LS genes. Two suspected germline deletion in MSH2 were detected and were still under further verification. 18 (72%) deleterious mutations were detected in the 25 patients meeting 3 or 4 inclusion criteria and 12 (23%) were detected in 48 patients meeting 2 criteria.

Conclusions: To our knowledge, this is the first NGS based study focus on inherited EC in Asian population. The high frequency of positive results indicated that multi-gene panel testing could be recommended to the patients with high risk of hereditary EC. The selection criterion used in current study is feasible and at a high sensitivity for screening the suspected inherited individuals.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

967P Clinical relevance of circulating MACC1 and S100A4 transcripts in serum of ovarian cancer patients

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Background: Metastasis-associated in colon cancer 1 (MACC1) and S100 calcium binding protein A4 (S100A4) promote metastasis. Their overexpression in the tumor was proposed as a prognostic and/or predictive biomarker for a variety of solid malignancies, including ovarian cancer. However, clinical relevance of circulating MACC1 and S100A4 transcripts as blood-borne biomarkers for ovarian cancer is unknown. Therefore, the objective of our study was to systematically track serum levels of both transcripts in the course of surgery and adjuvant therapy and to analyze their clinical relevance for ovarian cancer.

Methods: The levels of MACC1 and S100A4 transcripts were analyzed in a total of 318 serum samples from 79 ovarian cancer patients (thereof 80% FIGO III or IV), including samples at primary diagnosis and at 4 follow-up time points in the course of treatment. MACC1 was relatively quantified by RT-qPCR and S100A4 was absolutely quantified by digital droplet PCR.

Results: MACC1 and S100A4 transcripts were significantly elevated in serum of ovarian cancer patients, compared to healthy controls (p < 0.0024;p < 0.001) and showed a highly concordant (CA125 independent) dynamic in the course of treatment. Higher levels of MACC1 and S100A4 at primary diagnosis paralleled advanced disease (p = 0.0023;p = 0.04) and predicted ineffective primary debulking surgery as well as a non achievement of a macroscopically complete tumor resection (p = 0.011;p = 0.006). Moreover, higher levels of MACC1 and S100A4 at primary diagnosis indicated poor DFS (0.0033;p = 0.0019) and OS (p = 0.001;p = 0.001).

Conclusions: This is the first liquid biopsy approach, systematically analyzing MACC1 and S100A4 transcripts in ovarian cancer and proposing their prognostic capacity at primary diagnosis.

Legal entity responsible for the study: TU Dresden.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

968P Outcomes of ovarian clear cell carcinoma (OCCC) of the Vall d’Hebron Hospital/Vall d’Hebron Institute of Oncology (VHIO)

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Background: OCCC is a rare entity linked to good prognosis at early stages but chemo-resistance and poor survival in advanced setting. Molecular heterogeneity is common in OCCC, with PI3K/mTOR pathway alterations as most common drivers. The VHIO oncology group

Results: Median age was 55 years (y), FIGO (2014) stage I 51%, II 11%, III 39%, IV 9%. Primary surgery was performed in 92% achieving optimal cytoreduction in 86%. All pts received first-line of platinum (Pt)-based ChT. With a median follow-up of 9.5 y, 345
50.6% pts relapsed (13.4%, 2.1%, 62.5%, 3%, 68%, IV 50%), median OS was 11.2 y (CI95%: 6-9.4). Factors significantly associated with relapse and death in univariate Cox models were ECOG performance status and stage at diagnosis (p < 0.001). At 1st and 2nd relapse, 58 and 30% remained PR-sensitive, respectively. Median PFS with therapies after 1st relapse in a PR-sensitive setting (91% Pt combos) was 12.6 months (m) (CI95% 9.5-25.4) and in PR-resistant setting (69% non-platinum GCT) 3 m (2.5-NA). In total, 18 pts (24%) had genomic profiling (7 PIFCA mut, 1 BRCA1 mut, 1 MSH6 mut, and 16 pts (21%) received experimental agents after 1st relapse (8 antiangiogenic, 4 targeted or immunotherapy unmatchd, 4 targeted matched (3 PIFIR inchi and 1 PARP inhi). Median PFS was 4.8, 5.6 and 9.6 m respectively. When compared to non-Pru in PR resistant setting increased PFS was found with matched targeted agents (HR = 0.26, CI95% 0.1-1).

**Conclusions:** As reported in the literature, in our cohort, OCCC are more frequent diagnosed at early stages having a better prognosis. In the relapse setting Pt sensitivity and Pt-based CTX imply better outcomes. However, in the PR-resistant setting targeted therapies results in better PFS compared to CTX. Molecular profiling allows to select matched agents which may improve outcomes in this poor prognosis population. Further research in molecular characterisation and matched targeted therapy is an unmet need.

**Legal entity responsible for the study:** Vall d’Hebron Institute of Oncology (VHIO).

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**969P**

A systematic review and meta-analysis of randomized controlled trials to evaluate the risk of gastrointestinal and hepatic toxicities in patients with recurrent ovarian cancer treated with poly adenosine diphosphate ribose polymerase inhibitors maintenance.

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**Background:** Inhibition of poly adenosine diphosphate ribose polymerase (PARP) enzymes resulted in synthetic lethality in ovarian cancer cells by terminating an alternative DNA repair pathway in homologous recombination deficient tumors. Many PARP inhibitors have shown to improve survival with noteworthy safety concerns. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of gastrointestinal (GI) and hepatic toxicities.

**Methods:** We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention GI toxicities and elevation of liver function tests (LFT) either aspartate oralanine aminotransferase as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Fixed effects model was applied.

**Results:** Three phase III RCTs with 1401 patients were eligible. The study arms used olaparib or miraparib or rucaparib while the control arms utilized placebo. The ran-domization ratio was 1:1 in all studies. The RR of all grade side effects were as follows: diarrhea, 1.29 (95% CI: 1.03 – 1.58, P < 0.015); dyspepsia, 1.73 (95% CI: 1.20 – 2.49, P < 0.003); nausea, 2.11 (95% CI: 1.86 – 2.40, P < 0.001); vomiting, 2.20 (95% CI: 1.76 – 2.75, P < 0.001); dysuria, 4.38 (95% CI: 3.00 – 6.41, P < 0.001); and elevated LFT, 4.74 (95% CI: 2.82 – 7.95, P < 0.001). The RR of high-grade side effects were as follows: diarrhea, 1.225 (95% CI: 0.992 – 1.521, P = 0.060); nausea, 4.35 (95% CI: 1.45 – 13.06, P = 0.049); vomiting, 3.39 (95% CI: 1.19 – 9.63, P = 0.012); and elevated LFT, 10.19 (95% CI: 2.47 – 42.06, P = 0.001).

**Conclusions:** Our meta-analysis demonstrated that PARP inhibitors increased the risk of all grades of GI and hepatic toxicities with a relative risk of 10.19 for grade 3 and 4 elevated LFT. These toxicities have significant impact on patients’ quality of life and may ultimately affect patient’s compliance. Timely intervention with appropriate supportive care is necessary.

**Legal entity responsible for the study:** Kyaw Zin Thami / Texas Tech University Health Sciences Center

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**970P**

Evaluation of chemotherapy response score and lymphocytic infiltration as prognostic markers in ovarian cancer patients treated with neoadjuvant chemotherapy.

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**Background:** Neoadjuvant Chemotherapy (NACT) is an alternative frontline treatment in patients with advanced Epithelial Ovarian Cancer (EOC). Histopathological assessment of tumor post NACT is an ideal mean of response to treatment. The present study aims to characterize the pathological response and to examine its prognostic significance in these patients.

**Methods:** Medical records of women with EOC treated at Alexandra Hospital from 2011 to 2016 were retrospectively identified. Clinopathological data, treatment and survival data were analyzed. EDS specimens were reviewed by study pathologist and Chemotherapy Response Score (CRS), Lymphocytic infiltration, necrosis and mitosis were assessed. Survival differences were estimated using the long-rank test.

**Results:** 55 patients with EOC treated with NACT were identified, 48 had complete clinical and pathological data. Median age was 63 years. All patients had high grade disease and 45 of them had serious comorbidities. At baseline 38 patients had stage IIIC disease and stage IV. All patients received Paclitaxel-Carboplatin combination for 3 cycles. 20 patients had complete debulking (no macroscopic residual disease). 18 had optimal (macroscopic disease <1cm) and 7 suboptimal. 22 patients received also bevacizumab as part of their treatment post IDS. CRS assessed at omentum predicted PFS when adjusted for age, stage, debulking status (complete, optimal, suboptimal) and post IDS bevacizumab administration (mPFS CRS 1vs2vs3: 11.9-14.19-15.95 months CI [7.4-18.3]). [12.2-20.7] [13.5-31.3]). Lymphocytic infiltration was associated with improved OS (log-rank test p = 0.022). Presence of necrosis and mitosis per HPF did not predict either PFS or OS. BRCA status was known for 19 patients and presence of BRCA1/2 mutations was strongly correlated with lymphocytic infiltration (p = 0.011) but not CRS (p = 0.801).

**Conclusions:** Our study confirms the predictive value of CRS in EOC patients treated with NACT and IDS, but also demonstrates the prognostic significance of lymphocytic infiltration in IDS specimens. The later was associated with presence of BRCA1/2 mutations with obvious therapeutic implications.

**Legal entity responsible for the study:** Michalis Liontos

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**971P**

**Embryonic protein nodal as a novel marker of progression and drug resistance in ovarian cancer.**

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**Background:** Cancer cells can exploit normally dormant embryonic stem cell pathways to promote cancer progression. Studying embryonic signaling pathways in aggressive cancers has led to the discovery of the re-expression of the embryonic protein Nodal. It maintains pluripotency and cell plasticity of human embryonic stem cells. In many cancers Nodal signalling promotes tumor growth and metastasis. The objective of this study is to investigate the role of Nodal as a potential biomarker of ovarian cancer (OC) progression and resistance to chemotherapy.

**Methods:** We applied bioinformatics approach and RNA sequencing to investigate the impact of Nodal on biological processes in OC cells and disease outcome in OC patients (TCGA data). In vitro assays designed to assess cancer stem cell phenotypes and chemoresistance in OC cells wherein Nodal was overexpressed, or knocked out with CRISP/Cas9 genome editing were conducted. We performed IHC staining of Nodal in tissue microarrays of high-grade serious OCs (HGSO) to evaluate prognostic significance of Nodal. HGSO samples were obtained from Ovarian Cancer in Alberta and British Columbia study (OVAL-BC) cohort of OC patients (563 HGSO samples).

**Results:** RNA seq data showed that Nodal induces transcriptional reprogramming in OC cells via altering immune response, metabolism and drug resistance gene expression. In vitro, we showed that Nodal is a stress response gene which expression and protein increased in OC cells after treatment with cisplatin/carboplatin and retained for 96h after drug withdrawal. OC cells overexpressing Nodal characterized by increased resistance to cytostatic drugs, tumorigenicity and cell plasticity (partial EMT and stem cell-like phenotype). Analysis of TCGA microarrays data and IHC staining of tissue microarrays of HGSOs determined that Nodal predicts poor overall and progression-free survival in HGSO patients.

**Conclusions:** Nodal predicts poor survival in HGSO patients and likely drives tumorigenic potential and resistance to platinum in OC cells by promoting cancer stem cell plasticity and upregulating target genes involved in immune response, drug
973P Bcl-2 proteins expression and response to navitoclax in platinum resistant/refractory recurrent ovarian cancer (PROC)


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Background: Here is no convincing active treatment for patients with PROC. Anti-apoptotic Bcl-2 proteins have been implicated in chemotheray (CT) resistance. In pre-clinical studies, we demonstrated promising activity of Navitoclax, an anti-apoptotic inhibitor of Bcl-2 family, in ROC tumors, suggesting a potential action in platinum resistant pts. We conducted a multicentric phase II trial of Navitoclax monotherapy and reported modest efficacy (ESMO 2017, abstract #2269). Here we aimed to describe the relationship between Bcl-2 protein expression and response to Navitoclax; we also reported response to subsequent line of CT.

Methods: Pts (N = 46) with high grade recurrent PROC received oral Navitoclax (150 mg daily for 7 days followed by 250 mg daily for 21 days) until disease progression or toxicity. All pts had a biopsy of relapsed disease before navitoclax initiation to assess the expression level of Bcl-2 proteins by histomorphometry (HCM), as low, medium or high. We first evaluated the efficacy of Navitoclax for pts with high BIM level, with or without other Bcl-2 proteins. As a next step, we evaluated the efficacy of Navitoclax in pts with high BIM expression combined with low Mcl-1 and/or phospho-ERK. Response to subsequent CT was also described.

Results: 44 pts (with median of 4 prior lines) were assessable for efficacy: PFS was 50 days [6-234] with partial response (PR), 15 stable diseases (SD). IHC data were available for 35 pts. BIM was highly expressed in 9 pts, 4 of them with PR/SD (p = 0.68). Among them, 7 had a low expression of Mcl-1 and/or phospho-ERK, of whom 4 with PR/SD, showing no evidence of relation with clinical response. After Navitoclax, 32 pts were retreated with CT: 4PR and 9SD were noted, including 11 pts with long response (6-13 months). Median delay from previous platinum-based treatment to subsequent CT was 9 months [2-23] for PR/SD pts. Especially, 12 pts received platinum after Navitoclax with high response rate (3PR/4SD, 38%), median delay from previous platinum-CT was 18 months.

Conclusions: BIM expression, alone or combined with Mcl-1 and/or pERK, is not predictive of Navitoclax benefit. High proportion of PR/SD pts response to platinum rechallenge; the potential implication of Navitoclax needs further explorations. Other Bcl-2 family proteins (activator BH3-only BID and PUMA) expression may be more relevant. This trial is granted by the French Cancer Research Hospital Program in 2011 and the Mariapia Bressan award in GINEPS 2014.


Legal entity responsible for the study: Centre Francois Baclesse.

Funding: Abbvie.

Disclosure: All authors have declared no conflicts of interest.

973P Expression of CD4, CD8 and Foxp3 and its clinical significance in neoadjuvant chemotherapy for locally advanced cervical cancer

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Background: Cervical cancer ranks first among gynecologic malignancies. Neoadjuvant chemotherapy combined with surgery is currently a recommended treatment for locally advanced cervical cancer, however the patient’s prognosis is still poor and easy to recur even if the chemotherapy works significantly. We need more effective assessment method for local advanced cervical cancer. Therefore, we evaluated relationship between chemotherapeutic effect and prognosis on the expression of immunological biomarkers including CD4+ , CD8+ and Foxp3 pre- and post-neoadjuvant chemotherapy for locally advanced cervical cancer.

Methods: CD4+ , CD8+ and Foxp3 expression by IHC in 45 cases of locally advanced (IB2-IBB) cervical cancer pre- and post-neoadjuvant chemotherapy, computer software was used to quantitatively analyzed. The relationship between IHC results and clinicopathological characteristics, chemotheraphy efficacy, PFS and OS was analyzed by SPSS software.

Results: The expression of CD4, CD8 and Foxp3 in locally advanced cervical cancer before and after neoadjuvant chemotherapy was not related to patients’ age and size of tumor (P > 0.05), which was related to FIGO staging and histological grade. The expression of CD4 and CD8 increased significantly after chemotherapy (P = 0.016, P = 0.009), while the expression of Foxp3 decreased significantly (P = 0.0102).

Conclusions: CD4, CD8 and Foxp3 are associated with tumor staging and pathological grading in neoadjuvant chemotherapy for locally advanced cervical cancer, and the expression change of CD8 and Foxp3 before and after chemotherapy can be used as an independent prognostic indicator.

Legal entity responsible for the study: Wen Di.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

974P Clinical study on the efficacy of apatinib treatment for advanced ovarian cancer after second-line chemotherapy failure

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Background: Ovarian carcinoma has the highest mortality rate among gynecologic malignancies. Primary drug resistance and multi-drug resistance are major clinical obstacles to treatment and is the main reason for the dismal 5-year survival rate of patients. Apatinib is independently developed in China as an effective small-molecule tyrosine kinase inhibitor. It mainly functions by competitively blocking the binding of VEGF with VEGFR-2 and auto-phosphorylation of VEGFR-2, thereby inhibiting the function of VEGF in stimulating endothelial cell proliferation and migration and reducing microvascular density to elicit its anti-tumor effects.

Methods: This study is a prospective, open label, single-arm clinical trial aimed to evaluate the efficacy and safety of apatinib mesylate as treatment after failure of second-line chemotherapy in patients with advanced epithelial ovarian cancer. The study enrolled 20 patients, and 17 were evaluated. Patients received an oral dosage of apatinib (500 mg or 250 mg) once daily for 28 days as an observation cycle. The efficacy of the treatment was evaluated after three treatment cycles. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were assessed.

Results: After 3 cycles of treatment, 6 (35.3%) and 2 (11.8%) patients achieved partial response (PR) and stable disease (SD), respectively. The ORR and DCR were 35.3% and 47.1%, respectively. The efficacy of apatinib was not significantly different between patients with initial dosages of 500 mg (ORR, 39.0%; DCR, 39.0%) and 250 mg (ORR, 42.8%; DCR, 71.4%). The median PFS was 2.2 months (95% confidence interval (CI), 1.0-8.9) and the median OS was 6.3 months (95% CI, 1.5-12.8m). The most common AEs were hypertension (70.6%), hand-foot syndrome (52.9%), and oral mucosa damage (35.3%).

Conclusions: In conclusion, oral apatinib treatment was efficacious, safe, and had no serious adverse effects in patients with advanced EOC who failed second-line chemotherapy.

Clinical trial identification: ChiCTR-OOC-16008034. Registration time: 2016-03-01.

Legal entity responsible for the study: Gynecologic Department of Traditional Chinese Medicine, Shanghai Hospital.


Disclosure: All authors have declared no conflicts of interest.
Background: Patients (pts) with advanced COCC have a significantly poorer prognosis than other Epithelial ovarian cancer (EOC) subtypes. Being able to predict which pts are more likely to relapse could assist with treatment and monitoring decisions. The system inflammatory score (SIS) aims to predict postsurgical prognosis for COCC by stratifying pts into 3 groups (gps). The Risk of Ovarian Cancer Relapse (ROVAR) score aims to predict ROR for EOC following first line treatment and stratifies pts into low/intermediate (int)/high gps. We attempted to validate both scores in a non-trial population.

Methods: We reviewed the medical records for pts with COCC treated at two UK gynaecological cancer centres between 2002 and 2017. Data comprising pt and tumor characteristics, treatment and outcome. Analysis was performed using Mantel Cox and Fisher Exact Tests.

Results: 119 pts; stage I (65), II (19), III (22), IV (10) and unknown (3). ROVAR was calculated for 90 (75%) pts; 24 (20%) had incomplete data, 6 (5%) excluded for other. Pts classified into low (20%), int (44%) and high (36%) gps. ROR for low or int gps vs high p = 0.0001; ROR for low vs int gps p = 1. Compared to low/int, pts in high-risk gp were younger 53.87 yrs (34.7-72) vs 57.91 yrs (35-74), had smaller tumours 106mm (45-240) vs 136mm (50-230), with increase in both hypercalcaemia (21% vs 5%; p = 0.006) and thromboembolic events (37.5% vs 10% p = 0.0047). SIS was calculated for 67 pts (36%); 39 (58%) had insufficient data, 13 (11%) excluded for other. Pts classified into gp R8 (34.3%), 1 (37.3%) and 2 (28.3%) with no statistical difference in PFS (p = 0.918) or OS (p = 0.849) between gps.

Conclusions: ROVAR significantly predicts ROR in COCC in pts with high vs low/int risk disease. Our data suggests that the features that promote treatment-resistance are linked to paraneoplastic phenomena and emerge early in tumour development, resulting in diagnosis at a smaller size in younger women. Another possibility is that these are two pathologically similar, but ultimately distinct, disease entities from the outset. Pts with high-risk disease may benefit from more intensive follow-up and, given the chemo-resistant phenotype of the disease, early enrolment in clinical trials.

Legal entity responsible for the study: Michael-John Devlin.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 976P Comparison of PFS data across different therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AI</th>
<th>CTA</th>
<th>PARPi</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI</td>
<td>1.14 (0.98, 1.35)</td>
<td>0.73 (0.63, 0.86)</td>
<td>1.15 (1.07, 1.24)</td>
<td></td>
</tr>
<tr>
<td>CTA</td>
<td>0.87 (0.74, 1.02)</td>
<td>0.64 (0.52, 0.78)</td>
<td>1.00 (0.87, 1.16)</td>
<td></td>
</tr>
<tr>
<td>PARPi</td>
<td>1.37 (1.16, 1.6)</td>
<td>1.57 (1.38, 1.92)</td>
<td>1.57 (1.36, 1.81)</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.87 (0.81, 0.93)</td>
<td>1.00 (0.86, 1.15)</td>
<td>0.64 (0.55, 0.73)</td>
<td></td>
</tr>
</tbody>
</table>

AI angiogenesis inhibitors, CTA chemotherapy agents, PARPi poly ADP ribose polymerase inhibitors.

Conclusions: PARPi is maintenance treatment improved PFS in ovarian cancer and was relatively safer in terms of AEs caused implications when compared to other therapies. This network meta-analysis provides valuable evidence and significant insights in treatment of ovarian cancer.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.

The role of bevacizumab plus front-line chemotherapy in patients with malignant ascites of ovarian cancer

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Background: Epithelial Ovarian Cancer (EOC) is a group of different types of cancer and is the most common cause of death among women. The time at diagnosis 75% of them have stage III – IV disease. The standard of care is the combination of a taxane plus a platinum (TC) compound whereas, the addition of bevacizumab (bev) as a part of first-line treatment (TC-bev) was evaluated in many trials and has been shown to improve the PFS but OS only in retrospective subgroup analysis. Patients with ascites appear to have more aggressive disease and less overall survival. We aimed to evaluate the role of TC-bev in EOC patients suffering from ascites. Ferris et al. proved that, ascites may predict the population of women more likely to derive long-term benefit from bevacizumab.

Methods: A multi-center observational, Phase IV study, which enrolled patients with stage IIIIV EOC was conducted (11.2011-06.2014) in Greece. 314 patients were treated with front-line TC-bev (n = 205 pts) or TC (n = 109 pts) according to the physician’s choice. There were two independent cohorts of patients with similar characteristics. 83 (40.5%) and 40 (36.7%) in the TC-bev and TC groups presented with ascites. The data were collected from the patients’ records; the study has been approved by the institutional review board (IRB) of the participating centers.

Results: Patients treated with TC-bev experienced a better overall response rate (ORR) (68.7% Vs 59.5%) and less progression disease (PDI) compared to patients received TC (13.2% Vs 30.8%). It is worth mentioning that the Complete Response (CR) was 20.5% and 10% in the TC-bev and TC respectively. Partial Response (PR) was 48.2% and 43% respectively. Both of arms showed the expected toxicity and Bev-Tc was well tolerated. The median PFS was 18.1mos and 10.3mos in the TC-bev and TC group respectively (p < 0.001). OS is not mature (mOS has not reached in the TC-bev group and it is 22.5mos in the TC group) (p = 0.023). The 3 year survival rate was 55.3% and 50% in the TC-bev and TC respectively.

Conclusions: Patients with advanced or metastatic ovarian cancer and ascites are in high risk group and have worse OS and PFS. The addition of Bevacizumab to TC offer survival benefit in patients with stage III/IV EOC and ascites. We need largest studies to confirm these observations.

Clinical trial identification: NCT01982500.

Legal entity responsible for the study: The Authors.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.
Clinical trial identification: NCT03100006.

Legal entity responsible for the study: National Cancer Centre Singapore.

Funding: OncoQuest Inc.


Background: Cervical cancer (CC) is the fourth most common malignancy worldwide and 85% of new cases are diagnosed in low and middle-income countries. CC impacts women health quality of life (HQoL) although the association between socioeconomic factors and HQoL is not well described in the literature. We aim to evaluate HQoL in patients newly diagnosed with CC in Brazil.

Methods: This is a prospective, observational cohort study (EVITA) that included patients from 16 institutions in Brazil. Main eligibility criteria were age ≥ 18 years, newly diagnosed stage I to IV invasive CC. Data were collected during a medical visit and from medical charts. HQoL was assessed at baseline using EORTC QLQ-C30 and CX24 questionnaires. Educational level and household income were assessed as a continuous variable and categorized for this analysis as < 8 vs ≥ 9 years of education (21 vs 32; P = 0.0022). Other quality of life measures were not different among educational level and household income subgroups.

Conclusions: This is the most comprehensive evaluation of HQoL in cervical cancer in Brazil. Our study found that patients with advanced stage at diagnosis had worse quality of life. In patients newly diagnosed CC socioeconomic factors were of limited association with HQoL.

Clinical trial identification: NCT02671071.

Legal entity responsible for the study: Latin American Cooperative Oncology Group.

Funding: Roche.

Disclosure: All authors have declared no conflicts of interest.

Orogovomab (orego) and nivolumab (nivo) as a combinatorial immunotherapy strategy for recurrent epithelial ovarian cancer (EOC): ORION-01 phase Ib cohort


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Background: Oregon is an anti-CA 125 cancer vaccine whereas nivolumab is a programmed death-1 inhibitor. Both agents are clinically active in advanced EOC. We hypothesize that their combination will elicit a systemic CA 125 specific T cell response which is synergistic, safe and clinically efficacious in EOC patients (pts).

Methods: Pts with EOC, fallopian tube or primary peritoneal carcinoma who have received ≥2 prior chemotherapy lines were recruited in this phase Ib/IIa study. Study objectives were to characterize the safety and tolerability of orego + nivo, and determine the recommended dose for expansion (RDE) (both single agent). The combination was administered as a continuous infusion at a dose of 0.2mg Q4W (dose level 1) + nivo 240mg Q2W. Lower doses of orego were specified in case of dose-limiting toxicities (DLT). A minimum of 6 and maximum of 18 pts would be accrued for dose finding. Additional 14 pts will be treated at RP2D in the dose expansion cohort.

Results: 6 pts with median age 61 years (range 52.0 – 63.0) and EOC/PERGOM tumor status had 1 received at dose level 1. All had EOC (4 high grade serous, 2 clear cell) and a median of 4 (range 3 – 9) treatment lines before study entry. No DLT were observed. Treatment-related adverse events (AE) included grade 1 events of arthralgia, rash, transaministitis, fatigue, and anorexia. 23 (53.3%) pts experienced grade 1-2 thyroid-related immune-related adverse events (AE). No serious adverse events (SAE) were observed but they were deemed unlikely/not related to study treatment, including 2 episodes of grade 4 sepsis in 1 pt who eventually suffered of progressive disease (PD). Dose delay of orego and nivo occurred in 1 pt because of hospitalization for fever (SAE) followed by scheduling reasons. Dose omissions of nivo occurred in 2 pts due to grade 3 seizures in 1 pt, and grade 1 thrombosis in another. Analysis of exploratory immune correlate(s) is underway and will be reported at the meeting.

Conclusions: Orego 2mg Q4W with nivo 240mg Q2W was selected as the RDE/RP2D to treat EOC. Further evaluation of safety and efficacy of this novel combination is ongoing in our dose expansion cohort.

980P Genomic characterization of vulvar squamous cell carcinoma

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Background: Despite an increasing incidence, vulvar squamous cell cancer (VSCC) is still a rare disease. So far two etiological pathways have been described: A high-risk human papillomavirus (HPV)-dependent route and an HPV–independent pathway often associated with lichen sclerosus. To date, therapeutic strategies in VSCC are not influenced by molecularpathological information and therapeutic options for advanced or recurrent disease are limited.

Methods: Whole exome sequencing of DNA isolated from 34 VSCC samples and matched normal tissue for each individual was performed on an Illumina HiSeq4000. Short variant discovery was carried out using BWA and MuTect2. Variants were annotated using ANNOVAR. For the detection structural variants and copy number aberrations, Pindel, ADTEx and FREEC were employed. Presence of HPV integration sites was assessed using Bowtie2.

Results: All pts (median age 60) received surgery with (partial) vulvectomy as primary treatment. In 82% a surgical staging of the goins was performed. FIGO stages were: n = 5 IB, n = 13 II, n = 5 III and n = 7 IVa (n = 7 unknown). 10/34 (29.4%) samples were HPV positive (all HPV16). 17.6% pts suffered from recurrence (4 local, 2 groin, 1 pelvis) after a median of 10 months. TP53 mutations were most commonly detected, with 41% (14/34). Additionally, we observed mutations in the following genes, which were affected in at least three samples: MUC1A (7/34), SPIS2 (4/34), AKAP9 (4/34), TDRD15, PKD1L1, FCQ10, RABP2, FBXW7, VPS13C, MDGA2, SCN9A, VEPH1, ABC2A, KIAA0368, NCA32, GCC2, MYCIP2, PRF39, WDR49, ZNF729, UTRN, ANKRD36, GRAM1D, ADGRV1 in 3/34 samples. Significantly less mutations were detected in pts with a OS ≥ 48 months (p = 0.032). However, there was no significant difference in OS or OS between HPV positive and negative tumors (p = 0.78 and 0.92). In an univariate analysis there was a significant correlation between HPV negative tumors and TP53 mutations (p < 0.0081). No correlation between PT status, TNM status, tumor size or number of mutations and HPV status was detected.

Conclusions: The key mutation in vulvar cancer affects TP53. This first work and prospective analysis of whole exome sequencing of VSCC with corresponding normal tissue has the potential to identify further key mutations and therewith new targets for the treatment of VSCC.

Legal entity responsible for the study: The authors.

Funding: Hamburger Krebsgesellschaft.

Disclosure: All authors have declared no conflicts of interest.
Background: An estimated 12,820 women in the United States (US) will be diagnosed with cervical cancer this year, with 4,210 deaths from the disease. The economic and humanistic burden of cervical cancer has not been adequately studied.

Methods: This was a retrospective, cross-sectional analysis of Medical Expenditure Panel Survey (MEPS) data from 2006–2013. Cervical cancer cases were identified using ICD-9 CM code 180 or clinical classification software code 26. The control group consisted of women without a diagnosis of cancer. Study outcomes included healthcare resource use (institutional inpatient and outpatient, ER, and physician office visits), healthcare costs, activities of daily living (physical, cognitive, social, and activity limitations), quality of life measures (general health, SF-12v2 physical component score (PCS), mental component score (MCS), EQ-5D and SF-6D health utility, and HQ-2 depression severity). Multivariate generalized linear models (GLMs) were controlled for key sociodemographic and clinical covariates were conducted to compare study outcomes in cervical cancer cases to non-cancer controls.

Results: The analytic cohort consisted of 275,246 cervical cancer cases and 146,061,609 non-cancer controls. Cervical cancer cases were significantly older (mean age: 42.03 vs 36.98 years), and had a higher comorbidity burden (mean Charlson comorbidity index: 1.06 vs 0.66) as compared to non-cancer controls (all p < 0.05). Results from the GLMs suggested that cervical cancer cases had significantly higher institutional outpatient costs ($1,610 vs $802), physician visit costs ($2,422 vs $1,321), and total healthcare costs ($10,031 vs $4,913) (all P < 0.05) compared to controls. Cervical cancer patients had a 1.99 (odds ratio [OR]: 1.99; 95% CI: 1.23 to 3.22) and 2.56 (OR: 2.562; 95% CI: 1.78 to 3.68) times as likely to report activity limitations and poor general health as compared to controls. Cervical cancer patients had a significantly lower PCS, MCS, EQ-5D health utility, and HQ-2 depression severity (all P < 0.01).

Conclusions: Cervical cancer is associated with significant economic burden, activity limitations, and quality of life impairment among ambulatory women in the US.

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

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


Risk of fatigue and neuropathy in patients with advanced cancer treated with olaparib: A meta-analysis of randomized controlled trials


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Background: Poly ADP ribose polymerase (PARP) inhibitors are a new class of drugs that are currently being studied in several malignancies. Olaparib is FDA-approved for patients with advanced breast cancer and advanced ovarian cancer. Fatigue is the most common symptom associated with advanced cancer and treatment. Neuropathy is also a treatment related adverse event associated commonly with platinum and taxanes. We did a systematic and up to date review of the literature and a meta-analysis of randomized controlled trials (RCT) to characterize the risk of fatigue and neuropathy associated with olaparib use.

Methods: Published databases were searched for articles published till February 2018. The search was restricted to randomized controlled trials (RCTs) with olaparib and were selected according PRISMA. Safety profile from each selected study was evaluated for all-grade and high-grade fatigue and neuropathy events in control/placebo and olaparib arms. Summary incidences and the relative risk (RR), with 95% confidence intervals, of all-grade and high-grade events were calculated using random-effects or fixed-effects model based on the heterogeneity of selected studies.

Results: A total of 7 trials were selected, and included a total of 1750 patients with advanced ovarian, gastric or breast cancer. 746 patients received placebo/control treatment and 1004 received olaparib alone or in association with control. All-grade fatigue was increased by 55% (HR 1.55; 95% CI 1.14-2.09) (all P < 0.05) compared to controls. Cervical cancer patients had a 1.99 (odds ratio [OR]: 1.99; 95% CI: 1.23 to 3.22) and 2.56 (OR: 2.562; 95% CI: 1.78 to 3.68) times as likely to report activity limitations and poor general health as compared to controls. Cervical cancer patients had a significantly lower PCS, MCS, EQ-5D health utility, and HQ-2 depression severity (all P < 0.01).

Conclusions: Cervical cancer is associated with significant economic burden, activity limitations, and quality of life impairment among ambulatory women in the US.

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

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

Disclosure: All authors have declared no conflicts of interest.

Risk of cancer associated death in younger vs older patients with FIGO stage I endometrial cancer

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Background: Although age is considered a traditional risk factor for relapse in stage I endometrial cancer, whether it impacts endometrial cancer-related death is unclear. We aimed to assess disease risk factors, overall survival (OS), disease-free survival (DFS), and cancer-specific survival, in patients >70 (OP) vs <70 (YP) years of age with or without adjuvant therapy.

Methods: We reviewed medical records of all patients who underwent surgery for stage I endometrial cancer between 2000 and 2013 in British Columbia, Canada. Descriptive, logistic regression, multivariate Cox regression and competing risks analyses were used to evaluate patient outcomes.

Results: 365 OP and 1063 YP were included (n = 1428). No significant differences were found between OP and YP with regards to disease risk factors such as stage IB disease and lymphovascular invasion (LVI). However, OP had higher odds of non-endometrioid histology (OR 1.88, p < 0.001). 22.6% OP and 77.3% YP received adjuvant chemotherapy (CT) (OR 0.209 and 2.73 P < 0.05). OP received adjuvant radiotherapy (RT). When adjusted for histology, LVI and grade, YP were more likely to receive CT (OR 2.10, p < 0.009); no significant difference in odds of receiving RT was found between YP and OP (OR 0.86, p = 0.33). OP experienced higher odds of relapse (OR 1.78, p < 0.001) and worse OS (HR 1.22, p < 0.001) than YP after adjusting for risk factors. 10-year OS (endometrioid: 61.9 vs 89.2%, non-endometrioid: 46.1 vs 85.8%, p < 0.001) and DFS (endometrioid: 86.7 vs 91.9%, non-endometrioid: 69.6 vs 84.5%, p < 0.001) were worse for OP. Controlling for risk factors, OP experienced a higher incidence of endometrial cancer-related death than YP (HR = 2.09, p < 0.001).

Conclusions: In patients with stage I endometrial cancer, patients >70 years had higher odds of having non-endometrioid histology as well as relapse and death due to endometrial cancer, yet were less likely to receive adjuvant CT. Appropriate adjuvant therapy should be considered regardless of age, as recurrent disease is still a significant cause of mortality in older patients with stage I endometrial cancer.

Legal entity responsible for the study: BC Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
PFS and safety are summarised below. In multivariable Cox regression analysis, neither age nor number of comorbidities was prognostic for PFS.

Conclusions: Older patients were more likely to receive single-agent chemotherapy, have ongoing comorbidities and have worse surgical outcome than their younger counterparts. However, median BEV exposure, incidence of grade 3/4 AEs and median PFS were similar in younger and older patients. Grade ≥ 3 AEs were more common in patients with ≥ 3 comorbidities but BEV was similar.

Clinical trial identification: NCT01863693.

Editorial acknowledgement: Medical writing assistance was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd, Ashbourne, UK), funded by Roche Products Ltd.

Legal entity responsible for the study: Roche Products Ltd.

Funding: Roche Products Ltd.


985P
Prolonged survival (SV) associated with pulmonary metastasectomy (PM) for carcinomas of the cervix (CC)

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Background: CC is a public health problem in developing countries. Dissemination is typically lymphogenic but can develop hematogenous metastases. Chemotherapy alone is associated with a median SV of 13 months on metastatic disease. In selected cases with isolated lung metastases (LM), PM is associated with prolonged SV.

Methods: Observational, retrospective cohort. Patients (ptes) with CC who underwent PM at the National Cancer Institute (INCan) Mexico from January 2005 to December 2017. Primary end-points were Overall Survival (OS) and Disease-Free Survival (DFS). Secondary end-points were morbidity and mortality of PM.

Results: A total of 29 ptes were identified. Squamous carcinoma was primary histology in 21 (72.4%). Most presented with advanced tumors at initial diagnosis, 11 (37.9%) stage III and 7 (24.1%) stage IV. Unilateral nodules were seen in 27 (93.1%) and a single nodule was present in 24 (82.4%). Nodules were diagnosed as metastatic (after 6 months of diagnosis) in 21 (72.4%). Surgery was the initial treatment in 25 (86.2%) and only 4 (13.8%) received pre-operative chemotherapy. A wedge resection was performed in 16 (55.2%), interestingly, a lobectomy was needed in 12 cases (41.4%) and 1 case required a pneumonectomy. One case developed hemithorax requiring exploration for a 90-day morbidity of 3.4% and 90-day mortality was 0%. An R0 resection was achieved in 26 (69.7%). On pathological analysis, only in 20 ptes (69%) LM were confirmed, in the other ptes a benign condition was diagnosed. Postoperative chemotherapy was indicated in 12 cases. Median follow up was 101.5 months (6 – 260). For SV analysis only ptes with proved LM were included. Median OS has not been reached, 5-year OS 35%. Median DFS 100 months (6.4 -193.5) Only R2 resection (p=0.05), no postoperative chemotherapy (p=0.025) and disease relapse (p=0.007) were statistically significantly associated with a worst SV.

Conclusions: In our cohort, PM is associated with better OS than chemotherapy alone. Although some ptes required a lobectomy, a very low morbidity and zero mortality in our cases is very encouraging. PM should be considered as fundamental part of multidisciplinary treatment in cases of CC with isolated LM.

Legal entity responsible for the study: Jose Francisco Corona-Cruz.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 984P

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Age, years</th>
<th>No. of comorbidities</th>
</tr>
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<tbody>
<tr>
<td>&lt;70 (n = 219)</td>
<td>≥70 (n = 80)</td>
<td>&lt;3 (n = 109)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>160 (73) 59 (27)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>65</td>
<td>200 (91)</td>
<td>70 (88)</td>
</tr>
<tr>
<td>No microscopic residual disease</td>
<td>11 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>56 (26) 58 (26)</td>
<td>13 (16) 27 (34)</td>
</tr>
<tr>
<td>1</td>
<td>11 (5) 94 (43)</td>
<td>6 (8) 34 (43)</td>
</tr>
<tr>
<td>Pre-existing hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>49 (22)</td>
<td>33 (41)</td>
</tr>
<tr>
<td>2</td>
<td>11 (5)</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Pre-existing diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13 (6)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>2</td>
<td>214 (98) 2 (1) 3 (1)</td>
<td>71 (89) 9 (11) 0</td>
</tr>
</tbody>
</table>

*Stage III with ≥ 1 cm residuum, any stage N, or no surgery.
**Includes essential hypertension.
†Includes high protein level in urine.
‡Gastrointestinal perforation, febrile neutropenia, cardiac arrest, pneumonia, metastases to meninges.
§Abdominal pain, pneumonia aspiration. AE = adverse event.
Results: Of the 153 patients, 56 (37%) experienced at least one of the three AEs evaluated within the first three months after niraparib initiation, and 49 (32%) experienced only grades 1/2 AEs. Among the 153 patients, fatigue was reported for 24% (36/153) (CI 17.4% - 31.6%); nausea for 16% (25/153) (CI 10.5% - 22.2%) and thrombocytopenia for 14% (21/153) (CI 8.3% - 19.2%). Of the 21 patients with thrombocytopenia, 3 were grade 3/4 severity (2% of overall). Among the patients, 4% (6/153) had a dose interruption, 1% reduced their dose (17/153), and 2% discontinued niraparib altogether (3/153) due to AEs.

Conclusions: While over 60% of patients in the phase 3 clinical trial reported experiencing the three AEs observed in the study, only 37% reported such in real-world usage. This difference may be due to the higher dosing in the trial study (initial dose of 300 mg/day vs. 200 in the observational study). Additional real-world research is needed to understand the effects of niraparib dosing on AEs.

Legal entity responsible for the study: Clarity Pharma Research, LLC.

Funding: Tesaro, Inc.

Disclosure: All authors have declared no conflicts of interest.

Table: 987P

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<tr>
<th>NIMES-ROC</th>
<th>PRIOR USE OF ANTIANGIOGENICS</th>
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</thead>
<tbody>
<tr>
<td>Yes (n = 96)</td>
<td>No (n = 62)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>62 (39-81)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41 (42.7)</td>
</tr>
<tr>
<td>1</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>28 (29.2)</td>
</tr>
<tr>
<td>Papillary/serous cancer</td>
<td>75 (78.1)</td>
</tr>
<tr>
<td>Platinum sensitivity</td>
<td></td>
</tr>
<tr>
<td>Partially platinum-sensitive ROC (PFI &gt;12 m)</td>
<td>66 (68.8)</td>
</tr>
<tr>
<td>Fully platinum sensitive ROC (PFI &gt;12 m)</td>
<td>50 (52.1)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td>Prior surgery, n (%)</td>
<td>88 (91.7)</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>95 (99.0)</td>
</tr>
<tr>
<td>Prior platinum-based therapy, n (%)</td>
<td>96 (100)</td>
</tr>
<tr>
<td>Prior bevacizumab, n (%)</td>
<td>81 (84.4)</td>
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</table>

Table: 987P Continued

<table>
<thead>
<tr>
<th>NIMES-ROC</th>
<th>PRIOR USE OF ANTIANGIOGENICS</th>
</tr>
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<tbody>
<tr>
<td>Number of T+PLD cycles, median (range)</td>
<td>6.0 (1-34)</td>
</tr>
<tr>
<td>In-patients only</td>
<td>24 (25.0)</td>
</tr>
<tr>
<td>Out-patients only</td>
<td>58 (60.4)</td>
</tr>
<tr>
<td>Both</td>
<td>8 (8.3)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Progression-free survival (PFS), months (95% CI)</td>
<td>17.7 (13.2-nr)</td>
</tr>
<tr>
<td>PFS at 6 months, months (95% CI)</td>
<td>70.9 (60-79)</td>
</tr>
<tr>
<td>PFS at 12 months, months (95% CI)</td>
<td>39.1 (27-51)</td>
</tr>
<tr>
<td>Overall survival (OS), months (95% CI)</td>
<td>17.7 (13.2-nr)</td>
</tr>
<tr>
<td>Compete response (CR)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>25 (26.0)</td>
</tr>
<tr>
<td>Not evaluable / Missing</td>
<td>15 (15.6)</td>
</tr>
</tbody>
</table>

*Patients may be represented in multiple categories. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PS, performance status; ROC, recurrent ovarian cancer; T, trabectedin.

158 patients from 50 sites across Europe were evaluated. Median number of trabectedin+PLD cycles received per patient was 6, with 95 patients (59.6%) receiving ≥6 cycles and up to 34 cycles. Median treatment duration was 22.2 weeks (range: 3-124), with no statistical difference concerning prior use of antiangiogenics, and mostly on an outpatient basis (≥80% of patients). Bevacizumab was the most used antiangiogenic in 84% of patients. With 73 PFS events and 32 deaths recorded, median PFS (11.4 months; 95% CI: 10-14) and OS (see Table) was significantly larger in patients not pretreated with antiangiogenics (PFS: p < 0.009; OS: p < 0.018). Non-angiogenic pretreated patients also obtained better overall response rate (ORR = 47% vs 32%) and disease control rate (ORR = SD: 79% vs 58%). A total of 108 trabectedin-emergent adverse reactions (TEAR) occurred. Most common grade 3/4 TEARs were neutropenia (29%) and asthenia (4%). The toxicity profile between subgroups was not different from that of the overall population.

Conclusions: Our results confirm that trabectedin+PLD is active in patients with PSROC with an acceptable and manageable safety profile. Overall our data favorably compare with those of the pivotal OVA-301 trial (NCT00113607) and suggest major benefits in patients non-pretreated with antiangiogenics who obtained significantly longer PFS.

Clinical trial identification: NCT02825420; ET-D-031-14.

Editorial acknowledgement: The authors would like to acknowledge Adnan Tanović (PharmaMar) for providing writing assistance for the manuscript.

Legal entity responsible for the study: PharmaMar, S.A.

Funding: PharmaMar, S.A.

Disclosure: All authors have declared no conflicts of interest.

987P Trabectedin plus pegylated liposomal doxorubicin (PLD) in patients with platinum-sensitive recurrent ovarian cancer (PSROC) regardless of prior use of antiangiogenics: First results of an observational, prospective study

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Background: The non-interventional NIMES-ROC phase IV trial (NCT02825420) aimed to evaluate trabectedin (1.1 mg/m²) + PLD (30 mg/m²) in real-life clinical practice and given in accordance with the marketing authorization for patients with PSROC regardless of previous anti-angiogenic treatment.

Methods: Eligible patients were adults with PSROC who have received ≥1 cycle of trabectedin+PLD before inclusion. The primary endpoint was to assess the PFS according to investigator criteria.

Results:
Table: 988P Clinical endpoints for Ctx before and after IT

<table>
<thead>
<tr>
<th></th>
<th>OC (n = 18)</th>
<th>CC (n = 8)</th>
<th>EC (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ctx pre</td>
<td>IT</td>
<td>Ctx post</td>
</tr>
<tr>
<td>Median PFS (95% CI) months</td>
<td>9.62 (7.8-11.4)</td>
<td>3.43 (1.9-12.4)</td>
<td>8.2 (2.97-NA)</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>61%</td>
<td>11%</td>
<td>39%</td>
</tr>
<tr>
<td>CBR (%)</td>
<td>72%</td>
<td>44%</td>
<td>44%</td>
</tr>
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**B989P** Benefit from subsequent conventional cytotoxic chemotherapy (CTX) to immunotherapy (IT) in patients (pts) with gynaecological malignancies (GM)

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**Background:** IT has been a breakthrough for the treatment of many tumour types, nevertheless it’s use in GM remains an area of ongoing clinical research. Early evidence suggests that IT treatment may sensitize to subsequent CTxs. Our aim was to investigate the efficacy of pre- and post-IT CTxs in a cohort of GM.

**Methods:** From 2014 to 2017, 60 GM pts were treated with IT in phase I/II trials at Vall d’Hebron Hospital. Data was retrospectively collected from those pts who received Ctx pre- and post-IT. Endpoints: Progression free survival (PFS), clinical benefit rate (CBR) at 6 months (m) and overall response rate (ORR).

**Results:** A total of 28 (47%) pts (18 ovarian cancer (OC), 8 cervical cancer (CC) and 2 endometrial cancer (EC)) with median age of 53 (31-77), ECOG 0-1 (95%) and 2 medium (1-5) pre-IT CTx lines were identified. IT was single agent PD1/L1 inhibitor in 46% of cases, the remaining receiving a combination of IT drugs. Median PFS on IT was 3.0m (2.0-5.3), CBR was 36% and ORR 10%. Platinum-based CTx was given to 83% of the patients pre-IT and 50% post-IT. The table summarizes clinical endpoints stratified by tumor type. Of note, 2 OC pts had longer PFS with platinum-based CTx post-compared to pre-IT (15.9 vs 5.4 m and 21.4 vs 16.5 m). Such pattern was not observed in any pt with CC or EC. There was no association between benefit on IT and pattern of response to pre-IT Ctx.

**Conclusions:** A significant proportion of heavily pretrated GM pts are still treated with Ctx after failure of IT. Although limited by sample size, our study did not show signals of improved sensitivity to Ctx post-IT. GM pts retained the potential to respond to subsequent Ctx. Further studies are needed to define the optimal timing of IT and to define potential predictors of improved Ctx benefit.

**Legal entity responsible for the study:** Vall d’Hebron Institute of Oncology (VHIO).

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**B990P** Identification research and application for protein phosphorylation modification sites in human ovarian carcinoma

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**Background:** Phosphorylation modification, as one kind of protein post-translational modification (PTM), increases the diverse protein functions such as cell signaling, protein folding, enzymatic activity, protein degradation, and their subcellular location. However, the subcellular phosphoproteomic of ovarian carcinoma mitochondrial proteins hasn't been elucidated.

**Methods:** Here, an 8-plex isobaric tag for relative and absolute quantification (iTRAQ) proteomics was used to identify mitochondrial expressed proteins (mEPs) and phosphorylation modification sites of ovarian carcinomas relative to controls, followed by bioinformatics analysis.

**Results:** The iTRAQ based proteomics identified 5115 proteins and 99 phosphorylated proteins with quantitative information from purified mitochondrial samples, and 262 proteins were significantly related to overall survival in ovarian cancer patients. Interestingly, the results demonstrated that cancer cells exhibit an increased dependence on lipid metabolism, such as biosynthesis of unsaturated fatty acids, butanoate metabolism, fatty acid degradation, fatty acid metabolism, which might play an important role in ovarian carcinoma invasion and metastasis. Moreover 33 proteins related to lipid metabolism as potential markers for the development of ovarian carcinoma were identified. Additionally, 3 drug-associated phosphorylation proteins and 3 phosphoprotein sites as tumor markers in the plasma were obtained. The 99 phosphorylated proteins and TCGA data were integrated, thus obtained 9 important proteins. Among those, ESRP6 were highly related with lipid metabolism. In cells with increased Hsp60 levels both the amounts of total mitochondrial short-chain acyl-CoA dehydrogenase (ACADs) proteins and folded ACADs were increased, which may influence mitochondrial protein folding and lipid metabolism.

**Conclusions:** The current study provides a large-scale mitochondrial proteomic profiling and mitochondrial phosphoproteome with quantitative information, a certain number of proteins with the potential biomarkers, drug targets and a novel vision in the lipid metabolism bio-mechanism of human ovarian carcinoma.

**Legal entity responsible for the study:** Hunan Engineering Laboratory for Structural Biology and Drug Design, Xiangya Hospital, Central South University.

**Funding:** Xiangya Hospital Funds for Talent Introduction (to XZ), the grants from China “863” Plan Project (Grant No. 2014AA020610-1 to XZ), the National Natural Science Foundation of China (Grant No. 81372798 and 81572278 to XZ), and the Hunan Provincial Natural Science Foundation of China (Grant No. 14J1008 to XZ).

**Disclosure:** All authors have declared no conflicts of interest.

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**9999P** Enhancing prognosis prediction using nodal SUVmax and HPV status in cervical squamous cell carcinoma

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**Background:** A risk stratification model using metabolic variables on PET/CT combined with other known prognostic factors has not been proposed. To evaluate the prognostic classification model for predicting tumor recurrence using metabolic parameters on F-18 FDG PET/CT, status of human papillomavirus (HPV) infection and known prognostic variables in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy (CCRT).

**Methods:** A total of 129 patients with cervical squamous cell carcinoma who underwent initial CCRT were eligible for this study. The clinical, pathological parameters, HPV status and metabolic parameters of pre-operative F-18 FDG PET/CT were used for analysis. Univariate and multivariate analysis for disease-free survival (DFS) were performed using traditional prognostic factors, metabolic parameters and HPV infection. Classification and regression decision tree (CART) was used to establish new classification.

**Results:** Among 129 patients, 29 patients (22.5%) had recurrence after a median follow-up of 60 months (range, 3–125 months). In univariate analysis, FIGO stage, tumor size, status of para-aortic lymph node metastasis, Nodal SUVmax, HPV positive were statistically significant in DFS. Multivariate analysis revealed that tumor size, paraaortic lymph node metastasis, nodal SUVmax and HPV infection status were independent prognostic factors. CART analysis classified the patients into three groups. First node was nodal SUVmax and HPV status was second node for patients with nodal SUVmax ≤7.49 (p < 0.001). Group A (nodal SUVmax >7.49 and HPV negative), group B (nodal SUVmax >7.49 and HPV positive) and group C (nodal SUVmax >7.49). There was significant difference of DFS among 3 groups (p = 0.0012).

**Conclusions:** The present study revealed that the nodal SUVmax on F-18 FDG PET/CT and HPV infection status before CCRT are powerful independent prognostic factor for the prediction of disease free survival in patients with cervical squamous cell carcinoma who underwent initial CCRT. Furthermore, simple prognostic classification model using nodal SUVmax and HPV infection status can provide classification of recurrence.

**Legal entity responsible for the study:** The authors.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Background: Approximately 15% of ovarian cancer (OC) incidence is attributed to germ-line mutations in BRCA1 or BRCA2 genes. Being a distinct biological subset of OC disease, BRCA1/2–driven cancers are usually characterized by good response to chemotherapy. However, even if OC patient undergoes complete surgical cytoreduction and potentially effective systemic therapy, the probability of the tumor relapse is high. This study aimed to compare some essential clinical features of OC relapses in hereditary vs. sporadic OC.

Methods: We identified 212 women with relapsed high-grade serous OC, who were treated in the N. N. Petrov Institute of Oncology within years 2000–2014, underwent complete primary (n = 113) or interval (n = 99) surgical debulking, and had available clinical data for analysis. 66 women were BRCA1/2–germline mutation carriers and 146 were mutation negative. Recurrences were classified according to anatomical location (local, regional, distant, markers), type (systemic or discrete) and pattern of spread.

Results: As expected, median PFI (platinum-free interval) in BRCA1/2 carriers was longer as compared to sporadic cases (13.2 months vs. 8.0 months) [p < 0.001]. The proportion of OC cases with PFI > 12 months was significantly higher among BRCA1/2 carriers [38/66 (58%) vs. 51/146 (35%), p = 0.003]. There was no statistical difference in the frequency of distant relapses between these groups [10/66 (15%) vs. 31/146 (21%), p = 0.4]. Systemic recurrences (i.e., multiple lesions) occurred significantly more frequently in sporadic cases as compared to patients with BRCA1/2 mutation [58/146 (40%) vs. 30/66 (46%), p = 0.02] and were associated with shorter duration of PFI [p = 0.003]. The proportion of patients who could be subjected to the local treatment (locoregional discrete recurrence with lymphatic/transcoelomic spread) was higher among BRCA1/2 mutation carriers than non-carriers [29/66 (44%) vs. 45/146 (31%), p = 0.045].

Conclusions: BRCA1/2–driven OC are characterized by more favorable mode of relapse than sporadic high-grade serous ovarian cancers.

Legal entity responsible for the study: N. N. Petrov Institute of Oncology.

Funding: Russian Science Foundation [grant number 14-25-00111].

Disclosure: All authors have declared no conflicts of interest.
Background: Low grade serous carcinomas (LGSC), accounting for approximately 10% of the ovarian tumors, are associated with a better prognosis compared to high-grade serous carcinomas (HGSC). Nevertheless, we are confronted with a challenging treatment, since the median age at diagnosis is younger (55.5 years versus 62.6 years), standard platinum-based chemotherapy is less effective and most importantly, it has treatment strategies in Germany.

Results: From December 2017 to January 2018, a total of 180 participants took part in the survey (28% head physicians; 46% senior physicians). The median age was 49 years.

Methods: An anonymous, digital multiple-choice questionnaire, including 38 questions, was developed and provided to gynaecologists, gynaecologic oncologists and oncologists via Internet.

Results: Of 180 participants who took part in the survey (28% head physicians; 46% senior physicians). The median age was 49 years.

Conclusion: The results of this study underline the uncertainty in the treatment of LGSC. The implementation of our own treatment strategies and a prospective register for LGSC in Germany, in particular, would be necessary and planned.

Legal entity responsible for the study: North-Eastern German Society of Gynecological Oncology (NOGGO), Berlin, Germany.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
months. Eight patients were treated with surgery, 15 with whole brain radiotherapy (RT), 5 with stereotactic RT and 4 patients received systemic treatment at the moment of BM diagnosis. Median follow up was 18.7 months and median OS was 10.8 months. Factors associated to OS were as following: platinum sensitivity recurrence (HR 0.34, CI95% 0.12-0.96; p = 0.049), higher number of previous treatment lines (HR 1.57, CI95% 1.12-2.19; p = 0.008), ECOG performance status (HR 2.52, CI95% 1.24-5.08; p = 0.010), and longer interval from initial diagnosis to BM (p = 0.025). Notably, number of brain metastasis, largest tumor size and progression outside CNS were not related to survival.

Conclusions: Factors related to sensitivity to platinum therapy and BM as early event during the course of disease seem to be more related to survival than factors usually related to survival in BM from other cancers.

Legal entity responsible for the study: A.C. Camargo Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

998TIP Pamiparib, a novel PARP 1/2 inhibitor, monotherapy for gBRCAm patients with recurrent ovarian, fallopian, and primary peritoneal cancer: An open-label, multicenter, phase II trial in China

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Background: Poly (ADP-ribose) polymerase inhibitors (PARPs) represent a class of antitumor agents that exert their cytotoxic effects by inhibiting PARP activity. PARPis are also capable of trapping PARP proteins complexes on damaged DNA, further aug- menting cell death. Pamiparib is a selective PARP1/2 inhibitor with potent PARP trap- ping ability that can cross the blood-brain barrier and has demonstrated antitumor activity in both in vitro and in vivo nonclinical tumor models harboring BRCA gene mutations (BRCAmut), and other homologous recombination deficiencies. In Phase I studies (NCT02361723; NCT03339315), single-agent pamiparib was generally well tol- erated and showed antitumor activity, notably in patients with high-grade non-mucio- nous ovarian cancer (HGOC). Antitumor activity was observed in patients with BRCA mutant and BRCA wild type ovarian cancers, whose tumors were either sensitive or had platinum-resistant disease. Data from these Phase 1 studies support the recommended Phase 2 pamiparib monotherapy dose of 60 mg PO BID.

Trial design: In this ongoing study of pamiparib in China (NCT03339195), patients with HGOC harboring germline BRCAmut who have received ≥2 prior lines of therapy are being enrolled in the Phase 2 part of the study. Patients with either platinum-sensitive (progression occurring ≤6 months after last dose of platinum) or platinum-resistant (progression occurring >6 months after last dose of platinum) HGOC are eligible. Germline BRCAmut status is identified or confirmed by central testing before enrollment. Approximately 180 patients with HGOC (platinum-sensitive, n = 80; platinum- resistant, n = 20) will receive pamiparib 60 mg PO BID until disease progression. The primary objective is to assess overall response rate according to RECIST v1.1; secondary objectives include assessment of pamiparib’s safety, tolerability, and pharmacokinetic profile. Evaluation of antitumor activity will include an estimation of overall and pro- gression-free survival, as well as duration of clinical response.

Clinical trial identification: NCT03339195.

Editorial acknowledgement: Medical writing and editorial support was provided by Regina Switzer, PhD (Suicent/Choice Medical Communications, Chicago, IL).

Legal entity responsible for the study: BeiGene, Ltd.

Funding: BeiGene, Ltd.

Disclosure: T. Gu, K. Zhang, J. Liang, S. Mu, R. Ge, H. Yang, V. Huang, R. Brachmann, L. Wang, M. Li: Employee: BeiGene. All other authors have declared no conflicts of interest.

1000TIP OPINION: A single-arm, open-label, phase IIb study of olaparib maintenance monotherapy in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSROC) and without germline BRCA mutations (non-gBRCAm)

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Background: Olaparib (tablet formulation) is approved in the US for maintenance treatment of PSROC based on 2 pivotal studies (Study 19 [NCT00735345], SOLO2 [NCT01874535]), which showed a significant progression-free survival (PFS) benefit. In Study 19, clinical benefit was observed in pts with or without BRCA mutations, supporting the hypothesis that platinum sensitivity is a surrogate marker for homologous recombination deficiency (HRD). This study was designed to further prospectively explore olaparib activity in non-gBRCAm pts.

Trial design: This single-arm, open-label, multicenter, phase 3b study (OPINION; NCT03402841) was designed to assess the efficacy and safety of olaparib maintenance therapy in women with non-gBRCAm, high grade serous or endometrioid PSROC. Eligible pts (≥18 y, ECOG PS 0–1, ≥2 lines of prior platinum therapy [PT], and in response [CR/PR] to last PT) will be treated with olaparib 300 mg tablets twice daily until disease progression or unacceptable toxicity. Primary endpoint is investigator-assessed PFS (RECIST v1.1). Secondary endpoints are time to first subsequent therapy or death, time to treatment discontinuation or death, chemotherapy-free interval, PFS by tumor HRD status, and health-related quality of life (EORTC QLQ C-30). Safety and tolerability also will be assessed. Exploratory endpoints are overall survival, evaluating treat- ment impact and disease state on health state utility (EQ-5D-5L), and PFS in pts stratified by molecular subgroups (including mutations in HR repair genes, microsatel- lite instability status, TP53 mutation status, and tumor mutational burden score). Correlation between HRD status from tumor and circulating tumor DNA in matched pts also will be explored. A sample size of 230 pts was opted for adequate level of precision for PFS estimation, with mean 95% CI width at ±10 mos after first pt is

999TIP OVARIO: A single-arm, open-label phase II study of maintenance therapy with niraparib + bevacizumab (bev) in patients (pts) with advanced ovarian cancer (OC) after response to frontline platinum-based chemotherapy (chemo)

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Background: Most pts with advanced OC will experience recurrence within 2 years of initial platinum-based treatment. An unmet need exists for therapies that delay disease recurrence. Niraparib (Zejula®) is a selective poly (ADP-ribose) polymerase (PARP) 1/ 2 inhibitor approved for maintenance in pts with recurrent OC, regardless of BRCA or homologous recombination deficiency (HRD) status. Bev is a VEGF inhibitor approved in OC for treatment and maintenance therapy. Targeted therapies + VEGF inhibition showed synergy in preclinical models. Induction of intratumoral hypoxia downregulating BRCA and RAD51 may sensitize tumours to PARP inhibition and lead to apoptosis via contextual synthetic lethality. Niraparib + bev is being explored in the treatment setting in the ongoing phase II 1/2 AVANOVA trial, which has shown that nira- parib can be safely combined with bev. In OVARIO, niraparib + bev will be evaluated in the maintenance setting in pts with advanced OC who have recovered from primary debulking surgery and responded to frontline platinum-based chemo with bev.

Trial design: Target enrolment is 90 pts, regardless of BRCA or HRD status, with stage 3b and 4 epithelial ovarian, fallopion tube, or peritoneal cancer. Pts must achieve complete or partial response or no evidence of disease after frontline platinum-based chemo with bev. The starting dose of niraparib will be based on baseline body weight and/or platelet count. Pts weighing ≥77 kg with a platelet count of ≥ 150,000/μL will receive 300 mg qd. Pts weighing <77 kg or with a platelet count of <150,000/μL will receive 200 mg qd. The bev dosage will be 15 mg/kg qw up to 15 months. Pts will be treated continuously until disease progression or unacceptable toxicity. The primary objective for OVARIO is progression-free survival at 18 months. Secondary objectives include overall survival, time to first subsequent therapy, and safety and tolerability.

Clinical trial identification: NCT03336693.

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Legal entity responsible for the study: Tesaro, Inc.

Funding: Tesaro, Inc.


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A phase II clinical trial of veliparib and topotecan in patients with platinum resistant ovarian cancer


Background: Preclinical observations indicate that addition of PARP inhibitors to topoisomerase I-directed agents such as topotecan results in increased antitumor efficacy in vitro and in vivo. However, when veliparib or olaparib were combined with conventional 5-day topotecan in patients, the regimens were quite myelosuppressive. In contrast, a phase I trial of veliparib in combination with weekly topotecan, a less myelosuppressive but routinely used regimen, demonstrated a manageable safety profile and early signs of activity. This was manifested by responses or disease stability for 4 months in 52% of patients, particularly in ovarian cancer patients with deleterious germline repair pathway mutations. Therefore, a phase 2 clinical trial is now underway.

Trial design: This single arm, multi-center clinical trial is open and available at Experimental Therapeutics Clinical Trials Network (ECTION) sites in the US. The primary endpoint is response rate and the secondary endpoint is progression free survival. Correlative goals include assessing differences in toxicity and efficacy based on BRCA1/2 mutation status as well as evaluating the association between pretreatment tumor cell levels of topoisomerase 1, PARP, HR, BRC fashionable and P-glycoprotein and response. Eligible patients must have platinum resistant ovarian, primary peritoneal or fallopian tube cancer and have received 2 or fewer prior chemotherapy regimens or have performance status of 0, 1 or 2; adequate bone marrow, renal and hepatic function are also required. No prior PARP inhibitor therapy is allowed.

Clinical trial identification: NCT01012817.

Disclosure: All authors have declared no conflicts of interest.
reduce long-term complications associated with chemoradiation and improve patient quality of life.

**Trial design:** Eligible patients are women aged ≥ 18y diagnosed with invasive cervical cancer stages IB2, IIA or IIB. The stage will be assessed by clinical examination and confirmed by pelvic MRI, CT of upper abdomen and CT of thorax. ECOG PS 0-1 and adequate organ function are required. Two hundred and forty-four patients will be randomly assigned to one of two arms. In arm 1, patients will receive standard chemoradiation (cisplatin 40mg/m² IV: D1, D8, D15, D29 and D36 in concomitancy with external radiation 50.4Gy fractionated in 28 sessions of 1.8Gy followed by brachytherapy in four insertions of 7 Gy). In arm 2, patients will receive intravenous neoadjuvant chemotherapy (cisplatin 75mg/m² D1 plus paclitaxel 80mg/m² D1, D8 e D15, each 21 days, 3 cycles. After each cycle, the patient will be evaluated to verify toxicity and tumor response. After the third cycle, the patients with a complete clinical response or substantial tumor reduction (tumor restricted to cervix ≤4 cm), confirmed by pelvic MRI will undergo Piver-Rutledge class III abdominal hysterectomy and pelvic lymphadenectomy 3-6 weeks after the last cycle. Patients with tumor progression or severe toxicity after any cycle of neoadjuvant chemotherapy, or with inoperable tumor after the third cycle of neoadjuvant chemotherapy will be treated with definitive standard chemoradiation. The primary end point will be 5-years overall survival. Secondary endpoints will include survival free of disease, the rate of operability and complete pathological response in the neoadjuvant arm. The study is ongoing; one patient has been included, and three more are under preliminary evaluation for eligibility.

**Clinical trial identification:** UTN: U1111-1213-5169.

**Legal entity responsible for the study:** Division of Gynecologic Oncology - Department of Gynecology and Obstetrics - Ribeirão Preto Medical School - University of São Paulo.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
HAEMATOLOGICAL MALIGNANCIES

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Final overall survival results of frontline bortezomib plus rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) vs R-CHOP in transplantation-ineligible patients (pts) with newly diagnosed mantle-cell lymphoma (MCL): A randomized, open-label, phase III (LYM-3002) study

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A revised international prognostic score system for Waldenström’s macroglobulinemia

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Copanlisib monotherapy activity in relapsed or refractory indolent B-cell lymphoma: Combined analysis from phase I and II studies

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Impact of initial treatment (tx) on HRQoL and outcomes in patients (pts) with newly diagnosed multiple myeloma (NDMM) without intent for immediate transplant (SCT): Results from the Connect\textsuperscript{R}MM registry

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PD CD13 and CD33 CAR-T cells for the treatment of myeloid malignancies

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The identification of the AXL/Gas6 signalling axis as a key player of myelodysplastic syndrome (MDS) and the potential of the oral selective AXL inhibitor bemcentinib in the treatment of MDS


1009PD

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ALK positive anaplastic large cell lymphoma: Molecular diagnosis and minimal residual disease monitoring

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1010PD

1011PD

Intensified 14-day rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP14) compared to RCHOP21 in patients with newly diagnosed diffuse large B cell lymphoma (DLBCL): A systematic review and meta-analysis of randomized controlled trials

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1011PD

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1012PD Evaluation of safety, tolerability and efficacy of temsirolimus in patients (pts) with relapsed or refractory mantle cell lymphoma (rel/ refr MCL) in routine clinical practice

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1013PD A comparative study of 18F-FDG PET/CT with bilateral bone marrow trephine biopsy for assessment of bone marrow infiltration by lymphoma

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1014PD Phase I/II, first in human trial with M7583, a Bruton’s tyrosine kinase inhibitor (BTKi), in patients with B cell malignancies

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1015PD A prospective study of first-line Helicobacter pylori eradication therapy in treating localized extragastric mucosa-associated lymphoid tissue lymphoma

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1016PD Bendamustine and rituximab followed by 90Y-ibritumomab tiuxetan for relapsed follicular lymphoma: A preliminary analysis of a multicenter, prospective phase II study (BRiZ2012)

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1017P Estimating the incidence of cryptogenic organising pneumonia in chronic lymphocytic leukaemia patients: A real-world cohort study

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Background: Cryptogenic Organising Pneumonia (COP) is an understudied lung disease characterised by presence of granulation tissue within the alveolar ducts and alveoli. While prognosis of patients with COP is generally positive there remains a paucity of information on the conditions in the academic literature. This abstract presents the largest real-world study of COP in Chronic lymphocytic Leukaemia (CLL) patients to date.

Methods: A retrospective cohort study utilising the IMS Pharmetrics Plus database. A CLL patient cohort was identified using ICD9/10 codes; patients with previous history of COP prior to CLL diagnosis were excluded from the analysis. As a comparator, a random 9% sample of all patients with no history of CLL was taken. Crude Incidence rates (CR) of COP were estimated in both groups. A Poisson regression model (PRM) was
fitted to estimate the age and sex adjusted incidence rate ratio (IRR) of experiencing COP in CLL patients versus those with no history of CLL. Tests for trend were conducted for age and sex.

Results: A total of 64,773 CLL and 2,301.48 non-CLL patients were included in the study. The CLL cohort comprised of 59% males with a total of 436 patients experiencing COP. The non-CLL cohort comprised of 47% males with 1,971 patients experiencing COP. The CR of COP in the CLL cohort was 2.4 (95% CI 2.2-2.61) per 1,000 person-years (py) and 0.20 (95% CI 0.19-0.21) per 1,000 py in the non-CLL cohort. An age and sex adjusted PRM estimated an IRR of 7.7 (95% CI 6.9-8.8; p-value <0.001). A significant trend of increasing COP incidence was observed for age (p-value <0.001).

However, no differences found for gender.

Conclusions: This study indicated that CLL patients had a higher rate of experiencing an episode of COP as opposed to non-CLL patients, adjusted for age and sex. As COP is difficult to distinguish from the infectious and non-inflammatory pulmonary process in CLL patients, awareness of this increased risk may lead to earlier diagnosis and institution of treatment of COP. The role of co-morbidities and co-medications will be investigated in further analyses.

Legal entity responsible for the study: Gilead Sciences

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Progression of disease within 2 years (POD24) is a clinically significant endpoint to identify follicular lymphoma patients with high risk of death

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Background: Follicular lymphoma (FL) is an indolent non-Hodgkin’s lymphoma with heterogeneous outcomes among patients. Casulo et al (ICO 2015) showed that progression of disease within 2 years (POD24) after diagnosis for FL patients treated by R-CHOP was associated with poor outcomes, needing further validations before using it as a standard endpoint to evaluate treatment efficacy. We investigated the POD24 predictive value for all patients treated or not with R-CHOP in our institution (Nantes Medical University, France).

Methods: Patients with grade 1, 2 or 3A FL treated from 2007 were registered in our local database (approved by French authorities, CNIL) and included in the present retrospective monocentric study, with up-dating of patient’s outcomes. FL diagnosis was performed by local pathologist experts (members of the national LYSA-pathologist group, France).

Results: Between 2007 and 2016, 317 patients with confirmed FL were included. At diagnosis: 24 did not receive any treatment (Wait and watch), 259 were treated with Rituximab (R) (including R alone in 98 cases), 143 received an anthracycline-containing regimen (mainly R-CHOP-like), 5 received bendamustine-containing regimen, radiotherapy alone in 11 cases and another chemotherapy regimen in 36 cases (mainly R-COP). Second line treatment (N = 131) consisted of chemotherapy in 91 cases, R alone in 37 cases. After first line therapy, 61 patients relapsed or died within 2 years (POD24+), 99 patients after 2y, including 21 transformations, and 154 patients did not progress or die (missing = 5). At the time of the present analysis, the median follow-up is 5.4 years. Median PFS is 58.2 months. OS at 16.1 years and 5y are 98.4% (97.0-99.8), 95.1% [92.6-97.6] and 92.5% [89.3-95.9] respectively. The 5y OS was statistically worst for POD24+ patients (82% [71.9-93.5]) than for POD24- patients (93.3% [88.98-97.8]) (p = 0.0011). Age at diagnosis (>60), performance status (PS > 1), FLIPI, FLIPI2 scores (high) and transformation are predictive of OS in univariate analysis. PS (≥1) at diagnostic is predictive of POD24+.

Conclusions: POD24+ is predictive of a worse OS regardless of first line treatment nature and can be recommended as a relevant endpoint for clinical trials.

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Impact of genetic polymorphisms on prognosis and survival of diffuse large B-cell lymphoma

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Background: DLBCL is the most common subtype of NHL in adults. The efficacy of chemotherapy in DLBCL patients has significantly increased in the last 10 years. Growing evidence has shown genetic and environmental factors are involved in the etiology and prognosis of DLBCL. Genetic polymorphisms can influence the individual susceptibility and clinical outcome for different types of Lymphomas. The aim of this study was to investigate the genetic polymorphism of glutathione S-transferase P1 (GSTP1), a prognosis factor for patients with DLBCL.

Methods: 136 patients with DLBCL, 36 men and 80 women, median age 47 y.o were included in the study. The patients received R-CHOP-like regimens. Genomic DNA was extracted from blood samples. GSTP1 polymorphism (c. 313 A > G, p. Ile105Val) were analyzed by Allelic Discrimination Real-Time PCR.

Results: A homozygous for the GSTP1 genotype was detected in 65/136 (47.8%) patients, heterozygous A313G – in 57/136 (42%) and 14/136 (10.2%) were homozygous for the G313G genotype of DLBCL (p < 0.05). The GSTP1 genotype distribution was confirmed to Hardy-Weinberg equilibrium (q2 = 0.85 p = 1.01). The frequency of the homozygous wild genotype of the GSTP1 was significantly higher in patients with advanced disease vs patients with early stages of DLBCL (57% vs 43%, p < 0.05). The ORR was 76% (104/136) during the follow-up (median – 16 months; range 25–96 months, 41% of patients (56/136) had relapse or progression and 42 (31%) of them died during the follow-up period. We found an association of GSTP1 homozygous wild genotype with an unfavorable prognosis of DLBCL. The A313A genotype was strongly associated with increased risk of the DLBCL r/r disease as compared with A313G or G313G genotypes (23% vs 14% vs 4%, respectively, p < 0.05). 5-years EFS for patients with A313A GSTP1 genotype was lower compared to patients with A313G or G313G genotypes (42% vs 52%; p = 0.05). Thus, the A313A genotype impacts survival of DLBCL.

Conclusions: Results suggest the genotype of the GSTP1 (A313A) is associated with unfavorable prognosis of DLBCL, reduce EFS rate. Results can be promising, but further investigations might provide a possible application of this marker as a prognosis factor of DLBCL.

Legal entity responsible for the study: Olga Novosad.

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Long term treatment outcome of patients with refractory or relapsed Hodgkin’s lymphoma in the anthracycline era: A single-center intention-to-treat analysis

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Background: High dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is currently the treatment of choice for refractory or relapsed Hodgkin’s lymphoma (HL) and cures up to 50% of patients. However, its applicability is restricted to selected eligible patients and/or responding to salvage chemotherapy. The aim was to compare outcomes after salvage regimens with and without HDCT and ASCT in HL patients who failed or relapsed after ABVD or BEACOPP regimens.

Methods: From 836 patients with newly diagnosed HL registered in the MRCC database between 1998 and 2017 there were identified 131 patients with refractory disease (Gr.1, n = 89), early (Gr. 2, n = 31) or late (Gr.3, n = 11) relapse. At first relapse, patients had median age 30 years (range, 17 to 69), male, 46%, stage III/IV, 70%, B symptoms, 28%. 101 patients, 76 (38%) received standard CT regimens (51) when HDCT was not available (n = 64) or contraindicated (12). HDCT was initiated in 52 (42%) patients, but withdrawn in 38 of them (adverse effects, 9, progression, 24, low cytopenias, 5). ASCT was performed in 17 (31%) patients.

Results: Median follow-up time after first failure for survived patients (79 of 131, 60%) was 60 months (8-186). Durable second remissions were achieved in 10 (59%) of 17 patients after ASCT and in 50 (40%) of 76 patients after ST. In an intention-to-treat (ITT) analysis median freedom from second failure (F2F2) after HDCT and ST was, respectively, 4 vs. 15 months in Gr.1 (p = 0.018) but did not differ (15 and 16 months) in Gr.2; Gr.3 was too small for ITT. Median overall survival (OS) after HDCT and ST was, respectively, 22 vs. 158 months in Gr.1 (p = 0.036) and 42 vs. 52 months in Gr.2 (n.s.).

Conclusions: This single center analysis demonstrates the effectiveness of standard CT regimens as first-line salvage in patients not eligible for HDCT/ASCT. It also demonstrates the high failure rate due to inadequate chemo-responsiveness at salvage in patients referred to HDCT. An effect not accounted for in studies analyzing only outcome following HDCT/ASCT.

Legal entity responsible for the study: Viacheslav Vladimirovich.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.


Background: Bone and kidneys are among the main affected organ systems in symptomatic multiple myeloma (MM) and may be associated with debilitating complications. Thus, bone health and renal protection are at the core of MM management. Bisphosphonates (BP) are recommended for prevention of bone complications in all newly diagnosed symptomatic MM patients, but BPs are also potentially nephrotoxic and are cleared by the kidneys. This study describes the routine clinical use of BP among MM patients in Denmark.

Methods: Adult patients newly diagnosed with MM between 01.01.2005 and 30.06.2015 were identified in the Danish National Multiple Myeloma Registry, and information on BP treatment in first-line (1L) anti-MM therapy was analyzed.

Results: Among 2,633 MM patients with information on BP treatment in 1L treatment in 1L, 1,838 (69.8%) patients received BP. Median time from MM diagnosis to BP treatment was 19 days (IQR: 9, 35). Receipt of BP among 1L-treated patients by therapy was: 79.4% (635/799) in autologous stem cell transplant recipients, 75.0% (793/1,058) in patients treated with conventional chemotherapy, and 70.2% (903/1,286) in those treated with bortezomib-, lenalidomide-, or thalidomide-containing regimens. Among the BP-treated patients, 67.2% (341/513) had no recorded hypercalcemia at MM diagnosis, 81.0% (1,489/1,838) had a record of skeletal-related events (SRE) in the 12 months before MM diagnosis, and 80.0% (1,470/1,838) had a record of osteolytic foci at 1L. An additional 43% patients had a record of osteolytic foci but no record of BP treatment. Patients without a record of BP treatment had higher prevalence of overall hospital-registered comorbidity, anemia, or higher ISS stage at MM diagnosis than patients with a record of BP treatment. Severe renal impairment (stages 4-5) was recorded at MM diagnosis in 31.8% of patients with no BP record and in 12.6% of patients with BP record at 1L start.

Conclusions: In newly diagnosed MM patients receiving 1L, co-administration of BP and anti-MM therapy is widespread, though less prevalent in patients with renal impairment or comorbidity burden.

Legal entity responsible for the study: Aarhus University.

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Role of liposomal doxorubicin as a first line agent with VTd regimen in newly diagnosed multiple myeloma

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Background: Triple drug regimens are standard of care in newly diagnosed Multiple Myeloma (MM). Studies show 4 drug regimens to be highly active. In an economically backward country like India, newer drugs and Autologous transplant may not always be feasible because of financial constraints. We studied the effect of adding Pegylated Liposomal Doxorubicin (PLD) to standard regimen on the Response Rates (RR).

Methods: 60 newly diagnosed cases of MM were included in this double armed prospective, observational, comparative study. Patients were randomly assigned into 2 arms (30 Patients in each arm). Arm A consisted of VTd regimen (Inj. Bortezomib Day (D)1, D8, D15, D22 1.3mg / m2, Tab. Thalidomide Daily 100mg, Inj. Dexamethasone D1, D8, D15, D22 40 mg / once in 28 days). Arm B consisted of VTdG regimen (PLD D1 i.v 30mg / m2 + VTd). Hematological and biochemical parameters were noted at baseline and after completion of 4 cycles. Response assessment was done as per the criteria defined by International Myeloma Working Group (IMWG). The outcomes between the two treatment arms in terms of RR were compared.

Results: The differences in sCR rates were clinically very significant. However, on application of Pearson chi-square test significance p of 0.118 was seen, which maybe attributed to the lower power of the study. Poorer responses noted were highest in the 71-80 age group. Both the regimens were equally effective in ISS B patients. Neutropenia, thrombocytopenia, infections, mucositis, edema, diziness/malaise and DVT were not significantly different between the two arms (P > 0.05). Palmar–plantar erythrodysesthesia (PPE) was the only new complication seen in (10%) VTdG group. Grade 3-4 toxicities were similar in both arms.

Conclusions: The role of liposomal doxorubicin in first line setting as a 4th agent along with triple drug regimen in treatment of MM looks promising, especially in countries with financial constraints for the newer drugs. Larger studies are needed to validate this.

Legal entity responsible for the study: Scientific and Ethics Committee at HCG Hospital, Bangalore, India.
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Disclosure: All authors have declared no conflicts of interest.

Impact of prior bortezomib therapy on the incidence of lenalidomide-induced skin rash in multiple myeloma: A propensity score-matched multi-institutional cohort study

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Background: Rash is a well-known toxicity induced by lenalidomide (LEN) therapy in multiple myeloma (MM). LEN has immunomodulatory effects activating function of effector immune cell such as T-cells, which may result in rash onset. Conversely,

The f2-microglobulin is associated with the prognosis in patients with peripheral T-cell lymphoma, not otherwise specified

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Background: Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of tumors and subdivided into specified and not otherwise specified (NOS) types. Clinically, the International Prognostic Index (IPI), Prognostic Index for T-cell lymphoma, and Bologna score have been the prognostic model to discriminate the prognosis of patients with PTCL-NOS. However, no simple prognostic marker has been satisfactory in predicting treatment outcomes in patients with PTCL-NOS.

Methods: From Sep 2005 to Aug 2016, we identified 94 patients diagnosed with PTCL-NOS initially treated with CHOP or CHOP-like regimens. Event-free survival (EFS) was calculated from the date of diagnosis to the date of disease progression, treatment failure, relapse, or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause. The cut-off of serum β2 microglobulin (B2MG) was defined as > 3.2 mg/L.

Results: Among 94 patients, 41 (43.6%) patients showed B2MG > 3.2 mg/L. 37 (39.4%) patients showed B symptoms. According to IPI scores, 19 (20.2%) patients belonged to the low risk group (L1), 25 (26.6%) to the low-intermediate (LI), 29 (30.9%) to the high-intermediate (HI), and 21 (22.3%) to the high (H). Complete response (CR), EFS, and OS were associated with B2MG, B-symptoms, performance status, lactate dehydrogenase, extranodal involvement, Ann Arbor stage, and IPI risk group in univariate analysis. After multivariate analysis, B2MG was associated with CR (> 3.2 mg/L vs. ≤ 3.2 mg/L, odd ratio [OR]: 4.053, 95% confidence interval [CI]: 1.34–12.503, P = 0.015), EFS (hazard ratio [HR]: 1.721, 95% CI: 1.026–2.818, P = 0.040), and OS (HR: 1.449, 95% CI: 0.803–2.615, P = 0.218). IPI risk group was associated with CR (L1/LI vs. HI/H, P = 0.022), EFS (P = 0.001), and OS (P = 0.001). In 50 patients of HI/H risk group, B2MG showed association with CR (OR: 5.464, 95% CI: 1.256–23.774, P = 0.024), EFS (HR: 2.160, 95% CI: 1.095–4.260, P = 0.026), and OS (HR: 2.158, 95% CI: 0.979–4.759, P = 0.057).

Conclusions: B2MG could be a simple prognostic factor for the patients with PTCL-NOS. B2MG > 3.2 mg/L was associated with worse prognosis of patients with PTCL-NOS, especially in HI/H risk group. The larger scaled study is warranted to confirm our result.

Legal entity responsible for the study: Byeong Seok Sohn.
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bortezomib (BOR), another key drug of MM therapy, has strong immunosuppressive effects decreasing CD4+ T-cell count. Although the two drugs have different immuno-
ological aspects, the association between prior BOR therapy and LEN-induced rash has not been reported.

Methods: We conducted a four-institutional cohort study. Eligible MM patients treated with initial LEN therapy were divided into two propensity score-matched cohorts according to presence or absence of prior BOR therapy. The primary endpoint was the incidence of rash. The secondary endpoint was the incidence of eosinophilia. Non-economic factors were matched.

Results: One-hundred forty-four patients were evaluated. The incidence of rash was 35 (50/144 %), of which 34 (17/50%) were discontinued LEN therapy due to rash. The medium time to rash onset was 8.3 days after LEN initiation. Each cohort contained 43 patients after performing propensity-score matching. As compared to in the absence of prior BOR therapy, the incidence of rash was significantly lower in the presence of prior BOR therapy (10% vs 53%, p = 0.04). Median period of BOR therapy was significantly shorter in patients with rash, as compared with those without rash (109 days vs 164 days, p = 0.046). Also, the patients with rash showed significantly higher incidence of eosinophilia than those without rash, within one month after LEN initiation (28 vs 8%, p < 0.01).

Conclusions: Prior BOR therapy could reduce the incidence of LEN-induced rash. LEN-induced rash may be characterized by eosinophilia, suggesting that LEN enhance Th2 immune responses. Regarding the patients failed to continue LEN therapy due to rash, they may have a chance of LEN re-treatment after adequate BOR therapy.

Legal entity responsible for the study: Satoshi Doke.

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Prognostic factors of clinical use in acute myeloid leukemia

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Background: The heterogeneity in acute myeloid leukemia (AML) is influenced by disease and host-specific factors. In recent years, independent molecular factors and host characteristics that affect prognosis have been described. Nevertheless, data is needed to warrant their clinical use.

Methods: We retrospectively reviewed data on 356 AML patients from October 2008 to June 2017, including age, Charlson Comorbidity Index (CCI), ECOG performance status (PS), laboratory parameters (complete blood count, bone marrow blasts, lactate dehydrogenase) and disease factors (de novo or acute myelogenous leukaemia [AML]; germline alterations). The 2017 European Leukemia Net genetics risk stratification (GRS) was used. Univariate and multivariate Cox regression analysis was performed.

Results: The intensive chemotherapy (IC) group comprised of 241 patients, median age 58 years (y), 95% having PS ≤ 1, 67% CCI ≤ 2 and 22% were sAML. GRS was 23% favorable, 44% intermediate, 27% adverse and 6% unknown. Median overall survival (OS) was 15 months (mo), with 28% 3y-OS. In multivariate analysis (Table), age older than 60y (median 6 vs vs 21mo), PS ≥ 2 (median 7 vs 15mo) and higher risk GRS (median 5mo favorable vs 13mo intermediate and 1mo adverse) impacted on survival. The non-IC group included 112 patients, median age 67y, 76% having PS ≤ 1, 6% CCI ≤ 2 and 37% were sAML. GRS was 12% favorable, 49% intermediate, 24% adverse and 15% unknown. Median OS was 5mo, with 10% 3y-OS. In multivariate analysis (Table), age older than 60y (median 2 vs 17mo), PS ≥ 2 (median 1 vs 5mo) and higher risk GRS (median not reached in favorable vs 4mo intermediate and 1mo adverse) impacted on prognosis.

Conclusions: In spite of the high number of recognized risk factors, in real-life only GRS, age and PS were of clinical use to predict survival in both IC and non-IC sets. In our sample, there was no significant impact of AML, CCI and laboratory parameters. Efforts are needed to identify more factors that aid clinical decision in the treatment of AML.

Legal entity responsible for the study: Clinical Hematology Department, Centro Hospitalar São João, EPE.

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Conclusions: We did not find correlation between presence of compound mutation and probability to respond therapy or progression. Analyze higher number of sample is needed. Indeed, the importance to detect clones harboring high resistance mutation such as T315I earlier could help the clinician to choose the therapy to avoid clone progression.

Legal entity responsible for the study: Instituto Nacional do Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1031P Combination of chemotherapy and radiation improve the prognosis of primary diffuse large B-cell lymphoma of the tonsil

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Background: The most common histological type of tonsil lymphoma is diffuse large B-cell lymphoma (DLBCL). Treatment approaches that have used include surgery, chemotherapy (CTx) alone, radiation (RT) alone, and combination of both. We reviewed our data and evaluate treatment outcome of patient with DLBCL of the tonsil.

Methods: Retrospective review of 114 stage I-II DLBCL patients between 1995 and 2010. Forty-five (39.5%) patients had stage I disease and B-symptoms were present in 20 patients (17.5%). 17 (14.9%) patients received CTx alone, 63 (55.3%) RT alone, and 34 (29.8%) CTx and RT. We reviewed 114 patients who had stage I-II disease at the time of the study. Chi-square test was performed to estimate overall patients' survival.

Results: The median age was 59 years and 61% of patients were males. Low to lower intermediate by International prognostic index (IPI) was 97.9%. LDH level. Overall CR rate was 73.5% and seven (13.9%) of the patients who had achieved CR had recurred. The median follow-up was 28 months. Five year disease-free survival (DFS) and overall survival (OS) were 86.8% and 82.5%, respectively. Significant prognostic factors included age < 60 years old (OS, P = 0.011), LDH ≥ upper normal limit (OS, P = 0.003; DFS, P < 0.001), IPI > 0 (OS, P = 0.007; DFS, P = 0.034) and combination of CTx and RT (OS, P = 0.025; DFS, P = 0.038). Germinial center (GC) and non-GC phenotype were not predictors of outcome in localized DLBCL of the tonsil. Chemomunotherapy-treated patients with rituximab did not show a significantly better OS and DFS than those without rituximab. On multivariate analysis: LDH – upper normal limit (DFS: hazard ratio [HR], 14.958; 95% CI, 2.474-90.432, P = 0.003; OS, HR, 9.341; 95% CI, 1.635-53.361, P = 0.012), and combination of CTx and RT (DFS, HR, 1.088 95% CI, 0.009-0.834; P = 0.1034, OS HR, 1.112; 95% CI, 0.014-0.918, P = 0.841), retained statistical significance.

Conclusions: The DFS and OS rates were significantly better for patients receiving combination of CTx and RT. A combined treatment, consisting of CTx and RT (with RT dose of ≥ 45 Gy), results in a satisfactory outcome in patients with localized primary DLBCL of tonsil.

Legal entity responsible for the study: Consortium for Improving Survival of Lymphoma.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1032P The impact of serum microRNA-21 on outcome of diffuse large B-cell lymphoma patients

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Background: The utilization of circulating microRNAs (miRNAs) as non-invasive diagnostic and predictive tools have become substantial and promising scope of cancer research. The link between the aberrant expressions of various miRNAs and the pathogenesis of diffuse large B-cell lymphoma (DLBCL) has been revealed by multiple studies. This study planned to investigate the relative expression levels of serum miRNA-21 and to demonstrate its potential prognostic impact in DLBCL patients who were treated by cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (R-CHOP) protocol.

Methods: Polymere chain reaction (PCR) based technique was used to analyze serum miRNA-21 relative expression levels in 65 DLBCL patients prior to immunochemotherapy in comparison with 35 healthy individuals. Receiver operating characteristic curve analysis was used to gauge the optimal miRNA-21 cutoff and Kaplan-Meier method was performed to estimate overall patients’ survival.

Results: Serum miRNA-21 overexpression was significantly observed in DLBCL patients compared to the control group (P < 0.001). MiRNA-21 expression levels were closely associated with stage, C-reactive protein (CRP), lactate dehydrogenase (LDH) and β2 microglobulin (P < 0.001; P = 0.02; P = 0.003; P = 0.001 respectively). However, there was no relationship with other characteristics, such as gender, age, B-symptoms, extranodal site involvement, international prognostic index (IPI) and initial response to therapy (all P > 0.05). Overall survival was significantly worse in patients with high miRNA-21 expression levels compared to those with low expression levels (P < 0.01).

Conclusions: Serum miRNA-21 may be employed as valuable non-invasive diagnostic and prognostic marker in DLBCL patients treated with R-CHOP regimen.

Legal entity responsible for the study: The Authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Methods: Pts were randomized to receive bosutinib 500 mg once daily (QD) or imatinib 400 mg QD. The primary endpoint was complete cytogenetic response (CCyR) rate at 12 mo. We compared efficacy and safety of bosutinib and imatinib in Indian and non-Indian pts after 48 mo of follow-up. Efficacy was assessed in the intent-to-treat population; safety was assessed in all pts who received ≥1 dose of study drug.

Results: In all, 54 Indian pts (median age 34.5 y; 61% male) and 448 non-Indian pts (median age 48.5 y; 36% male) were randomized to receive bosutinib (n = 25 and n = 225 [2 untreated], respectively) or imatinib (n = 29 and n = 223 [1 untreated]). At 12 mo, major molecular response (MMR) and CCyR rates, respectively, for bosutinib vs imatinib were 44% vs 24% and 72% vs 86% in Indian pts, and 37% vs 26% and 70% vs 78% in non-Indian pts (Table). After 48 mo of follow-up, cumulative MMR and CCyR rates, respectively, for bosutinib vs imatinib were 64% vs 69% and 84% vs 97% in Indian pts, and 68% vs 67% and 78% vs 79% in non-Indian pts. The most frequently reported treatment-emergent adverse events (TEAEs; any grade) with bosutinib were diarrhea (48%) and thrombocytopenia (36%) in Indian pts, and diarrhea (73%) and nausea (39%) in non-Indian pts. 8 pts in the entire study were lost to follow-up while on-treatment; 7 (6 bosutinib; 1 imatinib) were from Indian sites.

Table: 1033P

<table>
<thead>
<tr>
<th>Sokal Risk Group, n (%)</th>
<th>Indian pts</th>
<th>Non-Indian pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Bosutinib</td>
<td>11 (44)</td>
</tr>
<tr>
<td></td>
<td>Imatinib</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Medium</td>
<td>Bosutinib</td>
<td>11 (44)</td>
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<td></td>
<td>Imatinib</td>
<td>106 (47)</td>
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<tr>
<td>High</td>
<td>Bosutinib</td>
<td>3 (12)</td>
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<tr>
<td></td>
<td>Imatinib</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cumulative response, any time on-treatment, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMR</td>
<td>64 (45–83)</td>
<td>68 (61–74)</td>
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<tr>
<td>CCyR</td>
<td>84 (70–98)</td>
<td>78 (73–84)</td>
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<tr>
<td>Response at 12 mo, % (95% CI)</td>
<td></td>
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</tr>
<tr>
<td>MMR</td>
<td>44 (25–64)</td>
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<tr>
<td>CCyR</td>
<td>72 (64–80)</td>
<td>70 (64–76)</td>
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<tr>
<td>Probability of retaining response at 48 mo (95% CI)*</td>
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<td>2 (7)</td>
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<tr>
<td>Overall survival, n (%)</td>
<td>96 (72–99)</td>
<td>95 (91–97)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Kaplan–Meier estimate
AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CI=confidence interval; CML=chronic myeloid leukemia; MMR=major molecular response

Conclusions: Response rates for bosutinib were comparable between Indian and non-Indian pts. MMR rates were higher for bosutinib vs imatinib at 12 mo, but not 48 mo, in Indian pts; comparison of bosutinib vs imatinib was limited by the small number of Indian pts. TEAEs were consistent with the known bosutinib safety profile, although Indian pts had a lower rate of diarrhea than non-Indian pts.

Clinical trial identification: NCT00574873.

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Funding: Pfizer Inc.

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1034P

A prospective multicenter study of primary breast lymphoma in the rituximab era: Prognostic implications of beta 2 microglobulin and interleukin-6 & interleukin-10


Background: Primary breast diffuse large B-cell lymphoma (DLBCL) is a rare entity representing ≤2% of extra-nodal non-Hodgkin lymphoma. We aimed to define clinical profile, prognostic factors and the incidence of the central nervous system (CNS) relapse in the era of rituximab and clarify the prognostic value of beta 2 microglobulin(B2M), interleukin-6 (IL-6) and interleukin-10(IL-10).

Methods: Between Jan 2012 to Dec 2016, a prospective analysis of 28 patients presenting to 7 academic Egyptian centers. All patients were females. Only patients with newly diagnosed stage I and II disease DLBCL were included. Patients with evidence of baseline CNS disease and patients with hepatitis B and HIV were excluded. All patients were scheduled to receive R-CHOP protocol plus involved-field radiotherapy. The prognostic significance of B2M, IL-6 and IL-10 were assessed.

Results: About 75% presented with breast mass, 4 cases with inflammatory symptoms, 3 cases were discovered by mammography. Right breast was more involved (65%). 86% had ≤1 ECOG performance status, and LDLN elevated in 39% and 18% had B symptoms. HCV was positive in 32% (9 patients). Stage I was detected in 57%. The stage-modified International prognostic index was ≤1 in 54%. Ten cases underwent breast surgery (2 modified radical mastectomy, 8 conservative breast surgery). Complete response was achieved in 23/28 (82%) with median follow-up of 28 months, 39% of patients had relapsed, contralateral breast was the site of initial relapse in two cases, 11% developed CNS relapse and 21% in other nodal and extranodal sites. Three year disease free survival and overall survival were 68% and 79%. Favorable prognostic factors according to univariate analysis were stage I, tumor size < 5cm, B2M, IL-6 and IL-10; while for multivariate analysis they were IPS < 1 and B2M, IL-6 and IL-10.

Conclusions: Primary breast DLBCL has high rate of CNS relapse in spite of era of rituximab so CT or MRI of CNS is necessary during follow-up. Prophylaxis to CNS should be considered in the initial treatment to improve outcome. In addition, assessment of pretreatment serum levels of B2M, IL-6 and IL-10 in newly diagnosed DLBCL may indicate a possible prognostic role.

Legal entity responsible for the study: Lobna Ezz el-arab.

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Disclosure: All authors have declared no conflicts of interest.

1035P

Experience in treatment of newly diagnosed multiple myeloma patients with renal failure required dialysis

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Background: About 2–4% of patients with newly diagnosed multiple myeloma (MM) present with severe dialysis required renal failure (RF), which is associated with significant morbidity and early death. The aim of this article was to analyze own experience in treating this category.

Methods: During 10.2014–12.2017 the sixty-two patients with severe RF with a glomerular filtration rate (eGFR) <30 ml/min/1.73m2 were enrolled in this retrospective study. All patients received bortezomib-based regimens: 41 (66.1%) VDC; 2 (3.2%) PAD; 12 (19.4%) VD and 7 (11.3%) VMP. Seven (11.3%) patients underwent high-dose therapy with ASCT. IMWG (2010) renal response criteria were used. Myeloma response was evaluated using the standard IMWG (2006) criteria.

Results: At the time of presentation 48 (77%) patients required dialysis. The mean eGFR was 6.0 (95% CI 4.4–7.6) for patients requiring dialysis (Group A) and 22.2 (16.4–29.2) ml/min/1.73 m2 for those (Group B) a dialysis independence (P < 0.001). Mean level of involved free light chain (iFLC) was 7400 (3440–10840) mg/l vs 2900 (780–3020) mg/l respectively (P < 0.001). The median time from RF to start of MM chemotherapy comprised 39 and 21 days for two groups respectively. Six (9.7%) patients died within the first 60 days of therapy (induction mortality). At least minimal renal response (> > MRenal) documented in 23.5% and 57% patients respectively. If the duration RF before initiation of MM treatment was >1 month no one patient required dialysis restored a renal function. Among all patients, overall myeloma response (> > PR) documented in 81% cases, including 39.6% very good partial response (VGPR) and 14.6% complete response (CR) after two years overall survival (OS) was 67.8 ± 6.4% without any different between groups.

Conclusions: In conclusion, our data indicate that bortezomib-based triplets are associated with a significant probability of renal response. In at least a 23.5% of patients
with MM presenting with dialysis-requiring severe RF may improve their renal function and discontinue dialysis. Unfortunately, our results are inferior to the literature data according to which up to 50% of patients become independent of dialysis. Legal entity responsible for the study: Evgeniya Zhenlova.

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Disclosure: All authors have declared no conflicts of interest.

1036P Immunohistochemical (IHQ) classification of DLBCL into CGB and non-CGB subtypes to predict survival after chemotherapeutic therapy at the Virgen de la Victoria University Hospital

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Background: It is known that diffuse large-B-cell lymphoma (DLBCL) is a clinically heterogeneous entity. The most important clinical predictor of survival is the International Prognostic Index, which does not provide information regarding the heterogeneity of biology of tumors. Two major subtypes of DLBCL have been identified by gene expression profiling (GEP) and classified by cell of origin into germinal center B-cell-like (GCB) and activated B-cell-like (ABC). GEP has become a reliable method for predicting the outcome of patients with DLBCL treated with R-CHOP chemotherapy. However, it is not easily applicable to clinical practice. Several IHC algorithms have been developed to assign patients into GCB and non-GCB subtypes.

Methods: We retrospectively analyzed 142 patients diagnosed of de novo DLBCL from 1999 to 2017 at our Hospital treated with chemotherapy. DLBCL was classified using the Hans algorithm into GCB and non-GCB subtypes. The primary end-point was progression-free survival (PFS) according to the Hans algorithm, that it was estimated by the Kaplan–Meier method.

Results: The percentage of GCB and non-GCB subtypes was 54% and 46%, respectively. After a median follow-up of 37 months, the median progression-free survival was 100 months in the global population. No significant differences were found in PFS, although there was a trend to favor GCB subtype (PFS at 24 months 70% in GCB group and 59% in non-GCB group, with a median of 60 months in non-GCB and not reached in GCB group, p = 0.177). Despite of being a retrospective study and the low median follow-up of patients, in GCB subtype there was a trend towards better overall survival (OS) (2-year OS: 72% vs. 68%), not statistically significant (p = 0.661).

Conclusions: In our study there is a lack of evidence supporting the use of the Hans algorithm for stratifying patients into distinct prognostic groups, probably due to the low median follow-up. Rather, GEP remains the preferred method for predicting prognosis. IHQ for subclassification of DLBCL is feasible and reproducible, but the harmonization of techniques and centralized consensus review is necessary.

Legal entity responsible for the study: Laura Galvez Carvajal.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1037P Quality of life evaluation in acute leukemia patients receiving induction chemotherapy

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Background: Over the past decades, special attention has been paid to study of quality of life (QoL) indicators in hematological patients receiving chemotherapy (CT). Nowadays QoL is conceptually viewed as an important complement to traditional objective evaluation measures. Aim. To assess QoL in patients with acute leukemia (AL) depending on the presence of concomitant ischemic heart disease (IHD) during the induction CT.

Methods: Our study involved 83 patients with newly diagnosed AL, of which 19 were lymphoblastic, 64 – myeloid leukemia, aged 16–72, 43 (51.8%) men, 40 (48.2%) women, according to ECOG-I-II. Patients received standard induction CT. According to concomitant IHD patients were divided into groups: I (n = 47) – AL without cardiovascular diseases, II (n = 36) – AL with concomitant IHD. Patients were evaluated using SF-36 questionnaire to calculate physical and mental health components before treatment and after 2 induction courses of CT reaching remission.

Results: The indicators of physical and mental QoL components in patients of both groups before CT were significantly lower compared with healthy respondents. After reaching the remission in patients of group I, all QoL parameters improved, with the exception of bodily pain and social functioning. The average physical status indicators in patients of groups I and II did not significantly change. At the same time, the psychological status of patients improved: in group I in 1.5 times (40.9 ± 2.25 vs 27.1 ± 2.77 before CT, p < 0.05), in group II – in 1.3 times (37.7 ± 2.82 vs 28.3 ± 2.37 before CT, p < 0.05). Minimum values of all scales after CT were characteristic for patients with concomitant IHD in group II. Differences between groups were not statistically significant in all scales, except for the index of physical activity (41.7 ± 1.36 vs 46.6 ± 2.02; p < 0.05). However, in comparison with the data of practically healthy respondents, QoL of patients with AL after CT remained significantly lower.

Conclusions: The QoL evaluation in patients with AL with comorbid IHD during induction CT is an important component of the management of oncological patients, which allows individualizing the approach to each patient in the presence of this type of comorbidity.

Legal entity responsible for the study: Ukrainian Medical Stomatological Academy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1038P PET-CT as a prognostic factor in patients with early stages in primary diagnosed Hodgkin lymphoma

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Background: Nowadays, there are different guidelines in diagnostics and PET-guided treatment of lymphomas. But questions about benefits and predictive role of PET-CT in pts with early-stage Hodgkin lymphoma (HL) still remain debatable. Here we report results of Ukrainian multicenter retrospective study about the role of PET-CT in early-stage HL pts.

Methods: 56 patients, with stages I-II, were registered in the study between August 2012 and Feb 2018 in 9 Ukrainian hematological centers. Metabolic PET-CT imaging was performed according to standard protocols. The threshold of positivity was set for a residual uptake higher than the liver background (Deauville score (DS) 4 and 5).

Results: Median age of patients at diagnosis was 29 years (range 18–50), 16 (28.5%) male and 40 (71.5%) pts were female. Bulky disease (>10 cm in any dimension) were presented in 4/56 (10.7%) of pts, B-symptoms – in 16/56 (28.5%) and extranodal disease had 4/56 (7%). Median follow-up was 24 months from diagnosis. Interim PET (PET2) was performed in 50 pts at 15 ± 3 days (range, 5–26) after 2xABVD or 2xBEACOPP cycles. Interim PET-CT was assessed as DS 1-2 in 34 patients (60,7%), DS 3 in 11 (19,6%), DS 4-5 in 5 pts (8,8%). In total, disease progression was documented in 5/56 (9%). Among them, 2/5 (40%) patient were PET2-positive (PET2+) and 3/5 (60%) PET2-negative (PET2–). (p > 0.05). There were no registered deaths from the refractory disease. We did not find any significant difference between EFS rate in pts with PET2+ vs PET2– (log-rank test, p = 0.4). 47 pts have proceeded for end-of-treatment PET-CT (PET3). Results showed 3/47 pts (6,3%) were PET3+ and PET3– were 44/47 (93,7%), (p > 0.05). EFS was compared and assessed depending on DS. Achieved rate of 3-year EFS in pts with PET3 DS 1-2, DS 3 and DS 4-5 were 94,4%, 50% and 0%, respectively (p < 0.006).

Conclusions: End of treatment PET-CT plays an important role in patients with early-stage HL and could be a beneficial prognostic factor. However, there is still need for prospective confirmation of interim PET-CT as a prognostic factor.

Legal entity responsible for the study: Tetiana Skrypnyk.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1039P Assessment to predict survival and risk of progression in patients with newly multiple myeloma in different age groups

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Background: Treatment options and outcomes for multiple myeloma (MM) pts were greatly changed over the last 10 years. Treatment according to different age groups requires careful consideration of the balance between maximizing efficacy and acceptable tolerability.

Methods: 100 pts (median age: 63, range 34–80; m: 63, f: 37) were registered in NCI from Jan 2006 to Jan 2018. 19% (19/100) of patients received M2, MP, DAV therapy (group1), 40% (46/100) – thalidomide-based (group2) and 35% (35/100) - PI-based regimens (group3). In 28% patients (24/100), del13, and del17p13 were assessed. The primary endpoint was EFS and OS.
Results: For 100 pts the OBR was 70%. We recorded 39% relapses in the follow-up after the 1st line therapy (median = 10.9 months; range 2-129). 61.1% vs 47.8% with 17.1% relapses were diagnosed in group1 vs group2 vs group3, respectively (p < 0.05). 3-year EFS for group was 18% vs 30% in group1 and 20% vs 30% for group2 vs group3, respectively (p < 0.002). ROC analysis confirmed bortezomib-based regimens improved EFS in MM patients without age correlation (Se = 81%; Sp = 54%; AUC = 0.7, p = 0.0001). EFS was higher in the group 2 pts >65 y.o. vs >65 y.o (40% vs 18%, p < 0.05). 3-year OS was 65% vs 45% in younger pts vs elderly pts, respectively (p = 0.019). Thrombosis complications in group 2 were compared in pts >65 y.o (20%) vs ≤ 65 y.o (7.7%), (p < 0.05). 3-year EFS and OS were similar in the group 3 (p = 0.4). Also, neurotoxicity was the same in different age groups (58% vs 60%). 50% vs 33.8% cases of disease progression had patients who received doublet and triplet regimens, respectively (p < 0.05). ROC analysis confirmed doublet regimen association with lower EFS pts >65 y.o (Se = 50%; Sp = 100%; AUC = 0.7, p = 0.04). Median EFS in pts with del1p13 was lower without any correlation with age (19.9 vs 27.9 months). We did not find any significant association between patients with del13 or (14:14) and clinical outcome of MM.

Conclusions: Bortezomib-based regimens are still in a priority for the 1st-line treatment in different age groups. Thalidomide might be an option for younger pts, because thromboembolic events are more frequent in elderly pts. To achieve better response in the 1st-line therapy, it is preferable to use triplet regimens in pts <65 and >65 years old.

Legal entity responsible for the study: Olga Nosovad.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Impact of bisphosphonate and anti-myeloma therapy on bone turnover markers in multiple myeloma

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Background: Bone involvement is a defining feature of symptomatic multiple myeloma (MM). There is little information on changes in bone mineral metabolism that occur with bisphosphonates and anti-myeloma medication.

Methods: Newly-diagnosed MM patients were prospectively enrolled from January to December 2017. Serum bone turnover markers estimation (CTX, PINP, and Osteocalcin (OC)), DEXA scan, and Tc99 bone scintigraphy were assessed at baseline. Antimyeloma drugs and monthly bisphosphonates were given as per institutional protocol. Bone turnover markers were re-assessed at 3 months.

Results: 24 patients were enrolled. Median age was 55 years (35 – 76 years); 79.16% males. Bone pains and anemia were most common (renal failure 45.8% and hypercalcaemia 45.8%). IgG subtype was most common (52%) [IgA 21%, light chain 16%]. 83.3% had ISS stage II disease; mean β-2 microglobulin was 17.81 (≤ 25.16) mg/mL. 70.83% patients had multiple lytic lesions and 29.16% had baseline fracture. On DEXA scan, 41.67% had osteopenia and 12.5% had osteoporosis. All bone markers showed a graded but statistically insignificant correlation with the extent of bone involvement, P > 0.05. Baseline CTX levels in patients with pathological fractures were significantly higher. Baseline β-2 microglobulin significantly correlated with CTX (r = 0.44) and PINP (r = 0.43); OC showed no such correlation. At 3 months, a significant decline was seen in CTX levels (69.66 (± 20.84) vs 1.16 (± 2.19), P < 0.001); minimal rise was seen in PINP and OC levels, P > 0.05. Fall in CTX levels in patients receiving VTD regimen was significantly greater than VCD regimen, P = 0.012. The decline in CTX among patients exclusively treated with zoledronate was significantly larger than those who received initial chondronate followed by zoledronate, P = 0.017. At 3 months, overall response rate was 79% (CR 16.7%, VGPR 50%, PR 33.3%).

Conclusions: The bone turnover markers significantly correlated with β-2 microglobulin. Bisphosphonates and anti-myeloma medications considerably reduced CTX (bone resorption marker) but had a trivial effect on PINP and OC. Larger prospective studies with longer follow up are required to interpret dynamics of bone turnover markers in myeloma.

Legal entity responsible for the study: PGIMER, Chandigarh.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1041P Comparison of ALL and Control (ITP) (n = 50)

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<th>Parameters</th>
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<tr>
<td>Platelet (μL)</td>
<td>9356.73 ± 5048.05</td>
<td>12240 ± 4576.02</td>
<td>NS</td>
<td>150000-450000</td>
<td></td>
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<tr>
<td>Prothrombin time (seconds)</td>
<td>14.1 ± 1.43</td>
<td>14.72 ± 2.13</td>
<td>NS</td>
<td>11-14</td>
<td></td>
<td></td>
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<tr>
<td>Activated partial thromboplastin time (seconds)</td>
<td>29.66 ± 1.99</td>
<td>29.77 ± 2.13</td>
<td>NS</td>
<td>25-35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT (seconds)</td>
<td>251.1 ± 37.97</td>
<td>260.16 ± 51.2</td>
<td>NS</td>
<td>100-155</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (unit)</td>
<td>22.17 ± 6.43</td>
<td>19.56 ± 4.55</td>
<td>0.371</td>
<td>9-35</td>
<td></td>
<td></td>
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<tr>
<td>PF (unit)</td>
<td>1.54 ± 0.72</td>
<td>0.94 ± 0.83</td>
<td>0.007</td>
<td>1.6</td>
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</table>

Both the groups were matched for platelet count. There was no statistically significant difference between two groups when prothrombin time and activated partial thromboplastin time were compared. On sonoclot analysis, the ACT did not show any difference in the two groups, and though clot rate (CR) was different in two groups, it was not statistically significant. However, platelet function (PF) was significantly lower in the ALL than the ITP group (Table).

Conclusions: This is the first study to the best of our knowledge demonstrating the use of sonoclot in ALL with severe thrombocytopenia. We conclude that sonoclot, a point of care device, can assess the risk of bleeding amongst patients with ALL.

Legal entity responsible for the study: Kundan Mishra.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Clinically actionable mutations identified in Korean patients with high-risk acute lymphoblastic leukemia

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Background: Identification of clinically actionable mutations in cancer is essential for catalyzing precision oncology based on risk stratification. Currently, little is known about the mutation profile of high-risk acute lymphoblastic leukemia (ALL) in Korean patients. We aimed to develop a multigene panel for ALL and to investigate clinically actionable mutations in the Korean patients with high-risk ALL.

Methods: We developed a multigene panel targeting 102 genes with diagnostic, prognostic, or therapeutic significance in ALL and validated it using reference materials and clinical samples. The mutation analyses were done in a total of 18 patients with high-risk ALL (T lymphoblastic leukemia (T-ALL, n = 7), B lymphoblastic leukemia in relapse (relapsed B-ALL, n = 5), and Philadelphia chromosome-positive ALL (Ph+ ALL, n = 6). High-risk ALL was categorized based on clinical findings and laboratory tests including immunophenotyping, chromosome analyses, fluorescence in situ hybridization, and RT-PCR. Clinically actionable mutations were selected based on a four-tiered system recommended by Association for Molecular Pathology in 2017.

Results: A total of 28 clinically actionable mutations including 6 novel mutations were identified in 83% of the patients. The most frequent alterations in Korean patients were loss of function mutations of KMT2C (78%), followed by mutations of NOTCH1 (17%) and SUZ12 (11%). There is to date no evidence of the frequency of KMT2C mutation among T-ALL, relapsed B-ALL, and Ph+ ALL, while mutations in NOTCH1 and

1040P

Assessment of bleeding risk by sonoclot in acute lymphoblastic leukemia

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Background: At the same level of thrombocytopenia, patients with acute lymphoblastic leukemia (ALL) receive more prophylactic platelet transfusion in comparison to immune thrombocytopenia (ITP). Routine investigation can’t differentiate the risk of bleeding between ALL and ITP. Sonoclot is a global test of coagulation, a bed side tool, also assesses platelet function. It is widely used in cardiac surgery and hepatology to assess need for blood plasma and platelet transfusion. Aim of the study was to evaluate role of sonoclot in assessing the risk of bleeding in ALL with severe thrombocytopenia.

Methods: In this prospective observational study, twenty-five cases of ALL and fifty cases of ITP (control) were included. All patients included had platelet counts lower than 20000/μL and there was no evidence of any active bleeding. Blood samples were evaluated by conventional coagulation tests as well as by Sonoclot. Sonoclot measures activated clotting time (ACT), clot rate (R1) and platelet function (PF).

Results: Abstracts Annals of Oncology
SUZ12 were observed only in T-ALL. Additional 8 genes including NT5C2 and KRAS were mutated. Furthermore, potential germline pathogenic variants were discovered in 3 patients including one previously diagnosed as neurofibromatosis type 1.

**Conclusions:** This study showed that KMT2C mutations were recurrently observed in Korean patients with high-risk ALL. The KMT2C mutation status could be an effective risk stratification strategy for Korean patients with ALL. This study provides clinically actionable mutational portrait of high-risk ALL, albeit in a limited number of patients and gives novel insight into genetic heterogeneity of the disease.

**Legal entity responsible for the study:** Pusan National University Yangsan Hospital Institutional Review Board.

**Funding:** Biomedical Research Institute in Pusan National University Yangsan Hospital.

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** AML is a heterogeneous hematologic malignancy. For patients who are ineligible for standard treatment, relapsed from prior remission, or failed prior treatment, only few options are available for further treatment and the responses are limited. A recent study has identified dihydroorotate dehydrogenase (DHODH) as a critical enzyme in the myeloid differentiation of human AML blast. At present there is no specific molecular marker to identify likely responders to DHODH inhibition. ASLAN003, a potent small molecular DHODH inhibitor, which has completed phase 1, has demonstrated the ability to induce differentiation in AML cell lines, xenograft models, and the primary AML blast obtained from patients. ASLAN003 has shown a safe and tolerable profile in prior phase I studies.

**Trial design:** A multicenter, single arm phase II A study to evaluate ASLAN003 as monotherapy in patients with AML who are ineligible for standard therapy. The primary objective is to determine the optimum dose of ASLAN003 based on the efficacy, safety and tolerability profile, of doses already studied in healthy volunteers. Safety will be assessed based on Adverse Events and other safety measures including vital signs, laboratory tests, electrocardiography. Efficacy will be assessed using the Overall Complete Remission Rate (OCRR, % of complete remission (CR) + complete remission with incomplete hematologic recovery (CRi)). Secondary objective is to assess the pharmacokinetics (PKs) of ASLAN003 and its metabolite and to further assess the efficacy based on relapse-free survival and clinical benefit rate (CBR, % of partial remission + CR + CRi). Exploratory objectives is to exam the myeloid differentiation effects of ASLAN003 ex vivo and explore the possible relationships between the clinical response and AML molecular profile. The study contains 3 cohorts (ASLAN003 100 mg, 200 mg, and 300 mg once daily). Accrual has started on December 2017, with planned enrollment for 6 patients for each cohort. Safety data will be listed and summarized. Exploratory objectives is to exam the myeloid differentiation effects of ASLAN003 ex vivo and explore the possible relationships between the clinical response and AML molecular profile. The study contains 3 cohorts (ASLAN003 100 mg, 200 mg, and 300 mg once daily). Accrual has started on December 2017, with planned enrollment for 6 patients for each cohort. Safety data will be listed and summarized. Overall AML response data will be listed and summarized showing frequency and proportion of the best response, OCRR and CBR by dose levels. Concentrations and PK parameters will be listed and summarized using descriptive statistics.

**Clinical trial identification:** Clinical trial information: NCT03451084.

**Legal entity responsible for the study:** ASLAN Pharmaceuticals.

**Disclosure:** M. McHale: Chief Operating Officer and holds stocks: ASLAN Pharmaceuticals. H-J. Shih, J. Kwek: Employee: ASLAN Pharmaceuticals. N. McIntyre: Statistical consultant: ASlan Pharmaceuticals. B. Lindmark: Employee, senior management team and CMO: ASLAN Pharmaceuticals; Holds stock and stock options: ASLAN Pharmaceuticals. All other authors have declared no conflicts of interest.
HEAD AND NECK CANCER, EXCLUDING THYROID

10460  A phase Ib/II study (SCORES) of durvalumab (D) plus danvatirsen (DAN; AZD9150) or AZD5069 (CX2i) in advanced solid malignancies and recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC): Updated results


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10450  A phase II window of opportunity study of preoperative olaparib (O) with cisplatin (C) or durvalumab (D) or olaparib alone in in patients with operable squamous cell head and neck carcinoma (HNSCC) (OPHELIA)

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Preliminary results from a phase II trial of tipifarnib in squamous cell carcinomas (SCCs) with HRAS mutations

A. Liu1, N. Chau2, J. Baumari1, K. Binde3, A. Chintakuntlawar4, M.E. Cabanillas5, D.J. Wong1, J. Braham Garcia1, M.S. Bruse4, V. Born1, C. Ewen1, M. Razeghi1, V. Mishra1, K. Bracken1, D. Wages1, C. Schulz1, A. Guaitberto1

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4Medical Oncology, Mayo Clinic, Rochester, MN, USA
5Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

1048O M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients (pts) with advanced SCCHN: Results from a phase I cohort

B.C. Cho1, A. Daste2, A. Ravaud3, S. Salas4, N. Isambert5, E. McClay6, A. Awada6, C. Borel7, J. Gulley1, L. Ojala1, C. Helwig1, P.A. Rolfe1, N. Penel1

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3Medical Oncology, CEPCM Assistance Publique des Hôpitaux de Marseille, Marseille, France
4Medical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France
5Medical Oncology, Institute for Metabolism Research & Education, California Cancer Associates for Research & Excellence, Inc, Encinitas, CA, USA
6Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
7Medical Oncology, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France

PD Pembrolizumab for recurrent head and neck squamous cell carcinoma (HNSCC): Post hoc analyses of treatment options from the phase III KEYNOTE-040 trial


1Drug Development and Innovation, Institut Cure, INSERM U900 Research Unit, and Versailles-Saint-Quentin-en-Yvelines University, Paris, France
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3Targeted Therapy, The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust, National Institute of Health Research Biomedical Research Centre, London, UK
4Medical Oncology, Instituto Portugues de Oncologia do Porto Francisco Gentil, Porto, Portugal
5Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy
6Hematology & Oncology, Samsung Medical Center, Seoul, Republic of Korea
7Medical Oncology, Hospital Universitario Ramon y Cajal, Madrid, Spain
8Oncology, Cliniques Universitaires Saint-Luc et Université Catholique de Louvain, Brussels, Belgium
9Hôpitaux Universitaires de Genève, Geneva, Switzerland
10Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA
11Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA
12Medical Oncology, Yale University School of Medicine and Yale Cancer Center, New Haven, CT, USA
13Medical Oncology, Merck & Co, Inc, Kenilworth, NJ, USA
14Department of Medicine – Department of Hemato-Oncology, Centre Hospitalier de l’Université de Montréal, Montréal, QC, Canada
Results of a phase II study evaluating monalizumab in combination with cetuximab in previously treated recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)


1ENT, Lung, Sarcomas and GIST, Centre Léon Bérard, Lyon, France, 2Oncology, Centre Oscar Lambret, Lille, France, 3Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA, 4Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, 5Early Phases Cancer Trial Center, APHM, AMU, Marseille, France, 6Medical Oncology, Institut Gustave Roussy, Villejuif, France, 7Medical Oncology, Hopital Lacassagne, Nice, France, 8Hematology/Oncology, The University of Chicago Medical Center, Chicago, IL, USA, 9Oncology, Stanford University Medical Center, Stanford, CA, USA, 10Medical, Innate Pharma, Marseille, France, 11Oncology, Abramson Cancer Center, Philadelphia, PA, USA
1050PD  Phase Ib/II, open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naïve patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)

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1051PD  Comparison of patient populations identified by different PD-L1 assays in head and neck squamous cell carcinoma (HNSCC)

M. Scott1, S. Wildsmith2, M. Ratcliffe3, H. Al-Masri3, P.W. Scorer1, C. Barker1, M.C. Rebelatto4, J. Walker5
1IMED Biotech Unit, Precision Medicine Laboratories, Precision Medicine and Genomics, AstraZeneca, Cambridge, UK, 2IMED Biotech Unit, Oncology Companion Diagnostics Unit, Precision Medicine and Genomics, AstraZeneca, Cambridge, UK, 3Anatomic Pathology & Clinical Pathology, Hematogenix, Tinley Park, IL, USA, 4Experimental Pathology, Translational Sciences-Research, MedImmune, Gaithersburg, MD, USA

1052PD  Predictor of effectiveness of treatment intensification on overall survival in head and neck cancer (HNC)

K. Zakeri1, F. Rotolo2, B. Lacas2, L.K. Vitzthum1, Q-T.X. Le3, V. Gregoire4, J. Overgaard5, J. Tobias6, B. Lacas6, M.K. Parmar8, B.A. Burtness9, M.G. Ghis10, G. Sanguineti11, B.O'Sullivan1, C. Fortpied13, J. Bourhis14, H. Shen1, J-P. Pignon12, B. O'Sullivan12, C. Fortpied13, J. Bourhis14, H. Shen1, J. Harris15, J-P. Pignon12, L.K. Mell1
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1054PD Concurrent cisplatin and dose escalation with intensity-modulated radiotherapy (IMRT) versus conventional chemo-radiotherapy for locally advanced (LA) head and neck squamous cell carcinomas (HNSCC): GORTEC 2004-01 randomized phase III trial


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1053PD Genomics features (GF) and integration with MRI radiomics features (RF) to develop a prognostic model in oral cavity squamous cell carcinoma (OSCC)

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1055PD Surrogates of immunologic cell death (ICD) and chemoradiotherapy outcomes in head and neck squamous cell carcinoma (HNSCC)

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Cetuximab + platinum-based therapy (PBT) as a first-line treatment for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN): An observational study (ENCORE)

Elderly patients with head and neck cancer selected based on FGFR mRNA overexpression

Background: The EXTREME regimen (cetuximab + PBT ≤ 6 cycles followed by cetuximab-alone maintenance until progressive disease [PD]) was the first treatment in 80 years to significantly improve disease control and overall survival (OS) vs PBT in patients (pts) with first-line (1L) R/M SCCHN (median progression-free survival [PFS], 5.6 vs 3.3 months; median OS, 10.1 vs 7.4 months). ENCORE is a multinational, observational, prospective, open-label study investigating the real-world treatment practices, efficacy, and safety of the EXTREME regimen in 1L R/M SCCHN. The primary objective was to characterize the ways the 1L R/M treatment regimen is administered in SCCHN.

Methods: This study (EMR 06202-566) enrolled 225 pts with previously untreated R/M SCCHN from Italy, France, Portugal, Russia, Algeria, and South Africa, who were planned to receive 1L treatment with cetuximab + PBT.

Results: 221 pts were evaluable. Median age was 64 years, 76% were male, and 85% had an ECOG performance status of 0 or 1. 51% of patients had recurrent disease, 9% had recurrent and metastatic disease, and 40% had metastasis at first presentation. 40% of patients received cisplatin, and 59% received carboplatin. Only 54% of patients received 5-fluorouracil (5-FU). 14% had previously received cetuximab as part of their locally advanced setting. 206 pts (93%) were planned to receive cetuximab maintenance until PD, and 97 of the 202 pts with known stop date (48%) received cetuximab maintenance. Median PFS was 6.5 months (95% CI, 5.4–7.6), and median OS was 10.2 months (95% CI, 8.5–12.6). Serious adverse events occurred in 36% of pts, with 3% related to cetuximab.

Conclusions: The ENCORE trial showed, in an international real-world setting, OS and PFS with 1L cetuximab + PBT that were comparable to what was observed in the randomized, phase 3 EXTREME study. Notably, the EXTREME regimen was feasible in an unselected population and was adapted in a substantial proportion of patients, with almost half of them not receiving 5-FU. Final data will be presented at the congress.

Clinical trial identification: Trial Protocol Number: EMR 06202-566.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking, and was funded by Merck KGaA, Darmstadt, Germany.

Legal entity responsible for the study: Merck KGaA.

Funding: Merck KGaA.

Disclosure: C. Le Tourneau: Honoraria: MSD, Bristol-Myers Squibb, Roche, Amgen, Novartis, Merck Serono, Nanobiotix. All other authors have declared no conflicts of interest.

Elderly patients with locally advanced head and neck squamous cell carcinoma treated with NBTXR3 nanoparticles activated by radiotherapy: A phase I trial

Background: Elderly patients (pts) with head and neck squamous cell carcinoma (HNSCC) represent 25% of the affected population. They are not always eligible to the same treatment of younger pts, thus require new therapies. NBTXR3, injectable hafnium oxide nanoparticles activated by radiotherapy (RT), was developed to increase the local deposit of energy within the tumor. It is currently evaluated in a phase I trial for locally advanced HNSCC in elderly and frail pts.

Methods: So far, 16 pts ≥65 years ineligible for surgery and cisplatin, the non-surgical standard of care, or intolerant to cetuximab, but eligible for RT with stage III or IV HNSCC of the oral cavity/oropharynx were treated with a single NBTXR3 intratumoral (IT) injection. A 3 + 3 dose escalation design was applied with dose levels at 3%, 10%, 15%, 22% of baseline tumor volume followed by intensity-modulated RT (IMRT; 70 Gy / 35 fractions / 7 weeks). Primary endpoints were determining the Recommended Dose and of Dose Limiting Toxicities (DLTs). NBTXR3 leakage in...
nearby healthy tissues and efficacy per RECIST 1.1 response via MRI were evaluated. Pts are followed until disease progression/study cut-off date.

**Results:** Enrollment is at the fourth level at 22% (5 pts) and complete for the first three at 5% (3 pts), 10% (3 pts), 15% (5 pts) with no early DLTs. Two adverse events (AE, asthma, grade 1; oral pain, grade 2) related to NBTXR3 and four AEs (two tumour hemorrhage, grade 1; asthma, grade 1; oral pain, grade 2) related to the IT injection were reported. NBTXR3 persistence in the tumor with no leakage was assessed per CT scan between 24h and 7 weeks post injection. In 13 evaluable pts, the best response per RECIST 1.1 on investigator assessment were 6 CR, 4 PR, 3 NC.

### Table: 1058P

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**Conclusions:** Current results indicate a safe and well tolerated profile for NBTXR3 even at the highest doses highlighting an encouraging perspective in the elderly. This population strongly medical need of which few HNSCC trials answer.

**Clinical trial identification:** NCT01946867.

**Legal entity responsible for the study:** Nanobiotix.

**Funding:** Nanobiotix.

**Disclosure:** All authors have declared no conflicts of interest.

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**1058P** Long lasting responses to adoptive T-cell therapy in relapsed EBV-related nasopharyngeal carcinoma

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**Background:** Epstein-Barr virus (EBV)-related Nasopharyngeal carcinoma (NPC) is a highly chemoradio-sensitive cancer. However, when relapsing without surgical or reirradiation options, NPC carries a dismal prognosis; survival >2 years being reported in 7-14% metastatic (1-2). We have previously achieved disease control using autologous EBV-specific cytotoxic T lymphocytes (CTL) in refractory/ relapsed pts following conventional treatments (3). The aim of the present study was to evaluate outcomes in pts receiving T-cell therapy after first line chemotherapy (CT) for recurrent disease.

**Methods:** Sixteen patients (13 males, median age 41 yrs) with metastatic (n=12, 7/12 with visceral metastasis, and 5/12 with bone and nodes lesions) or locally recurrent (n=4) NPC received 2 administrations of EBV-specific CTL at a total cell dose/infusion of 1.5-3 x 10^6, following completion of first line CT. The best response after first line CT had been progressive disease (PD) in 4 pts, stable disease (SD) in 3, partial response (PR) in 5 and complete response (CR) in 4.

**Results:** No adverse events were recorded, following CTL therapy. Among patients in CR after first-line CT, 3 remain in CR at 58, 76 and 77+ months, while one patient relapsed, but attained a long-lasting CR after treatment with 2nd-line CT. In the 12 patients treated with persistent disease (PR, SD, PD), the best response observed after CTL therapy, in some cases (3/12) associated with 1suSsequent of CT or radiotherapy, was PD in 8 patients, and CR (range 39-78+ months) in 4. At a median follow-up of 64 months, 8/16 patients are alive with no evidence of disease. Among the factors associated with positive outcome are response to first-line CT, and metastatic disease with limited tumor burden.

**Conclusions:** EBV-specific CTL therapy administered following first line CT for recurrent NPC, is safe and associated with remarkable clinical benefit in some patients, including long-lasting CR.

**Legal entity responsible for the study:** Fondazione IRCCS Policlinico San Matteo Pavia.

**Funding:** Fondazione IRCCS Policlinico San Matteo, Ricerca Corrente RCR.

**Disclosure:** All authors have declared no conflicts of interest.

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**1060P** Radiotherapy alone for human papillomavirus-related locally advanced oropharyngeal squamous cell carcinoma: A single-arm, phase II study

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**Background:** Oropharyngeal squamous cell carcinoma (OPSCC) is divided into two entities: human papillomavirus-related (HPV-related) and HPV-unknown. Although it is established that patients with HPV-related locally advanced OPSCC (LA-OPSCC) survive significantly better than those with HPV-unknown LA-OPSCC when treated with chemoradiotherapy (CRT), CRT remains the standard treatment for HPV-related LA-OPSCC. Given the young generation being more prone to be affected by HPV-related OPSCC, patients suffer from severe late toxicity associated with CRT for a long time. The hypothesis has emerged that patients with HPV-related LA-OPSCC could be well managed by de-intensiﬁed treatment, resulting in long-term less morbidity without compromising survival. A series of clinical trials are in progress to certify this hypothesis.

**Methods:** We did a single-arm, phase II trial, enrolling patients with newly diagnosed, biopsy-proven, stage III or IV (excluding T4 and/or N3) OPSCC, positive for both p16 and HPV DNA. Patients received intensity-modulated radiotherapy alone for 70 Gy in 35 fractions. The primary endpoint was response at 11th week after treatment, assessed on RECIST and PCRICST.

**Results:** Between August 2013 and November 2016, 39 patients were enrolled with a median age of 64 years (range: 49-83). The majority of patients (24, 62%) had ≥30 pack-years smoking history. 35 (90%) patients showed complete response on RECIST and/or complete metabolic response on PCRICST. One patient had regional recurrence, and two had distant metastasis. The 2-year overall survival rate and progression-free survival rate was 96% and 91% (95% CI, 76-99 and 75-97), respectively. During treatment 10 patients had grade 3 adverse events, but no grade 4 events were reported. 7 patients had gastrostomy tube placed during treatment, but no patient was dependent on gastrostomy tube at 4 weeks after treatment.

**Conclusions:** Radiotherapy alone was associated with high disease control and an improved toxicity proﬁle. Radiotherapy alone has the potential to replace CRT as the standard treatment for HPV-related LA-OPSCC.

**Clinical trial identiﬁcation:** UMIN000008953; Release date: 09/20/2012.

**Legal entity responsible for the study:** Osaka University.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no confict of interest.

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**1061P** Molecular screening in advanced cancer patients with head and neck cancers: A retrospective analysis of the MOSCATO-01 trial

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**Background:** Advanced and metastatic head and neck (HN) cancers are a heterogeneous tumour with poor outcome as few therapeutic options are available. Until now, no accepted genomic proﬁles can lead to an oriented treatment. We performed a retrospective analysis of the MOSCATO-01 trial for patients with advanced and metastatic HN cancer.

**Methods:** Patients included in MOSCATO-01 trial underwent biopsies for molecular screening analyses by Comparative Genomic Hybridisation Array, Next Generation Sequencing or RNA Seq. Patients were treated by targeted treatment on the molecular alteration screening. Progression-free survival (PFS) ratio was the primary endpoint corresponding to PFS2/PFS1 (PFS2: PFS in patients treated according to molecular alteration; PFS1: PFS in patients treated with usual treatment).

**Results:** 129 patients (12.4%) with advanced or metastatic HN cancers were included in MOSCATO-01 trial among 1035 patients. The most frequent histologic type was squamous cell carcinoma (62.7%), followed by adenocarcinoma and kystic adenocarcinoma (6.5% each) and mucoepidermoid carcinoma (3.7%). Patients were in most of the cases heavily pre-treated, as 65% of them received 3 lines of prior systemic treatment. More than 60% of the patients had a R0/R1 score at 0. 107 patients (82.9%) who underwent a biopsy, 45 (42%) presented potential targetable molecular alterations: PIK3CA, ERBB2, NOTCH and MET where the most frequent targeted changes: PIK3CA, ERBB2, NOTCH and MET where the most frequent targeted
molecular alterations. Moreover, 33.3% of them (n = 15) had a targeted treatment: 9 patients in phase I trial and 6 with off label use therapeutic. The median progression free survival of the 15 patients treated according to molecular alteration was 1.7 months (0.2-6.95). The PFS ratio was above 1.3 for 40% of the patients.

**Conclusions:** MSCCA-0104 for HN cancers showed that a large proportion of patients have cancer with actionable molecular alteration, with benefit on PFS ratio of oriented treatment guided by molecular screening. Precision medicine in advanced HN cancers could bring new therapeutic options in these hard to treat cancers.

**Legal entity responsible for the study:** Christophe Massard.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1062P** Pembrolizumab and afatinib for recurrent or metastatic head and neck squamous cell carcinoma

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**Background:** Head and neck squamous cell carcinoma (HNSCC) is an important malignancy in Taiwan. Anti-PD-1, including nivolumab or pembrolizumab (pembro), had shown the efficacies against recurrent or metastatic (R/M) HNSCC. Afatinib, an irreversible EGFR tyrosine kinase inhibitor (TKI), had showed its activity against head and neck squamous cell carcinoma. In vitro and animal study showed that afatinib can inhibit macrophage function, increase antigen presentation, and augment the T cell response. The role of afatinib for cancer immunotherapy have not been explored in human. We hypothesized that adding afatinib with pembro may improve the treatment efficacy for patients with R/M HNSCC.

**Methods:** For HNSCC patients who decided to take pembro, the combination with afatinib would be discussed between the physician and the patient. Pembro was planned for 4 cycles. Afatinib was prescribed concurrently with pembro, and will be kept after discontinuation of pembro, until disease progression. For patients taking pembrolizumab and afatinib (P+ A), the medical records were reviewed. Patients who have mono-therapy with pembrolizumab or afatinib before the P + A were excluded. REGIST.1.1 were used for evaluating tumor response.

**Results:** From Nov. 1, 2016 to Sep. 30, 2017, 41 R/M HNSCC patients (pts) took P+ A. The median age was 59 years, and 38 pts were men. The cancer types were: oral cavity: 29 pts, oropharynx: 5 pts, and hypopharynx: 7 pts. The initial treatments were: pembrolizumab 200mg; 27pts, 2mg/kg; 14pts. Eighteen pts are platinum naive, and 23 pts are platinum refractory. Until Mar. 30, 2018, the median follow-up was 7.6 months. The clinical response was: CR / PR 24/41 (58.5%, 95% CI: 42.8% - 74.3%), SD: 9/41, PD: 8/41. The median PFS was 7.5 (9.0-9.3) months. The median of OS was not reached. The most common toxicities were: diarrhea 56%, skin rash 44%, mucositis 32%, and hand-foot-skin reaction 24%. The incidence of grade 3 or 4 toxicities was 3/41. No pneumo-

**Conclusions:** The addition of afatinib with pembrolizumab showed good efficacies and tolerable toxicities. Biomarker studies are ongoing. Further confirmatory prospective trial is indicated.

**Legal entity responsible for the study:** Hsiang-Fong Kao.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1063P** A multicenter phase II trial of paclitaxel, carboplatin and cetuximab (PCE) followed by chemoradiotherapy in patients with unresectable locally advanced squamous cell carcinoma of the head and neck (SCCHN)

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**Background:** Induction chemotherapy (IC) often compromises the compliance of following chemoradiotherapy (CRT) in LA-SCCHN. In particular, impaired compliance of cisplatin (CDDP) during CRT negatively affects outcomes. Here, we aimed to assess the feasibility and efficacy of paclitaxel (PTX), carboplatin (CBDCA), and cetuximab (Cmab) as IC for unresectable LA-SCCHN.

**Methods:** Patients with biopsy-proven, unresectable LA-SCCHN were enrolled. IC consisted of CBDCA AUC = 1.5, PTX 80mg/m² and Cmab with an initial dose of 400mg/m² followed by 250mg/m² administered weekly for 8 weeks. Following IC, CDDP (200mg², 4 days x 3 cycles) and concurrent radiotherapy (78GY/35F) were started. Primary endpoint was the rate of CRT completion, defined by (1) completion of planned CDDP relative dose intensity (RDI) ≥ 80%, and (2) completion of radiotherapy within 2 weeks after planned completion date. PCE was planned to be deemed effective if the Bayesian posterior probability (PP) that the rate of CRT completion was > 65% exceeded 84%.

**Results:** 35 patients were eligible and received study treatment. Cases were hypopharynx/oropharynx/larynx in 17/17/1 patients, all stage IV (stage IVA: 24, stage IVB: 11). Of 35 patients, 34 (97%) completed IC and 32 received CRT (FAS). Of 32 FAS cases, the rate of CRT completion was 96.9%, and the study’s primary endpoint was therefore met (PP = 99.9% > 84%). Mean cumulative dose and RDI of CDDP in CRT was 232.5mg (160-240mg) and 100% (66.7-100%), respectively. Response rate was 88.6% in the IC phase and 93.8% in the CRT phase. 2-year rates of local progression, distant metastasis, event-free survival and overall survival were 34.9%, 16.7%, 51.5% and 83.5%, respectively. Main grade 3 toxicities included neutropenia (11%), skin rash (6%), and anemia (6%) in the IC phase; and oral mucositis (31%), neutropenia (13%), and radiation dermatitis (13%) in the CRT phase. No grade 4 toxicity or treatment-related death was seen.

**Conclusions:** PCE as IC was feasible, with promising efficacy and no effect on compli-

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**1064P** Cetuximab in combination with platinum-based chemotherapy or radiotherapy in patients with recurrent and/or metastatic SSCHN in clinical routine: Updated interim results of the prospective SOCCER study

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**Background:** Cetuximab in combination with platinum-based chemotherapy followed by cetuximab maintenance until progression significantly prolonged overall survival (OS) in patients with line recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) (EXTREME trial).

**Methods:** SOCCER is an ongoing German prospective, non-interventional study to evaluate symptom control in patients with recurrent and/or metastatic SCCHN treated with cetuximab in combination with platinum-based chemotherapy or radiotherapy in clinical routine. Descriptive statistics were used for the current interim analysis (data cut-off 8 DEC 2017) focusing on efficacy outcomes.

**Results:** This interim analysis involves 399 patients (median age: 62.0 years (range 29-89 years), 82.2% male, ECOCG 0-1: 74.2%, 61.9% metastatic disease) who received at least one dose of cetuximab. In 289 of 399 patients cetuximab was applied in combination with platinum-based chemotherapy (CT) only (163 cis- (41.3%), 124 carboplatin (31.3%)), in 80 patients (20.1%) in combination with radiotherapy (RT) only; and other regimens in 30 patients (7.9%). Current median duration of cetuximab therapy was 6.1 weeks in combination with CT and 12.9 weeks in combination with CT. Median observation time was 11.7 months (reverse Kaplan-Meier estimate). In the 231 patients with available response data (CR, PR, SD, PD) the objective response and disease control rate were 45.0% and 80.5%, respectively. Median progression-free survival and OS after start of cetuximab therapy was 5.5 and 9.3 months (5.2-9.3 months for the cetuximab + CT and 8.7/9.3 months for the cetuximab + RT).

**Conclusions:** Interim results of the non-interventional SOCCER study indicate that efficacy outcomes of cetuximab in combination with platinum-based CT under routine conditions are in line with the results of the EXTREME trial.
**Background:** The randomized phase III Study CA209141, Nivolumab (N) demonstrated significant overall survival benefit as treatment for platinum refractory R/M SCCHN and is now approved for these patients. N has a manageable safety profile compared to chemotherapies commonly used in patients with platinum-refractory R/M SCCHN. The main objective of the study is to provide additional insight into the frequency of high-grade AEs related to N and their impact on overall survival.

**Methods:** Between August 2017 and October 2017, 75 patients were included in the multicenter, open-label, non-controlled phase II safety study TOPNIVO. The main inclusion criteria were patients with platinum refractory R/M SCCHN with progressive disease, ECOG 0-2. Patients received N 1 mg/kg every 2 weeks intravenously over 30 minutes. We report here the safety results of the first three months of treatment.

**Results:** Of 73 patients treated with N, median age was 64 yrs, 73% were male, 23% were ECOG 0; 62%, 15%, 2, 81% were current or former smoker. The primary site of cancer was oral cavity 27%, oropharynx 34%, larynx 19%, hypopharynx 19%. 36% had loco regional relapse, 34% had metastatic disease and 30% had both. 48% had received one prior line of chemotherapy and 32% two prior lines. 35 pts (51%) received at least 6 administrations of N during the first three months of treatment. 5% of administrations were delayed, mainly for intercurrent disease. 38 pts (52%) ended N within the first three months of treatment. 6.7 months and 20.1 months, respectively. Grade 3/4 adverse events included neutropenia (91%), febrile neutropenia (FN) (39%), anemia (22%), appetite loss (17%), and fatigue (13%). The FN rate was significantly lower in the pts with platinum-refractory R/M SCCHN with progressive disease compared to chemotherapies. 5% of administrations were delayed, mainly for intercurrent disease. ORRs according to primary tumor site and histology are shown in the table below.

**Conclusions:** The incidence of grade 3/4 AEs was less than with platinum-refractory chemotherapy. The SAE rate was lower compared to what has been described previously. The primary endpoint was objective response rate (ORR). No treatment-related deaths were observed.

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**Legal entity responsible for the study:** Merck Serono GmbH, Darmstadt, Germany.

**Funding:** Merck Serono GmbH, Darmstadt, Germany.

**Disclosure:** M. Hecht: Research funding: Novartis, MSD, AstraZeneca; Honoraria: BMS, Merck Serono; Travel support: Merck Serono, MSD, TEVA. D. Hahn: Travel grants, honoraria for advisory boards and speaker: Merck. R. Hahn: Honoraria as speaker and consultant: Merck; C. Belka: Honoraria and advisory boards: Merck; D. Hofmann: Employee and stock ownership: Merck. R. Fiebiku: Honoraria as speaker and advisory boards: Merck Serono; Research funding: MSD, AstraZeneca; Honoraria: Roche, Merck Serono, Fresenius; MSD Travel support: Roche, Merck Serono, Fresenius, MSD. All other authors have declared no conflicts of interest.

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<th>Table: 1066P Objective response rates according to primary tumor site and histology</th>
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<tr>
<th>Tumor Site</th>
<th>Adenoid cystic carcinoma</th>
<th>Adenocarcinoma, not otherwise specified</th>
<th>Salivary duct carcinoma</th>
<th>Sebaceous carcinoma</th>
<th>Mucoepidermoid carcinoma</th>
<th>NUT midline carcinoma</th>
<th>Acinic cell carcinoma</th>
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<tr>
<td>Salivary gland</td>
<td>2/4</td>
<td>2/3</td>
<td>2/3</td>
<td>0/1</td>
<td>6/11</td>
<td></td>
<td></td>
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<tr>
<td>Nasal cavity/pananasal sinus</td>
<td>1/3</td>
<td></td>
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<tr>
<td>Ocular</td>
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<td></td>
<td>2/2*</td>
<td>1/1</td>
<td>1/3</td>
<td>2/5</td>
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<td>Oral cavity/lip</td>
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*complete response
1067P Multicenter phase II trial of nab-paclitaxel and cisplatin (AP) followed by chemoradiation therapy (CRT) for locally advanced head and neck squamous cell carcinoma (HNSCC)

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Background: The results of two consecutive phase II trials of patients with locally advanced HNSCC showed a relapse rate of 13% after nab-paclitaxel, cisplatin and 5-FU and cetuximab (APFC) followed by CRT (Cancer 2013) and 3% after AP (no 5-FU) and CRT (Clin Trials 2011). The complete response (CR) rate for the primary tumor site after 2 cycles of APFC was 53% and AP 77%. A comparison of APFC and CRT to APF and CRT showed no benefit of cetuximab (Oncal Oral Radiation 2017). In this phase II trial, we hypothesized similar efficacy with AP (no 5-FU) and CRT.

Methods: Eligibility criteria were similar to prior trials: stage III-IV oropharynx (OP), nasopharynx (NP), sinonasal, hypopharynx (HP), and primary tumor site after 2 cycles of APFC was 53% and AP 77%. A comparison of APFC and CRT to APF and CRT showed no benefit of cetuximab (Oncal Oral Radiation 2017). In this phase II trial, we hypothesized similar efficacy with AP (no 5-FU) and CRT.

Results: Characteristics of the 40 enrolled patients: mean age 57 years (range 42-77), smoker 6%, male 90%, and ECOG 0 (78%). Tumor characteristics: TxNx (68%), T2 (58%), and human papillomavirus (HPV) associated OPSCC (73%) or HPV-unrelated HNSCC (27%). The CR rate at the primary tumor site after 2 cycles AP was 70% (28 patients). Primary tumor site biopsies obtained following 2 cycles AP in 29 patients showed no cancer in 24 (83%). Post-cycle 2 biopsies showed no cancer in 19 of 20 evaluable patients with clinical CR. Median follow-up was 12.0 months (range 0.1-19.6). Relapse rate was 8% (3 patients).

Conclusions: The CR rate at the primary tumor site after 2 cycles of AP was not inferior to that with AP. Deletion of 5-FU from AP did not reduce tumor response. Clinical trial identification: NCT02573493.

1068P Cetuximab in combination with methotrexate (MTX) as first-line treatment in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A phase Ib randomized phase II study versus single agent MTX

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Background: First-line palliative treatment in R/M SCCHN consists of the combination of cetuximab with cisplatin and 5-FU with a median progression free survival (PFS) and overall survival (OS) of 5.5 and 10.1 months, respectively, at the expense of substantial toxicity. Single agent MTX has minimal side effects, but response rate, gain in PFS and OS are limited. We hypothesized that adding cetuximab to MTX could improve PFS without adding major toxicities. Because this combination had not been tested before, we first performed a phase Ib study followed by a randomized phase II study.

Methods: In the phase Ib study, patients (pts) with previously untreated R/M SCCHN were treated with weekly MTX 40 mg/m² and cetuximab 250 mg/m², after a loading dose of cetuximab 400 mg/m². The primary objectives of the phase Ib study were feasibility and safety of the combination of cetuximab and MTX. In the phase II study pts were randomized to either MTX or the combination (1:1). The primary objective of the phase II study was to detect an increase in median PFS from 3 to 5 months with combination vs single agent MTX. Secondary endpoints were toxicity and OS.

Results: Six pts were included in the phase Ib study. No dose limiting toxicities were observed, median PFS was 24.6 weeks (range 7.5-55.0). In the phase II study 45 pts were included, 15 pts received MTX (73% male, median age 64 years (range 50-77)) and 30 pts cetuximab and MTX (77% male, median age 69 years (range 46-80)). In the phase II study median PFS was significantly different: 8.0 weeks (range 3.0-39.0) in the MTX arm and 17.0 weeks (range 3.9-76.6) in the combination arm. Nine pts in the combination arm experienced a serious adverse event (SAE), 3 were possible treatment-related (pneumonia, pneumonitis and hypersensitivity reaction) compared with 5 pts with an SAE in the MTX group, all unrelated. OS and detailed toxicity results will be presented later.

Conclusions: The combination of cetuximab and MTX in pts with R/M SCCHN is feasible. This randomised phase II study met its primary endpoint: a significantly longer PFS in the cetuximab and MTX combination arm, while toxicity was acceptable.

Clinical trial identification: NCT02054442.

1069P Phase II study of biweekly TPFLL induction chemotherapy for locally advanced squamous cell carcinoma of head and neck

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Background: The induction chemotherapy (ICT) with triweekly TPFLL had been considered as an effective treatment in locally advanced squamous cell carcinoma of head and neck (SCCHN). However, the treatment needs inpatient care and may have more toxicities for Asian patients. We conducted a phase 2 study of alternative biweekly TPFLL as induction chemotherapy and evaluated the outcome and toxicities.

Methods: Patients with locally advanced SCCHN were enrolled in the study. Induction chemotherapy with Docetaxel 50mg/m², cisplatin 50mg/m², 5-fluorouracil 2500 mg/m² and leucovorin 250 mg/m² was administered biweekly for six cycles, followed by local treatment including concurrent chemoradiotherapy, bio-radiotherapy or surgery plus adjuvant RT. Our primary endpoint is response rate after ICT.

Results: Total 58 patients were enrolled in the study from June 2014 to September 2015. The median age is 58 years (30 to 89 years). The patients’ characteristics were mentioned as: primary site of oral cavity/oropharynx/hypopharynx: 18/25/15; stage IVA/IVB: 33/25; male/ female: 54/4; performance status ECOG 0-1/2/3:5/17/4. In the oropharyngeal cancer patients neither p16 nor HPV16 status was not studied. Of those 58 patients, 56 patients received at least 4 cycles of chemotherapy. The overall response rate after ICT was 89.6% (CR: 31% PR: 58.6%). Two patients escaped during induction chemotherapy. Grade 3/4 neutropenia was 25/9%, grade 3/4 mucositis was 1.7%, grade 3/4 diarrhoea was 1.7%. Infection rate was 15%. The response rate after following treatment was 75 % (CR: 66.0%, PR: 9.0 %). The median follow-up time was 31.8 months. The overall 3 years PFS/OS was 34.3%/56.1%. Local recurrence rate was 29.3% and distant metastasis rate was 10.3%. Six patients had second primary tumor (10.3%). The 3 years PFS of patients with CR/PR were 59.3%/25.5%. The 3 years OS of patients with CR/PR were 81.7%/49.1%.%.

Conclusions: Biweekly TPFLL induction chemotherapy has excellent response rate in locally advanced SCCHN. In addition, the grade 3/4 adverse event was acceptable. The patients achieved CR after induction chemotherapy had very good outcomes.

Clinical trial identification: CMU1103-REC2-038.

Legal entity responsible for the study: Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital.

Funding: Sanofi, Taiwan branch.

Disclosure: All authors have declared no conflicts of interest.
Phase II study of CC-486 in previously treated patients (pts) with locally advanced/metastatic nasopharyngeal cancer (NPC): Final results

R. Meia Nina, R. Bossi1, A. Hansel1, C. Huet1, L.F. Lictra1, E.H. Tanrı1, P. Cherf1, J. Miller1, L.L. Sun1, T. Fadda1
1Medical Oncology, Catalan Institute of Oncology (ICO Baladala), Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; 2Medical Oncology, Università degli Studi di Torino, Ospedale San Giovanni Battista, Turin, Italy; 3Medical Oncology, Genova University Hospital, Genoa, Italy; 4Medical Oncology, China Medical University Hospital, Taichung, Taiwan; 5Head and Neck Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy; 6Medical Oncology, National Cancer Center, Seoul, South Korea; 7Medical Oncology, Princess Margaret Hospital, Toronto, ON, Canada; 8Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Second/third-line treatment (Tx) options are limited for pts with NPC. The efficacy and safety of CC-486 were assessed using Simon’s optimal 2-stage design in a phase 2 study. The predefined criterion for advancement to stage 2 (>4 complete/ partial responses) was not met. Here, we present final results from stage 1.

Methods: The single-arm, open-label study (NCT02269943) included pts with locally advanced/metastatic NPC who had ≥1 prior Tx, including ≥2 platinum-containing regimens. Pts received CC-486 300 mg orally on d 1-14 of a 21-d cycle until disease progression/unacceptable toxicity. The first 4 Asian-Pacific (AP) pts received CC-486 200 mg; if well tolerated, subsequent AP pts received 300 mg. Primary endpoints (per independent review assessment [IRA]) were: overall response rate, progression-free survival; Key secondary endpoints: overall survival, disease control rate, safety, pharmacokinetics (PK).

Results: Median age of 36 enrolled pts was 54 y. Most were male (81%), had EGOG PS of ≤ 1 (97%), and had ≥ 2 prior systemic anticancer Tx (58%); 36% were AP. Pts received a median of 0.9 Tx cycles; 44% had ≥ 1 dose interruption and 39% had ≥ 1 dose reduction. 22 pts died: 1 on- and 21 post-Tx (> 28 after last dose); 18 died due to disease complications. The table shows efficacy outcomes. PK analysis showed rapid absorption; exposure was comparable between doses. However, large inter-pt variability and small pt numbers did not allow definitive conclusions. All 36 safety-evaluable pts had ≥ 1-15 emergent adverse event (AE). Common TEAEs included neutropenia (38%) and febrile neutropenia (11%).

Conclusions: The safety profile of CC-486 in pts with NPC was consistent with that in other solid tumors and of azacitidine. CC-486 monotherapy did not show sufficient clinical activity in the selected pt population to support further development in these pts.
**1075P** Safety and efficacy of nivolumab (nivo) in platinum-refractory recurrent/metastatic head and neck squamous cell (PR/RM HNSCC) patients (pts): Real-life experience


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**Background:** PR/RM HNSCC pts present a poor prognosis. In the randomized phase 3 trial CheckMate141, nivo showed benefit in OS with manageable toxicity. In our region, nivo is available for clinical practice since April 2017. Aim: to evaluate the safety and activity of nivo in a real-world setting.

**Methods:** This multicenter, retrospective analysis included PR/RM HNSCC pts treated with nivo 3mg/kg every 2 weeks at 7 centers from Valencia region. We assessed demographic, safety (CTCAE v4.0 criteria), response evaluation (RECIST 1.1) progression-free survival (PFS) and OS. Pts included in the analysis should have received >1 dose of nivo.

**Results:** A total of 50 pts were treated between May 2017 and April 2018. At the time of this analysis 38 patients were evaluable (updated data of the complete cohort and follow-up will be presented in ESMO congress). Nivo was administered as first-line palliative treatment in 8 pts (21.1%), as second-line in 18 pts (47.4%) and in third or subsequent lines in 12 pts (31.6%). The median number of doses administered was 5 (range 1-26) with 6 one-week treatment delays due to respiratory infections. Analysis of concurrent antibiotic therapy is pending. The objective response rate was 9 (23.7%) with 9 partial responses, whereas 9 pts (23.7%) had stable disease. No confirmed hyperprogression was observed. Median time since last dose of platinum was 2.9 months (range 0-24) with 10 pts with a period time longer than 6 months. With a median follow-up of 6 months (range 1-16), median PFS was 3.4 months.

**Disclosure:** All authors have declared no conflicts of interest.

**Results:**

- **Characteristics:** All (n = 675)  
  - *Age* (mean±SD): 49.52269 ± 11.91209  
  - *BMI* (kg/m²) (mean±SD): 23.26 ± 4.08  
  - *Smoking Status* Non-smoking Previous Current Missing: 419 135 100 29  
  - *T stage* T1-T2 T3-T4: 359 316  
  - *N stage* NO N1-N2 N3: 75 516 73  
  - *Stage at diagnosis* Stage 1 Stage 2 Stage 3 Stage 4: 4 117 306 33 137 78

- **Adjuvant chemotherapy (n = 595):**  
  - *Age* (mean±SD): 48.96639 ± 11.63714  
  - *BMI* (kg/m²) (mean±SD): 23.25 ± 4.10  
  - *Smoking Status* Non-smoking Previous Current Missing: 367 120 84 26  
  - *T stage* T1-T2 T3-T4: 309 286  
  - *N stage* NO N1-N2 N3-N4: 62 463 60  
  - *Stage at diagnosis* Stage 1 Stage 2 Stage 3 Stage 4 Stage 4a Stage 4b: 1 1 1 1 1

- **Active survival (n = 80):**  
  - *Age* (mean±SD): 53.425 ± 13.4473  
  - *BMI* (kg/m²) (mean±SD): 23.35 ± 4.00  
  - *Smoking Status* Non-smoking Previous Current Missing: 49 13 15 3  

- **p-value:** 0.002 0.16 0.824 0.454 0.075 0.054 0.255

**Conclusion:** No significant differences were observed in the analysis between the groups. Nivo was administered as first-line palliative treatment in 8 pts (21.1%), as second-line in 18 pts (47.4%) and in third or subsequent lines in 12 pts (31.6%). The median number of doses administered was 5 (range 1-26) with 6 one-week treatment delays due to respiratory infections. Analysis of concurrent antibiotic therapy is pending. The objective response rate was 9 (23.7%) with 9 partial responses, whereas 9 pts (23.7%) had stable disease. No confirmed hyperprogression was observed. Median time since last dose of platinum was 2.9 months (range 0-24) with 10 pts with a period time longer than 6 months. With a median follow-up of 6 months (range 1-16), median PFS was 3.4 months.
Comparison of 3-weekly cisplatin versus 3-weekly carboplatin in patients with locally advanced nasopharyngeal carcinoma (LA-NPC) receiving concurrent chemoradiotherapy (CCRT): A multicenter retrospective study


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Background: Although CCRT with high-dose cisplatin remains the standard protocol for patients with LA-NPC, carboplatin has been used as an alternative especially for cisplatin-ineligible patients. However, the comparable efficacy of these 2 regimes is still unclear. This study aimed to compare the efficacy and tolerability of 3-weekly carboplatin with 3-weekly cisplatin.

Methods: From May 2005 to November 2014, we retrospectively reviewed medical information for 787 LA-NPC patients treated with CCRT from 3 university hospitals in Thailand. Chemotherapy regimen would be either cisplatin (75-100 mg/m2) or carboplatin (AUC-5 to 6), followed by adjuvant chemotherapy (platinum plus 5-fluorouracil). Tolerability and survival were analyzed and compared.

Results: Patient demographics, baseline characteristics, and treatment for the patients were shown in the table. During CCRT, 52% of patients in the cisplatin arm completed the 3 planned cycles of treatment, compared to 88% in the carboplatin arm (P < 0.0001). Fifty-six percent of patients in the cisplatin, whereas only 5% in the carboplatin arm required dose reduction of chemotherapy due to toxicities (P < 0.0001). At the time of analysis, the 5-year disease-free survival was 60% (95% confidence interval [CI], 56 to 63) and 62% (95% CI, 50 to 72) (P = 0.21), and 5-year overall survival was 74% (95% CI, 70 to 77) and 67% (95% CI, 56 to 77) (P = 0.19), in the cisplatin and carboplatin groups, respectively.

Conclusions: Carboplatin showed similar efficacy to that of cisplatin with better tolerability and could be used as an alternative regimen.

Legal entity responsible for the study: Research University Network: Head and Neck Working Group.

Funding: Research University Network (Thailand).

Disclosure: All authors have declared no conflicts of interest.

1077P Comparison of concurrent chemoradiation therapy plus induction chemotherapy with cisplatin, fluorouracil and docetaxel versus gemcitabine and cisplatin in advanced nasopharyngeal carcinoma

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Background: Induction chemotherapy treatment for nasopharyngeal carcinoma (NPC) is controversial. The aim of this study was to evaluate the treatment outcomes and toxicities between two induction chemotherapy regimens, with both followed by concurrent chemoradiotherapy.

Methods: A retrospective study of 113 patients with eligible NPC (stage III–IV NPC with non-distant metastases) treated at the West China Hospital Cancer Center between May 2009 and Dec 2014 was conducted. Among them, 58 patients received cisplatin, fluorouracil, and docetaxel (five cycles) and 55 received gemcitabine and cisplatin (GP) induction chemotherapy. Both groups received CCRT incorporating IMRT and cisplatin-based chemotherapy.

Results: The average follow-up time was 51.4 (16.8–98.3) months. Ninety-four patients (83.2%) were alive after 36-months follow-up. The median overall survival (OS) and progression-free survival (PFS) time were 48.3 and 39.7 months, respectively. The 1, 3, and 5-year OS for the TPF regimen was 87.9% and 87.4% with GP chemotherapy (P = 0.928). The 3-year PFS of the TPF regimen was 84.5%, while it was 83.5% for the GP group (P = 0.537). OS (Log-Rank P = 0.928) and PFS (Log-Rank P = 0.651) did not differ significantly between the two groups. Patients in the TPF induction chemotherapy plus CCRT group, did not show better LRFs outcomes in comparison to those in the GP induction group (Log-Rank P = 0.073). Furthermore, DMFs rates were not different between the treatment groups (Log-Rank P = 0.892).

Conclusions: There were no significant differences in adverse toxicities or treatment efficacy between the chemotherapy regimens in the treatment of locoregionally advanced NPC. Furthermore, the adverse toxicities were similar and could be tolerated. However, the TPF group had a high proportion of grade 3 or 4 adverse reactions.

Legal entity responsible for the study: Lei Liu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1076P

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<th>Variables</th>
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<th>P-value</th>
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<tr>
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<td>Cisplatin (n = 710)</td>
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<tr>
<td>Median age (years)</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Sex (n [%]) Male</td>
<td>500 (70)</td>
<td>56 (73)</td>
</tr>
<tr>
<td>Smoking Yes (n [%])</td>
<td>225 (32)</td>
<td>47 (61)</td>
</tr>
<tr>
<td>Comorbidity Yes (n [%])</td>
<td>96 (14)</td>
<td>18 (23)</td>
</tr>
<tr>
<td>WHO classification I (n [%])</td>
<td>2 (0.3)</td>
<td>110 (15.6)</td>
</tr>
<tr>
<td>WHO classification II (n [%])</td>
<td>289 (41)</td>
<td>38 (56)</td>
</tr>
<tr>
<td>WHO classification III (n [%])</td>
<td>308 (43)</td>
<td></td>
</tr>
<tr>
<td>WHO classification IV (n [%])</td>
<td>161 (22.7)</td>
<td>38 (49)</td>
</tr>
<tr>
<td>Missing (n [%])</td>
<td>338 (47.6)</td>
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</tr>
<tr>
<td>Median baseline Cr (mg/dL)</td>
<td>0.87</td>
<td>0.94</td>
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</tbody>
</table>

Conclusions: Genomic profiling and matched therapy for recurrent or metastatic malignant salivary gland tumors

E.R. Malone1, R. Jiang1, A. Spreafico1, I. Weinreb2, S. Jennings1, L.L. Siu1, A. Hansen1

1Medical Oncology, Princess Margaret Cancer Center, Toronto, ON, Canada, 2Laboratory Medicine Program, University of Toronto, Toronto, ON, Canada

Background: MSGT are rare with limited systemic treatments. This ongoing trial is a single-institution, prospective study in advanced MSGT involving 2 phases: genomic profiling followed by treatment with either genomically matched or unmatched therapy. The aim is to determine response rates as per RESIST v1.1 in patients (pts) with MSGT treated with matched or unmatched therapy.

Methods: Pts with recurrent/metastatic MSGT with archived paraffin-embedded tumor samples were enrolled in the profiling phase. Following pathology review and DNA extraction, targeted next generation sequencing was performed in a CLIA certified laboratory. Immunohistochemistry for androgen receptor (AR) and fluorescence in-situ hybridization for HER2 and ALK was done. Successfully profiled pts then proceeded to treatment phase when their disease was progressing to receive a matched therapy via early phase clinical trials or approved agents. If no actionable mutations were identified or no matched agents were available, pts could receive selinexor, an oral selective inhibitor of nuclear export (SINE) that inhibits XPO1 at a dose of 60mg twice weekly. Non-progressing pts remained on active surveillance.

Results: Since July 2014, 38 pts (19M/19F, median age 62 yrs [range 37-85]) have been enrolled in the profiling phase. Disease subtypes include adenoid cystic (n = 19), salivary duct (n = 8) and other (n = 11). Four pts failed screening due to lack of tissue, 4 tumor samples are currently being analysed. Of the 30 evaluable pts, 13 (43%) had at least one actionable mutation. Aberrations included PIK3CA (6), FGFR2 (3), PTEN (2), AR (4), BRAF (2), HER2 amplification (1), HER2 mutation (1), KIT (1), EGFR (1) and MET (1). Eight pts were treated with genomically matched therapy and 7 received selinexor. See table for outcomes.

Disclosure: All authors have declared no conflicts of interest.
Conclusions: Genomic profiling may be integrated into clinical care for pts with MSGT permitting pts to receive targeted therapy. This is an ongoing study, we will present updated data at the conference.

Clinical trial identification: NCT02069730.

Legal entity responsible for the study: Princess Margaret Cancer Center.

Funding: Princess Margaret Cancer Center/Karyopharm.

Disclosure: A. Spreafico: Consultant and advisory board: Merck, BMS, Novartis; Research support: Genentech/ Roche, Merck, GleaveBlackKline, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, Karyopharm. All other authors have declared no conflicts of interest.

Table: 1078P

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<th>Matched Treatment</th>
<th>Selinexor</th>
<th>Median Duration of treatment</th>
<th>9 months (mo)</th>
<th>4mo</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Median overall survival</td>
<td>192mo</td>
<td>21.3mo</td>
</tr>
<tr>
<td>Stable disease rate</td>
<td>88% (7/8)</td>
<td>86% (6/7)</td>
<td></td>
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<tr>
<td>Progressive disease rate</td>
<td>12% (1/8)</td>
<td>14% (1/7)</td>
<td></td>
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</table>

Background: Treatment response to androgen deprivation therapy (ADT) in androgen receptor (AR)-positive salivary duct carcinoma (SDC) is 18-50%. The cause of ADT-resistance is unknown. We aim to predict treatment response through analysis of functional AR-pathway activity.

Methods: Patients who received palliative ADT (n = 28) for locally recurrent or metastatic SDC were selected. ADT consisted of bicalutamide or combined androgen blockade. AR-pathway analysis was performed in all patients. For this, RNA was extracted from annotated, formalin-fixed paraffin embedded sections from tumor tissue prior to treatment. For quantitative measurement of functional AR pathway activity, mRNA expression of the AR pathway target genes was measured using one-step RT-qPCR, and clinical response (PR, SD, PD) was determined.

Results: AR pathway activity score was divided in tertiles. Patients with highest AR-pathway activity score were more likely to respond to ADT (p = 0.0267, two-sided Fisher exact), while highest incidence of progression free survival (PFS) was found in the lowest AR activity group. Median OS was 30 months vs 17 months in the high and low AR activity group. Tertile 1 31.91-65.38, Tertile 2 43.71-50.35, Tertile 3 33.10-43.55.

Conclusions: Functional AR pathway activity measured by this new method was predictive for clinical response to ADT in this small retrospective SDC cohort. Extended validation of clinical utility in a larger patient cohort is in preparation.

Legal entity responsible for the study: Radboud University Medical Center, Nijmegen, the Netherlands.

Funding: Dutch Salivary Gland Cancer Patient Platform and Radboud Oncology Fund.

Disclosure: D. van Strijp, J.B.A. van Zon, A. van de Stolpe: Employee, corporate research funding: Philips Research. S. Neerken: Employee, corporate research funding: Philips Healthworks. All other authors have declared no conflicts of interest.

Table: 1079P

<table>
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<th>AR-pathway activity (range)</th>
<th>Response (number of patients)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
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<tr>
<td>Tertile 1 31.91-65.38</td>
<td>0 PR 15 SD 9 PD 21</td>
<td>12</td>
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<tr>
<td>Tertile 2 43.71-50.35</td>
<td>0 PR 2 SD 7 PD 21</td>
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<tr>
<td>Tertile 3 33.10-43.55</td>
<td>3 PR 4 SD 25 PD 5</td>
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Applications: Functional AR pathway activity measured by this new method was predictive for clinical response to ADT in this small retrospective SDC cohort. Extended validation of clinical utility in a larger patient cohort is in preparation.

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Disclosure: D. van Strijp, J.B.A. van Zon, A. van de Stolpe: Employee, corporate research funding: Philips Research. S. Neerken: Employee, corporate research funding: Philips Healthworks. All other authors have declared no conflicts of interest.

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Conclusions: Genomic profiling may be integrated into clinical care for pts with MSGT permitting pts to receive targeted therapy. This is an ongoing study, we will present updated data at the conference.

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Disclosure: A. Spreafico: Consultant and advisory board: Merck, BMS, Novartis; Research support: Genentech/ Roche, Merck, GleaveBlackKline, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim, Karyopharm. All other authors have declared no conflicts of interest.

Table: 1081P

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<td>Progressive disease rate</td>
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</table>

Background: SMM is a rare entity with no specific treatment. Little is known about SMM molecular profile, a low rate of genetic alterations has been described compared to cutaneous melanoma. We aimed to screen for several genetic alterations in SMM.

Methods: From 1988 to 2017, we collected 20 formalin-fixed paraffin primary tumors blocks from SMM patients and 12 local recurrences and/or distant metastasis from the same patients. We analyzed the spectrum of mutations in KIT (exons 9, 11 and 17) by standard PCR followed by Sanger sequencing, NRAS gene (exons 2, 3 and 4) by pyrosequencing and BRAF gene (exon 15) by Taqman PCR. Finally, RET, ALK and ROS1 fusions and gene expression levels were determined by nCounter.

Results: We identified gene mutations in 6/20 cases (30%). We found 2 cases (10%) with mutations in NRAS gene (both in exon 2: G12V), 3 cases (15%) with mutations in KIT (all in the exon 11: R863K, G566R, M552D) and 1 case (5%) with KRAS mutation (G12A). No BRAF mutations were detected. Interestingly, we found discrepancies in the NRAS mutational status of tumor samples obtained from 2 patients. In the first case, at diagnosis, we identified the NRAS mutation in 1 of 2 samples, and in 2 of 3 samples at the time of local recurrence. In the second case, the NRAS mutation was present at diagnosis but only in 2 of 4 samples of distant recurrence. Finally, nCounter did not reveal RET, ALK no ROS1 gene fusions or mRNA overexpression in any sample.
Conclusions: In our series of SNMM, we have found mutations in 6/20 tumors (30%) in KIT, NRAS and KRAS genes. No fusions or overexpression were found for ALK, ROS1 or RET genes. To our knowledge, this is the first reported study on these genes. We plan to further characterize this orphan population by analyzing immune-related genes.

Legal entity responsible for the study: Georgia Anguea.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1083P

1083P

Programmed death-ligand 1 (PD-L1) expression and HPV-associated p16 in oropharyngeal squamous cell carcinoma (OSCC) treated with primary curative radiotherapy (RT)

T. Steiniche1, J.G. Enskær1, J.K. Lilla-Fischer1, J. Georgesen1, P.T. Vo1, M. Busch-Sørensen2, D.R. Chirovsky1, D. Cheng2, D. Aurora-Garg2, R. Swaby3, J. Overgaard1

1Pathology, Aarhus University Hospital, Aarhus, Denmark; 2Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark; 3Pharmacopoeiology, MD - Merck & Co, USA, Kenilworth, NJ, USA; 4Busch-Sørensen Consulting ApS, Væn, Denmark; 5Outcomes Research, MSD - Merck & Co USA, Kenilworth, NJ, USA; 6Medical Oncology, Merck & Co Inc, North Wales, PA, USA.

Background: PD-L1 expression in malignancies contributes to an immunosuppressive microenvironment and disruption of anti-tumoral immune responses. Data are limited on the association between PD-L1 expression and survival in OSCC, overall and by HPV status. We explored the prognostic effect of PD-L1 and p16 in localized or locally advanced OSCC treated with primary RT.

Methods: Patients (pts) diagnosed with OSCC from 2000-12 were identified from the Danish Head and Neck Cancer database (DAHANCA). PD-L1 expression was measured using the A ventilation/diagnostic test (Ventana Pathology, MD - Merck & Co, USA). TPS was significantly associated with MIDS (Chi square = 5.030). A statistical analysis of the clinical endpoints, overall or by p16 status. After adjustment for other covariates did not change the results.

Conclusions: PD-L1 expression is not prognostic. TPS was significantly associated with HPV status (Chi square = 0.005). The findings support the importance of PD-L1 expression in the context of HPV status. Further studies to confirm these findings are warranted.

Legal entity responsible for the study: The Danish Head and Neck Cancer Group (DAHANCA).

Funding: Merck & Co, Inc.


1083P

Dynamics of immune checkpoint molecule (ICM) expression in immune cell subsets during curative conventional therapy of head and neck squamous cell carcinoma (HNSCC)

A. Garg1, S.S. Jeske1, K.K. Punigami1, C. Brunner2, J. Kraus2, H. Kester3, J. Döscher4, T.K. Hoffmann5, P.J. Schuler6, S. Laban7

1Department of Otolaryngology and Head & Neck Surgery, University Medical Center Ulm, Ulm, Germany; 2Institute for Medical Systems Biology, Ulm University, Ulm, Germany; 3Analysis and Visualization of Alteration Data (AVATAR), a novel bioinformatic analysis tool for prostate cancer. The study included 6 patients with HNSCC treated with curative conventional therapy. Immune cell subsets were isolated from peripheral blood mononuclear cells (PBMC) at baseline, and post-surgery, mid-CRT, end of CRT, 3, 6, 9, 12 months post end of treatment (EOT).

Results: Compared to baseline, surgery had no significant impact on ICM expression. PD1 were significantly lower at 3 and 6 months post EOT. CD8/CD41 and CD19/CD27 were significantly decreased from 3 to 12 months post EOT. CD4/CD27 were significantly lower from mid-CRT until 12 months post EOT, whereas CD4/CD27 and Treg/CD327 were significantly decreased from 3 to 12 months post EOT. CD4/CD28 and Treg/CD4 increased mid-CRT until 3 months post EOT, but significance was not confirmed after correcting for multiple testing.

Conclusions: Whereas surgery alone seems to alter ICM expression, CRT has a significant impact on the expression of PD1, Treg and CD27. CD28 seems to increase during CRT. These results reveal a rational for the combination of PD1 inhibitors with CRT. Combining such a treatment with CD40 inhibitors may be a promising strategy.

Clinical trial identification: NCT03053661.

Legal entity responsible for the study: University Medical Center Ulm.

Funding: Deutsche Forschungsgemeinschaft (GRK2254).

Disclosure: T. K. Hoffmann: Advisory board member: Merck Sharp & Dohme; Lecture fees: Merck Sharp & Dohme, Merck Serono. P.J. Schuler: Advisory board member: Bristol Myers Squibb. S. Lahm: Advisory board member: AstraZeneca, Merck Sharp & Dohme; Lecture fees: Bristol-Myers Squibb, Merck Serono. All other authors have declared no conflicts of interest.

1084P

Multibioptic optimization reveals distinct cancer-testis antigen patterns by primary site and human papilloma virus status in head and neck squamous cell carcinoma

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Background: Most previous vaccination attempts in cancer immunotherapy have been focused on a single antigen. Consequently, the expression of the selected antigen needs to be determined before trial inclusion resulting in a high screening failure rate. The establishment of a multi-antigen vaccine may improve the coverage of potential patients, especially if the selected antigens are semipersonalized for clinical patient subgroups.

Methods: Analysis and Visualization of Alteration Data (AVATAR), a novel bioinformatic software tool for multi-objective optimization of large datasets, was used to analyze publicly available datasets of transcriptome data from The Cancer Genome Atlas (TCGA) and a dataset from Gene Expression Omnibus (GSE40774). Cancer-testis antigens (CTA) were selected as model antigens for multi-objective optimization based on the primary tumor site and HPV-status. Dichotomized data were pooled and edited resulting in a cohort of 865 patients, of which 125 were HPV-positive (HPV+). Primary tumor sites included were oral cavity (n = 208), oropharynx (n = 150) and larynx (n = 208).

Results: Selecting 10 CTA genes for the whole cohort results in a coverage of 89.3%. When optimizing gene selections for each primary tumor site, distinct 10-gene selections are revealed improving the coverage in the respective group markedly. Antigen selections overlap only to a minor degree with the solutions for all patients or other patient groups. Even in predominantly HPV+ primary sites such as OC and L, antigen selections are remarkably different from each other. When optimizing for HPV-status, distinct selections were found for optimal coverage in the respective patient group overlapping only in one gene.

Conclusions: AVATAR can be used to identify antigen selections with optimal coverage within a specified patient group. A semi-personalized antigen selection based on multi-objective optimization may be a useful strategy to plan trials for antigen-specific vaccination.

Legal entity responsible for the study: University Medical Center Ulm.

Funding: Deutsche Forschungsgemeinschaft (GRK2254).

Disclosure: S. Lahm: Advisory board member: AstraZeneca, Merck Sharp & Dohme; Lecture fees: Bristol-Myers Squibb, Merck Serono; J. Eic: Employment, stock ownership; Bristol-Myers Squibb, Merck Serono; J.-H.G. Ramansee: Employment; Bristol-Myers Squibb; P.J. Schuler: Advisory board member: Bristol Myers Squibb. All other authors have declared no conflicts of interest.
Background: HPV-related oropharyngeal cancer (OPC) patients have favorable prognosis, but around 20% fail to treatment. The HPV16-ES oncoprotein increases recycling of activated-epidermal growth factor receptor (EGFR) to the cell surface, enhancing factor signal transduction. Our aim was to evaluate viral HPV16-ES oncogene expression as well as EGFR and its activated form, phosphorylated EGFR (pEGFR), protein levels as biomarkers for clinical outcome in a retrospective cohort of OPC patients.

Methods: Formalin-fixed-paraffin-embedded OPC were collected from pathology archives. Samples containing HPV-DNA were further subjected to HPV E6*I mRNA detection and p16INK4a immunohistochemistry (IHC). HPV 16-positive cases were evaluated for HPV16-ES (RT-PCR) and E6*I*EGFR IHC. A stratified random sample of HPV-negative cases was evaluated for E6*I*EGFR. Overall survival (OS) and disease-free survival (DFS) estimates were calculated.

Results: Among the 788 OPC patient samples from a retrospective cohort, 54 were HPV16-positive and 213 were HPV-negative. HPV16-ES expression was found in 41 samples (77.4%). Expression of EGFR was observed in 37.7% vs 70.8% HPV-16 positive and HPV-negative samples, respectively; (adjusted Odds Ratio (OR) = 0.1595%, Confident Interval (CI) 0.04-0.56). Expression of pEGFR followed an inverse pattern with 39.6% and 24.9% detection in HPV16-positive and HPV-negative samples, respectively; (adjusted OR 1.80 (0.48-6.17)). Within HPV16-positive cases, no association between HPV16-ES and EGFR or pEGFR was observed. The combination of HPV status and EGFR or pEGFR expression were predictors of OS and DFS.

Conclusions: HPV16-ES is highly expressed on HPV16-positive OPCs. Interestingly, HPV16-positive cases expressed more pEGFR than HPV-negative cases as expressed significantly more EGFR. The combinations of HPV status and EGFR or pEGFR expression are useful biomarkers for prognosis outcome in OPC patients.

Legal entity responsible for the study: Instituto Catalán de Oncología.

Disclosure: All authors have declared no conflicts of interest.

1086P
Combined analysis of gene expression profiles in 2 preoperative trials with afatinib and cetuximab in head and neck squamous cell carcinoma

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Background: Only a minority of head and neck squamous cell carcinoma (HNSCC) patients (pts) respond to targeted agents acting on epidermal growth factor pathway. We investigated the changes of gene expression profiles in 2 preoperative window of opportunity trials, to allow a further investigation in mechanisms of response.

Methods: Thirty and 20 pts with similar characteristics were treated for 2 weeks before surgery with afatinib (EORTC 90111-24111 NOCI HNSCC trial, Ann Oncol 2017) and cetuximab (Schmitz S, Ann Oncol 2013), respectively. The gene expression profile obtained by microarray platform was compared by a paired analysis pre and post treatment. Gene sets were defined according to GSEA and only sets with q-value FDR < 0.05 differences were considered. Clinical response was analysed according to primary endpoint of the trials (FDG-PET response).

Results: Pre- and post-targeted treatment paired histological samples from 20 and 15 pts were evaluable for gene expression, from afatinib and cetuximab series, respectively. The following gene sets were commonly downregulated by the treatment: G2M checkpoint, MYC and EZF targets and MTOC. On the opposite, the gene sets which resulted upregulated were: angiogenesis, epithelial-mesenchymal transition, inflammatory response and NOTCH signaling. A substantial overlapping of molecular alteration between the 2 series has been observed, thus allowing a further meta-analysis combining the 2 datasets to analyse profiles associated to response. Preliminary data in afatinib series showed a strong downregulation of hypoxia gene signature only in responding pts.

Conclusions: In 2 independent studies with afatinib and cetuximab in window of opportunity setting, we observed similar molecular alterations induced by the drugs. Further insights in the pathways involved in response to both drugs are ongoing.

Legal entity responsible for the study: Paolo Bossi.

Funding: AIRC and Italian Ministry of Health.

Disclosure: P. Bossi: Advisory Board: Merck Serono, J-P. Machiels: Advisory board: Boehringer-Ingelheim. L.F. Licitra: Advisory board and research supports: Merck Serono, Boehringer Ingelheim. All other authors have declared no conflicts of interest.
Analysis of immune and genomic landscapes of patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) treated with pembrolizumab in the INSPIRE study

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Background: Despite the survival gain observed with anti-PD-1 agents in R/M HNSCC, responses are modest and no predictive biomarkers have been validated. We investigated immune and genomic biomarkers of response in a prospective cohort of R/M HNSCC patients (pts) treated with pembrolizumab 200 mg IV QW in the INSPIRE study.

Methods: Pts had blood samples (BS) collected at baseline (BL) and on treatment (OT) at cycle 3 (week 9); fresh tumor biopsies (FTB) were collected at BL and OT (week 6-9). Analyses included tumor whole exome sequencing and immunophenotyping by flow cytometry of FTB and BS; tumor PD-L1 staining (clone 22C3) using modified proportion score. Response rate (RR) using RECIST 1.1. Median progression-free survival (PFS) and overall survival (OS) estimated by Kaplan-Meier method. Time to progression (TTP) was estimated using cumulative incidence method. Univariable analyses of genomic and immune parameters were conducted to identify response predictors.

Results: Seventeen pts were enrolled: median age 62 years (48-71); smoking history: >10 pack-year (PY); T3/T4 = 11; oral cavity = 7; oropharynx = 6 (5 HPV +); larynx = 4; Platinum-refractory = 15; > 2 prior lines of therapepy = 4; PD-L1 < 1% = 9; RR = 3 partial responses (PR), 10 stable disease (SD), 4 progressive disease (PD). Median follow-up was 4.9 months (0.6-19.3); TTP 9.7m (3.5-not reached (NR)). Pts with PR had >10 PD-L1 > 1% and no local recurrence. Pts with PR + SD had less proliferating k67+, FoxP3+ T regulatory cells (Tregs) in blood compared to PD pts (p<0.05). Seven pts had FTB for analysis (1 PR, 3 SD, 3 PD): patient with PR (HPV+ oropharynx) had less immunosuppressive Tregs via lower expression of CTLA-4 and CD39 in BL tumor and increased proliferating Tregs at paired OT FTB. Tumor somatic coding mutation burden and percent genome copy alteration in FTB at BL (N = 9) did not predict response (PR = 0) but a trend was observed with percent loss of heterozygosity (p=0.15).

Conclusions: This preliminary data suggest peripheral and tumor T-regs might play a critical role in R/M HNSCC pts treated with anti-PD1 agents. Dynamic immune-cell changes were more informative than BL genomic markers.

Clinical trial identification: NCT02644369.

Legal entity responsible for the study: Princess Margaret Cancer Centre.

Funding: Merck

Disclosure: A. Specific: Consultant and advisory boards: Merck, Bristol-Myers Squibb, Novartis. L.L. Stiu: Advisory board: Merck; Funding to institution (Princess Margaret Cancer Centre) to conduct clinical trials: Merck. A. Hansen: Research support: Genentech/Roche, Merck, GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Boston Biomedical, Boehringer-Ingelheim. All other authors have declared no conflicts of interest.

CIGALT1 predicts poor prognosis and is a potential therapeutic target in head and neck cancer

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Background: Head and neck squamous carcinoma (HNSCC) accounts for more than 600,000 cases annually worldwide. Glycosylation is the most common post-translational modification of proteins, and aberrant glycosylation is a hallmark of cancers. Core 1,3-galactosyltransferase (C1GALT1) controls the crucial step in O-glycosylation and promotes malignant behavior in various cancers. However, its role in HNSCC remains unclear.

Methods: Immunohistochemistry was performed to analyze expression of CIGALT1 in 133 HNSCC tumors. Student-t, Kaplan-Meier analysis, and Cox regression analyses were used to analyze correlation of CIGALT1 expression with clinicopathological factors and survivals. CRISPR/Cas9 system was used to knock out CIGALT1. MTT assay, transwell migration, and Matrigel invasion assays were carried out to evaluate HNSCC cell viability, migration, and invasion, respectively. Human phospho-RTK array and Western blot analyses were performed to evaluate signaling pathways. ELISA was used to evaluate EGF-EGFR binding affinity. Mass spectrometry was used to identify O-glycopeptides on EGFR. Molecular docking simulation was used for searching CIGALT1 inhibitors. In vivo effects of CIGALT1 and its inhibitor were evaluated in NOD/SCID mice.

Results: CIGALT1 was overexpressed in HNSCC tumors and predicts poor survivals. CIGALT1 overexpression enhanced whereas CIGALT1 knockdown/knockout suppressed cell viability, migration, and invasion in HNSCC cells. Mechanistically, CIGALT1 modulated O-glycosylation of EGFR and enhanced EGF-EGFR binding affinity, leading to increased EGFR signaling and malignant phenotypes. Using mass spectrometry, we identified five O-glycopeptides on EGFR, among which four are within the ligand binding domain. Itraconazole, a CIGALT1 inhibitor, directly bound to CIGALT1 and changed O-glycans on cell surfaces and EGFR. Targeting CIGALT1 with CRISPR/Cas9, shRNA, or itraconazole was able to significantly suppress tumor growth in NOD/SCID mice.

Conclusions: Our findings indicate CIGALT1 as an attractive therapeutic target for HNSCC.

Legal entity responsible for the study: National Taiwan University Hospital.

Funding: Ministry of Science and Technology National Taiwan University Hospital, Hoinchu branch.

Disclosure: All authors have declared no conflicts of interest.

Table: 1090P Frequency of PIK3CA mutations in HNSCC in southern Thailand

<table>
<thead>
<tr>
<th>Location of HNSCC</th>
<th>% PIK3CA mutation</th>
<th>Overall % PIK3CA mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity carcinoma</td>
<td>0 (0/61)</td>
<td>0 (0/61)</td>
</tr>
<tr>
<td>Hypopharyngeal carcinoma</td>
<td>0 (0/21)</td>
<td>8 (2/23)</td>
</tr>
<tr>
<td>Frequency of mutation</td>
<td>8 (2/23)</td>
<td>17 (4/23)</td>
</tr>
<tr>
<td>in three exons</td>
<td>6 (6/73)</td>
<td>10 (10/96)</td>
</tr>
</tbody>
</table>

Conclusions: Our study showed more frequency of PIK3CA mutations in hypopharyngeal carcinoma than oral cavity carcinoma. These results suggest that its mutation may be more involved in the carcinogenesis, and hypopharynx should be primary site of interest for further studies.

Legal entity responsible for the study: Unit of Medical Oncology, Faculty of Medicine, Prince of Songkla University.

Funding: Faculty of Medicine, Prince of Songkla University.

Disclosure: All authors have declared no conflicts of interest.

References:

NCT02644369.

1090P Frequency of PIK3CA mutations in head and neck squamous cell carcinoma (HNSCC) in southern Thailand

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Background: Phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations have been reported in many cancers including HNSCC. The presence of mutations have shown to associate with prognosis and might predict response to phosphoinositide 3-kinase (PI3K) inhibitors. However, the frequency of mutations varies among different primary locations, so this might be relevant to distinguish the possibility of treatments and outcomes among HNSCC. In this study, we examined the frequency of PIK3CA mutations in patients with oral cavity and hypopharyngeal carcinoma.

Methods: Ninety-six fresh biospies consisted of 73 oral cavity and 23 pyriform sinus carcinoma were collected for DNA extraction. DNA samples were first investigated to ascertain a reference mutational points in PIK3CA exons 4, 9 and 20. We subsequently designed two probes labelled with two different fluorescent dyes for the wild-type and mutated alleles. Multiallele analysis was further carried out by using allele-specific real time PCR.

Results: We identified mutations in 10% of patients (10 out of 96 HNSCC, specimens). Among 10 mutant specimens, there were 5 missense mutations (2 samples in exon 9 (ES45K) and 3 samples in exon 20 (H1047R)), and 5 silence mutation in exon 20 (T1025T). None of mutation was found in exon 4. Exon 9 mutation was detected in 2 out of 96 cases and was merely from hypopharyngeal carcinoma. In exon 20, 8 mutations were found (2 hypopharyngeal carcinoma and 6 oral cavity carcinoma). Overall frequency of mutations in three exons were 8% and 17% in oral cavity and hypopharyngeal carcinoma, respectively.

Conclusions: Our study showed more frequency of PIK3CA mutations in hypopharyngeal carcinoma than oral cavity carcinoma. These results suggest that its mutation may be more involved in the carcinogenesis, and hypopharynx should be primary site of interest for further studies.

Legal entity responsible for the study: Unit of Medical Oncology, Faculty of Medicine, Prince of Songkla University.

Funding: Faculty of Medicine, Prince of Songkla University.

Disclosure: All authors have declared no conflicts of interest.
**Results:** The median follow-up time was 61.1 months, with a range from 1 months to 91 months. The 3-year OS, LFS, RFS, DMFS, and DFS were 86.9%, 96.7%, 97.1%, 93.3%, and 82.6%, respectively. For LRFS and DMFS, the proposed eighth edition had superior prognostic value to the AJCC/UICC 7th edition for LRFS and DMFS and lead a better distinction between adjacent T stages of nasopharyngeal carcinoma patients without cervical lymph node metastasis. The proposed eighth edition was found to be significant both by the seventh and the proposed 8th editions. The difference between T1 and T3, T1 and T4, T2 and T3, and T2 and T4 by the proposed eighth edition were found to be significant (P = 0.024, P = 0.004, and P = 0.041, respectively), however, there was no significant difference between T1 and T3, T2 and T3 by the seventh edition (P = 0.204, and P = 0.215). In addition, the difference between T1, T2, T3 with T4 were found to be significant in DFS (P = 0.000, P = 0.000, and P = 0.037) and there was no significant difference between T1 and T2, T2 and T3 (P = 0.162) by the seventh edition and there was significantly different between T2 and T4 (P = 0.026) by the proposed 8th editions. Multivariate analysis demonstrated that age, T stage of the proposed 8th editions and chemotherapy were independent prognostic factors for OS, LFS, RFS, DMFS, and DFS. The AIC value was smaller for the 8th edition compared to the 7th stage grouping. The C-index value was larger for the 8th edition compared to the 7th edition grouping. The C-index value was larger for the 8th edition compared to the 7th edition grouping.

**Conclusions:** IMRT with elective neck irradiation provides excellent local-regional control for NPC patients without cervical lymph node metastasis. The proposed eighth editions had superior prognostic value to the AJCC/UICC 7th edition for LRFS and DMFS and lead a better distinction between adjacent stages of nasopharyngeal carcinoma patients. The proposed eighth edition was found to be significant both by the seventh and the proposed 8th editions. The difference between T1 and T3, T1 and T4, T2 and T3, and T2 and T4 by the proposed eighth edition were found to be significant (P = 0.024, P = 0.004, and P = 0.041, respectively), however, there was no significant difference between T1 and T3, T2 and T3 by the seventh edition (P = 0.204, and P = 0.215). In addition, the difference between T1, T2, T3 with T4 were found to be significant in DFS (P = 0.000, P = 0.000, and P = 0.037) and there was no significant difference between T1 and T2, T2 and T3 (P = 0.162) by the seventh edition and there was significantly different between T2 and T4 (P = 0.026) by the proposed 8th editions. Multivariate analysis demonstrated that age, T stage of the proposed 8th editions and chemotherapy were independent prognostic factors for OS, LFS, RFS, DMFS, and DFS. The AIC value was smaller for the 8th edition compared to the 7th staging system. The C-index value was larger for the 8th edition compared to the 7th staging system.

**Legal entity responsible for the study:** Fudan University Shanghai Cancer Center.

**Funding:** Has not received any funding.

**Disclosure:** The author has declared no conflicts of interest.

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**Validation of the clinical AJCC/UICC TNM 8th edition for human papillomavirus related oropharyngeal squamous cell carcinoma (OPC)**

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**Background:** With the growing interest in treatment de-intensification strategies for human papillomavirus positive (HPV+)- oropharyngeal squamous cell carcinoma (OPC), accurate patient stratification has become essential for patient selection. The aim of this study was to validate the prognostic ability of the AJCC/UICC TNM 8th edition (8th Ed) for HPV+ OPC.

**Methods:** Patients with HPV+ OPC treated with curative (chemo)radiotherapy (CRT) between 2004 and 2017 were classified according to the TNM 7th edition (7th ED) and the new clinical TNM 8th Ed. HPV status was determined by p16 immunohistochemistry staining. The 5-year overall survival (OS) was estimated using the Kaplan–Meier method and groups were compared using the log-rank test. Harrell’s C-index was used as model of measure performance.

**Results:** A total of 333 OPC were identified of whom 100 were HPV+. The median follow-up was 67.3 months (IQR: 30.09, 99.9). The 5-year OS of the 7th Ed was stage I 88.9% (95% CI 0.76 to 0.99), stage II 73.0% (95% CI 0.69 to 0.87), stage III 45.8% (95% CI 0.22 to 0.80), stage IVa 71.4% (95% CI 0.57 to 0.86) and stage IVb 29.8% (95% CI 0.14 to 0.54). With the TNM 8th Ed, the 5-year OS of stage I, II and III were 91.6% (95% CI 0.76, 1.97), 75.4% (95% CI 0.59 to 0.95), and 38.0% (95% CI 0.21 to 0.67). On Cox regression analysis, when compared to stage I, OS was significantly lower for stage II (P = 0.02, Hazard ratio (HR) = 4.24 (95% CI 1.27 to 14.13)) and for stage III (P = 0.01, HR = 5.40 (95% CI 1.69 to 17.26)).

**Conclusions:** The TNM 8th Ed provides better OS stratification than the 7th Ed for HPV+ OPC following (C)RT, better prognostic models are needed due to the lack of differentiation between stage II and stage III. This study supports the idea that the 8th Ed introduces the opportunity for further research in patient selection and personalized treatment for HPV+ OPC.

**Legal entity responsible for the study:** The ethics committee of the University Hospitals of Leuven.

**Funding:** Grant from Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society.

**Disclosure:** S. Deschuymer: Grant: Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society. All other authors have declared no conflicts of interest.

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**Clinical prognostic factors in patients (pts) with recurrent and/or metastatic (RM) head and neck cancer (HNC) treated with cetuximab plus chemotherapy**

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**Background:** There is limited information about prognostic factors in RM HNC pts receiving first-line platinum-based chemotherapy and cetuximab. Moreover, we lack survival data in a real-world population, without the selection bias affecting pts enrolled in clinical trials.

**Results:** Nevertheless, there was no significant difference between stage II and III (p = 0.60, HR = 1.27 (95% CI 0.51 to 3.17)). The Harrell’s C-index for the TNM 8th Ed stage was 0.67.

**Conclusions:** Although the TNM 8th Ed provides better OS stratification than the 7th Ed for HPV+ OPC following (C)RT, better prognostic models are needed due to the lack of differentiation between stage II and stage III. This study supports the importance of further research in patient selection and personalized treatment for HPV+ OPC.

**Legal entity responsible for the study:** The ethics committee of the University Hospitals of Leuven.

**Funding:** Grant from Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society.

**Disclosure:** S. Deschuymer: Grant: Stand up to Cancer (Kom op tegen kanker), the Flemish cancer society. All other authors have declared no conflicts of interest.
Methods: We evaluated all consecutive pts treated from 1/2007 to 12/2016 in 6 Italian centres. The following baseline prognostic factors were investigated: sex, age, site of disease, tumor grading, HPV status for oropharyngeal cancer, performance status (PS), weight loss in the previous 3 months (<less than 10%), comorbidity (according to CAE-27), residual tumor at primary site, previous chemotherapy or cetuximab in curative setting, previous radiotherapy, platinum type (cisplatin/carboplatin, CBDDA), chemotherapy schedule (weekly±3-weekly), platinum and cetuximab doublet or with a third drug (i.e. 3FU or paclitaxel). For each potential predictor variable, Kaplan-Meier curves for OS and PFS were estimated, and a Log-rank test was used to compare survopsh in different levels of the variable. A Cox proportional hazard model was run including only predictors characterized by a significant (p < 0.05) Log-rank test.

Results: We analyzed 340 pts, with a median PFS/OS of 5.0/10.6 months. The 1-year and 3-year OS rate for all pts was 44.2% (CL: 39.1-50.0) and 7.8% (CL: 5.1-13.2). Only one out of two pts received a second-line therapy. In univariate analysis lower OS was associated with PS ≥ 2 (p = 0.001), residual tumor at primary site (p < 0.001) and CBDDA use (p = 0.012) while lower PFS was associated with paranasal sinus site (p = 0.008), PS > 0 (p = 0.001), CBDDA use (p = 0.035) and residual tumor at primary site (p < 0.001). All these predictors except for platinum type remained significant at multivariate analysis. Pts with clinical response to treatment carried a more favorable prognosis, while progressive disease as best response had a dismal median OS of 5.8 months.

Conclusions: In non-selected RM NPC pts, we obtained a median PFS and OS of 5.0 and 10.6 months, very similar to 5.6 and 10.1 months reported in Extreme trial (Vermorken et al. 2008). At baseline, PS and residual tumor at primary site could be defined as poor prognostics.

Legal entity responsible for the study: Paolo Bossi.

Funding: Has not received any funding.

Disclosure: P. Bossi, D. Ferrari, R. Depeni, G. Azzarello. Advisory board: Merck Serono. L.F. Licitra: Advisory board and research support: Merck Serono. All other authors have declared no conflicts of interest.

1095P Prognostic value of MRI-derived residual retropharyngeal lymph node delineation on intensity-modulated radiotherapy in nasopharyngeal carcinoma and a nomogram for the prediction of it

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Background: In nasopharyngeal carcinoma (NPC) patients with retropharyngeal lymph node metastasis, the requirement of intensity-modulated radiotherapy (IMRT), the incidence of magnetic resonance imaging (MRI)-derived residual retropharyngeal lymph node (RRLN) is not rare and its prognostic value is uncertain. In present study, we aim to investigate the prognostic value of MRI-derived RRLN and sought to develop a nomogram for the prediction of it.

Methods: A total of 922 patients with RLN metastasis without distant metastasis NPC treated with IMRT were enrolled in present study. The Kaplan-Meier survival curves and cox proportional regression model were used to assess the prognostic value of RRLN. The patients were then randomly assigned into the training cohort (n = 464) and the validation cohort (n = 277). Factors significantly associated with RRLN were identified and used to construct nomogram with multivariate logistic regression model. The discrimination and performance of nomogram were evaluated in training cohort and confirmed in validation cohort.

Results: The incidence of RRLN was 28.2%. The 5-year OS, DFS, DMFS, LRRFS of the RRLN group and non-RRLN group were 84.1% vs. 93.2%, 65.1% vs. 87.3%, 71.2% vs. 94.2% and 87.9% vs. 95.6%, respectively (for all rates, P < 0.05). Necrosis, extra-nodal neoplastic spread (ENS), minimum axial diameter (MAD) and the percentage volume of the GTV with excluding 95% of the prescribed dose (GTVex V95%) were identified as independent factors associated with RRLN and used to construct the nomogram. The nomogram showed favorable calibration and discrimination in training cohort (AUC, 0.74) and validation cohorts (AUC, 0.738). Patients with high-risk scores had a higher probability of developing RRLN than patients with low-risk scores in training cohort (OR, 3.183, 95% CI: 2.853-8.525) and validation cohort (OR, 6.977, 95% CI: 3.990-12.200).

Conclusions: MRI-derived RRLN was a negative independent prognostic factor for OS, DFS, DMFS and LRRFS in NPC patients with RLN metastasis who received IMRT. We constructed a nomogram based on clinical and radiological characteristics that predicted an individual’s risk of RRLN.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center.

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Disclosure: All authors have declared no conflicts of interest.

1096P Proteomic comparison based on 18FDG-PET/CT defined metabolic tumor volume in non-metastatic nasopharyngeal carcinoma

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Background: Various PET/CT based metabolic tumor volume (MTV) was found to influence the prognosis of non-metastatic nasopharyngeal carcinoma. The proteomic analysis of primary tumor was compared for 18FDG-PET/CT based MTV in non-metastatic nasopharyngeal carcinoma. We tried to find the potential biomarker related to MTV.

Methods: We respectively analyzed 110 patients with PET/CT confirmed non-metastatic nasopharyngeal carcinoma at our institution. MTV of primary tumor was defined with SUV2.5. The ROC curve was portrayed with treatment failure events of patients. With the optimal cut-off point of MTV, another 25 nasopharyngeal carcinoma patients were divided into two groups to compare the primary tumor proteomics. Proteomic analysis was conducted with the combination of iTRAQ and nano-RPLC-MS/MS. We analyzed the previous tumor specimens (97/110) to verify the potential biomarker found by proteomics.

Results: The area under the ROC curve (AUC) was 0.726. And the best cut-off point for MTV was 9.88 ml (≥10 ml). MTV <10 ml appeared a favorable disease-free survival (DFS, 93.5% vs. 81.3%, P = 0.035). A total of 7913 proteins were identified with proteomics, of which 360 had significant differences. In MTV≥10ml group, the expression of 244 proteins was up-regulated and the other 116 was down-regulated. According to GO analysis and clustering, these proteins were mainly localized in organelles (34%), cytoplasm (20%), extracellular matrix (13%), and plasma membrane (10%). They were involved in many biological processes and molecules features. R.E.GE suggested that these differential proteins participated in metabolism, migration and inflammation-related pathways. The PPI interaction network showed that the core proteins were mainly implicated in protein phosphorylation, signal transduction and cell adhesion. Higher TRIM29 protein expression was found in the MTV≥10ml group by immunohistochemistry (x2 =19.041, P < 0.001).

Conclusions: With proteomic comparison based on MTV, the differential proteins were closely related to tumor cell growth, migration, metabolism and immunity. Also, patients with MTV <10 ml had a favorable DFS. Lower expression of TRIM29 found in this group might be considered as a promising prognostic biomarker.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1097P Prognostic value of metabolic tumor volume in recurrent and/or metastatic head and neck squamous cell carcinoma treated with platinum-based chemotherapy

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Background: The standard first-line treatment for recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) is platinum-based chemotherapy, while the predictor of survival has yet to be established, except for tumor human papillomavirus (HPV) status. The present study aimed to evaluate the usefulness of metabolic tumor volume (MTV) measured on FDG-PET/CT in predicting survival of patients with R/M HNSCC after platinum-based chemotherapy.

Methods: Patients with R/M HNSCC treated with platinum-based chemotherapy as first-line treatment following FDG-PET/CT between 2006 and 2017 at Osaka University Medical School Hospital and Osaka International Cancer Institute were eligible. Exclusion criteria were nasopharyngeal carcinoma, ~60 days duration between FDG-PET/CT and chemotherapy initiation. FDG-PET/CT data were transferred into the workstation in the DICOM format. A total amount of MTV in the whole body was measured using a S UV-based automated contouring program (PETSTAT Viewer Ver. 2.2), with the SUV threshold being 2.5. Tumor HPV status was determined by p16 immunohistochemistry. The risk of death was assessed by Cox proportional hazard model.

Results: One hundred and four patients met the criteria. The median follow-up duration of surviving patients was 13.1 months (range, 3.2-79.6). The median MTV was 21.9ml (range, 0.0-1118.7). The median of death increased by 1.03 fold (95% confidence interval, 1.02-1.04; P < 0.0001) for every 10-ml increment of MTV, independently of tumor HPV status. The median overall survival was 15.3 months in patients with MTV larger than the median and 9.2 months in patients with MTV equal to or smaller than the median.

Conclusions: MTV is a useful predictor of survival in patients with R/M HNSCC after platinum-based chemotherapy. MTV needs to be considered in allocation for randomized clinical trials.
Title: The prognostic value of early tumor response in metastatic nasopharyngeal carcinoma patients treated with first-line chemotherapy


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

Background: The prognostic value of the early tumor response to first-line chemotherapy remains unknown in metastatic nasopharyngeal carcinoma (mNPC). The aim of this study was to explore the association between early tumor response (response at 6 weeks) and survival outcomes and to assess the relationship between best (response at 18 weeks) and early tumor response.

Methods: A total of 433 mNPC patients with measurable lesions, who received first-line chemotherapy between 2005 and 2016 were enrolled in this study. Response was assessed at completion of 6 weeks and 18 weeks of chemotherapy using RECIST1.1. To estimate in an unbiased way, the landmark method was used in this study. Log-rank test and Cox regression were used to analyze survival data. The correlation between early tumor response and best tumor response was measured by kappa agreement, Pearson correlation and receiver operating curves.

Results: The median follow-up time was 54.3 months (IQR: 38.6-67.9 months). Two hundred and sixty-five patients achieved tumor response at 6 weeks. From the 6-week landmark, patients with tumor response were significantly associated with better OS (hazard ratio, HR = 0.566, P < 0.001; median OS: 30.3 versus 21.7 months) and PFS (HR = 0.426, P < 0.001, median PFS: 9.2 versus 7.3 months) than the patients without. After adjusting for potential confounders, the early tumor response was an independent prognostic factor associated with OS (HR = 0.539, 95% CI, 0.428 to 0.679, P < 0.001) and PFS (HR = 0.467, 95% CI, 0.378 to 0.576, P < 0.001), respectively. There was a good correlation between the early and best tumor response (Kappa: 0.82; Pearson: 0.85). The sensitivity, specificity, positive and negative predictive values of early tumor response in predicting best response were 100%, 79%, 88% and 100%.

Conclusions: Early tumor response is an independent prognostic factor in determining survival. The early and best tumor response correlated very well. The data could provide a basis for trial design that addresses alteration of first-line chemotherapeutic. Validation studies are awaited.

Legal entity responsible for the study: Sun Yat-sen University Cancer Center. Funding: National Natural Science Foundation of China. Disclosure: All authors have declared no conflicts of interest.

Title: Potential clinical management changes in patients harboring locally advanced squamous-cell carcinoma of head and neck by incorporating pre- and post chemoradiotherapy 18FDG PET/CT: a prospective trial

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Background: The utility of performing 18FDG PET/CT in the tumor staging and as a clinical management tool in the post-123I-week chemoradiotherapy (CRT) in patients (pts) harboring locally advanced squamous-cell carcinoma of head and neck (LASCCCHN) has been established. The aim of this report is to evaluate the impact of incorporating a staging 18FDG PET/CT and post-CRT, for pts harboring 123I radiation and its planning changes were generated by detection of new regional metastatic lymph nodes or identification of primary tumor in 10 patients (20.4%). Post-radiotherapy 18FDG PET/CT was able to detect residual lymph node disease and residual primary disease in 3 and 1 pts respectively.

Conclusions: These findings confirm the clinical utility of performing pre and post CRT 18FDG PET/CT in pts harboring LASCCCHN. Clinical trial identification: Brazilian Clinical Trial Registry - ReBEC - RBR-9wwstd.

Legal entity responsible for the study: A.C. Camargo Cancer Center. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Title: Patterns of local failures and suggestions for reduction of clinical target volume for nasopharyngeal carcinoma patients without cervical lymph node metastasis

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Background: To investigate the initial irradiated dose of the recurrent site and local failures patterns after Intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma (NPC) patients with retropharyngeal lymph nodes (RLN) metastasis only, with the aim to demonstrate the adequacy and overall quality of the target volume definitions for further improvement of outcome and therapeutic ratio.

Methods: 382 newly diagnosed non-metastatic NPC patients were retrospectively enrolled, receiving elective neck irradiation to to levels II, III, VA. For patients with local failure, the location and extent of local failures were transferred to the pretreatment planning CT for dosimetric analysis. The dose of radiation received by GTV1 (gross tumor volume of recurrence) was calculated and analyzed with dose-volume histogram (DVH). Failures were classified as: “in-field” if 95% of GTV1 was within the 95% isodose, “marginal” if 20% to 95% of GTV1 was within the 95% isodose, or “outside” if less than 20% of GTV1 was inside the 95% isodose.

Results: With a median follow-up time of 61.3 months, 12 patients have developed local recurrence (10 cases available). The 5-year OS, LFS, RFS, DMFS and DFS were 87.8%, 95.2%, 99.1%, 93.3% and 82.5%, respectively. Dose conformity with IMRT was excellent and the recurrence was mainly within 3 years after the first treatment. The dosimetric analysis showed that 7 failures were classified as “in-field”, 2 failures as “marginal” and only 1 failures as “out-field”. Most local relapse site located just the same site of primary tumor and most anatomic sites were at low risk of concurrent bilateral tumor invasion.

Conclusions: IMRT with elective neck irradiation provides excellent local control for NPC patients without cervical lymph node metastasis. In-field failures are the main patterns for local recurrence and the radiosensitive subvolumes within the GTV are needed to be identified. We proposed suggestions for reduction of target volume during IMRT treatment for NPC patients.

Legal entity responsible for the study: Fudan University Shanghai Cancer Center. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Title: Target delineation and dose prescription for adaptive replanned intensity-modulated radiotherapy in nasopharyngeal carcinoma

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Background: To investigate the feasibility and benefits of target re-delineation and dose prescription for adaptive replanned radiotherapy in nasopharyngeal carcinoma (NPC) patients who underwent intensity-modulated radiotherapy (IMRT).

Methods: Fifty-four consecutive NPC patients who underwent IMRT were enrolled in this study. The replanning CT (CT- II) for each patient was generated at the 22nd fraction of the IMRT. In Plan-I, GTVnx-I was defined as all detected gross disease. The high-risk clinical target volume (CTV- I), as subclinical disease consisting of a 1-cm margin surrounding the GTVnx-I. The low-risk clinical target volume (CTV2), as 0.5- to 1.0-cm margin surrounding the CTV- I. In Plan-II, the GTVnx-II, as all detected gross disease detected after 22 fractions. CTV- I-II maintained the extent of the originally irradiated CTV- I, including the area in which the tumor disappeared/disolved after 22 fractions. The CTV2 was not delineated. The doses prescribed were as follows: Plan-I, GTVnx/I/GTV2 35-45 Gy/25 F; PCTV1/GTV2 47.5-54 Gy/25 F; PCTV2 45-55 Gy/25 F; and Plan-II: GTVnx/I/GTV2 15-15.5 Gy/7 F; PCTV1/GTV2 11.5-45 Gy/7 F. The parameters were compared. Clinical outcomes and toxicities were evaluated.

Results: The median reductions in the GTVnx, GTVnd-R, bilateral parotids and bilateral submandibular glands were 25.07%, 38.17%, 23.43% (left), 21.12% (right), 23.37% (left) and 23.00% (right) (P < 0.05), respectively; bilateral RPLN and GTVnd-L disease. Downstaging N1 to N0 was registered in 2 pts. Suspected distant metastatic disease was registered in 2 cases (lung 1, bone 1). Primary occult tumor was identified in 3, and secondary synchronous colorectal tumor was diagnosed in one case. Radiotherapy planning was driven by detection of new regional metastatic lymph nodes or identification of primary tumor in 10 patients (20.4%). Post-radiotherapy 18FDG PET/CT was able to detect residual lymph node disease and residual primary disease in 3 and 1 pts respectively.

Conclusions: These findings confirm the clinical utility of performing pre and post CRT 18FDG PET/CT in pts harboring LASCCCHN. Clinical trial identification: Brazilian Clinical Trial Registry - ReBEC - RBR-9wwstd.

Legal entity responsible for the study: A.C. Camargo Cancer Center. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.
exhibited median reductions of 22.50% (left), 25.00% (right), and 32.80% (P < 0.05), respectively. The average V95% of PTVnx reached nearly 100% in the two plans. Plan-II significantly reduced the Dmax in the optic chiasma, thyroid gland, hypo- pharynx, spinal cord, brain, primary, oropharynx, and oropharynx, and oropharynx with Plan A (P < 0.05). Recurrence did not occur in the regression area, and the acute re- actions were mild. The 3-year OS/LRFS/DMFS rates were 93.3%/90.5%/91.4%, respectively.

Conclusions: Adaptive replanned IMRT in NPC provided a new perspective for target re-delineation and dose prescription. The results of this study showed significant dosi- metric and clinical benefits without recurrence and reducing survival.

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Disclosure: The author has declared no conflicts of interest.

1102P
Significance of pre-treatment F-18 FDG PET/CT parameters in nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

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Background: The aim of this study was to assess the prognostic significance of parame- ters derived from pretreatment18 fluorodeoxyglucose positron emission tomogra- phy/computed tomography (F-18 FDG PET/CT) for patients with nasopharyngeal carcinoma (NPC) received intensity-modulated radiation therapy (IMRT). Furthermore, the functional information provided by PET/CT may offer the feasibility of biological conformity in tumor target delineation and dose planning.

Methods: We retrospectively reviewed 82 NPC patients who underwent pretreatment F-18 FDG PET/CT and received IMRT between 2010 and 2013. Maximum standard- ized uptake value (SUVmax) and metabolic tumor volume (MTV) of the primary tumor were measured by F-18 FDG PET/CT. MTV might be viewed as a collection of absolute SUV values equal to or greater than a certain threshold on each axial image of PE/CT. The ROC curve was used to determine the appropriate cut-off point of SUVmax and MTV. The prognostic significance of MTV, SUVmax was assessed in the study. Meanwhile, the paper studies the relation between SUVmax MTV, and primary tumor volume (PTV). Receiver operating characteristic (ROC) analysis was used to determine the optimal MTV cut-off value.

Results: Positive correlations between PTV and MTV, SUVmax and MTV were found. PTV, SUVmax, and MTV were significant predictors of survival. The 3-year progres- sion-free survival (PFS) for SUVmax ≥ 8.20 and SUVmax ≥ 8.20 were 91.1% and 73.0% (p = 0.02). With furthermore analysis, patients having tumor with lower MTV had higher 3-year PFS than patients having tumor with higher MTV. The percentage of the MTV≥ 80% in PTV was 14.6% ± 15.7% (95% CI: 11.25-18.13).

Conclusions: Our study indicated that PET/CT-derived parameters, SUVmax and MTV, are very important in assessing prognosis and making radiotherapy planning. Patients having tumor with lower MTV had higher 3-year PFS than patients having tumor with higher MTV. It is necessary to give more aggressive treatment for patients with higher MTV. The MTV≥ 80% might be an appropriate quantitative definition of hypoxic sub-volumes for radiotherapy boost to improve the therapeutic effect.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

1103P
Sentinel lymph node biopsy for clinically NO oral squamous cell carcinoma

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Background: Despite advances in early detection, diagnosis, and treatment of oral squa- mous cell carcinoma (OSCC), the survival for patients with early stage OSCC remains at 80% for the past 30 years. Nodal status is still the most significant prognostic factor of OSCC. Therefore, early detection of the cervical lymph nodes metastasis is expected to increase survival. Sentinel lymph node biopsy (SLNB) is a widely accepted procedure in various human malignancies. In clinically NO (cNO) OSCC cases, SLNB has received considerable attention for its role in deciding whether to perform neck dis- section. In this study, we assessed the efficiency of SLNB for cNO OSCC in a single-institu- tion experience.

Methods: A total of 135 patients with cNO OSCC underwent SLNB between 2001 and 2016, of which 128 were clinically T1 and T2. The primary site was tongue, gingiva, oral floor, buccal mucosa, and lip in 49%, 36%, 7%, 6%, respectively. The location of the sentinel lymph node (SLN) was determined by radiosotope (RI) method with pre- operative lymphoscintigraphy and intraoperative use of a handheld gamma probe and/or dye method and evaluated by histopathological examination and genetic analysis.

Results: SLNB was performed with RI method (90%) or dye method (10%). SLNs were successfully identified with RI method (100%) and dye method (70%). The average number of SLN/case was 1.9 with RI method and 2.3 with dye method. The rate of SLN identified side was 85% in supratentorial, 8% in bilateral, and 6% in contralateral. Twenty two of 135 patients (16%) had metastasis-positive SLN. Thirteen patients with negative SLN developed the latent neck lymph node metastasis. The sensitivity, specificity, and accuracy was 62.5% (22/35), 100% (100/100), and 90.4% (122/135), respectively.

Three-year overall survival rate for SLN-negative patients was 95.6% (108/115).

Conclusions: SLNB is a minimally invasive and highly reliable method staging the cN0 for patients with OSCC. Patients with negative SLNB showed more excellent neck con- trol rate and the SLNB provides more accurate staging than elective neck dissection or wait and see.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1104P
An insight on head and neck cancer management in China

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Background: As no Chinese data has evaluated the oncologists’ strategy for treatment and management of the head and neck cancer (HNC), this survey investigated Chinese oncologists’ treatment strategy in HNC.

Methods: This survey was conducted during October 2017 to January 2018 in 100 ran- domly selected tertiary Chinese hospitals from 21 cities. The plan was to include 300 non-randomly selected Chinese oncologists to know their responses on HNC. The investigating stages included: development of a questionnaire after consulting 9 experts in HNC, execution of a pre-test by 40 oncologists from 5 cities; reliability and validity evaluation followed by finalisation of the questionnaire; and conduct of formal investi- gation with oncologists. Results for all evaluations were presented as percentages.

Results: Of the 296 questionnaires received, 272 were considered valid. Among valid respondents, 65.1% oncologists reported nasopharyngeal carcinoma as the most com- mon HNC, followed by laryngeal/hypopharyngeal (22.1%) carcinoma. 71.3% oncolo- gists acknowledged having a multidisciplinary team for HNC treatment in their hospitals. Prescribed regimens for recurrent/metastatic HNC included taxane ± plati- num (TP), taxane-cisplatin-5fluorouracil (TPF), platinum monotherapy (PF), PF, TF and others (45.2%, 27.9%, 21%, 2.2% and 3.7%). Oncologists (77.6%) add target therapy to chemotherapy as the first line therapy in recurrent/metastatic cancer. For locally advanced HNC, anti-EGFR would be preferred by 84.2% oncologists. 39.0% oncologists reported considering inclusion of targeted therapy at combined radical radiotherapy and chemotherapy stage. HPV was believed to be associated with HNC prognosis by 72.0% oncologists; 1.9% oncologists disagreed and 26.1% were unsure. HPV testing rate was 67.3%. The reasons for not testing HPV were immature technical conditions (41.9%), no impact on treatment (40.8%), no consent by patients (25.0%) and low HPV incidence in Chinese HNC patients (18.0%).

Conclusions: In conclusion, oncologists in China have not fully followed international guidelines of HNC which might be due to practical considerations. These findings will provide future education for HNC management.

Legal entity responsible for the study: China Medical University

Funding: Merck Serono Co Ltd, Beijing, China.

Disclosure: All authors have declared no conflicts of interest.

1105P
Real-world outcomes and costs in patients with recurrent or metastatic squamous cell carcinoma of the head and neck

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Background: Overall survival (OS) of patients with recurrent or metastatic (R/M) squa- mous cell carcinoma of the head and neck (SCCHN) is extremely poor. New therapeut- ic options emerge but need to establish their economic value. The objective was to describe OS and costs in French R/M SCCHN patients.

Methods: The EGB, a random representative sample (1/97th) of the French national healthcare system claims database was used. All adult patients with a diagnosis of SCCHN with a first R/M between Jan 2009 and Dec 2014 were selected. Data were ana- lyzed from the index date (first chemotherapy) until patients’ death or Dec 2015 (mini- mum follow-up of 12 months). Two periods were distinguished: ‘chemotherapy treatment’ (CT) and ‘end-of-life’ (EoL) (from last CT to death). OS was estimated using the Kaplan-Meier method. Costs included all hospitalizations for SCCHN, con- sultations, medical devices, biology and imaging procedures, supportive and palliative
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Treatment patterns in elderly patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC): Results from an EORTC led survey

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Background: An increase in the number of elderly patients diagnosed with head and neck cancer is expected, but there is no consensus on what is the optimal treatment for patients >70 years with locally advanced disease. Geriatric assessment (GA) is recommended but not validated for guiding treatment decisions. We hypothesized that significant heterogeneity will exist across institutions in patterns of care delivered to elderly patients with LA-HNSCC and in the use of GA and assessment of quality of life (QoL).

Methods: Members of the EORTC, the European Head and Neck Society and national groups in Europe were asked to complete a questionnaire about treatment delivered and use of GA and QoL assessment in elderly patients with LA-HNSCC. Among 144 responding centers in Europe, 16 (11.3%) teaching hospitals, 26 (18%) community hospitals and 62 (43.2%) private clinics. Large differences in treatment patterns were found. For instance, for oropharyngeal carcinoma, one third of the centers reported high frequencies of cetuximab use, while one in five centers treat >40% of elderly patients with chemoradiotherapy (CRT) (3 x 100 mg/m2, q3w) for the treatment of LA SCCHN. The International guidelines recommend the use of high-dose platinum chemotherapy (70 mg/m2 x 3, q4w) to achieve a significantly lowered OS. Predictive factors would help to select patients who are suitable for an optimal cumulative dose of cisplatin.

Results: Investigators from 111 centers replied, including 90 (81.1%) academic centers, 16 (14.4%) community hospitals and 5 (4.3%) private clinics. Large differences in treatment patterns were found. For instance, for oropharyngeal carcinoma, one third of the centers indicated that they treat <5% of elderly patients with chemoradiotherapy, while 18 centers (16.2%) treat >40% of elderly patients with chemoradiation. More than half of the centers hardly or never use cetuximab in elderly patients with hypopharyngeal carcinoma, while one in five centers treat >20% of the elderly patients with cetuximab. Furthermore, 3 centers (2.7%) treat <5% of elderly patients with oral cavity cancer with surgery and postoperative radiotherapy, while 73 centers (65.7%) offer this treatment to at least 40% of their elderly patients. Fourteen centers (12.6%) routinely perform GA while 43 centers (38.7%) never do, and 39 centers (35.1%) sometimes do. QoL is assessed on a routine basis in one fifth of the centers.

Conclusions: Large differences exist across institutions in the patterns of care delivered to elderly patients with LA-HNSCC. Prospective studies are required in this population to learn how to use GA, how to improve QoL and ultimately improve treatment outcome. For that, consensus on standard of care is essential.

Legal entity responsible for the study: EORTC.

Disclosure: S. Oosting. Research grants (paid to institution): Pfizer, Novartis, Celldex. All other authors have declared no conflicts of interest.

Table: 1107P Multivariable model

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low comorbidity</td>
<td>2.61</td>
<td>(0.95-7.21)</td>
<td>0.006</td>
</tr>
<tr>
<td>Moderate comorbidity</td>
<td>3.17</td>
<td>(1.24-8.11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe comorbidity</td>
<td>6.24</td>
<td>(2.08-18.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin &lt; 13.6 g/dL</td>
<td>1.92</td>
<td>(1.04-3.55)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stage II</td>
<td>2.57</td>
<td>(0.87-7.58)</td>
<td>0.009</td>
</tr>
<tr>
<td>Stage III-M</td>
<td>4.10</td>
<td>(1.15-14.67)</td>
<td>0.03</td>
</tr>
<tr>
<td>NO: Watchful waiting</td>
<td>2.82</td>
<td>(0.98-8.12)</td>
<td>0.05</td>
</tr>
<tr>
<td>Therapeutic neck dissection</td>
<td>2.57</td>
<td>(1-6.60)</td>
<td>0.05</td>
</tr>
<tr>
<td>PLR (platelets to lymphocytes ratio) &gt; 66</td>
<td>3.98</td>
<td>(0.88-17.93)</td>
<td>0.07</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>2.88</td>
<td>(1.28-4.66)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusions: We described the account of comorbidity assessment as a prognosis factor of resectable OSCC. We provide the importance of additional clinical and easily accessible information to tumor stage, capable of discriminating prognostic risk factors in resectable OSCC.

Legal entity responsible for the study: The Clinical Research Ethics Committee of Aragon (CEIC-A).

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Disclosure: All authors have declared no conflicts of interest.

Can concomitant diseases predict the compliance with cisplatin plus RT in patients with LA SCCHN? An exploratory endpoint analysis of the COMPLY trial

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Background: International guidelines recommend the use of high-dose platinum chemotherapies (CRT) (3 x 100 mg/m², q4w) for the treatment of LA SCCHN. The clinical benefit of CRT decreases with lower cumulative dosage. Dose reductions to ≤ 200 mg/m² lead to a significantly lowered OS. Predictive factors would help to select patients who are suitable for an optimal cumulative dose of cisplatin.

The importance of comorbidity assessment in patients with oral squamous cell carcinoma (OSCC): Could the adult comorbidity evaluation – 27 (ACE-27) provide an additional information?

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Background: Disease stage is the most powerful prognostic factor in OSCC but is not accurate enough to identify highest risk patients. Other patient-related conditions as comorbidity add relevant prognostic value. We show the importance of the comorbidity assessment in contrast to other historic prognostic factors.

Methods: Retrospective review of patients with resectable OSCC from 2011 to 2014. Baseline pretreatment comorbidity data were collected according to ACE-27. Clinical, pathological, presurgical blood samples and treatment data were collected. Kaplan-Meier and Cox proportional hazards modeling were used to determine associations with OS (Overall Survival), DSS (Disease-Specific Survival) and DFS (Disease-Free Survival).

Results: Among 215 patients, median age was 67 years (range 32-96). Median follow-up was 51 months (1-78). 74% suffered at least one previous comorbid condition. 3 year OS, DSS and DFS were 68%, 77% and 65%, respectively. The multivariable model is showed in the table. Suffering a severe comorbidity had the highest prognostic value, greater than present a locally advanced OSCC. [HR = 6.24; 95%CI=2.08-18.67p < 0.001].
Methods: The COMPLY trial included patients with LA SCCHN from Germany and Switzerland. Eligible patients were treated in 2013/2014. The planned target dose of cisplatin had to be > 200 mg/m². Compliance was defined as an administration of > 200mg/m² cisplatin. R/U ASCCHN, as transplanted treatment or participation in other clinical trials were excluded. The exploratory objective was to identify a predictive score for therapy compliance with platinum-based CRT. A multiple logistic regression analysis was performed to identify independent explanatory variables associated with compliance with cisplatin. Only independent variables with a p-value < 0.15 in the univariate analysis were considered for multiple logistic regression analysis.

Results: 184 patients in 9 sites were included. Median age was 61.0 years, 82.6% were male, 167 patients (90.8%) were ECOG 0-1. A significant difference in treatment compliance with cisplatin was shown for patients with concomitant musculoskeletal/connective tissue disorders (odds ratio for absence of disease vs. presence: 9.43; 99% CI: 1.20, 74.02; p = 0.03) and respiratory, thoracic and mediastinal disorders (odds ratio for absence of disease vs. presence: 6.39; 95% CI: 1.47, 29.48; p = 0.01) by system organ class. The probability of treatment compliance with cisplatin, being an estimate from a scoring system developed for the study, was 43.4% in subjects with absence of both disorders while the treatment compliance was 8.9% in subjects who presented with either one of the disorders and 1.2% in subjects with both disorders.

Conclusions: These exploratory results indicate that subjects without musculoskeletal/connective tissue and respiratory, thoracic and mediastinal disorders as concomitant diseases were more likely to have received cisplatin > 200 mg/m².

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Compliance of acute hematologic and renal toxicities in two chemotherapy schedules of cisplatin for epithelial cell carcinoma of head and neck

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Background: Standard approach for treatment of locally advanced head and neck carcinoma is concurrent chemoradiation with cisplatin 100mg/m² every three weeks. However, prescribing cisplatin at this dose is associated with increased toxicity that can interrupt and compromise treatment results. Many centers use alternative schedules of weekly cisplatin at doses of 30-40mg/m² per week.

Methods: In this study, 77 patients with head and neck cancer were randomized in a phase II clinical trial to compare toxicity for two cisplatin schedules, 100mg/m² three weekly and 40mg/m² weekly.

Results: The incidence of grade 3-4 hematologic events was not significantly different between the two groups, but the mean level of glomerular filtration rate in the three weekly group was significantly higher than the weekly group. There was no significant difference between the two groups in terms of mean overall treatment time and mean dose of cisplatin. Cisplatin cumulative dose > 200mg/m² was higher in the weekly group, but no significant difference was observed. The main reason for treatment interruption was neutropenia for the three-weekly group, but in the weekly group, it was renal dysfunction for chemotherapy delay, and thrombocytopenia for radiotherapy break.

Conclusions: Weekly prescribing cisplatin can lead to higher cumulative doses, which may improve treatment outcomes. The incidence of grade 3-4 hematologic events was not significantly different between the two groups; However, the weekly schedule was associated with a higher drop in GFR, requiring further investigation.

Legal entity responsible for the study: Shahid Beheshti University of Medical Science.

Funding: Research and Development Center of Shahid Beheshti University of Medical Science.

Disclosure: All authors have declared no conflicts of interest.

Patient reports of mouth symptoms after radiotherapy treatment for head and neck cancer: An international survey

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Background: People with head and neck cancer frequently have symptoms that are caused by their disease or by their treatments, which may significantly impact on their quality of life living with and beyond cancer. This international research survey captured a self-reporting survey by people who had had radiotherapy (RT) treatment for head and neck cancer about their experience of oral symptoms, including Dry Mouth (Xerostomia).

Methods: This survey was designed by patients, and then submitted for ethical approvals in collaboration with a healthcare researcher. The international survey was open to anyone over 18 who has had treatment for head and neck cancer, whether or not they currently have symptoms of Dry Mouth. The electronic survey was only in English and the ethical permissions granted that patients who wished to take part could request assistance if needed; due to illness, fatigue, confidence in accessing the internet, or English literacy. Participant recruitment was supported through a wide range of networks including healthcare practitioners, charities and patient support groups. The average time to complete the 18-item survey was under 10 minutes, including both multiple choice and open questions. The statistical analysis reflected correlations between the participant demographics and self-report of symptoms. An interpretative analysis of free text responses highlighted patient values and priorities.

Results: Over 100 individuals responded, from across UK, US, Canada, Australia, India and mainland Europe. The analysis demonstrates patterns between the patient demographics, types of radiotherapy treatments, time since treatment, and current symptoms. This is the first time that this original dataset will be presented. The findings also generated insights into the self-reported impact of these symptoms on patients' quality of life.

Conclusions: This study comprises important evidence of patients' experiences and symptoms following RT treatment. The cross-sectional dataset also indicates the global view of recent and current RT treatment approaches. Future collaborative research by healthcare researchers, patient groups and relevant pharma is imperative. This research will be presented by a Patient Advocate.

Legal entity responsible for the study: University of Central Lancashire.

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Risk factors for aspiration pneumonia during concurrent chemoradiotherapy or bio-radiotherapy for head and neck cancer

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Background: Aspiration pneumonia (AP) is one of the most important side effects in chemoradiotherapy (CRT) and bio-radiotherapy (BRT) for patients (pts) with head and neck cancer (HNC). AP is involved in on-cancer related mortality in HNC pts. However, the relation between AP during CRT or BRT and treatment outcomes in HNC pts has not been identified. The aims of this study were to assess the influence of AP on treatment outcomes, and to identify clinical risk factors for AP during definitive CRT or BRT for HNC pts.

Methods: We retrospectively assessed the data of pts with locally advanced HNC who received definitive CRT or BRT at Shizuoka Cancer Center (August 2006 to December 2016). AP was defined as a clinical condition that met all the following criteria: (i) pts with both subjective and objective symptoms of pneumonia; (ii) the presence of aspiration was suspected clinically (choking or delayed swallowing) or by endoscopy or video-fluoroscopy exam; (iii) no evidence of micro-organisms that cause atypical pneumonia.

Results: Of 374 HNC pts who received CRT or BRT, 95 (25.4%) developed AP during treatment. The study cohort of 374 pts had the following features: median age 65 years (range: 19-83); male/female, 322/52; performance status <12/23, 196/109/143; number of metastatic sites 1/2/3/4, 96/60/27/4; primary site larynx/oesophagus/larynx/other/oral cavity, 57/48/15/22/21/10/14/17/1; T-classification 1/2/3/4/5, 32/136/86/92/82; N-classification (UICC 7th) 1/2a/b/2c/2d, 76/54/19/134/75/16; induction chemotherapy 1/2, 273/101; chemoradiotherapy regimen cisplatin/carboplatin/5-fluorouracil, 278/64/32. AP was significantly associated with treatment response of CRT or BRT (multivariate-adjusted odds ratio for complete response 0.55, p < 0.029). Multivariate analyses identified four independent factors for AP, including poor oral hygiene, high N-classification, hypopalbuminemia before treatment, and inpatient treatment.

Conclusions: AP during CRT or BRT has a detrimental effect on treatment response in HNC pts. Careful attention should be paid to AP in HNC pts with these risk factors receiving CRT or BRT.
**1113P** Nutritional support dependence after curative chemoradiotherapy in head and neck cancer: A supplementary analysis of a phase II trial (JCOG0706S1)


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**Background:** Curative chemoradiotherapy (CRT) for locally advanced head and neck cancer (LA-HNC) causes severe acute and late adverse reactions, including nutritional support dependence. The aim of this supplementary analysis of a previous single-arm phase II study of CRT with 81±1 cisplatin for unresectable LA-HNC (JCOG0706), which demonstrated promising efficacy (CancerSci2015;166:726) was to explore risk factors of laryngo-esophageal dysfunction-free survival (LEDFS) and nutritional support dependence over 12 months (NSD12M).

**Methods:** The study population comprised 45 patients (pts) in the JCOG0706. Risk factors of LEDFS and NSD12M were analyzed using Cox regression models and logistic regression models, respectively, with consideration to the pts’ laboratory data just before CRT. Radiation fields were reviewed to analyze the relationship between the extent of irradiated fields and functional outcomes.

**Results:** Proportions of alive without nutritional support at registration and 2, 6, 12, and 24 months after registration were 82.2%, 55.6%, 68.9%, 77.8%, and 64.4%. All six pts who received nutritional support at 12 months remained tube feeding-dependent thereafter. With a median follow-up period of 3.5 years of all pts, 3-year LEDFS was 48.9%. For LEDFS, the hazard ratio was 0.42 in pts with nutritional support at registration (vs. without nutritional support; 95% confidence interval [CI] 0.17-1.04). For NSD12M, odds ratio was 6.78 in pts with hemoglobin less than the median value of 13.4 g/dL (vs. higher than or equal to the median; 95% CI 24.16-36.85); and was 6.00 in pts with albumin less than the median value of 3.9 g/dL (vs. higher than or equal to the median; 95% CI 11.32-34). Primary sites in disease-free pts with NSD12M were the oropharynx (N=2) or hypopharynx (N=1), and all their pharyngeal constriction muscles were irradiated with a curative dose of 70 Gy/35 fr.

Conclusions: Functional outcomes were affected by severe dysphagia requiring nutritional support before CRT, and lower pretreatment values of hemoglobin and albumin. These risk factors should therefore be taken into consideration in planning treatment strategy for pts with LA-HNC.

Clinical trial identification: UMIN000001272.

Legal entity responsible for the study: JCOG.


**Disclosure:** All authors have declared no conflicts of interest.

**1114P** Comparison of treatment outcomes and tolerability of patients with recurrent (R) nasopharyngeal carcinoma (NPC) and metastatic disease at diagnosis (M1): A retrospective analysis

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**Background:** In current clinical trials and practice, patients with R and M1 NPC are considered the same entity and typically received similar systemic treatments. However, natural history, treatment outcomes and tolerability of systemic chemotherapy between both groups remains unknown.

**Methods:** R and M1 NPC patients were identified. Patient characteristics, treatment modalities, tolerability, and survival outcome were retrospectively abstracted. Tolerability of chemotherapy was defined by dose reduction, hospitalization, delayed, and/or termination of chemotherapy.

**Results:** A total of 144 NPC patients (R=98, M1=46) were analyzed. In R patients, locoregional recurrence and distant metastasis were observed in 30% and 46%, respectively. In R group, median time to recurrence was 16.6 months. Median OS of M1 patients was not different from R group (12.9 vs 11.8 months; p=0.09). However, patients with M1 had shorter OS when compared with locoregional group (12.3 vs 20.7 months; p=0.01). Patients who received doublet had longer OS than single agent chemotherapy in both groups. There was no different in OS between 1st line cisplatin- and carboplatin-based chemotherapy in R group (44.2 vs 19.3 months; p=0.15), but significant difference in M1 patients (14.7 vs 12.3 months; p=0.05). Tolerability to systemic chemotherapy were comparable among R and M1 NPC patients.

**Table: 1114P**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Metastasis at diagnosis N=46 (%)</th>
<th>Recurrence N=98(%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Patient Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Median age (range)</td>
<td>56(29.79)</td>
<td>50(19.79)</td>
<td>0.17</td>
</tr>
<tr>
<td>-male</td>
<td>34 (73.9)</td>
<td>75 (76.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>-smoker</td>
<td>21(45.7)</td>
<td>42(42.9)</td>
<td>0.84</td>
</tr>
<tr>
<td>ECOG 0-1 ≥2 chemotherapy</td>
<td>41 (89.1)</td>
<td>95 (96.9)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>1st line</td>
<td>15 (32.6)</td>
<td>28 (28.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>&gt; =3rd line</td>
<td>7 (15.2)</td>
<td>11 (11.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>doublet single</td>
<td>32(69.6)</td>
<td>53(54.1)</td>
<td>11 (11.2)</td>
</tr>
<tr>
<td>cisplatin carboplatin</td>
<td>22(47.8)</td>
<td>10(21.7)</td>
<td>12(12.2)</td>
</tr>
</tbody>
</table>

**Conclusions:** There was no different in tolerability and survival of R and M1 NPC patients. Physicians should expect similar outcomes of R and M1 NPC patients who received systemic chemotherapy.

It remains unclear whether the efficacy and the safety, especially in nephrotoxicity, for CRT of HNC patients with cisplatin dose 100mg/m² or 80mg/m² are different.

**Methods:** We reviewed medical records of NPC patients who received CRT in our institute retrospectively. The primary objectives of this study were to evaluate the nephrotoxicity and the rate of patients treated with cumulative dose of cisplatin 200mg/m² or more.

**Results:** During January 2014 to October 2017, 261 HNC patients who received CRT were treated. The starting dose of cisplatin were 80mg/m² in 118 patients vs 100mg/m² in 143 patients, respectively. There were more patients over 70 years who received cisplatin in 80mg/m² than 100mg/m² (27.1% vs 4.2%, p<0.001). The mean Creatinine Clearance (Cr) obtained using the Cockcroft-Gault at baseline was significantly lower in 80mg/m² than 100mg/m² (87.82 vs 97.28, p=0.0022). There were no significantly different in patient’s other characteristics as follows gender, performance status, pathology. The incidence of Grade 2 or higher elevation in creatinine was 2.1% in 80mg/m² group and 4 (2.8%) in 100mg/m² group, respectively (p=0.554). The rate of change in CCR showed no difference between both groups (-5.73% in 80mg/m² vs -7.63% in 100mg/m², p=0.2927). Either, the rate of cumulative dose of cisplatin ≥200mg/m² was significantly higher in 100mg/m² (97.2% vs 72.0%, p<0.001). 2-year PFS rate was not significantly different between 80mg/m² and 100mg/m² in oropharynx (89.9% vs 88.2%, p=0.7766) and in hypopharynx/ larynx (70.28% vs 80.92%, p=0.4740), respectively.

**Conclusions:** Cisplatin dose of CRT for HNC patients in 100mg/m² was feasible without increasing the nephrotoxicity and the rate of cumulative dose of cisplatin ≥200mg/m² was higher compared to 80mg/m². Legal entity responsible for the study: Tomoyo Oguri.

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

Impact of the multidisciplinary approach on the survival of squamous head and neck cancer in our institution

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Background: Our hospital has about 650 beds. Since 2008, the multidisciplinary tumour team (MDT) evaluates once a week, all new cases of head and neck cancer, approximately 75% of the year. The main objective is to ascertain the 2-year survival of patients with squamous cell cancer of the head and neck (HNSCC) treated by a MDT and without an MDT, determining whether there are statistically significant differences.

Methods: Observational retrospective study of two cohorts, which aims to analyse the survival in the cohort by an MDT (Cj); those from 01/01/2005 to 12/31/2008) with respect to the cohort without an MDT (C2, 01/01/2009 to 12/31/2012). We included all patients with a histopathological diagnosis of HNSCC at our centre. With access to the Pathological Anatomy database, the records of the MDT, the medical history, we collected the primary endpoint (survival at 2 years) and characteristics related to the patient, tumour, treatment and tracking (date and cause of death). Definitive sample consists of 408 patients, 208 in pre-MDT cohort and 208 in post-MDT cohort. A descriptive analysis is given of the demographic, clinical and epidemiological characteristics of the sample and a survival analysis with rates calculated using the Kaplan Meier method. The log-rank test was used to assess the differences in survival between cohorts, and a Cox proportional-hazards regression model was used to perform the univariate and multivariate survival analysis.

Results: Our population presents age (mean) 64.2y (SD 12.4), male 82.6%, ECOG 0–2, larynx malignancy 51.5%, laryngeal location, tumour stage IVA 31.6%. Treatment with surgery (S) and with radiotherapy (RT). Nutritional intervention aimed to reach 30 kcal/kg/d. Group B was treated with conventional diet guidance at first, appropriate nutritional intervention will be given when serious malnutrition (PG-SGA >1) appeared. Weight and nutritional questionnaires (NRS 2002, PG-SGA) were collected at the baseline, before, during and after CRT.

Conclusions: The population served in our area presents demographic and clinical and epidemiological characteristics similar to those of other series published in our country. There is a statistically significant improvement in the survival of patients treated by MDT, this approach being an independent variable of better prognosis in terms of overall survival in our study (HR 0.696).

Legal entity responsible for the study: M. J. Martínez-Ortiz.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

Prophylactic versus reactive nutritional supplement in local advanced nasopharyngeal carcinoma patients receiving radical chemoradiotherapy

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Background: The aim of this study was to investigate the effect of prophylactic versus reactive nutritional supplement on nutritional status and treatment tolerance in local advanced nasopharyngeal carcinoma (NPC) patients receiving neoadjuvant chemoradiotherapy (NACT) and concurrent chemoradiotherapy (CCRT).

Methods: NPC patients were randomly assigned to prophylactic nutritional intervention group (A) or the control group (B). Patients in group A were supported with enteral nutrition supplement except daily diet from the beginning of radiotherapy (RT). Nutritional intervention aimed to reach 30 kcal/kg/d. Group B was treated with conventional diet guidance at first, appropriate nutritional intervention will be given when serious malnutrition (PG-SGA >1) appeared. Weight and nutritional questionnaires (NRS 2002, PG-SGA) were collected at the baseline, before, during and after CRT.

Results: From October 2016 to May 2018, 114 patients from our cancer center were randomly assigned to the group A and B (58 vs 56). The completion rates of NACT and RT were 88.6% and 100%, 80.7% of patients completed CCRT (A vs B = 90% vs 71%, P = 0.013, 95%CI 0.266-2.3, grade 2-3 anorexia reaction were observed in 26.3% and 25.7% of patients. Though more serious radiation reactions were observed in group B, no statistical difference between group A and B (42 w 30.4% and 21% vs 27%, P > 0.05). All patients experienced weight loss during the NACT and CCRT. Comparing to baseline, the rate of weight loss >5% and >10% before, during, after RT and 1 month after RT were 3.5%, 29.9%, 29.8%, 64.7% and 0, 4.4%, 18.4%, 31%. The overall incidence of PG-SGA ≥4 and ≥5 were32.6%, 39%

95.9%, 100%, 78.7% and 2.3%, 10.5%, 50%, 72.3%, 14.8%, respectively. But the repeated measures showed that the difference of weight loss and PG-SGA scores between two groups were not significant (P > 0.05).

Conclusions: Malnutrition risk was gradually increased during the treatment of NPC. Prophylactic nutritional intervention can improve the tolerance of concurrent chemoradiotherapy, but it has no advantage in weight loss and scores of short-term nutritional assessments.

Clinical trial identification: NCT02948699.
Legal entity responsible for the study: Zhejiang Cancer Hospital.
Funding: Nutricia.
Disclosure: All authors have declared no conflicts of interest.

A randomized phase III study to evaluate the value of the omission of prophylactic neck dissection for stage I/II tongue cancer

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Background: The standard local treatment for early-stage tongue cancer with no clinical lymph node metastasis is partial glossectomy. However, whether or not prophylactic neck dissection (ND) should be performed has been controversial. In 2015, D’Cruz et al. reported that prophylactic ND contributes to the improvement of overall survival (OS) for clinical T1-2N0 tongue cancer regardless of the depth of invasion (DOI). However, considering the occult lymph node metastasis of 30% and disadvantages associated with prophylactic ND such as cosmetic issues and complications including accessory and facial nerve paralysis, partial glossectomy alone can still be regarded as a treatment option for patients (pts) carefully selected by DOI, provided there is appropriate follow-up with full use of computed tomography (CT) and other diagnostic imaging modalities to detect recurrence early enough to conduct salvage surgery.

Trial design: We have commenced a phase III randomized controlled trial to confirm the non-inferiority of glossectomy alone compared to glossectomy with prophylactic ND (standard arm) in terms of OS. Historologically proven stage I/II tongue cancer with DOI >10 mm by enhanced magnetic resonance imaging is eligible. The selection based on the DOI is a novel aspect of this study. We set the key inclusion criterion of DOI as >0 mm and DOI < 3 mm according to the data from D’Cruz et al. and pts with DOI > 3 and DOI > 10 mm are classified as T3 according to the 8th TNM classification. The primary endpoint is OS. The secondary endpoints include relapse-free survival (RFS), local-DFS, proportion of non-resectable recurrence, proportion of neck lymph node recurrence, major and minor adverse events. We assumed a 5-year OS of 85% in the standard arm and set the non-inferiority margin at 7.5%. The sample size was set at 440 pts, with a one-sided α of 5%, power of 70%, an accrual period of 5 years, and a follow-up period of 5 years. For follow-up observation, CT is essential at 3, 6, 12, 18, and 24 months postoperatively and then annually thereafter. Enrollment launched November, 2017 and five pts were enrolled as of April 2018.

Clinical trial identification: UMIN000030098.
Legal entity responsible for the study: National Cancer Center.
Funding: The grant for practical research for innovative cancer control from the Japan Agency for Medical Research and Development (AMED) (JP18ck0106438) and the National Cancer Center Research and Development Fund (29-A-3).
Background: Locally advanced SCCHN is associated with a high risk for local recurrence and distant metastases. Treatment includes a combination of surgery, radiation therapy and chemotherapy to optimize the chances for long-term disease control and improved survival. After definitive local therapy, patients (pts) are monitored for local recurrence and/or distant metastases as standard of care. No effective systemic adjuvant treatment has been identified. Atezo is an anti–programmed death-ligand 1 (PD-L1) monoclonal antibody that prevents PD-1 from binding to its receptors PD-1 and B7.1, thereby restoring anti-tumor immunity. Efficacy results from a cohort of pts with recurrent/metastatic SCCHN in the Phase 1/II PCD94896g study suggest that atezo offers a potential therapeutic benefit. The objective of IMvoke010 (NCT03432137) is to evaluate the efficacy and safety of adjuvant atezolizumab in pts with locally advanced SCCHN who are at high risk for disease recurrence or progression following definitive curative therapy. Trial design: IMvoke010 is a global, double-blind, placebo-controlled, randomized Phase III trial enrolling pts who have completed definitive local/regional therapy for Stage III human papillomavirus (HPV)-positive oropharyngeal carcinoma or Stage IV A or IV B HPV-negative SCCHN involving the oral cavity, oropharynx, larynx, or hypopharynx and are at high risk for disease recurrence or progression. Approximately 400 pts will be randomized 1:1 to receive placebo or atezo 1200 mg Q3W for up to a year (24 cycles) or until unacceptable toxicity, disease recurrence or progression. Pts with nasopharyngeal carcinoma, metastatic disease, or progressive disease during or at completion of definitive local therapy will be excluded. Stratification factors include HPV status, response to definitive local therapy and whether primary surgery was performed as part of definitive therapy. Primary endpoints are independent review facility-assessed event-free survival (EFS) and overall survival. Key secondary endpoints include investigator-assessed EFS, safety, and patient reported outcomes. Exploratory biomarkers will also be assessed.

Clinical trial identification: NCT03452137.

Editorial acknowledgement: Medical writing assistance for this presentation was provided by Steffen Bieneke, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.

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

Funding: F. Hoffmann-La Roche, Ltd.

Background: Nasopharyngeal carcinoma is a distinct disease entity with high incidence in South East Asia and behavioral risk factors (e.g., betel quid chewing, tobacco smoking) are important. Axial CT and MR imaging can be used to assess primary tumor and nodal disease. Treatment with concurrent chemoradiotherapy (CRT) has been proven to be effective in patients with stage III or IV (pts) NPC, with a 5-year overall survival (OS) rate of 20% to 35%. With improved locoregional control, dissemination to ipsilateral and contralateral neck lymph nodes has been reported to improve the OS in both early and advanced stage NPC. The addition of pembrolizumab (MK-3475, anti-PD-1) to CRT in the treatment of stage III or IV NPC is investigational. Pembrolizumab has been approved for the treatment of >100 cancer types, including metastatic laryngeal, oropharyngeal, and head and neck squamous cell carcinoma (HNSCC).

KEYNOTE-412: Phase III study of pembrolizumab plus chemoradiation vs chemotherapy alone for locally advanced nasopharyngeal carcinoma (HNSCC)


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Background: Preclinical data suggest improved tumor growth control and survival when radiation therapy (RT) is combined with a PD-1 inhibitor. Pembrolizumab is effective for treatment of recurrent/metastatic HNSCC, and initial results from a phase I b study suggest that pembrolizumab plus chemoradiation therapy (CRT) is tolerable in patients with locally advanced (LA) HNSCC. KEYNOTE-412 (NCT03040999) is a phase 3, randomized, placebo-controlled, double-blind trial to determine efficacy and safety of pembrolizumab plus CRT and as maintenance therapy vs placebo plus CRT in LA-HNSCC.

Trial design: Eligibility criteria are age ≥18 years; newly diagnosed, treatment-naïve, oropharyngeal p16-positive (any T4 or N3), oropharyngeal p16-negative (any T3-T4 or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4 or N2a-N3) SCC; evaluable tumor burden (RECIST v1.1); and ECOG performance status 0/1. Patients will be randomly assigned (1:1) to receive pembrolizumab 200 mg every 3 weeks plus cisplatin-based CRT (n = 342) or placebo plus cisplatin based CRT (n = 342). Treatment will be stratified by KRAS (wild-type or mutant) and ECOG performance status. The primary endpoint is objective response rate (RR) per RECIST v1.1 assessed by blinded independent central review. Secondary endpoints are duration of response, disease control rate (complete or partial response or stable disease for ≤12 weeks), progression-free survival, OS at 24 months, time to locoregional recurrence (LRR), and grade 3-4 toxicities

Pembrolizumab in patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC)


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Background: There are no approved treatments or standard of care for recurrent or metastatic cSCC. Effectiveness of common therapies for cSCC is limited. Recurrence effective for SCC of the head and neck (HNSCC) may also be effective for cSCC. Pembrolizumab is a programmed death 1 (PD-1) inhibitor that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Evidence of pembrolizumab efficacy and safety has been shown in patients with recurrent or metastatic HNSCC in the phase 1b KEYNOTE-012 study. The single-arm, open-label phase 2 KEYNOTE-629 trial will be conducted to evaluate the efficacy and tolerability of pembrolizumab in patients with previously treated recurrent or metastatic cSCC (NCT03324442).

Trial design: Patients will be given pembrolizumab 200 mg every 3 weeks by intravenous infusion, continued for 35 doses (~2 years) or until disease progression, unacceptable toxicity, or patient/physician decision to withdraw. Patients will be evaluated to determine necessity of neck dissection 12 weeks after completion of CRT. Primary end point is event-free survival and secondary end point are overall survival, safety, and patient-reported outcomes. Biomarkers will be analyzed in patients and placing endpoint. Recruitment is ongoing in 12 countries and will continue until ~780 patients are enrolled.

Clinical trial identification: NCT03324442. Trial initiated September 15, 2017. Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Matthew Graywacz, PhD, of the ApotheCom pembrolizumab team (Yardley, PA, USA). This assistance was funded by Merck & Co, Inc, Kenilworth, NJ, USA. Legal entity responsible for the study: Merck & Co, Inc.

Funding: Merck & Co, Inc.


Pembrolizumab in patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) (NCT03324442)
A randomized phase II study of cisplatin plus radiotherapy versus durvalumab plus radiotherapy followed by adjuvant durvalumab versus durvalumab plus radiotherapy followed by adjuvant tremelimumab in intermediate risk, HPV-positive, locoregionally advanced oropharyngeal squamous cell carcinoma (LA-OSCC) (Canadian Cancer Trials Group HN.9)


Background: Definitive cisplatin-based chemoradiotherapy (CRT) in patients (pts) with locoregionally advanced head and neck SCC is associated with acute and long-term toxicities. Immunotherapy, such as anti-PD-L1 and anti-CTLA4 antibodies, are actively being investigated in this disease setting. HN.9 evaluates a chemotherapeutic sparing approach in pts with HPV bodies, are actively being investigated in this disease setting. HN.9 evaluates a chemotherapeutic sparing approach in pts with HPV

Trial design: CCTG HN.9 is a non-comparative, randomized phase II study in intermediate risk HPV+ LA-OSCC. Pts will be randomized at a 1:1:1 ratio to: CRT (arm A); immunotherapy (RT) with durvalumab (durva) followed by durva maintenance (Arm B); RT followed by durva and tremelimumab (treme) maintenance (Arm C). Treatment schedule: 70 Gy/35 over 7 weeks (RT) + cisplatin 100mg/m2/d 22, 43 (Arm A); RT + durva 150 mg Q4W for 4 doses (Arm B); RT followed by durva Q4W for 4 doses (Arm C). Key eligibility criteria: intermediate risk HPV + LA-OSCC; adequate organ function; no autoimmune disorders; no immunosuppressive therapy. Pts will be stratified by smoking status, age, ECOG PS and other relevant clinical parameters. The primary objective is to estimate the efficacy of the 3 treatment arms in terms of event-free survival (EFS). Secondary objectives: overall survival, loco-regional control; distant metastasis-free survival; quality of life and swallowing assessments; economic evaluation. Correlative studies include: immunohistopathology, radiomic, ctDNA, microbiome analyses. The planned sample size is 240 pts over 2.5 years with 3 years of follow-up. The assumed new treatment will improve 3-years EFS from 83% to 91%, with one-sided type I error of 0.1, 1.8 pts/cm, the study will have 80% of power to reject the null hypothesis (3-year EFS rate is 83% or lower). Study activation: April 2018. Clinical trial identification: NCT03410615.

Editorial acknowledgement: Supported by AstraZeneca.

Legal entity responsible for the study: Canadian Cancer Trial Group.

Funding: AstraZeneca.


Randomized, phase II study of ficitluzumab with or without cetuximab in patients (pts) with cetuximab-resistant, recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HN SCC)

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Background: Cetuximab, an anti-EGFR monoclonal antibody (mAb), is approved for R/M HNSCC but only a minority benefits. c-Met and EGFR signaling converge at the FER/AVL and AKT/PKB nodes. Preclinical evidence shows that c-Met can drive tumor intrinsic resistance to EGFR inhibition. Ficitluzumab is an IgG1 mAb against HGF, the sole ligand for cMet. We recently completed a phase Ib study evaluating ficitluzumab and cetuximab in pts with cetuximab-resistant, R/M HNSCC (Bauman JE et al, ASCO 2017). Twelve pts were treated; 11 were platinum-refractory. Grade 3 adverse events included edema, hypalbuminemia, infection, and thromboembolism. No DLTs were seen. Median progression-free survival (PFS) at the recommended phase II dose (RP2D) was 6.0 mos (90% CI = 2.0 – not reached). Confirmed overall response rate (ORR) was 17% (90% CI = 0.28%). Clinical benefit rate was 67%. Serum Veristrat, a proteomic classifier predictive of differential treatment benefit from anti-EGFR therapy, did not correlate with PFS. We designed a randomized phase II trial evaluating ficitluzumab with or without cetuximab in patients with cetuximab-resistant, R/M HNSCC. The combination arm follows the hypothesis that continued anti-EGFR blockade may overcome reciprocal compensation between the EGFR and cMet pathways.

Trial design: This is a multicenter phase II trial with a randomized, non-comparative, 2-arm design (Arm A: ficitluzumab and Arm B: ficitluzumab + cetuximab) in pts with R/M HNSCC after failure of cetuximab. Key eligibility criteria include: R/M HNSCC; cetuximab resistance (recurrence during or within 6 mos of cetuximab-radiation or palliative cetuximab) EGCOG:0-1; mandatory baseline research biopsy. The primary objective is to assess the efficacy of ficitluzumab, with or without cetuximab, as measured by PFS. To test this hypothesis that either regimen historical PFS from 2 months to 22 months requires 66 eligible patients. Disease control rate and survival. Biomarkers to be correlated with efficacy include tumor HGF/Met dimers, phospho-Met, and immunoscores and serum Veristrat. Two of 66 patients have enrolled.

Legal entity responsible for the study: University of Arizona Cancer Center.

Funding: University of Arizona Cancer Center; Aveo.

Disclosure: The author has declared no conflicts of interest.

Annals of Oncology

1127O 

A personal neoantigen vaccine, NEO-PV-01, with anti-PD1 induces broad de novo anti-tumor immunity in patients with metastatic melanoma, NSCLC, and bladder cancer

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1128O

Pre-specified interim analysis of a randomized phase IIb trial of trastuzumab + nelipeptimut-S (NeuVax) vs trastuzumab for the prevention of recurrence demonstrates benefit in triple negative (HER2 low-expressing) breast cancer patients

D.F. Hale1, E.A. Mittendorf2, T.A. Brown1, G.T. Cliftan3, T.J. Vreeland2, J. Myers1, K. Peace1, D. Jackson1, J. Greene1, J. Holmes1, G.E. Peoples4

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1129O

Stage 2 enrollment complete: Sitravatinib in combination with nivolumab in NSCLC patients progressing on prior checkpoint inhibitor therapy

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1130 Responses and durability of clinical benefit in renal cell carcinoma treated with pegilodecakin in combination with anti-PD-1 inhibitors

N.M. Tannir1, A. Naing2, K.P. Papadopoulos3, D.J. Wong4, W.M. Korn5, R. Aljumaily6, K.A. Autio7, S. Pant2, T.M. Bauer8, A. Drakaki4, N. Daver9, A. Hung10, M. Oft11, J. Leveque12
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1131PD Preliminary results of phase I/II study of SENL-B19 chimeric antigen receptor T cell therapy in pediatric and adult patients with relapsed/refractory acute lymphoblastic leukemia (r/r-ALL)

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Clinical efficacy of T-cell therapy after short-term BRAF-inhibitor induction in checkpoint inhibitor resistant metastatic melanoma patients

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A phase IIa trial to assess the safety and efficacy of BL-8040 and pembrolizumab in patients with metastatic pancreatic adenocarcinoma (PDAC)


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A phase Ia/IIb trial of the CXCR4 inhibitor X4P-001 and nivolumab for advanced renal cell carcinoma (RCC) that is unresponsive to nivolumab monotherapy

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Characterization of the immune tumor microenvironment (TME) to inform personalized medicine with immuno-oncology (IO) combinations

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Discrepancy of tumor neoantigen burden between primary lesions and matched metastases in lung cancer

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First in human study with GSK3359609 (GSK609), inducible T cell co-stimulator (ICOS) receptor agonist in patients (Pts) with advanced, solid tumors: Preliminary results from INDUCE-1

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Novel small-molecule RORc agonist immuno-oncology agent LYC-55716: Safety and efficacy in a phase IIA open-label, multicenter trial

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Phase I study of KN035, a novel fusion Anti-PD-L1 antibody administered subcutaneously in patients with advanced solid tumors in the USA


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Association between immune-related adverse events and efficacy in patients treated with anti-PD-(L)1

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Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma: Data from a French multicentric cohort


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Background: Therapeutic options for second line metastatic pancreatic ductal adenocarcinoma (PDAC) are limited with FOLFOX or FOLFIRI having mOS of 5-6 months. PDAC has low tumor mutational burden and tumor infiltrating CD8+ T cells are rare, which may explain why immune-oncology approaches to date have been less than promising. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFN-γ and the expression of MHC, and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Pegilodecakin (5 ug/kg) in combination with FOLFOX. 21 out of 25 pts progressed on prior gemcitabine containing regimen and did not receive prior platinum containing therapy.

Table: 1143P

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Pegilodecakin N Prior Therapies</th>
<th>ORR</th>
<th>CR</th>
<th>DCR</th>
<th>mPFS</th>
<th>mOS One-Year</th>
<th>Two-Year</th>
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<tr>
<td>E (ITT)</td>
<td>19 (21) (1-5)</td>
<td>15.8</td>
<td>10.5</td>
<td>73.7</td>
<td>2.6</td>
<td>10.2</td>
<td>42.9</td>
</tr>
</tbody>
</table>
| E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations), ITT (intent to treat); All treated/safety population: n = 25; 25 pts were treated with pegilodecakin (5 ug/kg) in combination with FOLFOLX. 21 out of 25 pts progressed on prior gemcitabine containing regimen and did not receive prior platinum containing therapy.
| Subjects with OS > 8 mos had 75-250 CD8+ T cells/mm² in the retroperitoneal tumor and had a clonal expansion of new T cell clones in the blood. Data cut on 05/01/18; Median follow-up 26.4 months (22.0-32.0 months).

Methods: In a 353 patient phase 1/1b dose escalation and expansion study conducted in the US from 2013 to 2017, 21 heavily pretreated metastatic PDAC subjects received pegilodecakin in combination with FOLFOLX. Responses were assessed by iREC. CD8+ T cell activity was determined by IHC and TCR clonality in the blood.

Results:

Conclusions: Pegilodecakin in combination with FOLFOLX is well tolerated in patients with metastatic PDAC, and has a reduced incidence of FOLFOLX related neutropenia. Immune activation and overall survival are encouraging in this advanced PDAC population.

Clinical trial identification: NCT02099449

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oli, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

Responses and durability of clinical benefit in pancreatic ductal adenocarcinoma (PDAC) patients treated with pegilodecakin (AM0010) in combination with 5-FU/LV and oxaliplatin (FOLFOX)


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Background: Therapeutic options for second line metastatic pancreatic ductal adenocarcinoma (PDAC) are limited with FOLFOX or FOLFIRI having mOS of 5-6 months. PDAC has low tumor mutational burden and tumor infiltrating CD8+ T cells are rare, which may explain why immune-oncology approaches to date have been less than promising. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFN-γ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and metastatic dissemination. 

Results:

Table: 1143P
Background: Responses in NSCLC to agents targeting the PD-1/PD-L1 axis are correlated with PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB), and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells. Pegilodecakin also up-regulates IFN-γ and the expression of MHC, which stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also reduces tumor inflammatory processes such as angiogenesis and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies.

Methods: In a 353 patient phase 1/1b dose escalation and expansion study, 34 pre-treated NSCLC subjects received pegilodecakin with pembrolizumab or nivolumab. Responses were assessed by iREC. PD-L1 was tested with the 22C3 IHC assay. TMB by whole exome sequencing and pre-treatment GEP by Nanostring.

Results: In a 353 patient phase 1/1b dose escalation and expansion study, 34 pre-treated NSCLC subjects received pegilodecakin with pembrolizumab or nivolumab. Responses were assessed by iREC. PD-L1 was tested with the 22C3 IHC assay. TMB by whole exome sequencing and pre-treatment GEP by Nanostring.

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1144P Responses and durability of clinical benefit in non-small cell lung cancer treated with pegilodecakin in combination with anti-PD-1 inhibitors

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Background: Responses in NSCLC to agents targeting the PD-1/PD-L1 axis are correlated with PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB), interferon associated mRNA Expression Profile (GEP) and the absence of liver metastases. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFN-γ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies.

Methods: In a 353 patient phase 1/1b dose escalation and expansion study, 34 pre-treated NSCLC subjects received pegilodecakin with pembrolizumab or nivolumab. Responses were assessed by iREC. PD-L1 was tested with the 22C3 IHC assay. TMB by whole exome sequencing and pre-treatment GEP by Nanostring.

Results: In a 353 patient phase 1/1b dose escalation and expansion study, 34 pre-treated NSCLC subjects received pegilodecakin with pembrolizumab or nivolumab. Responses were assessed by iREC. PD-L1 was tested with the 22C3 IHC assay. TMB by whole exome sequencing and pre-treatment GEP by Nanostring.

Table: 1144P

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1145P Responses and durability of clinical benefit in triple negative breast cancer patients treated with pegilodecakin monotherapy or in combination with platinum plus taxane-based chemotherapy


1Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA, 2Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 3Drug Development, Sarah Cannon Research Institute, Denver, CO, USA, 4Breast Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 5Drug Development, Sarah Cannon Research Institute, Denver, CO, USA, 6Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, 7Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 8Oncology, Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL, USA

Background: Late line, triple negative breast cancer (TNBC) is an unmet need. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin also up-regulates IFN-γ and the expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden and promotes immunosurveillance by expanding effector memory T cells (Mumm et al. 2010, 2011). Finally, pegilodecakin reduces tumor inflammatory processes such as angiogenesis and and metastatic dissemination (Oft 2017), the off-target auto-immune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies.

Results: Pegilodecakin when added to anti-PD-1 therapy in advanced NSCLC patients was associated with response rates and durability of benefit greater than has been seen with anti-PD-1 alone. Responses were seen in settings in which anti-PD-1 therapy has demonstrated limited benefit, such as absent PD-L1 expression, low TMB and/or the presence of liver metastases. These preliminary findings support further studies of pegilodecakin with anti-PD-1 therapies.

Clinical trial identification: NCT02009449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. Oft, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.
Methods: In a 353 patient phase 1/1b dose escalation and expansion study conducted in the US from 2013 to 2017, 18 heavily pretreated TNBC subjects received pegilodecakin alone (N = 8) or in combination with platinum and taxane-based chemotherapy (N = 4) or platinum and gemcitabine chemotherapy (N = 10). Responses were assessed by iRC.

Results: G3/4 TRAEs in monotherapy are anemia (38%), thrombocytopenia (38%) and fatigue (25%); and in the platinum/taxane combo: anemia (75%), neutropenia (75%), thrombocytopenia (75%), leukopenia (50%), and febrile neutropenia (25%); in carbogem combo: thrombocytopenia (60%), fatigue (30%) and anemia (20%).

Table: 1145P

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120 qkg Q 5D; 2Pegilodecakin 10 qkg + Carboplatin + Paclitaxel or Pegilodecakin 2.5 or 10 qkg + Carboplatin + Docetaxel or Pegilodecakin 10 qkg + Carboplatin + Paclitaxel + Carboplatin; 3Pegilodecakin 5.0 or 10 qkg + Carboplatin + Gemcitabine; 4Chemotherapy cohorts 1 & 2 combined; E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat); Data cut on 05.01.18.

Conclusions: Pegilodecakin in combination with platinum and taxane-based chemotherapy in advanced TNBC was associated with objective responses and durable clinical benefit as measured by disease control and overall survival. These preliminary findings support further studies of pegilodecakin in combination with standard of care chemotherapy in both later and earlier stages patients with TNBC.

Clinical trial identification: NCT02094449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. ORI, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1146P

Durability of clinical benefit in metastatic epithelial ovarian cancer patients treated with pegilodecakin monotherapy or in combination with platinum plus taxane-based chemotherapy

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1Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 2Investigative Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA, 3Biostatistics, ARMO BioSciences, Redwood City, CA, USA, 4Pre-Clinical and Clinical Development, ARMO BioSciences, Redwood City, CA, USA, 5Scientific Affairs, ARMO BioSciences, Redwood City, CA, USA, 6Drug Development, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA

Background: Checkpoint inhibition as monotherapy has limited success in advanced metastatic epithelial ovarian cancer (epOC) and strategies to increase immunogenicity are needed. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10 that stimulates activation, survival and clonal expansion of intra-tumoral, tumor antigen-specific CD8+ T cells. Pegilodecakin also up-regulates IFN-γ and expression of MHC, which enables tumor antigen presentation in neoplasias of low mutational burden (eg, epOC) and promotes immunosurveillance by expanding effector memory T cells (Mumma et al 2010, 2011). Pegilodecakin reduces tumor inflammatory processes such as angiogenesis and metastatic dissemination (ORI 2017), the off-target autoimmune side effects of immunotherapy and the inflammatory-related side effects of some chemotherapies. Preclinical data suggest synergy of pegilodecakin in reducing tumor volume when combined with platinum/taxane-based chemotherapy.

Methods: In a 353 patient phase 1/1b dose escalation and expansion study conducted in the US (2013-2017), 12 platinum-refractory, heavily pretreated epOC pts received daily pegilodecakin alone (N = 9) or in combination with platinum/taxane-based chemotherapy (N = 3). Responses were assessed by iRC.

Results: In monotherapy 4 (44%) had a PFS of more than 3.5 months and a survival of more than 14.7 months. No IRAEs were seen. G3/4 TRAEs in monotherapy: anemia (33%), fatigue (33%), thrombocytopenia (22%); in platinum/taxane combo: anemia (33%), diarrhea (33%), neutropenia (33%), thrombocytopenia (33%).

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1.0 or 20 qkg/; 2Pegilodecakin 10 qkg + Carboplatin + Paclitaxel or Pegilodecakin 10 qkg + Carboplatin + Paclitaxel or Pegilodecakin 2.5 qkg/ + Carboplatin + Docetaxel; 3E (evaluable - baseline tumor assessment + >1 post-baseline assessments, and no major protocol deviations); ITT (intent to treat); Data cut on 05.01.18.

Conclusions: Pegilodecakin alone demonstrated durable disease control with manageable toxicity in a proportion of treatment refractory epOC pts. Preliminary findings in a small subset of epOC pts who received pegilodecakin in combination with platinum plus taxane-based chemotherapy yielded promising results.

Clinical trial identification: NCT02094449.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.

Disclosure: A. Hung, M. ORI, J. Leveque: Employee: ARMO BioSciences. All other authors have declared no conflicts of interest.

1147P

Preliminary results from a phase I study of GBR 1302, a bispecific antibody T-cell engager, in HER2 positive cancers

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1University Hospital Carl Gustav Carus, Dresden, Germany, 2University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany, 3Clinical Sciences, Glenmark Pharmaceuticals Inc, Mahwah, NJ, USA, 4Drug Discovery, Glenmark Pharmaceuticals Inc, Mahwah, NJ, USA, 5Biometrics, Glenmark Pharmaceuticals Inc, Mahwah, NJ, USA, 6Biostatistics, Glenmark Pharmaceuticals Inc, Mahwah, NJ, USA, 7Glenmark Pharmaceuticals, S.A., Switzerland, 8Research, Mary Crowley Cancer Research Dallas, TX, USA, 9Charities, Comprehensive Cancer Center, Charité University of Medicine, Berlin, Germany

Background: GBR 1302 is a HER2xCD3 bispecific antibody engineered to direct T-cells to HER2 expressing tumor cells. This ongoing first-in-human study (NCT02829372) in subjects with HER2-positive cancers aims to evaluate the safety, tolerability, and preliminary efficacy of GBR 1302.

Methods: Adults with HER2-positive (immunohistochemistry 2+ or 3+) solid tumors with no available standard treatment receive GBR 1302 on Day 1 and Day 15 in 28-day treatment cycles at escalating dose levels, starting at 1 mg/kg. The primary endpoint includes determination of the maximum tolerable dose and safety profile of GBR 1302. Secondary and exploratory endpoints include pharmacodynamic (PD) testing for modulation of cellular and cytokine biomarkers.

Results: To date, 19 evaluable subjects for dose limiting toxicity (DLT) have been treated up to a dose of 790 mg/kg; dose escalation is ongoing. Grade (G) 1 to 2 infusion related reaction (IRR)/cytokine release syndrome (CRS) is the most common treatment emergent adverse event that has been observed in subjects treated at doses ≥100 mg/kg. The majority of subjects were managed with conservative treatment. 2 subjects experienced DLT events: one asymptomatic subject (100 mg/kg) was noted to have reduced left ventricular ejection fraction on routine echocardiogram at 4 weeks, which resolved spontaneously after treatment discontinuation; the second subject (300 mg/kg) experienced G4 IRR/CRS which required ICU care but resolved within 36 hours. Beginning at 30 mg/kg, CD3, CD4, and CD8 positive T-cell populations decreased within 6 hours of administration and recovered to levels at or above baseline by 48 hours. Dose-proportional, transient increases in cytokines (IL-2, IL-6, IL-10, IFN-γ, TNF-α), which peaked at 6 hours and began to normalize within 48 hours, were observed. No subjects have documented radiological response, but 2 subjects (HER2 3+; gastropathic adenocarcinoma and HER2 2+; breast adenocarcinoma) have prolonged disease stabilization lasting ≥4 months.

Conclusions: The combination of clinical findings and PD changes suggests T-cell activation with higher dosages of GBR 1302. Dose escalation is continuing and updated results will be presented.

Clinical trial identification: NCT02829372.

Editorial acknowledgement: Editorial assistance provided by Ashley Skorusa, PhD of Prescott Medical Communications Group (Chicago, IL) and funded by Glenmark Pharmaceuticals S.A., Switzerland.

Legal entity responsible for the study: Glenmark Pharmaceuticals, SA.

Funding: Glenmark Pharmaceuticals, SA.

Annals of Oncology


1148P A phase Ia study of a personalized TSA-CTL (tumor specific antigen-induced cytotoxic T lymphocytes) therapy in metastatic melanoma

B. Li, S. Qiu
Genomimmune Therapeutics, BGI-Shenzhen, Shenzhen, China

Background: Neoantigens are derived from tumor specific mutations and presented by MHC on cancer cells. The set of neoantigens likely bypass immune tolerance and less likely induce autoimmune because they are absent from normal cells. Targeting multiple neoantigens may significantly enhance the clinical efficacy of anti-tumor treatment with less toxicity. We present the proof-of-concept clinical application of personalized neoantigens induced T cell therapy.

Methods: This open-label phase Ia clinical trial is designed to test the safety and objective response of the tumor specific antigen-induced cytotoxic T lymphocytes (TSA-CTL). This study will enroll 9 advanced melanoma patients. Participants should have measurable metastases with at least one lesion that is resectable or tumor biopsies for DNA and RNA extraction. For each patient, we generate autologous TSA-CTLs based on neoantigens which identified through machine learning approaches with exome sequencing. Patients will receive 6 doses of TSA-CTL infusion. Toxicity (endpoint 1) will be defined by Common Terminology Criteria for Adverse Events v5.0, and objective response (endpoint 2) will be determined by the Response Evaluation Criteria in Solid Tumors.

Results: Seven patients have been enrolled so far and three of them have completed 3 cycles of TSA-CTL infusion. The fifth patient display pruritus grade 1. No other related adverse events just after the treatment were observed. We detected neoantigen-specific CD8+ T cells in peripheral blood through pMHC tetramer and found that neoantigen-specific CD8+ T cell increased after the TSA-CTL infusions for the third patient and the fifth patient. After three cycles of TSA-CTL infusion, the third and the fourth patient was assessed as SD with three metastasis’ regression and PR, respectively. Further treatment and analyses are ongoing.

Conclusions: No major direct side effects are observed. Although with very limited trial subjects, a few patients did show favorable responses. Our study highlights the promise of personalized cell therapy for tumor-specific T cells and provide guidance for the future development. Clinical trial information: NCT02959905. Clinical trial end date: Release date: November 9, 2016.

Legal entity responsible for the study: BGI-Shenzhen.

Funding: BGI-Shenzhen.

Disclosure: B. Li, S. Qiu: Employee: BGI Tech Solutions (Hong Kong Co. Ltd).

1149P Safety, tolerability, and pharmacokinetics of the OX40 agonist ABBV-368 in patients with advanced solid tumors

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Background: ABBV-368 is a novel humanized IgG1 agonist monoclonal antibody specific for human OX40, a TNF receptor superfamily member expressed on activated T regulatory cells. The proposed ABBV-368 therapeutic mechanism of action includes activation of T effector cells and inhibition of the suppressive capacity of T regulatory cells. This ongoing first-in-human, phase 1, two-part study (NCT03071757) is investigating the safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary anti-tumor activity of ABBV-368 in patients (pts) with advanced solid tumors.

Methods: Eligible pts include adults (≥18 years) with advanced or metastatic solid tumors. ABBV-368 was administered intravenously in a 3+3 dose-escalation design at doses ranging from 0.10 to 3.0 mg/kg every 2 weeks (4 cohorts). PK was assessed in cycle 1 and cycle 3. OX40 receptor saturation, Ki67 proliferation marker expression in peripheral blood immune cell subsets, and additional PD biomarkers were evaluated.

Results: As of Feb 12, 2018, 38 pts with advanced or metastatic tumors were enrolled in dose-escalation cohorts. Median age was 65 years (range, 38-78). No dose-limiting toxicities were reported during dose escalation. Overall, 15 (39.5%) pts reported grade (Gr) ≥3 treatment-emergent adverse events (TEAEs). Three (7.9%) pts reported Gr 3 TEAEs related to ABBV-368. Two investigator reported immune-related AEs were documented, including hypothyroidism; neither were serious. ABBV-368 PK was approximately dose-proportional from 0.1- to 3-mg/kg doses during cycle 1, with dose-dependent target saturation. Initial anti-tumor activity has been observed.

Conclusion: ABBV-368 was well tolerated; a maximum tolerated dose was not reached. Antitumor activity was observed at doses predicted to be biologically active. Further evaluation of ABBV-368 is ongoing in pts with advanced solid tumors.

Clinical trial identification: NCT03071757.

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Legal entity responsible for the study: AbbVie Inc.

Funding: AbbVie Inc.

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1150P Recombinant humanized anti-PD-1 monoclonal antibody (JS001) in patients with refractory/metastatic nasopharyngeal carcinoma: Preliminary results of an open-label phase II clinical study

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Background: Patients with metastatic nasopharyngeal carcinoma (NPC) who experienced disease progression after standard therapy have limited treatment options. NPC is closely associated with Epstein–Barr Virus (EBV) infection and has been reported to have high levels of PD-L1 expression and tumor infiltrating lymphocytes, favoring immune-therapy potential in treating NPC. JS001, a humanized recombinant IgG4 antibody against PD-1, selectively blocks the interactions of PD-1 with its ligands PD-L1 and PD-L2, and promotes antigen specific T cell activation. Phase I studies of JS001 in subjects with heavily pretreated solid tumors had demonstrated an acceptable safety profile in doses up to 10 mg/kg QSW.

Methods: Refractory/metastatic NPC Patients received JS001 3 mg/kg Q2W until disease progression or unacceptable toxicity. All patients were measurable disease were assessed for clinical response every 8 weeks. Tumor PD-L1 expression (SP142) and plasma EBV DNA levels were monitored for correlation with clinical response.

Results: Between Dec 22nd 2016 and May 4th 2018, 139 NPC pts were enrolled into the study. The median age was 46 years, 84% male (n = 117), with average 3 lines of prior systemic therapies. By Nov 13th 2017, treatment related AEs occurred in 84% patients, which were mostly grade 1 or 2, including fever (18.2%), hypothyroidism (18.2%), proteinuria (10.9%), fatigue (9.1%), TBL increase (9.1%), lekenopia (9.1%) and anemia (7.3%). Grade ≥3 treatment related AEs occurred in 14.5% patients. Out of 52 evaluable pts by Jan 18, 2016 partial responses (30.8% ORR) and 16 stable diseases (61.5% DCR) were observed. PD-L1+ pts had slightly higher ORR 38.5% and 63.4% DCR. Interestingly, an average drop of 47-fold plasma EBV DNA copy number was observed in responding pts, which typically preceded the radiographic identification of clinical benefits.

Conclusions: PD-1 mAb JS001 has demonstrated encouraging clinical activity in heavily pretreated NPC pts and a manageable safety profile. A change in plasma EBV DNA copy number might serve as a prognosis marker for NPC upon immunotherapy.

Clinical trial identification: NCT02915432.

Legal entity responsible for the study: Shanghai Junshi Biosciences Co.

Funding: Shanghai Junshi Biosciences Co.

Disclosure: H. Wu, H. Feng, S. Yan: Employee: Shanghai Junshi Biosciences Co. All other authors have declared no conflicts of interest.
Cemiplimab, a human monoclonal anti-PD-1, in patients (pts) with advanced or metastatic hematocarcinoma (HCC): Data from an expansion cohort in a phase I study

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Background: Cemiplimab (JAVI-01, MEDI5626) is an investigational, human monoclonal anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, currently in clinical development as monotherapy for the treatment of patients with advanced solid tumors. This study evaluated cemiplimab in an expanded cohort of advanced or metastatic HCC in patients (pts) who were not candidates for surgery and had progressed on, or could not tolerate, or refused first-line systemic therapy.

Methods: A total of 52 pts were enrolled (25 M/17 F), median (range) age was 65 (40–78) years; 24 pts (92.3%) had ≥1 prior systemic therapy; ECOG performance status was 1 in 19 pts (73.1%), 0 in 6 (23.1%) and missing in 1. Median duration of follow-up was 7.2 months (range: 0.1–15.5 months). By investigator assessment, 5 pts (19.2%) had partial response, 14 (53.8%) had stable disease, 6 (23.1%) had progressive disease and 1 was not evaluable. Median progression-free survival was 3.7 months (95% CI: 2.3–9.1). Five (19.2%) completed the planned 48-week treatment, and 21 (80.8%) discontinued prematurely, mainly due to disease progression (65.4%). Three of the 5 pts who completed planned treatment remained without disease progression at the last response assessment. The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (26.9%), decreased appetite, increased aspartate aminotransferase (AST), abdominal pain, pruritus, and dyspnea (each 23.1%). Grade ≥3 TEAEs occurring in ≥2 pts were hyponatraemia (3 pts), autoimmune hepatitis (2 pts) and increased AST (2 pts). Two pts (7.7%) had a TEAE resulting in death: 1 with pulmonary embolism that was considered unrelated to treatment and another with hepatic failure considered possibly related to treatment.

Conclusions: Cemiplimab demonstrated evidence of antitumour activity in pts with advanced or metastatic HCC. The safety profile is comparable with that of other anti-PD-1 inhibitors.

Clinical trial identification: NCT02383212.

Annals of Oncology

1154P A phase I study of MEDI1873, a novel GITR agonist, in advanced solid tumors
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Background: MEDI1873 is a novel GITR-ligand/IGG1 agonist fusion protein that binds the co-stimulatory glucocorticoid-inducible TNF receptor family-related protein (GITR) on CD4+ and CD8+ effector T cells and regulatory T cells. This Phase 1 study evaluated safety, maximum tolerated dose (MTD), pharmacokinetics (PK), immunogenicity, immunomodulatory effects and preliminary antitumor activity in pts with advanced solid tumors.

Methods: MEDI1873 was administered IV Q2W. During dose escalation (DE), it was evaluated in 2 single pt cohorts (1.5 and 3 mg), followed by 3 + 3 DE in 6 cohorts (7.5, 25, 75, 250, 500 and 750 mg). Pts with NSCLC, HNSCC or CRC receiving 75 or 250 mg were evaluated in pharmacodynamic (PD) cohorts using biopsies pretreatment and at day 29. All pts had flow cytometric assessment of lymphocytes pre- and on-treatment up to day 45. Antitumor response was assessed using RECIST v1.1.

Results: As of 1/20 clinical trials, 4 pts were dosed in the DE (28) and 12 cohorts. An MTD was not reached (maximum administered dose was 750 mg). Three DLTs occurred: Grade 3 worsening tumor pain at 250 mg, Grade 3 nausea and vomiting at 500 mg and Grade 3 non-STEM at 750 mg. Any-grade drug-related AEs occurred in 82.5% of pts, most commonly headache (25%) and infusion related reaction (IR, 20%). Grade 3 drug-related AEs occurred in 22.5% of pts; asymptomatic increase of 25% decrease in GITR/C21/C21+FOXP3+ T cells in 5 of 5 pts with evaluable cells. Immune PD changes were observed in 8 pts who underwent paired biopsies. Best overall response was stable disease (SD) in 42.5% of pts; 17.5% had SD

Clinical trial identification: NCT0283165, October 22, 2015

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Legal entity responsible for the study: MedImmune

Funding: MedImmune

Disclosure: C.S. Derlinger: Grant: MedImmune, during the conduct of the study; Grants and personal fees: Eli Lilly and Company; Grants: Bristol-Myers Squibb.

1154P A phase I study of MEDI1873, a novel GITR agonist, in advanced solid tumors
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1155P Phase I adoptive cellular therapy trial with ex-vivo stimulated autologous CD8+ T-cells against multiple targets (ACTolog) via IMA101 in patients with relapsed and/or refractory solid cancers

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Background: Adoptive cellular therapy in patients (pts) with solid tumors is limited due to lack of cancer targets with high specificity or relapse often associated with loss of single antigen (Ag) expression. To address multiple novel tumor Ags, we utilized Ag-specific T cells (IMA101) against cancer targets. Target positive tumors were identified by qPCR. Expression levels predictive for Ag presentation were determined by mass spectrometry. Autologous T cells against ACTolog targets are in vitro primed in the presence of Il-2 followed by HLA tetramer-guided cell sorting and expansion prior to infusion.

Methods: HLA A*02:01 positive pts with relapsed/refractory solid tumors are eligible for treatment if their tumors express >1 of 9 possible Ag targets from a predefined anti-gen warehouse. These pts undergo leukopheresis, followed by IMA101 cell manufacturing. Treatment consists of lymphodepletion (Fludarabine/Cyclophosphamide) followed by IMA101 infusion of up to 4 Ag-specific T cell products and IL-2.

Results: From 8/2017 to 5/2018, 86 pts were prescreened, 38 were HLA A*02:01 positive, 18 had tumor biopsy, 11 had leukopheresis and 3 were treated so far: hormone receptor pos, HER2 neg. breast cancer (36 yr, fem), srynaic sarcoma (28 yr, fem); and liposarcoma (36 yr, mal), No. of prior therapies, 12, 6, 8, respectively. Relative time to recovery was: ANC >1.0: day 41, 48, and 61; Platelets >50: day 47, no decrease <50, and 61. Pts developed Grade 1-2 cytokine release syndrome, without evidence of infec-

Clinical trial identification: NCT02876510

Legal entity responsible for the study: Immatics US, Inc.

Funding: Cancer Prevention Research Institute of Texas (DP150029).


Clinical trial identification: NCT02876510


1155P Phase I adoptive cellular therapy trial with ex-vivo stimulated autologous CD8+ T-cells against multiple targets (ACTolog) via IMA101 in patients with relapsed and/or refractory solid cancers

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Clinical trial identification: NCT02876510

Legal entity responsible for the study: Immatics US, Inc.

Funding: Cancer Prevention Research Institute of Texas (DP150029).


Clinical trial identification: NCT02876510
Phase I/Ii, open-label, multiple ascending dose trial of AGEN2034, an anti-PD-1 monoclonal antibody, in advanced solid malignancies: Results of dose escalation in advanced cancer and expansion cohorts in subjects with relapsed/refractory cervical cancer

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Background: AGEN2034 is a fully-human immunoglobulin (IgG) 4 monoclonal antibody targeting programmed death protein 1 (PD-1). The objective was to assess safety, maximum tolerated dose, preliminary efficacy, and pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of AGEN2034 in patients (pts) with advanced malignancies.

Methods: 50 pts were enrolled at dose cohorts of 1, 3, and 10 mg/kg. AGEN2034 is given intravenously Q2w for ≥2 years with cohorts at Q3w dosing at 6 and 10 mg/kg. A phase 2 expansion of AGEN2034 3 mg/kg Q2w in pts with relapsed/refractory cervical cancer is under way.

Results: 10 pts were enrolled at each dose level. Median age was 58 y, with ECOG scores 0–1. No dose-limiting toxicities were observed. Immune-related adverse events (AEs) consistent with this drug class were observed, including pneumonitis, colitis, diarrhea, rash, and pruritus. 21 of 30 pts had treatment-related AEs (TRAEs): 13 (43%) subjects discontinued (d/c) due to disease progression and 1 patient d/c due to TRAEs of hepatitis and pneumonitis. At the time of data cutoff, in 25 evaluable heavily pretreated pts, 3 partial responses (2 confirmed) were noted in pts with cervical, ovarian, and breast cancers in the 1 and 3 mg/kg cohorts. 13 patients had stable disease, including 5 of 5 patients with ovarian cancer. AGEN2034 demonstrates a dose-proportional Cmax of 19.6 µg/mL at 1 mg/kg and 73.6 µg/mL at 3 mg/kg in 12 pt samples analyzed in the first 2 cohorts. Average PD-1 receptor occupancy (RO) on circulating CD8+ and CD4+ effector memory T lymphocytes (n = 18) demonstrated >59% saturation at all dose levels at day 15 post infusion.

Conclusions: AGEN2034 is pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signals of clinical activity in cervical and ovarian cancers. PK and RO results are comparable to commercial PD-1 antagonists. Updated safety and efficacy results for the dose escalation and the relapsed cervical cancer cohorts will be presented.

Disclosure: Agenus Inc. (Lexington, MA, USA)

Phase I trial of a novel hTERT vaccination strategy addressing T effector cells and immune-suppressor mechanisms

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Background: Inability to generate activated T effector cells and the presence of strong suppressor mechanisms have limited cancer vaccine efficacy. Human telomerase reverse transcriptase (hTERT) is expressed in >90% of tumours but is HLA dependent, which has restricted its use to patients with a particular HLA haplotype. We sought to address these problems with a novel vaccination strategy.

Methods: Each vaccination was preceded by 10 days of metronomic low dose cyclophosphamide, designed to inhibit Treg cells. A vaccine consisting of T KERT peptide, predicted to bind HLA Class I and II proteins, not HLA restricted, was given 3-weekly ID. Adjuvants (Montanide and liposome-based) were used to optimise hTERT presentation. The primary objective was safety, with secondary objectives of immunological and clinical efficacy. Blood lymphocyte phenotype profiles were analysed ex vivo and post culture to identify activated T effector cells, checkpoint-regulatory T cells and Tregs. T cell receptor (TCR) sequencing was performed prior to and post vaccination.

Results: 17 patients (pts) have completed treatment. Vaccination was well tolerated, 1 withdrew following an injection site reaction. 4 pts (24%) had stable disease for ≥6 months (colorectal, lung, prostate, pancreas). Baseline activated T cells in pts (CD8+ / C4- / TCR- / Na+) were similar to healthy donors (HDs), but increased up to 3-fold post-vaccination (p = 0.017). T cells from 5 pts were cultured in vitro post-vaccination; peptide-specific activation of CD4+ and CD8+ T cells was seen in 4/5 and 3/5, respectively. Baseline checkpoint regulatory (PD-1+) CD8+ T cells were 8-10 fold higher in pts (CD8+ / p = 0.011; CD8+, p = 0.004) than HDs; post-vaccination

levels fell but remained > HDs. Post-treatment Tregs fell significantly (FOXP3+ / PD-1+, p = 0.016). TCR sequencing demonstrated the emergence of clonally expanded T cells, including hTERT-specific clones.

Conclusions: This pan-tumour generic vaccine was safe, with sustained disease stabilisation in a subset of patients with a range of tumour types. Immune-suppressor T cell numbers fell, and hTERT-specific T effector cells were generated.


Legal entity responsible for the study: King’s Health Partners.

Funding: Candles Charity.

Disclosure: All authors have declared no conflicts of interest.
1159P  Phase I/II study of spartalizumab (PDR001), an anti-PD-1 mAb, in patients with advanced melanoma or non-small cell lung cancer

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Background: Spartalizumab is a humanized IgG4 anti-PD-1 mAb, which has previously shown favorable PK and safety, and preliminary clinical activity. Methods: This Phase I/II, open-label, dose escalation/expansion study (NCT02404441) characterized the safety and efficacy of spartalizumab in patients (pts) with advanced solid tumors. In dose escalation, the recommended Phase II dose was declared as 400 mg Q3W (alternative: 380 mg Q4W). Here, we present expansion data for anti-PD-L1 naïve cohorts with advanced melanoma and NSCLC. PD-L1 expression was assessed centrally (Dako PD-L1 IHC 22C3 pharmDX).

Results: As of Nov 13, 2017, 61 pts with melanoma received 400 mg spartalizumab Q3W; 30% of pts were treatment-naive; 20% had ≥ 2 prior therapies, and all were anti-PD-L1 naïve. Suspected-related AEs (all grades) were fatigue (15%), decreased appetite (13%), nausea (8%), pruritus (8%), dyspepsia (7%) and rash (7%). ORR (confirmed responses) was 18% (16/61), including 2 CRs; 67% had baseline PD-L1 data; 63% were PD-L1– (TPS (confirmed responses) was 26% (16/61), including 1 CR. 41 pts (67%) had prior therapies; 27% had ≥2 therapies. Suspected-related AEs (≥5%) were diarrhea, nausea, decreased appetite, nausea, vomiting, pyrexia (12%) and rash (9%). ORR in both groups (Q3W: 38.4%, Q4W: 15.8% vs 9.5%). PK analyses confirmed flat dosing (Q3W vs Q4W) achieved drug exposure comparable with weight-based dosing. Conclusions: Spartalizumab was well tolerated with a manageable safety profile. Efficacy was observed in pts with NSCLC (Q3W and Q4W) and melanoma (Q4W), and was as expected given the high proportion of pts with PD-L1– disease. ORRs were higher in PD-L1– pts, corroborating previous findings that PD-L1 expression enriches for response to anti-PD-1 agents in certain tumor types. Clinical trial identification: NCT02404441, CPDR001X2101. Editorial acknowledgement: Editorial assistance was provided by Laura Hilditch of ArticulateScience Ltd.

Legal entity responsible for the study: Novartis Pharmaceutical Corporation.

Funding: Novartis Pharmaceutical Corporation.


1160P  Phase I/II evaluation of intratumoral INT230-6 for the treatment of solid tumors

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Background: INT230-6 is a formulation of cisplatin and vinblastine with an amphiphilic penetration enhancer to improve dispersion and diffusion into cancer cells. This is the first product designed for selective delivery into tumors with the potential to deliver high payload levels directly into cancer cells while sparing healthy cells. In colon 26 animal models, injection into a solitary lesion led to tumor necrosis, recruitment of dendritic cells into the tumor and activation of CD4 and CD8 T-cells. Injected tumors experienced high rates of complete response (up to 80%). Importantly, untreated lesions distal to the injection site also responded. Efficacy was synergistic when combined with checkpoint inhibitors.

Methods: Initial cohort enrolled subjects with advanced solid tumors with superficial lesions amenable to local injection. INT230-6 was administered intratumorally at a ratio of 1ml for each 4 cubic cm of tumor volume, once each month for a total of 5 cycles. Both the maximal dose into one tumor and the total dose (over multiple lesions) could be escalated on repeat cycles if no DLTs. Patients were monitored for safety weekly. Pharmacokinetic (PK) samples and peripheral blood were collected for flow cytometry and circulating cytokines. Subsequent cohorts of twice monthly injections into superficial tumors and monthly injection into deep tumors commenced after comprehensive review of safety data in superficial tumors.

Results: Thirteen subjects were treated with either melanoma, SCC, ovarian, chor- doma, cholangiocarcinoma or H&N into single or multiple lesions. PK analysis revealed negligible amounts of reduced platinum and vinblastine in blood, suggesting retention in the tumor compartments. No DLTs or drug related SAEs were reported. The most frequent adverse event was grade 1 or 2 injection site pain, or other local symptom (infection or blister). Subjectively, some injected lesions were noted to change as soon as 1 week with flattening and areas of necrosis. Conclusions: INT230-6 was safe when administered locally to tumors at doses given. Updated results will be presented including biomarker and response data. Additional cohorts including higher drug concentrations should be combined with an anti-PD1 antibody. Clinical trial identification: NCT03058289.

Legal entity responsible for the study: Ian B. Walters, MD.

Funding: ImmunoTherapeutics.

OMTX705, a powerful stroma-targeting ADC to treat invasive tumors with low response to immunotherapeutic anti-PD-1 treatments


Background: Microenvironment represents 20-60% of solid tumor mass and is increasingly recognized to play a key role in promotion, invasiveness and metastasis. Mounting evidence suggests that FAP-expressing CAFs, the predominant stroma cell type, is involved in the tumor immune response. A novel antibody-drug conjugate, OMTX705, was generated through CTS-based conjugation of a new anti-FAP humanized antibody, with high specificity and affinity, to a novel cytotoxin, using an optimized vcPABA linker.

Methods: In vivo studies were performed in patient-derived xenograft models for pancreatic and NSCLC cancer in immunodeficient and humanized mice. Tumor volume and animal weight were monitored 3 times a week over 4 weeks of treatment with OMTX705, administered intravenously at different doses, either as single agent or in combination with chemotherapy such as Gemcitabine or Paclitaxel, or immunotherapy such as Pembrolizumab. FACS and IHC analysis of CD45, CD25, CD3, CD4, CD8 and FoxP3 markers were performed on blood and tumor samples to study the effect of OMTX705 on immune system in these models.

Results: OMTX705 showed 100% tumor growth inhibition and regression in the PDO models used, both as single agent and in combination with Gemcitabine and Nab-Paclitaxel, Paclitaxel, or Pembrolizumab, without weight loss. When treated with OMTX705 in combination with chemotherapy, the response was maintained for a longer period without further treatment: re-growth of tumors was delayed and tumors kept responding upon re-treatment, showing lack of resistance to OMTX705 treatment. In combination with Pembrolizumab immunotherapy in a humanized PDO model for lung cancer, OMTX705 efficacy was even higher at lower dose, inducing full regression and significant delay in tumor recurrence, through CD8(+) T cell dependent immunomodulation.

Conclusions: FAP-targeted OMTX705 represents a potent novel strategy for cancer treatment at low doses, with high specificity and affinity, to a novel cytotoxin, using an optimized vcPABA linker.

Legal entity responsible for the study: Oncomatryx Biopharma, S.L.


Cemiplimab, a human monoclonal anti-PD-1, plus radiotherapy (RT) in advanced non-small cell lung cancer (NSCLC): Results from a phase expansion cohort (EC 2)


Background: Cemiplimab (REGN2810), a human monoclonal antibody to PD-1, has exhibited substantial antitumour activities in patients (pts) with advanced malignancies in a Phase 1 study. Most patients with advanced NSCLC do not respond to PD-1 inhibitor monotherapy. Here we report results of the Phase 1/2b, a combination regimi of cemiplimab plus RT in advanced NSCLC (NCT02383212).

Methods: pts with advanced NSCLC who had relapsed after or were refractory to at least first-line therapy and for whom palliative RT was clinically indicated, received cemiplimab 3 mg/kg every 2 weeks for up to 48 weeks plus RT (9 Gy x 3 times/week) given 1 week after first dose of cemiplimab) to a single lesion. The co-primary objectives were to evaluate the safety, tolerability, and efficacy of cemiplimab plus RT. Tumour measurements (of non-irradiated target lesions) were performed by RECIST 1.1 every 8 weeks.

Results: As of 1 Sept, 2017, 33 pts (22 M/11 F; median age 67.0 years [range, 47–82]) were enrolled; 66.7% and 30.3% had an ECOG performance status of 1 and 0, respectively; the status of one pt was unknown. Overall response rate (ORR; complete response [CR] + partial response [PR]) was 18.2% (95% CI: 6.3–30.3%) with a median duration of response of 14.9 months (95% CI: 5.3–14.9). Disease control rate (ORR + stable disease [SD]) was 72.6% (6 PRs + 18 SDs). The most common treatment-emergent adverse events (TEAEs) of any grade were decreased appetite (38.3%), fatigue (27.3%), and cough (24.2%). Grade ≥3 TEAEs occurring in ≥2 patients include anaemia (12.1%), hypophosphatemia, and urinary tract infection (each 6.1%). One patient had a TEAE of pneumonitis, considered related to study drug, with an outcome of death.

Conclusions: Cemiplimab plus RT demonstrated antitumour activity in pretreated pts with NSCLC. The safety profile is comparable with other anti-PD-1 agents and RT. The combination therapy regimen did not produce greater efficacy relative to which can be achieved with PD-1 inhibitor monotherapy for advanced NSCLC.

Legal entity responsible for the study: Regeneron Pharmaceutical Inc.; Sanofi.

**Clinical trial identification:** RPCEC0000017. Legal entity responsible for the study: Center of Molecular Immunology. Disclosure: M. Hernandez, C. Viada: Employed: Center of Molecular Immunology. All other authors have declared no conflicts of interest.

**Background:** Racotumomab-alum is an anti-idiotypic vaccine that induces immunological response against N-glycolylated gangliosides in NSCLC patients. Nimotuzumab is a humanized anti-EGFR monoclonal antibody that has shown activity in NSCLC patients. The aim of this study is to evaluate safety and efficacy of racotumomab-alum or nimotuzumab versus docetaxel as second line or switch maintenance therapy for advanced NSCLC.

**Methods:** This phase III, multicenter, open label, randomized trial is designed to enroll 743 stage IIIB-IV NSCLC patients, after first line therapy, with PS 0-2, with written informed consent. The primary endpoint is Overall Survival (OS). Patients are been randomized (2:2:1) to 3 arms: racotumomab-alum, nimotuzumab or docetaxel, and stratified according to response to first line (progressor or non-progressor patients). Racotumomab-alum treatment consists in 5 bi-weekly intradermal doses and re-immunizations every 4 weeks. Nimotuzumab arm receives 6 weekly infusions followed by bi-weekly doses. Docetaxel is used at 75 mg/m2 for 6 cycles, if there is no evidence of progressive disease after 3 cycles. As second-line therapy, both experimental drugs will be classified as non-inferior (NI) to docetaxel, if 1-year OS rate is 23.1% and HR C/T >0.76. [d0 (0,28), d0]. In HRe/C(T/2) using a 10% NI margin. Here we report the interim analysis in 255 progressing patients.

**Results:** 106 patients in racotumomab, 97 in nimotuzumab and 54 in docetaxel arm with at least 1 year follow up were analyzed (ITT). The median OS and 1-year survival rate were 4.67 months (CI: 4.0-5.3) and 14.5% with nimotuzumab, 4.85 months (CI: 3.7-5.9) and 23.5% with racotumomab-alum and 5.85 months (CI: 3.9-7.7) and 20.2% with docetaxel, respectively. Most frequent treatment-related adverse events were induration (10.7%), local erythema in injection site (8.8%) and arthralgia (8.2%) with racotumomab-alum; myalgia (12.1%), fever (7.9%) and nausea (7.0%) with nimotuzumab, and nausea (16.9%), asthma (13.2%) and vomiting (12.1%) after docetaxel. Conclusions: These data do not confirm the non-inferiority of racotumomab-alum or nimotuzumab versus docetaxel as second-line therapy. Both experimental treatments were safely administered at primary level of health assistance.

**Disclosure:** M. Hernandez, E. Neninger, E. Sanjiteestean, K. Camacho, N. Hernandez, R. Aranda, T. Acosta, Y. Gonzales, Y. Jimenez, M. Corella, R.A. Ortiz, L. Bella, A. Calanu, P. Pichs, M. Cala, Y. Flores, C. Viada, M. Robaina, T. Crombet: Employed: Center of Molecular Immunology. All other authors have declared no conflicts of interest.

**Funding:** Has not received any funding.

**Table 1163P Demographic and clinical characteristics of 22 patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MNAs-T cells plus PD1 inhibitors plus BSC (N = 11)</th>
<th>PD1 inhibitors plus BSC (N = 11)</th>
</tr>
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<tr>
<td></td>
<td>Disease Progression (N=4)</td>
<td>No Disease Progression (N=7)</td>
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<tr>
<td>Age – no(%): &lt;60</td>
<td>4 (100)</td>
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<tr>
<td></td>
<td>0 (0)</td>
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<td></td>
<td>2 (28.6)</td>
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<tr>
<td>Age – no(%): &gt; =60</td>
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<td></td>
</tr>
<tr>
<td>Sex – no(%): Male</td>
<td>3 (75)</td>
<td>3 (42.9)</td>
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<tr>
<td></td>
<td>1 (25)</td>
<td>4 (57.1)</td>
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<tr>
<td></td>
<td></td>
<td>3 (27.3)</td>
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<tr>
<td>Sex – no(%): Female</td>
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<tr>
<td>Previous treatments – no.</td>
<td>4 (7)</td>
<td>7 (11)</td>
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<tr>
<td></td>
<td>6 (11)</td>
<td>4 (7)</td>
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<tr>
<td>Cancer – no.</td>
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<tr>
<td>ECOG – no(%): 0</td>
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<td></td>
<td>1 (18)</td>
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<td></td>
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<td></td>
<td>3 (50)</td>
<td>1 (2)</td>
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<td>Stage – no.</td>
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<td>1 (2)</td>
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<tr>
<td>Peripheral IR Diversity – mean (SD)</td>
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<tr>
<td></td>
<td>0.76 (0.18)</td>
<td>1.2 (0.27)</td>
</tr>
</tbody>
</table>

**Conclusion:** The combined immunotherapy of MNAs-T cells and PD1 inhibitors is more effective than PD1 inhibitor alone in prolonging the PFS, and has a good safety. IR Clonality change shows its potential as a predictive biomarker.

**Disclosure:** All authors have declared no conflicts of interest.
Methods: A phase I multi-center study was conducted to evaluate the safety, tolerability, PK and anti-tumor activity of CS1001 in pts with advanced tumors. A 3+3 dose-escalation design was undertaken. Pts received CS1001 intravenously once every three weeks (Q3W). Safety and tolerability were assessed by monitoring adverse events (AEs). Tumor assessments were performed per RECIST v1.1 (solid tumors) or Lugano (lymphomas).

Results: As of 8 Apr 2018, a total of 19 Asian pts (median age 50 (31–74) yrs) with advanced tumors were treated by CS1001 Q3W across 5 dose-escalating cohorts (3 mg/kg, N = 3; 10 mg/kg, N = 4; 20 mg/kg, N = 3; 40 mg/kg, N = 3; 120 mg/kg, N = 6). All pts had received at least 1 prior line of anti-cancer treatment (median 2 [1–7]). Median duration of study treatment was 63 (6–172) days. 14 pts remain on study. No dose limiting toxicity was observed, and maximum tolerated dose was not reached. The most frequent treatment-emergent AEs were grade (G) 1/2 anemia (n = 7), nausea (n = 6), decreased appetite (n = 5), blood bilirubin increased (n = 4), protein urine present (n = 4), white blood cell count decreased (n = 4) and proinflammation (n = 4). Immune-related AEs (G1–3) occurred in 5 pts. No treatment-related serious AE was reported. PK analysis was conducted using observed CS1001 serum concentrations from 16 pts across all 5 cohorts. The PK of CS1001 was linear and the terminal elimination half-life was about 12 days. Among 12 efficacy evaluable pts, four achieved unconfirmed partial response and all remain on treatment. Three additional pts achieved a best overall response of stable disease.

Conclusions: CS1001 appears to be generally well tolerated in pts with advanced tumors, with a linear PK profile. The preliminary safety profile and anti-tumor activity support continued development and development of CS1001.

Clinical trial identification: NCT03312842, October 18, 2017.

Legal entity responsible for the study: CStone Pharmaceuticals (Su Zhou) Co., Ltd.

Funding: CStone Pharmaceuticals (Su Zhou) Co., Ltd.


Abstract: A novel dual inhibitor of IDO and TDO enhances anti-cancer immunity and synergizes with immune checkpoint blockade


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Background: Indolamine 2,3-dioxygenase (IDO) blockade is a new therapeutic strategy to enhance cancer immunity. However, IDO blockade alone cannot completely block the immunosuppressive tryptophan-kynurenine (Trypt-Kyn) pathway in the tumor microenvironment. Recent studies have demonstrated that Tryp 2,3-dioxygenase (TDO) is an alternative enzyme employed by various tumors that can be used as a target for the Trypt-Kyn pathway; therefore, here we developed an orally available dual inhibitor that targets IDO and TDO.

Methods: Small-molecule inhibitors for IDO and TDO were synthesized and screened by in vitro IDO/TDO enzyme and cell-based assays. CT26 colon or 4T1 breast tumor-bearing mice were treated with CB548 either alone or in combination with anti-PD1 antibody. We monitored tumor growth and analyzed the tumor microenvironment using flow cytometry, qPCR, and confocal microscopy.

Results: A lead compound, CB548, showed potent inhibition of IDO and TDO in the enzyme and cell-based assays with various human and murine cancer cell lines. Oral administration of CB548 revealed a good pharmacokinetic profile, and the conversion of Tryp to Kyn in tumors was effectively suppressed. Moreover, the CB548 monotherapy revealed a dose-dependent inhibition of CT26 colon or 4T1 breast cancer growth as well as markedly increased CD8+ T-cell infiltration in the tumor microenvironment. Additionally, the combination immunotherapy of CB548 and anti-PD1 antibody suppressed tumor growth to a greater extent than did the monotherapy, and led to durable tumor regression. There was no significant systemic toxicity with the CB548 treatment.

Conclusions: Overall, our study demonstrates that CB548, a novel IDO/TDO dual inhibitor, can elicit a robust anti-cancer immunity and synergistically inhibit cancer progression in combination with an immune checkpoint inhibitor.

Legal entity responsible for the study: CHA Bundang Medical Center.

Funding: This work was supported by the Bio & Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science & ICT of Republic of Korea.

Disclosure: J.S. Kim: Employee of the CMG Pharmaceutical. All other authors have declared no conflicts of interest.
Background: Cytotoxic T-lymphocyte–associated antigen (CTLA-4) and programmed cell death 1 (PD-1) pathway ligands have distinct roles in T-cell modulation; blockade of both has been synergistic in vitro and in the clinic. This study will assess safety and tolerability of AGEN1884 (anti–CTLA-4 human immunoglobulin [IgG]-1 monoclonal antibody [mAb]) in combination with AGEN2034 (anti–PD-1 human IgG4 mAb) in patients (pts) with advanced/refractory solid tumors, with expansion into select solid tumors.

Methods: A dose-escalation phase and expansion focusing on adult female pts with recurrent/metastatic cervical cancer that has relapsed after platinum-containing doublet treatment. Phase 1 (Ph1) pts (n=20) will be enrolled to 2 dose regimens of AGEN1884 + AGEN2034 (starting: 1 mg/kg AGEN1884 Q6w + 1 mg/kg AGEN2034 Q2w; escalating: 1 mg/kg AGEN1884 Q6w + 3 mg/kg AGEN2034 Q2w). Escalation phase primary endpoints: safety, determination of recommended Ph2 dose (RP2D); Ph2 (n=40) also includes best overall response assessment by Independent Endpoint Review Committee per RECIST 1.1. Secondary endpoints: AGEN1884 and AGEN2034 pharmacokinetic (PK)/pharmacodynamic (PD) profiles, objective response rate, duration of response, progression-free and overall survival.

Results: 7 pts at starting dose, 3 pts at escalating dose. No dose-limiting toxicity has been observed; most common toxicities observed were expected for therapeutic class. 8 pts experienced toxicity grade 1 or 2. Most common toxicities: diarrhea/nausea/vomiting, n=6; rash/pruritus, n=2; transaminases elevated, n=1; fever/illness, n=3; fatigue, n=2. There was 1 serious adverse event and grade 3 toxicity unrelated to study drug. No discontinuation due to study drug, no deaths observed. Median dose administered was 1 for AGEN1884, 3 for AGEN2034. Dose level 2 was determined for RP2D. Updated safety, efficacy, and PK/PD of AGEN1884 + AGEN2034 will be presented. Conclusions: AGEN1884 (1 mg/kg Q6w) + AGEN2034 (3 mg/kg Q2w) is well tolerated and being evaluated in Ph2 combination in 2L cervical cancer and other solid tumors.

Clinical trial identification: ACTRN12618000833279.

Disclosure: The Medicine Group, LLC (New Hope, PA, USA) and funded by Agenus Inc. (Lexington, MA). Legal entity responsible for the study: Agenus Inc. and subsidiary there of (current or former employee), Lexington, MA. This project is supported by the Division of Cancer Prevention, National Institutes of Health. A. Boudot 1, C. LeMire 1, T. Meniawy 1, C. F. Dupont 1, A. M. Gonzalez 1, M. Lim 1, D. Savinsky 1, M. Carini 2, S. Hu 2, H. Youssoufian 3, Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA. J. Szabo 1, D. Savinsky 1, M. Carini 2, S. Hu 2, H. Youssoufian 3, Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA. O. Shebanova 1, E. Dow 1, W. Ortuzar 1, J. S. Buell 2, R. B. Stein 3, H. Youssoufian 3, Agenus Inc. or subsidiary there of (current or former employee), Lexington, MA. 

\[ \text{References:} \]

Results: We observed that bivalent binding to HER2 provides a stronger association with HER2+ tumor cells than monovalent binding, but that locating the CD3-binding domains in the hinge regions of ABP-100 results in functionally monovalent binding to CD3. ABP-100 showed a similar safety profile (cytokine release) to the heterodimer molecule both in vitro and in vivo. In models of HER2+ cancer, however, ABP-100 showed highly potent antitumor activity, resulting in complete responses in mice at doses as low as 0.1 mg/kg with no evidence of tumor regrowth after treatments were stopped. Overall clinical efficacy of ABP-100 was strongly dependent on HER2 levels and synergistic effects were observed when ABP-100 was combined with a PD-L1 inhibitor.

Conclusions: The Tetrahelix format of ABP-100 provides a potentially more therapeutic index than monovalent bispecific formats that feature monovalent recognition of HER2. Moreover, because ABP-100 is designed to engage CTLLs, it provides a novel mechanism for treating HER2+ disease relative to current therapies. These data support the clinical development of ABP-100 in HER2+ solid tumors.

Legal entity responsible for the study: Abpro.

Funding: Abpro.


1117P Phase I expansion cohort results of cemiplimab, a human PD-1 monoclonal antibody, in combination with radiotherapy (RT), cyclophosphamide and GM-CSF, in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC)


Background: Most pts with R/M HNSCC do not respond to PD-1 inhibitor monotherapy. Cemiplimab is a human monoclonal anti-PD-1. An expansion cohort in the phase 1 study (NCT02388312) combined cemiplimab with other potential immune-supportive treatments for pts with R/M HNSCC.

Methods:Pts with R/M HNSCC who were refractory to at least first-line therapy and for whom palliative RT is clinically indicated received cemiplimab 3 mg/kg Q2W for up to 48 weeks plus RT (9 Gy x 3 times/week beginning 6–8 days after first dose of cemiplimab), cyclophosphamide (200 mg/m² every 14 days for 4 doses), and GM-CSF (100 µg daily for 7–8 days after each of the first 4 doses of cemiplimab). The co-primary objectives were to characterise the safety, tolerability, and efficacy of cemiplimab in combination with RT, cyclophosphamide and GM-CSF in pts with R/M HNSCC. Tumour assessments were performed by RECIST 1.1 Q8W.

Results: As of 1 Sept, 2017, 15 pts (9 M/6 F) had been enrolled. Median (range) age was 62.0 (45–78) years; ECOG performance status was 1 in 12 pts (80%), and 0 in 3 (20%); and 14 (93.3%) had received prior RT. The primary site of cancer was upper aerodigestive tract of head and neck. With a median (range) duration of follow-up of 3.3 (0.5–10.2) months, treatment is ongoing in 3 pts (20%) and 12 (80%) had discontinued, mainly due to disease progression/recurrence (53.3%). The most common treatment-emergent adverse events (TEAEs) of any grade were fatigue (40.0%), constipation (26.7%), dysphonia, maculopapular rash and pneumonia (each 20%). The only grade 3 or 4 TEAE that occurred in > 1 pts was pneumonia (13.3%). By investigator-assessment, there was 1 partial response (6.7%); disease control rate was 40.0% (95% CI: 17.4–67.7); 5 stable disease), 7 pts had progressive disease and 2 were not evaluable. Median progression-free survival by investigator-assessment was 1.8 months (95% CI: 0.1–7.4) months.

Conclusions: The combination therapy regimen did not demonstrate efficacy above that which can be achieved with PD-1 inhibitor monotherapy for R/M HNSCC.

Clinical trial identification: NCT02388312.


1172P A first-in-class, first-in-human phase I/II trial of CAN04, targeting interleukin-1 receptor accessory protein (IL-1RAP), in patients with solid tumors


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Background: CAN04 is a first-in-class fully humanized monoclonal antibody targeting IL-1RAP, a co-receptor for the IL-1R receptor which is expressed on human cancer cells.

Objective: CAN04 binds to IL-1RAP with high affinity in a manner that blocks signal transduction from IL-1 and IL-33 into the cells. Binding of CAN04 to IL-1RAP also allows NK cells to recognize tumor cells and subsequent killing by antibody dependent cellular cytotoxicity (ADCC).

Methods: The primary objective was to assess safety and tolerability of weekly CAN04 in order to define the Maximum Tolerated Dose/Recommended Phase 2 Dose. Patients with relapsed or refractory non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), breast or colorectal cancer were included in the initial part of the trial using a 3 + 3 dose escalation design. Key eligibility criteria were: ECOG ≤ 1, normal organ function and no bleeding disorder or coagulopathy. Tumor responses were evaluated according to RECIST every 8 weeks. Plasma samples were obtained for pharmacokinetic evaluation and for assessment of circulatory biomarkers of immunologic activity (e.g. IL-1α, IL-1β, IL-1RA, IL-6, IL-8, IL-33 and TNF-α).

Results: Nine subjects were enrolled across 3 initial cohorts (1-3 mg/kg). Demography: mean age 66 yrs (48-77); gender 5 M and 4 F; median number of prior lines of therapy 5 (range 2-11). No dose limiting toxicities (DLTs) were observed and MTD has not been reached yet. AEIs occurred mainly following the first dose and the most common AEs were: fatigue (60%), nausea (44%), pyrexia (44%), infusion related reactions (IRR) (44%) and pruritus (44%). AE grade 3 or 4: one grade 3 IRR following an initial dose of 1.0 mg/kg in cohort 3. Stable disease was achieved in 2/6 and progressive disease in 4/6 patients after 8 weeks of treatment.

Conclusions: CAN04 demonstrated a manageable safety profile in the initial 3 cohorts with no DLTs observed and the dose escalation will be continued as planned. The dose expansion phase of the trial will then evaluate CAN04 as monotherapy as well as in combination with standard of care therapy for NSCLC and PDAC in separate arms.

Clinical trial identification: NCT03267316.

Legal entity responsible for the study: Cantargia AB.

Funding: Cantargia AB.

Disclosure: A. Awada: Honorarium for advisory board: Cantargia AB. P.G. Ahlmol: Horizonary: Symton, Boehringer Ingelheim, Macrogenics, Amgen, Novartis; Travel grants: Amgen, Merck, Roche. L. Thorsen: Employee and shareholder: Cantargia AB. All other authors have declared no conflicts of interest.
### 1173P Immunostimulatory AdCD40L gene therapy in patients with advanced solid tumours

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Background: CD40-CD40L is a key activator of adaptive immunity. AdCD40L is a replication-deficient adenovirus carrying the CD40 ligand gene. We have conducted a phase I/II study (NCT01455259) for patients with advanced cancer receiving intratumoral injections of AdCD40L. Patients with metastatic malignant melanoma were treated in the first three cohorts in which we demonstrated that low dose cyclophosphamide before the first and fourth intratumoral injection given in the second and the third cohort was of clinical value with four patients surviving >1 year, while radiotherapy combination was not. In these patients, AdCD40L increased the Teffector to Tregulatory cell ratio showing its action via T cell activation. We now report the results of the fourth and final cohort treating patients with other solid malignancies.

Methods: Six patients with metastatic solid cancer underwent treatment with four weekly percutaneous intratumoral injections of 2.5X10^10 VP AdCD40L and low dose cyclophosphamide conditioning (300 mg/m^2) before the first and fourth injection. All patients had good performance status at inclusion. The primary tumor was kidney cancer (n = 2) or cholangiocarcinoma (n = 1), rectal (n = 1), ovarian (n = 1), and breast cancer (n = 1). Correlation analysis between immunological data and survival was performed.

Results: The treatment was generally well tolerated. Patients received the injection in metastases located in the liver (n = 4), lymph node (n = 1), or muscle (n = 1). The performance status for one patient improved during the treatment and this patient was therefore accepted for re-treatment. The median survival was 54 weeks ranging from 5 to 101 weeks compared to the melanoma patients that had a median survival of 27 weeks (5 to 220 weeks). Immunological data from five of the patients showed a significant negative correlation between IL10 concentrations at week 3 and survival (p = 0.0283). In addition, TNP3 and IL12 were higher post-treatment in the two patients with the longest survival.

Conclusions: Intratumoral injections of AdCD40L in combination with cyclophosphamide is feasible in patients with solid cancer. Desirable immune effects were noted and the potential of the treatment was also demonstrated in one patient who improved clinically.

Clinical trial identification: NCT01455259 Realise date: September 2011.

Legal entity responsible for the study: Gustave Roussy.

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### 1174P Patterns of progression to immune checkpoint targeted monoclonal antibodies in phase I trials

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Background: New patterns of progression under immune checkpoint targeted (ICT) monoclonal antibodies (mAb) have been described such as pseudoprogression (PsPD). Except for melanoma, variations between studies reveal difficulties to establish their real incidence. This study aims to assess different patterns of progression in ICT mAb phase I trials.

Methods: All patients participating in ICT mAb phase I trials at the Drug Development Department at Gustave Roussy for solid tumors excluding melanoma, were enrolled. Radiological evaluations according to RECIST 1.1 were correlated with prospectively registered patient characteristics and outcomes.

Results: Among 360 patients included between August 2015 and November 2017, 70.6% received ICT mAb combination: 58.3% with another ICT mAb, 27.9% with targeted therapy and 13.8% with radiotherapy. Patients received a median of 2 previous lines of therapy (range 0–10). The objective response rate was 17.2%. PsPD were observed in 10 (2.8%) of patients (1 NSCLC, 1 microsatellite-high colon cancer, 1 hepato- carcinoma, 2 renal, 2 bladder, 1 cervix, 1 thyroid and 1 thymic cancer). PsPD patients had a median PFS (until confirmed PD according to iRECIST) of 17.3 months (95% CI [8.4–N.R]) that was comparable to other responders patients PFS (median unreached 95% CI [13.8–N.R]); HR: 2.0, 95% CI [0.7–6.1]; p = 0.2). Dissociated responses (defined as a concomitant progressing and responding lesions) were reported for 4.2% of patients with a median PFS of 4.8 months (95% CI [0.0–15.6]) comparable to stable disease patients (median PFS 5.0 months 95%CI [4.3–6.4]; HR: 0.9, p = 0.6). Among the 203 patients who progressed at first evaluation, 139 (68%) were withdrawn from the phase I study at first assessment, whereas 64 (32%) continued ICT mAb and underwent another CT scan evaluation one-month later.

Conclusions: We showed a low rate of PsPD and dissociated response in a large cohort of patients excluding melanoma. Using iRECIST, 32% of progressing patients underwent another CT scan at one month confirming PD, which may delay the initiation of a new regimen. This work suggests that prognosis or on-treatment biomarkers are needed to identify early patients who should (or not) continue ICI treatment once a first progression is evidenced.

Legal entity responsible for the study: Gustave Roussy.

Funding: Has not received any funding.


### 1175P Prognostic value of response according to tumour growth rate in a phase I trial on vaccine therapy

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Background: Vaccine therapy INVAC-1 (a DNA vaccine encoding human telomerase reverse transcriptase (HTERT)), is a new class of anti-cancer agents and was evaluated in a Phase I trial (INVAC1-CT-101 study) in patients with advanced cancer. We propose to study tumour patterns of response on imaging evaluations of patients under vaccine in a retrospective CT study.

Methods: The tumour growth rate (TGR) of the tumour burden (sum of lesions) was calculated before and during therapy. Patients with decrease of the TGR after initiation of therapy were considered responders whereas patients with stability or increase of the TGR were considered non responders. Overall survival (OS) and response according to anatomical location were also analysed.

Results: 1019 patients were responders according to the tumour growth rate. The median [IQR] of OS was 9.6 month [6.8, 13.3] versus 5.3 month [5.1, 15.0] for non-responders (p = 1.3;10^-5). Regarding organ sensitivity to vaccine therapy, we observed that none of the liver metastases responded to treatment, whereas the majority of lymph node lesions responded.

Conclusions: The decrease of the tumour growth rate in patients treated by vaccine therapy INVAC-1 could predict a benefit in terms of overall survival. The efficiency could vary depending on the location of the metastases.

Legal entity responsible for the study: Invercys.

Funding: Invercys.

Disclosure: R. Defrance, T. Huet, D.P. Pierre, V. Doppler: Salaried: Invercys. L. Fournier: Funded: Invercys; Speaker fees: Novartis, Merck, Pfizer. All other authors have declared no conflicts of interest.
Background: Despite current treatment options in multiple myeloma (MM), most patients acquire resistance to therapy and relapse. As MM remains incurable, novel therapies are needed. A potentially promising approach is immunostimulatory therapy via an armed oncolytic adenovirus. The herein investigated LOAd viruses are serotype Ad5/35 chimera and therefore infect cells via CD46, which is often upregulated in MM. Viral replication is restricted to tumor cells due to a deletion in E1A. LOAd viruses express transgenes under the control of a CMV promoter. LOAd703 encodes for trimetric membrane-bound (TMZ) CD40L and 4-1BBL, whereas LOAd713 carries a gene encoding a single chain fragment against the IL-6 receptor in combination with TMZ-CD40L. IL-6 is identified as an essential growth and survival factor in MM. Hence, LOAd713 therapy may be of special interest as it not only induces immune cell activation via TMZ-CD40L but also blocks IL-6R signaling.

Methods: A panel of MM cell lines (ANBL-6, L363, LP-1, OPM-1, RPMI-8226, U266-B) were infected with LOAd viruses. Viral replication was evaluated with qPCR detecting viral DNA and viability was analyzed by flow cytometry. Surface expression of TMZ-CD40L, 4-1BBL and markers for an immunogenic phenotype were analyzed by flow cytometry. Cell culture supernatants were investigated by multiplex analysis.

Results: All MM cell lines were sensitive to LOAd infection, leading to viral replication and decreased viability. TMZ-CD40L and 4-1BBL were expressed in all cells infected with the respective viruses carrying the transgenes. LOAd infection induced an immunogenic phenotype with the upregulation of molecules that facilitate recognition and killing by the immune system. These included CD40, 4-1BB, Fas, HLA-DR, CD80 and CD96. In the supernatants of infected cells, the pro-inflammatory cytokine MIP-1α was increased in 4/6 cell lines. The suggested MM growth factor MCP-1 as well as sIL-2R were decreased in 3/6 cell lines.

Conclusions: LOAd viruses infected and replicated in MM cells. The encoding transgenes induced transgene expression and subsequently an immunogenic phenotype in infected cells. Immunostimulatory oncolytic LOAd viruses may be an attractive approach for MM therapy.

Legal entity responsible for the study: Upstate University, Department of Immunology, Genetics and Pathology, Loskog group.

Funding: The Swedish Cancer Society, The Swedish Research Council, Lokon Pharma AB

Disclosure: A. Loskog: CEO, board member, royalty agreement, research grant: Lokon Pharma AB; Advisor: Nexttobe AB; Board member: Hansa Medical, Bioimics; Chairman: Repovs Pharma, Vivolux; Royalty agreement: Alligator Bioscience. All other authors have declared no conflicts of interest.

Humanized knock-in mouse models for evaluating in vivo efficacy of immune-oncology drugs targeting stimulatory immune checkpoint molecules

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Background: Cancer immunotherapy is one of the most promising research areas in the field of cancer therapy. Many pharmaceutical and biotech companies in the world are devoting great effort to develop cancer immunity-related treated drugs. However, along the IO drug development process, in vivo efficacy models have always been a rate-limiting step.

Methods: In most cases, a human monoclonal antibody does not have mouse cross-reactivity. Mouse surrogate antibodies were often used in immune-competent syngeneic mouse models to evaluate in vivo efficacy of IO drugs. However, the efficacy of a surrogate antibody cannot fully represent the human drug in the clinical scenario. Therefore, we generated humanized knock-in mice to evaluate the in vivo efficacy of human IO antibodies.

Results: For example, human 4-1BB knock-in (B-h4-1BB) mice were generated with a chimera: 4-1BB receptor, which is recognized by stimulatory human 4-1BB antibodies. Additionally, more knock-in mice targeting stimulatory immune checkpoint molecules were developed and validated, such as B-hCD27, B-hCD40, B-hOX40, B-hGITR, B-hCD28, B-hICD28, etc.

Conclusions: All these mouse models respond well to the corresponding human IO antibodies, proving that they are powerful tools that can be used with purpose to conduct in vivo flow cytometry and human immunostimulatory immune checkpoint antibodies.

Legal entity responsible for the study: Beijing Biocytogen Co., Ltd.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1178P Tackling fraticide to manufacture clinical grade NKGD2-CAR T cells for cancer therapy

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Background: T cells bearing a chimeric antigen receptor (CAR) T-cell consisting of the fusion of the NKGD2 NK receptor with the intracellular domain of CD3eta (CYAD-01) can recognize eight stress ligands expressed in a large variety of cancers. However, activated T cells undergo stress and transiently express NKGD2 ligands (NKGD2L). Consequently, CYAD-01 T cells kill sister cells preventing the large-scale manufacturing of CYAD-01 for clinical application.

Methods: Inclusion of the PI-3K inhibitor LY294002 into the manufacturing process was the first strategy used as an initial effort focused upon blunting the activity of the CAR T cells. We subsequently developed a process that included a NKGD2 blocking antibody during the expansion phase of cell culture.

Results: LY294002 was shown to reversibly reduce NKGD2 expression at the cell surface. Consequently, this inhibitor partially controlled fraticide during manufacturing and enhanced viability post-thawing which enabled the initiation of the THINK (NCT03014801) clinical trial. As the trial moved through the dose-escalation phase towards the upper dose level (production of more than 10^9 cells), there was an increase in the level of manufacturing failures. This was largely linked to the effect of LY294002 upon T cell proliferation and the challenge faced manufacturing CAR T cells from patients with advanced cancer. Therefore, we subsequently developed a process that included a NKGD2 blocking antibody during the expansion phase of cell culture. This strategy enabled the expansion of CYAD-01 T cells to the levels required for the THINK clinical trial. After fine tuning the process, the CYAD-01 CAR T cells generated showed high comparability to the CYAD-01 CAR T cells produced in the first part of the trial. This process has been in place for the THINK trial since January 2018.

Conclusions: Together, these results indicate that when fraticide is an issue preventing clinical development, CAR T cells can be efficiently manufactured through PI-3K inhibition and antibody mediated receptor blockade.

Legal entity responsible for the study: Celyad SA.

Funding: Has not received any funding.


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Background: The NKGD2 receptor is a type II transmembrane glycoprotein playing an important role in anti-tumor responses. In humans, NKGD2 binds to eight ligands, MHCC class I-related chain MICA and B and unique long (UL16) binding proteins ULBP 1-6. The surface expression of NKGD2 ligands (NKGD2L) is highly regulated to avoid inappropriate immune responses in physiological conditions but is induced by various stress situations such as malignant transformation or inflammation. NKGD2L expression on tumors has been reported in the literature. However, a systematic study on all NKGD2L in a large array of normal tissues and tumor samples is lacking. Celyad is pursuing the clinical development of NKGD2 based chimeric antigen receptor (CAR) T cell therapy and robust data are thus required to adequately support this work.

Methods: We performed an extensive immunohistochemistry study on primary tumors and normal adjacent tissues from patients suffering from pancreatic, breast, ovarian, bladder, colorectal and lung carcinomas and on a series of normal tissues from non-cancer patients.

Results: NKGD2B were the most frequently and highly expressed. Interestingly the subset of triple negative breast cancers (TNBC) showed strong membranous staining for all NKGD2L on tumor cells making this patient subpopulation a very attractive therapeutics target for NKGD2-based therapies. There was no clear correlation between the expression of NKGD2L and the clinical stage of the tumors indicating that every stage of the disease could be targeted. In bladder, TNBC, CRC and pancreatic tumors, tumor cells were frequently stained for multiple NKGD2L implying that these tumors would not be susceptible to immune escape. Tumor-associated fibrovascular structures displayed generally membranous staining within the endothelial compartment suggesting that NKGD2-based CAR T therapy can target simultaneously both the tumor and the tumor microenvironment.

Conclusions: In conclusion, this extensive immunohistochemistry study supports the concept of targeting NKGD2L for cancer therapy.

Legal entity responsible for the study: Celyad SA.

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1180P  
Combination of pegilodecakin and docetaxel shows synergy in tumor rejection in immune resistant TNBC model

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Background: Immune checkpoint inhibitors (ICI) induce durable tumor responses and increased overall survival (OS) of cancer patients. Patients with low PD-L1, low tumor mutational burden (TMB) or without intra-tumoral CD8+ T cells, have a poor response rate to ICIs. Pegilodecakin (AM0010) is a pegylated recombinant human interleukin-10, which overcomes tumor immune escape by stimulating the activation, survival and donor expansion of intra-tumoral, tumor antigen specific CD8+ T cells. Pegilodecakin up-regulates IFNγ in CD8+ T cells and MHC expression, which facilitates antigen presentation even in tumors with low CD8+ T cells and low TMB. Here we explore the combination of Pegilodecakin with SOC docetaxel in an ICI resistant mouse triple negative breast cancer model.

Methods: 4T1 cells were established SC for two weeks prior to treatment. Pegilodecakin was administered at suboptimal doses, docetaxel was dosed at the MTD. Quantification of T cell infiltration and tumor cell death was quantified by IHC. Intra-tumoral and systemic cytokine and T cell activity were evaluated.

Results: Docetaxel did not induce regressions but inhibited tumor growth by 65%. Pegilodecakin alone induced tumor growth inhibition and delayed tumor regression in 75% of mice with an 80% reduction in tumor volume. Pegilodecakin + docetaxel led to a synergistic tumor control and complete responses in 75% of mice. While pegilodecakin induced T cell infiltration and tumor cell apoptosis with 95% of the measurable tumor being reduced to scar tissue, the tumor size initially continued to increase, indicative of pseudo-progression. In contrast, Pegilodecakin / docetaxel therapy led to a complete eradication of the tumor without pseudoprogression.

Conclusions: The determination of clinical efficacy of immune therapy can be difficult due to delayed immune responses and pseudoprogression related to immune effector cell infiltration. Here we show that largely necrotic tumors on pegilodecakin may have a delayed clearance despite overwhelming anti-tumor efficacy. The combination of immunotherapy with chemotherapy may facilitate clearance of the necrotic tumor mass leading to complete responses of measurable tumor burden.

Legal entity responsible for the study: ARMO BioSciences.

Funding: ARMO BioSciences.


1181P  
Mutations in interferon gamma and antigen presentation pathways are frequent in hyper/ultra-mutated (HiMut) tumors and could be relevant for tumor immune-editing processes in HiMut tumors

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Background: Tumors with a phenotype associated with a high mutational load such as POLE-mutated or those showing microsatellite instability (MSI) are more likely to have clinical responses to immune-checkpoints blockade therapy. Indeed, several clinical trials are currently on-going targeting PD-1 in a variety of cancer types. However, some of these patients do not respond to immunotherapy. Recently, mutations in JAK1 and JAK2 has been reported to be responsible for this resistance.

Methods: Here we explore the effect of functional mutations in genes in the interferon gamma (IFG) signaling and antigen presentation (AP) pathway in endometrial, colorectal, and gastric POLE-mutated and MSI tumors extracted from TCGA.

Results: As a result, we have found that POLE-MSI tumors accumulated more mutations in IFG and AP pathways than randomly expected. Using gene expression data, we corroborated that IFN pathway is under-expressed in IGAFP mutant tumors. MSI IGF/AP mutant tumors over-express T cell receptor pathway probably as a compensatory mechanism.

Moreover, when cell infiltration was assessed, these tumors have a tendency to present higher levels of cytotoxic lymphocytes than non-mutated tumors. However, they showed over-expression of pathways related to anti-PD1 resistance such as epithelial to mesenchymal transition or angiogenesis. These results suggest that despite being infiltrated, IGAFP mutant tumors are able to evade immune surveillance.

Regarding survival, although overall these tumors have a very good prognosis, we observed that IGAFP mutated endometrial tumors showed higher clinical grade than the non-mutated ones.

Conclusions: Based on these results, we show that regardless of cancer type, HiMut tumors with functional mutations in IFG and AP pathways shows a more aggressive phenotype, and present activation of cellular processes that have been related to immune-resistance, probably to evade destruction by a very active T-cell stroma due to the high amount of neoantigens. This phenotype is even more evident in ultra-mutated POLE tumors. Therefore, HiMut tumors could be exploited as a surrogate to understand mechanisms of immune-resistance.

Legal entity responsible for the study: Tomás Kirchhoff.

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1182P  
Anti-CTLA4 toxicity associates with genetic variation correlating with serum antibody diversity


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Background: While anti-CTLA4 immunotherapy (IT) improves survival in metastatic melanoma patients, it manifests with severe toxicity. Recently, we identified serum antibody signatures associated with toxicity outcomes following anti-CTLA4 IT. In this study, capitalizing on our recent data showing that the expression of autoimmunity risk genes is controlled by germline genetic variation in melanoma survival, we tested whether antibody profiles linked with IT-related toxicity are impacted by underlying genetic variation.

Methods: We have integrated serum data from 37 anti-CTLA4 IT-treated patients, profiled by HuProt human proteome array with germline whole-exome sequencing (WXS), comparing 28 patients with none/mild toxicity (CTCAE score 0-2) and 9 patients with severe toxicity (CTCAE score 3-5). The associations between toxicity and germline genetic variation were assessed by gene-burden analysis (SKAT). SKAT was integrated with differential proteome analysis of toxicity to identify individual proteins coded by genes and/or pathway enrichment putatively controlled by genetic variation associated with anti-CTLA4 related toxicity.

Results: The proteomic analysis identified 915 proteins that were differentially expressed (p < 0.05) in non/mild versus severe toxicity outcomes in anti-CTLA4 IT. SKAT analysis of genetic variation identified 1947 significant genes (p < 0.05) associated with toxicity, of which 78 were also significant (p < 0.05) in the proteome analysis. The functional pathway analysis of 78 proteins showed enrichment for the regulation of interferon production, and a significant enrichment was observed for molecular pathways involved in autoimmunity.

Conclusions: We present a novel framework integrating germline genetic information and serum protein expression levels to identify associations with toxicity in anti-CTLA4 IT. We found enrichment for interferon production and pathways involved in autoimmunity controlled by genetic variation. The data strongly support the importance of genetic variation in immune system regulation and its effect on IT-related toxicity.

The effect of genetic variants on protein expression is currently further tested in the context of toxicity response to IT treatment.

Legal entity responsible for the study: Tomas Kirchhoff.

Funding: NIH.

Disclosure: S. Hu: Scientist at CDB laboratories. J.S. Weber: Consulting or advisory role: Celldex, Ichor Medical Systems, Cam Biotherapeutics, Lion Biotechnologies, Pieris Pharmaceuticals, Altor BioScience, Bristol Myers Squibb, Merck, Genentech, Roche, Amgen, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, Abvive, Eisai, Cytox Therapeutics, Nektar, Novartis, Medivation, Selas Life Sciences, WindMILL, Stock and ownership options. Altor BioScience, Celldex, Cytox Therapeutics, Biond. All other authors have declared no conflicts of interest.

1183P  
PD-L1 expression is strongly associated with TIGIT, FOXP3 and LAG3 across advanced cancers, but not OX40, TIM3 and IDO


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Background: Multiple trials are ongoing to evaluate combinations of immune checkpoint inhibitors (ICIs) across a variety of tumor types. Most of these studies utilize programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors as a backbone. We interrogate the relationship of PD-L1 with other immune checkpoints to inform rational combination strategies.

Methods: We performed whole transcriptomic sequencing (RNA-Seq; ~200x106 reads/tumor) across 1,467 unselected advanced cases (NantHealth, Calver City, CA). Cases reflected 38 distinct histologies; the most common histologies were breast (17.8%), colon (9.5%) and lung (7.9%). High and low PD-L1 was delineated as the top
Pharmacodynamic (PD) changes in tumors and peripheral blood T cell receptor (TCR) repertoire in a phase I study combining OX40 (PF-04518600) and 4-1BB (utomilumab) agonistic monoclonal antibodies (mAbs)


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Background: PF-04518600 (OX40) and utomilumab (uto) are human IgG2 agonistic mAbs against the tumor necrosis factor superfamily receptors OX40 and 4-1BB, respectively. Both receptors play key roles in T cell survival, proliferation, and activation. PF-8600 has been shown to increase proliferation and activation of peripheral CD4 memory T cells and uto has a similar effect on CD8 memory T cells. Previous in vivo studies with PF-8600 and uto have demonstrated great success in stimulating anti-tumor T cell immunity in a wide variety of cancers, immunity has had very limited success in pancreatic cancer patients. PDAC is characterized by a highly immunosuppressive tumor microenvironment (TME), dominated by Myeloid Derived Suppressor Cells (MDSCs). Type 2 Tumor-Associated Macrophages (M2 TAMs), and T regulatory cells (Tregs). While the presence of these cell types in the PDAC TME is well characterized, much still remains to be understood about how they function within the TME and how they co-operate with each other and tumor-resident lymphocytes to regulate antitumor immunity.

Methods: Paired biopsy samples at baseline and week 6 were collected from 5 dose cohorts (0.1/20, 0.3/20, 0.5/10, 1.0/10, 3.0/10) of PF-8600 in mg/kg (fat dose of uto in mg/kg) during dose escalation. Biopsy tissues were analyzed by IFHC and RNAseq to evaluate the PD effects of PF-8600 + uto. CD3, CD8, CD45RO, and FoxP3 expression was measured by IHC. Changes in transcriptional profile were measured by RNAseq analysis and gene ranking-based gene set enrichment analysis. CD4/8 T cell populations were isolated from blood samples at the same time points. DNA was extracted and submitted for high-throughput sequencing of TCR.

Results: In an analysis of paired biopsy samples from dose cohorts including > 0.3 mg/kg PF-8600, OX40 was among the genes that showed increased expression. The top gene sets including significant enrichment by RNAseq were associated with immune activation. TCR sequencing revealed clonal expansion of CD4/8 T cells at all dose levels.

Conclusions: Increases in immune-related markers including OX40 and enrichment of gene sets associated with immune activation were observed in tumor tissue, providing evidence of an active, immunomodulatory mechanism for PF-8600 + uto. Peripheral CD4/8 T cell populations exhibited clonal expansion at all dose levels, further suggesting an immune-activating PD effect. Further evaluation of PF-8600 + uto safety, efficacy, and PD continues in NSCLC and melanoma cohorts.

1184P

# Using MultiOmyx™ to analyze correlations between immunosuppressive cells and tumor-infiltrating lymphocytes in the pancreatic tumor microenvironment


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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive forms of cancer with a five-year survival rate that has remained below 10% for the past two decades. While immunotherapy-based treatment in recent years has demonstrated great success in stimulating anti-tumor T cell immunity in a wide variety of cancers, immunity has had very limited success in pancreatic cancer patients. PDAC is characterized by a highly immunosuppressive tumor microenvironment (TME), dominated by Myeloid Derived Suppressor Cells (MDSCs), Type 2 Tumor-Associated Macrophages (M2 TAMs), and T regulatory cells (Tregs). While the presence of these cell types in the PDAC TME is well characterized, much still remains to be understood about how they function within the TME and how they co-operate with each other and tumor-resident lymphocytes to regulate antitumor immunity.

Methods: MultiOmyx™, a novel hyperplexed multi “omic” technology, enables visualization and characterization of multiple biomarkers on a single 4 μm tissue section. MultiOmyx protein immunofluorescence (IF) assays utilize a pair of directly conjugated Cyanine dye-labeled (Cy5, Cy3) antibodies per round of staining. Each round of staining is imaged and followed by novel dye inactivation chemistry, enabling repeated rounds of staining and deactivation for up to 60 protein biomarkers. In this study, MultiOmyx hyperplexed IF assay was utilized to measure CD11b, CD14, CD4, CD16, CD33, CD45RO, CD68, CD163, FoxP3, HLA-DR, Arginase1, PD-L1, PD-L2, granzymeM, Ki67, and PanCK protein expression from a single 4 μm FFPE section.

Results: Using the MultiOmyx™ multiplexing assay in combination with proprietary algorithms for specific biomarker classification, we will report on the correlation between the presence of monocytic MDSCs (CD11b+CD33+CD14+CD15-HLA-DR-), granulocytic MDSCs (CD11b+CD33+CD15-HLA-DR-), M2 TAMs (CD68+CD163+), Tregs (CD3+CD4+FoxP3+) and the activation state of TILs, as well as their spatial relationship in tumor tissue from patients with PDAC.

Conclusions: Using the MultiOmyx™ multiplexing assay will allow us to analyze correlations between immunosuppressive cells and TILs in the pancreatic TME.

Legal entity responsible for the study: NeoGenomics

Funding: NeoGenomics, a Pharma and Clinical services company.

Background: S-588410 is a cancer vaccine peptide composed of 5 HLA-A*2402-restricted peptides derived from 5 cancer-testis antigens, DEPDGC1, MPFHSPH1, URLC10, CDCA1, and KOC1, all of which have been found to be upregulated in esophageal cancer patients. The aim of this study is to evaluate the effects of S-588410 on the number of tumor-infiltrating CD8-positive lymphocytes (TIL and PD-L1 expression) in the tumor tissue before and after the short-term treatment with S-588410 in the pre-surgical treatment.

Methods: HLA-A*2402-positive patients (pts) with esophageal cancer who can start the treatment more than 30 days prior to the surgery were eligible. S-588410 was injected subcutaneously once weekly, 5 times or more in total. Tumor tissues of pre- and post-treatment were collected for immunohistochemistry (IHC) analysis for target antigens, CD8, PD-L1 and HLA class I. Peptide-specific CTLs in PBMC were evaluated using ELISPOT assay.

Results: As of April 13, 2018, total 15 pts were enrolled and tumor tissues of the first half of the pts 8 pts were analyzed. 8 pts received 3 to 6 injections of S-588410. All 5 antigens and HLA class I on tumor tissues were detected in all pts except for one whose tumor expressed 4 target antigens. CTL activity circulating in blood markedly increased in all pts at least for 1 of 5 peptides. IHC analysis demonstrated that TIL density and PD-L1 expression on post-treatment tissues clearly increased compared to the baseline; CD8 TIL density at baseline was <1% in 5 pts and 1%-10% in 3 pts and that for post-treatment 1%-10% in 2 pts, 10%-30% in 6 pts, and PD-L1 expression at base line was ≤1% in 7 pts and 1%-5% in one patient and that for post-treatment was ≤1% in one patient, 1%-5% in 4 pts and 5%-30% in 3 pts.

Conclusions: The short-term treatment with S-588410 generated peptide-specific CTL and markedly increased CD8 TIL density and PD-L1 expression on tumor tissue of esophageal cancer pts. These interim results suggest that the combination of S-588410 with anti- PD-1/PD-L1 antibody is expected to be more effective than monotherapy, particularly in pts with low TIL/PD-L1 status.

Clinical trial identification: UMIN000023324.

Legal entity responsible for the study: Shionogi & Co., Ltd.

Funding: Shionogi & Co., Ltd.


1187P Clinical implication of PD-L1 expression and TILs in male breast cancer: More hype or new hope? Results from the UMBREAC trial (NCT03240510)

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Background: Whether PD-L1 or TILs have any indication for prognosis in male breast cancer (MBC) patients remains unknown. In this study, we investigated the relationship between the expression and degree of PD-L1 and TILs and evaluated the prognostic value of these factors in MBC.

Methods: We retrospectively identified 150 MBC patients diagnosed between 2003 and 2013 at Salah Azaiez Cancer Institute. PD-L1, Stromal (str) CD8+ and CD4+ TILs were evaluated immunohistochemically. TILs levels were evaluated following 2014 International TIL Working Group guidelines.

Results: Fifty three percent of MBC patients had low str-CD8+ and 47% had moderate str-CD4+. No lymphocyte predominant breast cancer was identified. Only 12% of MBC patients had high str-CD8+ TILs and 11% had high str-CD4+ TILs. TNBC subtype and HER2 enriched tumors had higher median levels of str-CD8+ TILs, str-CD4+ TILs and str-TILs at diagnosis. On univariate analysis, higher levels of str-CD8+ TILs, str-CD4+ TILs and str-TILs were associated with better OS (p = 0.035, p = 0.043 and p = 0.040, respectively). Multivariate analysis identified str-CD8+ TILs and str-TILs as independent prognostic factors for OS (HR = 0.851 [0.706-0.997], p = 0.000) and HR = 0.69 [0.435-0.960], p = 0.043) respectively. High expression of PD-L1 was observed in 64.5% of MBC samples. Patients with high PD-L1 expression had significantly shorter overall survival (OS) than patients with low expression (p = 0.002, hazard ratio HR = 5 [2.624–10.642]). Multivariate analysis identified PD-L1 as independent prognostic factor for OS (p < 0.001, HR = 0.775 [0.680-0.870]).

Conclusions: PD-L1 expression, Str-CD8+ T cells and str-TILs represents promising novel biomarkers with prognostic significance in MBC. Thus, successful inclusion of these markers in prognostic clinical models is becoming a realistic hope in MBC.

Clinical trial identification: NCT03240510.

Legal entity responsible for the study: Institut Salah Azaiez.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1188P Identification of prognostic and predictive factors for durvalumab efficacy by modeling of tumor response and overall survival (OS) in patients with late-stage non-small cell lung cancer (NSCLC)

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Background: Durvalumab, a human anti–PD-L1 mAb, is currently approved for treatment of patients with Stage III unresctable NSCLC. The objectives of this analysis were to identify prognostic and predictive factors for tumor growth and shrinkage, as well as for OS in NSCLC patients treated with durvalumab.

Methods: Longitudinal tumor size (TS) and OS data obtained from NSCLC patients in Study 1108 (all comers) and ATLANTIC (Stage III and above) who received durvalumab were analyzed using a nonlinear mixed effect model that describes the growth and regression of sensitive and insensitive tumor cells, as well as delay in immune response relative to tumor killing. A linked OS-dropout model was developed by relating model-predicted tumor changes to OS and dropout probability over time. Potential prognostic and predictive factors were evaluated in a multivariate covariate analysis using the models.

Results: The longitudinal TS and OS data from NSCLC patients in both studies are generally well described by the models. Liver metastasis, neutrophil-to-lymphocyte ratio (NLR), EGFR mutation, and durvalumab clearance (CL) are identified as prognostic factors for tumor growth, and tumor cell PD-L1 expression (TC) and baseline tumor size as predictive factors for tumor killing (p < 0.01). The significant factors for OS after accounting for the tumor size changes included TC and immune cell PD-L1 expression (IC), NLR, lactate dehydrogenase, as well as CL (p < 0.01). Among all factors tested, NLR is the most influential factor on the predicted 1-year survival rates (~60% vs. 30% with NLR below and above the median [4.56]). Positive PD-L1 expression (TC or IC ≥ 25%) is predicted to result in ~10-20% increase in one-year survival rates. Increasing the cutoff value is not predicted to result in substantially greater improvement in the survival rate.

Conclusions: The modeling results provided quantitative assessments of the impact of various prognostic and predictive factors, as well as biomarker cutoff values on the efficacy of durvalumab in NSCLC patients, and can be used to inform patient selection criteria in future monotherapy or combination studies.

Clinical trial identification: NCT01693562.

Legal entity responsible for the study: MedImmune, LLC.

Funding: MedImmune.


1189P Intrinsically and extrinsically regulated expression of PD-L2 expression by transcription factor STAT3 or c-FOS in oncogene-driven non-small cell lung cancer

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Background: Treatment with antibodies that target programmed cell death 1 (PD-1) or its ligand programmed death ligand 1 (PD-L1) has demonstrated durable efficacy for various malignant tumors. Programmed death ligand 2 (PD-L2), which is another ligand for PD-1, has recently been shown to be implicated in tumor immune escape. The regulation of PD-L2 expression in tumor cells has remained unclear, however. We here examined intrinsically and extrinsically regulated expression of PD-L2 expression in NSCLC.
Methods: PD-L2 expression was evaluated by reverse transcription and real-time polymerase chain reaction analysis and by flow cytometry.

Results: BEAS-2B cells stably expressing an activated mutant form of the epidermal growth factor receptor (EGFR) or the EML4-ALK fusion oncogene manifested increased expression of PD-L2 at both mRNA and protein levels. Furthermore, treatment of NSCLC cell lines that harbor such driver oncogenes with corresponding EGFR or ALK tyrosine kinase inhibitors or depletion of EGFR or ALK by siRNA transfection suppressed expression of PD-L2, demonstrating that activating EGFR mutations or EML4-ALK fusion intrinsically induce PD-L2 expression. We also found that interferon-γ extrinsically induced expression of PD-L2 via STAT1 signaling in NSCLC cells. Oncogene-driven expression of PD-L2 in NSCLC cells was inhibited by knockdown of the transcription factors STAT3 or c-FOS. Interferon-γ also activated STAT3 and c-FOS. Knockdown of STAT3 or c-FOS decreased Interferon-γ-induced expression of PD-L2, suggesting that these proteins may also contribute to the extrinsic induction of PD-L2 expression.

Conclusions: Expression of PD-L2 is induced intrinsically by activating EGFR mutations or EML4-ALK fusion as well as extrinsically by interferon-γ, with STAT3 and c-FOS possibly contributing to both intrinsic and extrinsic pathways. Our results thus provide insight into the complexity of tumor immune escape in NSCLC.

Legal entity responsible for the study: an individual person.

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Disclosure: K. Azuma: Personal fees: AstraZeneca; Grants and personal fees: Boehringer Ingelheim, Ono Pharmaceutical, MSD Oncology, Bristol-Myers Squibb, and Chugai Pharma. I. Okamoto: Grants and personal fees: AstraZeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, MSD Oncology, L. C. Myers Squibb, Chugai Pharma, GSK, Astellas Pharma Novartis, Personal fees: Pfizer outside the submitted work. All other authors have declared no conflicts of interest.

1190P Microsatellite instability detection by targeted sequencing of cell-free DNA


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Background: Microsatellite instability (MSI) is a guideline-recommended biomarker used in assessment of prognosis and treatment choices, including checkpoint inhibitors recently approved for cancers with MSI-high (MSI-H) status. Plasma-based next generation DNA sequencing (NGS) tests are increasingly used for comprehensive genomic profiling of cancer; however, sensitive methods to detect MSI status from cell-free DNA (cfDNA) are not available for clinical patient care. Additionally, the impact of variable tumor shedding on MSI detection has not been evaluated.

Methods: We developed an accurate method to assess MSI status using targeted sequencing of cfDNA using the Guardant360© clinical platform across a many cancer types and a broad range of simple repeats. For each microsatellite locus, the number of differently-sized repeats in experimental samples is quantitated using a probabilistic log-likelihood-based score designed to accurately discriminate biological signal derived from cfDNA fragments of somatic origin from noise arising from technical artifacts. Loci are considered unstable if the likelihood score is greater than a threshold computed from a cohort of normal samples. MSI status of a sample is determined by the presence of a minimum 5 unstable microsatellite loci among the 91 scored.

Results: We simulated MSI high (MSI-H) samples across a range of tumor fractions by combining data from 82 healthy donor samples with in silico spike-ins of differentially sized repeats. Simulated data demonstrates a sensitivity of 94% at 0.2% (limit of detection) tumor content for an expected specificity of 99.9% estimated from healthy donor samples. When applied to a prospective test set of 134 advanced cancer samples, this method demonstrated 98.3% (125/127) specificity and 86% sensitivity (67/76) relative to standard tissue PCR-based MSI assessment across a cfDNA range of 0.1%-15%.

Conclusions: Targeted sequencing of cfDNA can enable highly accurate detection of MSI in cancer samples, even for samples with low tumor shedding. This novel approach enables non-invasive assessment of MSI status concurrent with comprehensive genomic profiling and allows potential access to immunotherapies for patients whose tumor types are not routinely tested for MSI.

Legal entity responsible for the study: Guardant Health, Inc.

Funding: Guardant Health, Inc.


1191P Immune checkpoints and T-lymphocytes as immunotherapeutic target in the treatment of sebaceous gland carcinoma

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Background: Immune checkpoint blockade strategies have gained attention in the treatment/prognosis of cancers via targeting the PD-1/PD-L1 pathway or in combination with the CTLA-4 blockade and are currently in clinical trials. The present study investigated the expression of PD-1, PD-L1, CTLA-4, CD4 and CD8 proteins and their prognostic value in the tumor microenvironment of sebaceous gland carcinoma patients (SGC).

Methods: Stromal and tumor cells expressing PD-1, PD-L1, CTLA-4, CD4 and CD8 protein were assessed in 52 cases of sebaceous gland carcinoma by Immunohistochemistry and their mRNA expression was measured by quantitative Reverse-Transcriptase PCR (qRT-PCR). Kaplan–Meier curves and Cox proportional hazard models, analyzed the correlation of proteins with clinicopathological parameters and disease-free survival.

Results: Pagetoid spread was the frequent histopathological high-risk factor in our study. Expression of PD-L1 was found to be more common in tumor cells than stromal cells. In univariate analysis, patients expressing PD-1 and PD-L1 in tumor cells were associated with reduced disease-free survival, whereas stromal-PD-L1 showed an increased survival of the patients (p < 0.05). However, in multivariate analysis, expression of PD-1 in tumor cells was found to be an independent prognostic factor for poor survival.

Conclusions: This is the first report describing the association of clinicopathological features and outcomes of immune checkpoint expression along with T-lymphocytes in sebaceous gland carcinoma. These results support the consideration that PD-1/PD-L1 pathway might play an important role in tumor microenvironment for mediating immune response in the pathogenesis of sebaceous gland carcinoma patients.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1192P Evaluation of OX40 receptor density, influence of IgG Isotype and dosing paradigm in anti-OX40-mediated efficacy and biomarker responses with PD-1 blockade

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Background: GS1374998 is an agonistic IgG1-anti-OX40 (aOX40) monoclonal antibody (mAb) that binds to OX40 receptors expressed on activated T cells. GS1374998 engages the immune system via several T cell-mediated pathways. The following studies examine 1) OX40 receptor expression and enumeration in T cell populations in patient tumors 2) influence of IgG isotype on GS1374998-mediated FcγRIIa engagement 3) dosage regimen effects on efficacy and pharmacodynamic response with the anti-OX40 anti-PD-1 (aPD-1) combination in preclinical models.

Methods: In vitro, an FcγRIIa reporter assay was used to compare GS1374998 with other IgG isotype variants and its combination with pembrolizumab. In vivo studies were performed to evaluate tumor growth and survival following concurrent and sequential dosing regimens of aOX40 ± aPD-1 in Abs. Biomarkers of response were monitored by flow cytometry, NanoString, TCRB sequencing and multiplex cytokine analysis.

Results: OX40 receptor density was observed as highest on intra-tumoral Tregs (compared to CD4 effectors and CD8 + T cells) in several primary tumor samples. FcγRIIa engagement correlated strongly with receptor density and was dependent on an IgG1 wild type Fc isotype. GS1374998 in combination with pembrolizumab increased inflammatory and Th1 cytokine production in human PBMCs. In vivo studies suggest that concurrent dosing of aOX40 with aPD-1 offers superior anti-tumor efficacy and survival compared to sequential regimens. Furthermore, combination with aPD-1 led to enhanced expression of inflammatory and Th1 cytokines, increased T cell activation, proliferation and cytotoxicity compared to either monotherapy. Concurrent treatment also significantly increased T cell clonal expansion in the periphery, increased clonality both in blood and tumor and induced migration of the expanded clones into the tumors over monotherapy.

Conclusions: Overall, the combination of aOX40 and aPD-1 elicited stronger qualitative and quantitative changes in immune markers both in vitro and in vivo. The potential synergy of concurrent dosing formed the basis for combining GS1374998 with pembrolizumab in phase I/II clinical studies.

Legal entity responsible for the study: GlaxoSmithKline Inc.

Funding: Has not received any funding.
1193P Impact of tissue processing and interferents on the reproducibility and robustness of a multi-plex gene expression assay measuring tumor inflammation

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Background: The Tumor Inflammation Signature (TIS) is an investigational use RNA expression assay on the NanoString nCounter Dx Analysis System, which provides a measure of tumor inflammation across multiple solid tumor types. TIS measures immune genes in tumors from multiple origins, and it is possible that inclusion of tissue-specific interferents, such as non-tumor lymphoid aggregates (NTLA) could influence TIS performance. Here we describe the validation of the reproducibility of the TIS assay from FFPE tissues and robustness of the TIS across 8 potential tissue interferents.

Methods: TIS includes both review of an H&E tissue slide by a Pathologist and sample processing of unstained slides by an assay user. Analytical validation of the reproducibility of the TIS assay from 3 different Pathologists and 3 different assay users was performed using at least 10 patient specimens for 11 different tumor types (>110 independent tumors tested) from excisional and core biopsies. The robustness of the TIS assay to potential tissue interferents (genomic DNA, adjacent non-tumor tissue, NTLA, mucin, hemorrhagic, necrotic, and fibrotic tissue) was also assessed.

Results: The assay was validated to be reproducible with >95% concordance in assay results between independent pathologists. The total standard deviation of the TIS score was less than 2% of the score range from tissue including different pathology review and users. The interference studies demonstrated that the presence of mucin, necrotic, hemorrhagic and fibrotic tissue did not influence TIS results. However, if not properly removed, contamination with large concentrations of genomic DNA, non-tumor tissue, and NTLA can reduce biomarker concordance by increasing the TIS score.

Conclusions: The analytical performance of the NanoString TIS assay has been validated to be reproducible by users and pathologists when potential interferents are removed as instructed in the assay procedures. TIS is well suited for decentralized clinical and use as a potential biomarker to enrich for patients based on their tumor inflammation across multiple solid tumors.

Legal entity responsible for the study: NanoString Technologies, Inc.

Funding: NanoString Technologies, Inc.

Disclosure: E. Harris, N. Dowidar, A. Bergdahl, S. Ferree: Employee, Stockholder at the time of the publication.

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1194P Translational endpoints in patients with metastatic microsatellite unstable colorectal cancer (MSI-CRC) treated with durvalumab plus monalizumab (anti-NKG2A)

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Background: The safety and preliminary efficacy of this combination (NCT02671435) was previously reported (ASCO 2018). Here, we present the results of baseline and longitudinal pharmacodynamic biomarker assessments in peripheral blood and tumor in patients with MSI-CRC treated with Monalizumab plus Durvalumab.

Methods: Peripheral biomarkers evaluated included NKG2A receptor occupancy (RO), and frequency and functional status of immune cells (N = 23). In tumors, changes in NK and CD8+ T cells in pre-treatment biopsies were measured by immunohistochemistry (IHC) (N = 7). Gene expression profiling of tumors was determined by RNAseq in N = 15 pretreated and N = 4 paired biopsies.

Results: In peripheral blood, full and sustained NKG2A RO was detected. Expansion of activated or proliferating NK cells was detected in 14/23 and 10/20 patients respectively, while increases in T cell proliferation (Ki67+) were observed at levels expected for Durvalumab monotherapy (1.3-2.4-fold). In an in vitro assay system, similar changes on TNF-α cell phenotyping were observed upon exposure to Monalizumab and Durvalumab. No consistent pharmacodynamics changes in tumoral NK and CD8+ cells by gene expression or IHC were observed. However, modulation of pathways associated with metabolism, DNA repair and cell cycle were detected in tumors on treatment.

Conclusions: In peripheral blood, pharmacodynamic effects consistent with the proposed mechanism of action of Monalizumab and Durvalumab were observed in patients with MSI-CRC.

Clinical trial identification: NCT02671435; February 22, 2016.

Legal entity responsible for the study: MedImmune.

Funding: MedImmune.

Disclosure: N. Standifer, M.L. Ascencio, C. Morehouse, H. Ghadially, J. Rodriguez Canelo, M.C. Rebollota, X. Song, D.C. Jones, L.I. 1, S. Marshall, S. Abdullah, M. Jure-Kunkel: Employee. All other authors have declared no conflicts of interest.

1195P Alterations in peripheral T cell subsets, T cell activation markers and immune checkpoint molecules in advanced pancreatic cancer patients receiving FOLFRINOX or gemcitabine + nab-paclitaxel

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Background: Efforts to develop successful immunotherapeutic treatments in pancreatic cancer have failed so far. One possible strategy might be the combination of established chemotherapeutic regimens (FOLFRINOX or gemcitabine plus nab-paclitaxel [gem-nab-pac]) with checkpoint inhibitors. The goal of the present pilot study is to provide a better understanding of alterations in the expression of T cell activation markers and immune checkpoint molecules in patients with advanced pancreatic cancer receiving FOLFRINOX or gem/nab-pac.

Methods: We conducted a prospective single-center study with selected advanced pancreatic cancer patients who received FOLFRINOX or gem/nab-pac between 2015 and 2017. Blood samples (15 ml heparinized blood, 10 ml serum) were taken at day 1 and 30 of first-line chemotherapy. Flow cytometry was performed using a LSRII Fortessa flow cytometer (BD Biosciences). CD3+ CD4- T cells were counted as well as the expression of FOXP3, PD-1, CTLA4, CCR7, CD62L, CD69, Tim3 and Lag3 on CD3+ T cells was analyzed.

Results: 25 eligible patients were included in the study. Two consecutive blood samples were available for 21 of these patients (FOLFRINOX: n = 18, gem/nab-pac: n = 3). We found a broad variability within T cell subsets and change of expression in T cell activation immune checkpoint molecules during therapy. While the majority of patients (n = 13/21, 62%) is still in follow-up, first results indicate a correlation of an increase of FOXP3+ T cells in peripheral blood during chemotherapy and worse outcome. No correlation between increase of PD-1 on peripheral T cells and prognosis was observed.

Conclusions: A comprehensive RNA based (nanostring nCounter®) analysis of intratumoral immune cell infiltration of all included patients is currently ongoing. It will provide further insights on the interplay between tumoral and peripheral (T cell) immunity during chemotherapy in advanced pancreatic cancer.

Legal entity responsible for the study: Stefan Boeck.

Funding: Friedrich-Baur Stiftung.

Disclosure: All authors have declared no conflicts of interest.

1196P Resistance to anti-PD-1 therapy is associated with the retention of CCRX3+ CD4+ CD8- T cells in blood

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Background: Immune checkpoint blockade has received significant clinical efficacy in the past decade in many malignancies. However, both primary and acquired resistance becomes one of the major obstacles that cannot be ignored, which seriously limits its clinical efficacy. To predict immunotherapy efficacy remains challenging. Dynamic
Cerebrospinal fluid lymphocytosis: A hallmark of neurological immune related adverse events (irAEs) during checkpoint inhibitor treatment

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Background: Checkpoint inhibitors have reshaped the oncology landscape, but their toxicity and side effects are not well understood. Here, we report the neurological symptoms and cerebrospinal fluid (CSF) analysis in patients with lymphocytic CSF pleocytosis during checkpoint inhibitor treatment.

Methods: We conducted this meta-analysis on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement. Two reviews independently completed a search of PubMed and Web of Science to identify relevant clinical trials. The search was conducted using keywords “nivolumab”, “pembrolizumab”, “atezolizumab” and “immune checkpoint”. The search included randomized controlled trials (RCTs) published in English.

Results: Eleven eligible studies, including 5,663 patients, were included in this meta-analysis. In our analysis, PD-1/PD-L1 inhibitor was associated with a 31% reduction in the risk of death (HR = 0.69, 95%CI: 0.64-0.74; P < 0.00001). In subgroup analysis, patients got overall survival (OS) benefit from PD-1/PD-L1 inhibitors regardless of PD-L1 expression, and a dose effect relationship between expression of PD-L1 and OS benefit was observed (Interaction, P = 0.00001). Patients with smoking history achieved greater OS benefits (HR = 0.69, 95% CI: 0.61-0.77; P < 0.00001) than never smoker (HR = 0.88, 95% CI: 0.70-1.11; P = 0.28). Compared with second or later line treatment, there was better OS benefits in first line treatment subgroup (Interaction, P = 0.02). The OS benefits were similar according to age (Interaction, P = 0.74), sex (Interaction, P = 0.43), performance status (Interaction, P = 0.68), central nervous system (CNS) metastasis (Interaction, P = 0.59), tumor histology (Interaction, P = 0.64) and treatment type (Interaction, P = 0.36). Conclusions: These results suggest changes in the white cell subpopulation count in pts who experience irAEs. Further studies are needed to confirm our findings.
1200P Serum biomarkers during the first cycle of anti-PD-1 antibody therapies in non-small cell lung cancer

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Background: PD-1 blockade by anti-PD-1 antibodies restore the function of exhausted T cells and release perforin, granzyme B and cytokines which induce cytotoxic activity against tumor cells. We examined serum perforin, granzyme B and immune modulators as biomarkers of response to PD-1 blockade in non-small cell lung cancer (NSCLC) patients.

Methods: Advanced NSCLC patients treated with nivolumab or pembrolizumab were studied. Serum were collected on days 1, 2, 8, and 15 for nivolumab and on days 1, 2, 8, 15, and 22 for pembrolizumab. Concentration of perforin was determined by enzyme-linked immunosorbent assay (ELISA) and ten immune modulators, including granzyme B, were measured by a multiplex immunoassay. Best objective response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients were followed more than 3 months.

Results: Plasma samples were obtained from 29 patients with nivolumab and 18 patients with pembrolizumab. With nivolumab, in 57% of responding patients, there were two aspects, (i) baseline levels of perforin concentration were higher in responders than in non-responders, or (ii) a ratio of perforin concentration on day 2 to the baseline was elevated (≥1.2). With pembrolizumab, there were no significant differences in baseline concentration between responders and non-responders. If patients who passed more than 3 months, 96% had advanced disease. In the remaining 77%, MG manifested clinically only after initiation of CPI. In the remaining 77%, MG manifested clinically only after initiation of CPI. Overall, 38% developed respiratory failure requiring mechanical ventilation, including 8 pts who needed urgent intubation. MG symptoms occurred with other irAEs (myositis, myocardiitis, polyneuropathy, and Guillain Barré Syndrome) in 15%. Most pts required treatment with high dose corticosteroids (90%), intravenous immunoglobulin (45%), and plasmapheresis (42%). Other treatments included azathioprine, mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; 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most were maintained on corticosteroids, anticholinesterase, azathioprine, or mycophenolate mofetil, and only one had active disease symptoms of MG was reported in 23%; most were maintained on corticosteroids, anticholinesterase, azath...
**Methods:** Patients rechallenged after irAE grade ≥2 induced by anti-PD1/PDL1 and referred at the multidisciplinary board of committee of immune toxicity (ITOX) of Gustave Roussy between August 2015 and December 2017 were included in this study. **Results:** One hundred eighteen patients had a confirmed irAE. Median age was 62. Tumour types were melanoma (25.4%, n = 50), lung carcinoma (22.9%, n = 27), colorectal cancer (8.5%, n = 10), lymphoma (7.6%, n = 9), renal cell carcinoma (7.6%, n = 9), urothelial (6.8%, n = 8) and others (21.2%, n = 25). IrAE distribution was grade 2 (n = 56, 47.5%), grade 3 (n = 44, 37.3%) and grade 4 (n = 18, 15.2%). IrAE toxicities were hepatitis (15.2%, n = 18), skin toxicities (14.4%, n = 17), pneumonitis (13.6%, n = 16), colitis (10.2%, n = 12), arthralgia (8.4%, n = 10), hematologic (7.6%, n = 9) muscular (6.8%, n = 8), neurologic (5.9%, n = 7), ocular (5.1%, n = 6) toxicities, lipoate increases (4.2%, n = 5), endocrine (4.2%, n = 5), nephrologic (2.5%, n = 3), cardiac toxicities (0.8%, n = 1) and infused related reaction (0.8%, n = 1). Forty patients (33.8%) were died and then rechallenged. Rechallenged and non-rechallenged patients didn’t differ in term of age, distributions and grades of toxicity and steroids use. Patients were rechallenged after an irAE grade 2 (n = 18, 42.5%), grade 3 (n = 17, 42.5%), grade 4 (n = 5, 12.5%); 40% (16/40) had no recurrence, 35% (14/40) had recurrence of the same irAE, 15% (6/40) experienced a new irAE, and 10% (6/40) had multiple irAE. No patient had died after rechallenge. IrAE recurrence rates were 3/5 for colitis, 3/6 for arthritis, 3/5 for hepatitis, 1/5 for pneumonitis, 1/5 for pancreatitis, 3/7 for neutropenia, 3/7 for skin toxicities. Recurrence rates were not different in grade 2 compared to grades 3-4. **Conclusions:** The rechallenge of ICI after mild or severe irAE was associated with 60% of irAE grade ≥2 recurrence or new irAE. Toxicity profile was acceptable but required a close monitoring. **Legal entity responsible for the study:** Department des Innovations Therapeutiques et Essais Pre´coces, Gustave Roussy, Universite´ Paris-Saclay. **Funding:** Has not received any funding. **Disclosure:** All authors have declared no conflicts of interest.

**1204P Long term disease control and abscopal effects by stereotactic radiotherapy for growing metastases during anti-PD1**

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**Background:** Recent reports have described the safety and clinical utility of combining anti-PD1 checkpoint inhibition with radiotherapy. Abscopal effects - radiotherapy inducing clinically meaningful distant responses in unirradiated sites - have been hypothesized, though clinical proof is scarce.

**Methods:** We analyzed efficacy and toxicity of combined stereotactic ablative radiotherapy (SABR) and anti-PD1 in consecutive melanoma and non-squamous cell lung cancer (NSCLC) patients that underwent stereotactic radiotherapy for a limited number of growing metastases during anti-PD1/PDL1 in our institute in 2017.

**Results:** Ten patients, 8 with metastatic melanoma and 2 with metastatic NSCLC, were included in this series. SABR was given at a median of 11.5 months (range 3-21 months) after the start of anti-PD1 treatment (nivolumab or pembrolizumab). A single radiation treatment was delivered in 8 patients, 2 simultaneously in 1 patient and 5 in the last patient. Disease control of the irradiated lesion was established in all 10 patients. With a median follow-up of 5.5 months (range 1-16 months) all patients were still alive without the need to start a subsequent systemic therapy. Additionally, abscopal effects, defined as a significant decrease of unirradiated metastases that were previously stable under immunotherapy, were seen in 4/10 patients after SABR. One patient developed a pneumonitis (outside high dose radiation field) shortly after SABR that was considered to be related to nivolumab. No other severe toxicities of the combined treatments were observed.

**Conclusions:** These data show that combining SABR and checkpoint inhibition for patients with oligo-progressive disease during PD1-inhibition is a strategy that can induce long-term disease control and additionally can lead to abscopal effects in unirradiated tumor sites. In order to explore feasibility for all patients with oligo-progressive disease during PD1-inhibition, prospective clinical studies are needed.

**Legal entity responsible for the study:** University Medical Center Utrecht. **Funding:** Has not received any funding. **Disclosure:** K.P. Suijkerbuijk: Consulting, Advisory relationship: Bristol-Myers Squibb, MS; Honoraria (institutions): Novartis, Roche. G. Groenewegen: Consulting, Advisory relationship: BMS, MSD; Speakers fee: Astellas; Honoraria received paid to institution. All other authors have declared no conflicts of interest.

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**1206P Incidence of immune related adverse events in patients 70 years old treated with anti-PD-L1 therapy**

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**Background:** Advanced age is an important risk factor of cancer and is associated with poor prognosis. Changes in the immune system called immunosenescence may occur with older age. However, the impact of aging on efficacy and safety of immune check-point inhibitors (ICI), such as anti-PD-(L)1, remains undetermined.

**Methods:** Patients with advanced solid tumours treated with an anti-PD-(L)1 agent monotherapy between June 2014 and October 2017 and prospectively included within the Gustave Roussy ICI-dedicated pharmacovigilance registry REHARM (Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie) were retrospectively reviewed. Incidence of immune-related adverse events (irAEs) of grade ≥2 was compared between patients aged ≥70 and <70 years old using Chi-squared test.

**Results:** Among the 615 patients included in the analysis, 191 were ≥70 years old (OP) and 424 <70 years old (YP). The median age of OP and YP were respectively 77 (70 - 93) and 59 (17 - 69). A total of 165 irAEs were included in the analysis (103 Grade 2 and 58 Grade 3-4). The overall occurrence of irAEs grade ≥2 was higher in OP compared to YP (33% versus 25%, p = 0.03). Statistical significance was lost when stratifying irAEs according to their severity grade, suggesting that this effect was not present in the same extent (the grade = 0.08 for Grade 2 and p = 0.13 for Grade 3-4). Anti-PD(L)-1 related deaths were registered in 1 OP and 3 YP (0.5% and 0.7% respectively; NS). The most frequent organs toxicities in OP was skin rash (49%), endocrine (14%), hepatic (10%), it was skin rash (28%), endocrine (25%), digestive (15%) in YP. Median time to

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PO-1 blockade in renal transplant patients with poor prognosis cancer and minimizing risk of organ rejection using comprehensive immune monitoring and screening techniques: A safety study

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Abstract:
Programmed cell death 1 (PD-1) inhibitors have exhibited significant efficacy in various types of cancer including non-small-cell lung cancer (NSCLC). PD-1 inhibitors are expected to be used increasingly as monotherapy or in combination. Pneumonitis is relatively uncommon but potentially fatal toxicity induced by anti PD-1 therapy. Although patients with apparent interstitial pulmonary edema are excluded from clinical trials of anti PD-1 therapy, patients with minimal interstitial opacities on chest CT scans can be treated with PD-1 inhibitors in the clinical practice. Little is known about the incidence of pneumonitis in such cases.

Methods:
Among patients with NSCLC treated with PD-1 inhibitors in our institution, we identified those who developed pneumonitis. We reviewed medical records and chest imaging studies. We investigated association between background factors including lung opacities on chest CT scan before anti PD-1 therapy and development of pneumonitis.

Results:
We analyzed a total of 79 patients treated with PD-1 inhibitors. At the baseline CT scan, ground glass opacities and reticular opacities were observed in 20 patients (25%) and 11 patients (14%), respectively. All of these interstitial opacities were very mild, and the case of obvious interstitial pulmonary edema was not observed. During the anti PD-1 therapy, pneumonitis developed in 16 patients (20%). Of the 20 patients with ground glass-opacities, ten patients (50%) developed pneumonitis, and of the 18 patients with reticular opacities, nine patients (50%) developed pneumonitis. Ground glass opacities and reticular opacities at baseline were significantly associated with the incidence of pneumonitis (p < 0.001 and p = 0.001, respectively). Among the 49 patients who did not have either of these opacities, three patients (6%) developed pneumonitis. There were no association between pneumonitis and other background factors such as presence of radiation pneumonitis or pulmonary emphysema.

Conclusions:
Ground glass opacities and reticular opacities on chest CT scan before treatment can be risk factors of pneumonitis, even if they are mild. For the patients without these opacities, anti PD-1 therapy appears relatively safe.

Legal entity responsible for the study: Aichi Cancer Centre Aichi Hospital

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

PO-1 inhibitor-related pneumonitis in patients with minimal interstitial lung shadows before treatment

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Background:
Programmed cell death 1 (PD-1) inhibitors have exhibited significant efficacy in various types of cancer including non-small-cell lung cancer (NSCLC). PD-1 inhibitors are expected to be used increasingly as monotherapy or in combination. Pneumonitis is relatively uncommon but potentially fatal toxicity induced by anti PD-1 therapy. Although patients with apparent interstitial pulmonary edema are excluded from clinical trials of anti PD-1 therapy, patients with minimal interstitial opacities on chest CT scans can be treated with PD-1 inhibitors in the clinical practice. Little is known about the incidence of pneumonitis in such cases.

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Legal entity responsible for the study: Aichi Cancer Centre Aichi Hospital

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Immuno therapy in the immune deficient: A treatment paradox?

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Background:
Patients with immunodeficiency are typically excluded from trials involving Immuno therapy, however they are at increased risk of developing malignancy. There is currently a lack of evidence to guide clinicians making difficult decisions in this cohort who have a theoretical risk of being unable to mount an adequate immune response.

Methods:
Patients diagnosed with Metastatic Melanoma treated with either single or dual immuno therapy regimes at University Hospital Southampton NHS Foundation Trust were identified through our electronic chemotherapy prescribing system. Those with a background of immuno suppressive states were analysed including high intensity chemotherapy or stem cell transplant for prior malignancy and HIV.

Results:
A total of 124 patients received Pembrolizumab monotherapy and 47 patients received Ipilimumab with Nivolumab. Six patients were considered immuno deficient, including three patients treated with cutaneous intent with intensive chemotherapy for prior lymphoma, one patient with HIV with undetectable viral load, one patient continuing on Brutinib treatment for Small Lymphocytic Lymphoma and one patient under a watch and wait approach for Chronic Lymphocytic Leukaemia. All patients in this group had any grade treatment related toxicity, with five experiencing severe grade 3-4 toxicity requiring hospitalisation. With a median follow up of 16.5 months no patients had reactivation of previous malignancy and all have had a complete radiological response and two patients had disease progression.

Conclusions:
In our cohort the majority of patients had a significant response to immuno therapy with toxicity managed without any long term comorbidities. All of these patients were able to mount an anti-tumour immune response despite concurrent immuno deficiency and experienced an increased incidence of toxicity when compared with other patients treated at our centre. Despite the limitations of a small retrospective series our data would support offering immuno therapy even in the context of apparent immuno deficient states.

Legal entity responsible for the study: University Hospitals Southampton

Funding: Has not received any funding.

Disclosure: J. Longley: ESMO Travel Grant. J. Karydis: Travel, accommodations, expenses. Delcath Systems. M. Wheeler: Consulting or advisory role: Roche, Novartis, MSD, Healthcare at Home; Travel, accommodations, expenses: MSD, Bayer, Bristol-Myers Squibb; Honoraria: Bristol-Myers Squibb, MSD Oncology, Pfizer, GlaxoSmithKline, Novartis, Delcath Systems; Research funding: Roche, GlaxoSmithKline, Novartis, MSD, Aveo, Bristol-Myers Squibb, Verastem, Merck Sharp & Dohme, Inovio Pharmaceuticals, BioNTech AG, Serametrix, Toulight Genetics, Delcath Systems; C. Ottensmeier: Consulting or advisory role: Bristol-Myers Squibb, Merck Sharp & Dohme, Immatics; Travel, accommodations, expenses: Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Delcath Systems; Research funding: Bristol-Myers Squibb, Verastem, Merck Sharp & Dohme, Inovio Pharmaceuticals, BioNTech AG, Serametrix, Toulight Genetics, Delcath Systems. All other authors have declared no conflicts of interest.
1214P Hyperprogression during immuno-checkpoint inhibitors (ICIs): A clinically significant problem?

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Methods: We retrospectively identified a series of 334 pts with miscellaneous advanced solid tumors treated with anti-PD1/PD-L1-containing ICI (mono or combo therapy) at our Institution. Inclusion criteria included imaging assessment at 3 timepoints: during reference period (from 3 months to 2 weeks before ICI baseline scan), before ICI therapy start (baseline scan, performed within 28 days) and during ICI treatment. Patients were considered HPD if they showed progressive disease (PD) by RECIST 1.1 at first radiological evaluation and a ≥ 2-fold increase of the TGR during ICI therapy compared to reference period. FISH analysis to evaluate MDM2 family gene amplification was performed in HPD cases whose paraffin embedded tumor material was available.

Results: 73 cases were initially excluded from our analysis due to lack of tumor assessment during ICI. Of the remaining pts, 109 reported PD at first evaluation. Of them, only 45 were available for the analyses, having all requested radiological exams previously available. Seven cases met HPD criteria: 3.5% of evaluable pts (7/197) and 6.4% of all the PD. No correlation with histology, age, serum biomarkers and type of ICI was found. FISH analysis for MDM2 family has been performed on 3 cases: one case showed amplification MDM4 gene (mean of signals ≥ 8); other cases showed only increased MDM4 ratio score of unknown significance.

Conclusions: Despite the limits of a retrospective analysis and small numbers, in our series HPD is a rare but clinically relevant event. The role of MDM2 family alteration as predictive biomarker is promising and deserves more investigations. Prospective studies including genomic and biological analysis are warranted.

Legal entity responsible for the study: Elena Fareì.

Funding: Has not received any funding.

Disclosure: F.G.M. de Braud: Advisor: BMS, Ignyta, MSD, Novartis, Pfizer, Amgen, Roche, Merck Serono, Servier. All other authors have declared no conflicts of interest.

1212P Pathogenesis, clinical evolution and outcomes of patients with immune checkpoint inhibitor induced acute liver injury: A multicentre study


Background: Immune checkpoint inhibitor (CPI) induced acute liver injury (ALI) is a frequently encountered toxicity occurring in up to 50% patients (pts). There is a lack of systemic evaluation of CPI induced ALI pathogenesis, clinical evolution and outcome of patients (pts).

Methods: Retrospective analysis was performed on pts with CPI induced ALI presenting to 6 UK oncology centres between 2013-17. Indices of ALI therapy complications and outcome were recorded. ALI grading was based on Common Terminology Criteria for Adverse Events.

Results: 65% (3657) pts received ipilimumab+nivolumab (N) or pembrolizumab (P) (combo groups) and 35% (2175) P or N alone (mono group). Median therapy duration to ALI onset was 96 days in the mono and 22 days in the combo group. At presentation, all pts had acute elevations in transaminases (ALT, median 325U/L [range 155-543], ALP 111U/L [72-250]). Immunglobulins and immunoglobulins were normal. One pt developed acute synthetic dysfunction without encephalopathy (Bilirubin 64μmol/L, INR 1.5). 79% received steroids (mean dose 1.3mg/kg). 34% MIF. Steroid refractory ALI was treated with anti-thymocyte globulin (ATG) in 4 pts. Pathological findings (n = 6 liver biopsies) revealed lobular hepatitis and myelo-lymphoid cell infiltrate/ aggregates (CD3+ c.ED8+, CD68+). Pts with severe, refractory (G4) ALI had significant reductions in circulating lymphocytes/monocytes. 63% (n = 35) had a temporal association between recent infection and ALI. 15% (n = 8) also received anti-TNFα therapy for colitis. This was not associated with more severe ALI and ALI resolved in all cases. 21% (n = 11) developed bacterial infections. Fungal sepsis (aspergillosis) occurred in all ALI (n = 4) treated patients. Overall no deaths were due to liver failure. 14 pts died with 13 due to disease progression and 1 due to immunotherapy related neuropathy. All deaths due to progressive disease were in pts whose ALI peaked at G3-4. Actuarial median survival was significantly lower in G3-4 (14.5 months) vs G1-2 (25 months) liver injury.

Conclusions: Our data report on the largest cohort of CPI induced ALI identifying disease evolution, markers of disease severity and strong correlation with increased morbidity and mortality.

Legal entity responsible for the study: The Royal Marsden Hospital.

Funding: The Royal Marsden Hospital & Imperial College London.

Disclosure: J. Larkin: Institutional research support: BMS, MSD, Novartis, Pfizer Consultancy: Elsai, BMS, MSD, GSK, Kymab, Pfizer, Novartis, Roche/Genentech, Secarna, Pierre Fabre, EUSA Pharma; Support: NIHR R/M/R Biomedical Research Centre for Cancer. All other authors have declared no conflicts of interest.

Results: 2,056 pts initiated 1L tx (full cohort), of which 628 pts went on to 2L tx; 42% received TOP and 58% other tx. Within 2L, mean age was 65y; 66% were white, 51% were female, 98% had a smoking history and 95% were treated in the community. Of 2L pts, 68% had extensive and 22% had limited disease at dx. 372 were PT-sensitive and 231 pts were PT-resistant. Upon matching for CheckMate 032 I/E, 903 pts were identified; 373 had incomplete matching. TOP sensitivity was based on a 90 day gap. Median, 1-y and 2-y overall survival (OS) by Kaplan-Meier was calculated from 2L initiation to death. Median duration of therapy (mDoT) was assessed. A matched 2L cohort was constructed using CheckMate 032 Inclusion/Exclusion criteria (IE).

Results: From Diagnosis

<table>
<thead>
<tr>
<th>Full Cohort</th>
<th>Median OS, months (95%CI)</th>
<th>1-year / 2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 2056)</td>
<td>11.6 (11.1,12.3)</td>
<td>48.6 / 22.0</td>
</tr>
<tr>
<td>Limited disease (n = 680)</td>
<td>19.6 (18.0,21.5)</td>
<td>71.9 / 42.3</td>
</tr>
<tr>
<td>Extensive disease (n = 1,263)</td>
<td>9.4 (8.9,9.9)</td>
<td>35.2 / 10.5</td>
</tr>
</tbody>
</table>

Results: From Initiation of 2L

<table>
<thead>
<tr>
<th>Matched Cohort</th>
<th>Median OS, months (95%CI)</th>
<th>1-year / 2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 628)</td>
<td>4.2 (3.7,4.7)</td>
<td>13.3 / 3.3</td>
</tr>
<tr>
<td>PT-sensitive (n = 372)</td>
<td>5.4 (4.6,6.2)</td>
<td>15.9 / 4.2</td>
</tr>
<tr>
<td>PT-refractory (n = 231)</td>
<td>3.0 (2.6,3.6)</td>
<td>9.1 / 2.9</td>
</tr>
</tbody>
</table>

From Diagnosis

| All (N = 903) | 12.5 (11.5,14.3) | 47.0 / 26.4 |
| Limited disease (n = 348) | 23.8 (20.0,29.5) | 72.0 / 49.5 |
| Extensive disease (n = 507) | 9.8 (8.9,10.6) | 37.9 / 12.1 |

Continued
Conclusions: This large retrospective data set highlighting 2L SCLC outcomes demonstrates poor survival in this setting under scoring the need for novel tx. Results from CheckMate 032 present ICI as a potential option for SCLC pts.

1215P

Sequential blockade of PD-1 and PD-L1 causes fulminant cardiotoxicity: From case report to mice model validation

Y.-J. Chen 1, W.-C. Huang 2, S.-Y. Liu 3, C.-C. Ko 3

1Department of Radiation Oncology, Mackay Memorial Hospital, Taipei City, Taiwan, 2Department of Surgery, Mackay Memorial Hospital, Taipei City, Taiwan, 3Department of Medical Research, Mackay Memorial Hospital, Taipei City, Taiwan

Background: In clinical practice, the sequential use of shifting from a programmed cell death 1 (PD-1) inhibitor to its ligand 1 (PD-L1) inhibitors in consideration of ineffectiveness or toxicity is becoming more common due to prolonged survival. We report a patient in whom fatal myocarditis developed after sequential use of PD-1 and PD-L1 inhibitors. To validate this finding, a syngeneic tumor-bearing mice model was used.

Methods: A 61-year-old woman with metastatic lung adenocarcinoma, who had received 5 doses of nivolumab (3 mg/kg) and then 1 dose of atezolizumab (1200 mg), complained of chest tightness and dyspnea 4 weeks later. The workup revealed sinus tachycardia, a normal Troponin I level (< 0.01 ng/mL), an elevated creatine kinase-myocardial band (CK-MB) level (10 mg/mL), and elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) level (2960 ng/mL). Serial echocardiograms revealed left ventricular ejection fractions declining from 66.3 to 59.2 %. Under a diagnosis of myocarditis, she was treated with intravenous methylprednisolone at 5 mg/kg/day and oral methylpredonale methylate at 1000 mg/day. The progressive clinical deterioration was noted with serial elevation of Troponin I, CK-MB and NT-proBNP levels up to 1.3, 24 and 157/6ng/mL, respectively. Cardiac arrest was noted later. The Balb/c mice bearing metastatic of CT26 colon cancer cells were treated with the PD-L1 and PD-L1 inhibitors for pathological and immunohistochemical studies.

Results: The pathology shows that the combination of anti-PD-1 and anti-PD-L1, either sequentially or simultaneously administered, caused myocarditis lesions with myocyte injury and patchy mononuclear infiltrates in the myocardium in all combination group mice (n = 3 for each). The myocarditis lesions were not seen in mice treated with anti-PD-1 or anti-PD-L1 alone. Marked expression of PD-L1 in infiltrating lymphocytes and expression of PD-1 in myocytes was noted only in mice with combination blockade, implying a possible role for pathogenesis of myocarditis.

Conclusions: The combinatory use of PD-1 and PD-L1 blockade, either sequentially or concurrently, may cause fulminant cardiotoxicity, and such usage should be cautious.

Legal entity responsible for the study: Mackay Memorial Hospital, Taipei, Taiwan.

Disclosure: All authors have declared no conflicts of interest.

Table: 1214P

<table>
<thead>
<tr>
<th>From initiation of 2L</th>
<th>median OS, months (95%CI)</th>
<th>1-year / 2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 254)</td>
<td>4.9 [4.0-6.2]</td>
<td>14.6 / 3.8</td>
</tr>
<tr>
<td>PT-sensitive (n = 158)</td>
<td>6.3 [5.6-7.5]</td>
<td>18.4 / 6.0</td>
</tr>
<tr>
<td>PT-refractory (n = 90)</td>
<td>2.7 [2.1-3.3]</td>
<td>5.6 / 1.9</td>
</tr>
<tr>
<td>CHECKMATE 032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIVO 3 mg/kg cohort (n = 98)</td>
<td>4.4 [3.0-9.3]</td>
<td>33 / NR</td>
</tr>
<tr>
<td>NIVO 1 mg/kg + IP 3 mg/kg (n = 61)</td>
<td>7.7 [3.6-18.0]</td>
<td>43 / NR</td>
</tr>
<tr>
<td>NIVO 3 mg/kg + IP 1 mg/kg (n = 54)</td>
<td>6.0 [3.6-11.0]</td>
<td>35 / NR</td>
</tr>
</tbody>
</table>

1216P

Impact of anti-infectious and corticosteroids on immunotherapy: Nivolumab and pembrolizumab follow-up in a French study

I.-P. Metges 1, E. Michaud 2, D. Deniel Lagadec 3, F. Mathurenda 4, A. Chasten 4, F. Grude 4

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Background: Immunotherapy is a new paradigm with EMA approval in melanoma and lung cancer. However, B Fouty and al has recently published a decrease of efficacy of immunotherapy via gut microbiome antibiotics influence and potential drug interactions between antibiotics/corticoids and immunotherapy associated with decrease of overall survival have been underlined too. The Observatory of Drugs, Medical Device and Therapeutic Innovations (OMEDIT) Bretagne/ Pays de la Loire (B-PL), in collaboration with French Regional Health Insurance System (FRHIS), wanted to carry out a study about the impact of these treatments on the efficacy of immunotherapy.

Methods: FRHIS (PL) has made an extract in its database for patients who initiated treatment with Nivolumab/Pdfoxo and Pembrolizumab/keytruda® between January 2016 and end of June 2017. Dispensing of antibiotics, corticoids and antifungals 60 days before initiation of immunotherapy and after the beginning of treatment (within 30 or 150 days after). The patient’s clinical data (age, sex, diagnosis, indication, grade III/IV side-effects, response rate, survival) would be crossed with the use or not of anti-infectious drug treatment in order to define the impact of taking these drugs on the treatment of immunotherapy.

Results: 798 patients were identified including 377 in 2016 and 421 in the first half of 2017: 148 with malignant melanoma and 650 with lung cancer. 763 were treated with nivolumab and 35 with pembrolizumab. Before the beginning of immunotherapy, 14% of these patients received an antibiotic; 17% a corticoid and 2% an antifungal. After the beginning of immunotherapy (within 30 days after), 8% received a corticoid, 6% an antibiotic and 2% an antifungal. Response to treatment, Progression Free Survival and Overall Survival (PFS and OS) in correlation with the use or not of these drugs for Bregagne and PL areas would be presented at the meeting.

Conclusions: The good use of immunotherapy was crucial to optimize the response rate and to increase OS. Use of anti-infectious and corticosteroids was usual in routine. Antibiotics were found to be prescribed in 20% of the patients receiving immunotherapy. Results about their impact in term of response, PFS and OS would be shown at the meeting.

Legal entity responsible for the study: Cancer Observatoire BPL, OMEDIT B and PL.

Funding: Has not received any funding.

Disclosure: I.-P. Metges: Trial coordination without remuneration: MSD. All other authors have declared no conflicts of interest.

1217P

Real-world safety of nivolumab in patients with non-small cell lung cancer (NSCLC) in Japan: Interim summary of post-marketing all-case surveillance

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Background: Nivolumab, a fully humanized anti-PD-1 antibody, was approved in December 2015 in Japan for the treatment of previously-treated, unresectable, advanced or recurrent NSCLC. A post-marketing all-case surveillance was imposed as a condition for approval, to accumulate real-world safety data for nivolumab, because clinical trial data were limited.

Methods: This all-case surveillance is an ongoing mandatory observational register, searching for new treatment-related safety issues. All NSCLC patients treated with nivolumab between 17 December 2015 and 31 March 2016 were registered and monitored for one year. Safety data were accumulated using case report forms (CRFs) in accordance with Good Post-Marketing Study Practice Ministerial Ordinance in Japan. This interim summary is based on data collected and summarized from patients whose CRFs were available by 3 January 2018.

Results: Overall, 3681 patients were enrolled from 17 December 2015 to 31 March 2016, with 3303 CRFs collected by 3 January 2018. The safety analysis set included 3297 of 3303 patients. Background characteristics of patients: median age was 67 years; 74% of patients were current or former smokers; 77% of patients had an ECOG performance status score of 0 (24%) or 1 (53%); 66% and 28% of patients had adenocarcinoma or squamous cell carcinoma, respectively. The frequency of adverse drug reactions of any grade was 45%. The most frequent (5% or higher) adverse events of special interest were interstitial lung disease (ILD, 9.1%; grade ≥ 3, 3.9%), thyroid dysfunction (8.7%; grade ≥ 3, 3.0%), hepatitis function disturbance (7.8%; grade ≥ 3, 2.4%), infusion reaction (5.4%; grade ≥ 3, 0.3%) and colitis/severe diarrhea (5.3%; grade ≥ 3, 3.3%). The overall survival rate at 1 year was 57% (95% CI, 35.2 to 83.6%). We will report updated data along with estimated risk factors for ILD.

Legal entity responsible for the study: Pulmonary Medicine and Oncology, Nippon Medical School, Tokyo, Japan.
Conclusions: Among Japanese patients with previously-treated, unresectable, advanced or recurrent NSCLC, nivolumab showed an almost consistent safety profile with clinical trial data except for frequency of IILD. The benefit-risk profiles should consistently be monitored.

Editorial acknowledgement: Content Ed Net.

Legal entity responsible for the study: Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb.

Funding: Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb.


**1218P Immune-related adverse events: Comparison of melanoma and non-small cell lung cancer patients treated with anti-PD1 therapy**

N Duma1, A.G. Azouzou1,2, Y. Yadav1, K. Hoversten1, C. Reed1, A.N. Steek1, Y. Lou1, T. Murthy1, T. Halldinman1, K. Leventakos1, R.W. Joseph1, R. Manochio1, R. Dranca1

1Medical Oncology, Mayo Clinic, Rochester, NY, USA, 2Medical Oncology, Mayo Clinic, Jacksonville, FL, USA, 2Internal Medicine, Mayo Clinic, Rochester, NY, USA

Background: Immune-related adverse events (IRAEs) represent a clinical challenge, potentially limiting the clinical benefits of immunotherapy. Data suggests nivolumab and pembrolizumab IRAEs rates are similar but no comparisons across tumor types exist. Therefore, we studied IRAEs in patients (pts) with metastatic melanoma and non-small cell lung cancer (NSCLC) treated with anti-PD1 therapy.

Methods: All pts with metastatic melanoma and NSCLC seen at the Mayo Clinic Rochester and Florida from 2015 to 2018 were reviewed. Patients that received prior immunotherapies or thoracic radiation were excluded. Chi-square test was used to estimate differences in categorical data.

Results: Out of 510 pts, 266 (52%) had melanoma and 244 (48%) NSCLC. Baseline characteristics were similar across groups, except for sex (NSCLC: 51% women; melanoma: 40% women), 80% of the pts with NSCLC received chemotherapy prior to immunotherapy compared to 14% of the pts with melanoma. 75% (206) of melanoma pts received pembrolizumab and 66% (161) of NSCLC pts received nivolumab. Higher rates of IRAEs were observed in the melanoma pts (55% vs 41%, <0.001) (Table). No difference in grade ≥ 3 IRAEs was observed. Melanoma pts were more likely to develop diarrhea/colitis and endocrinopathies compared to the NSCLC pts (19% vs 7%, p < 0.008, 13% vs 18%, p = 0.01, respectively). Contrarily, pts with NSCLC had higher rates of pneumonitis (14% vs 6%, p < 0.007). Most pts resumed the anti-PD1 agent after developing IRAEs (60% and 57%, respectively). In 31% of the pts experiencing IRAEs the anti-PD1 agent was permanently discontinued due to toxicity.

Conclusions: Patients with metastatic melanoma were more likely to develop IRAEs with anti-PD1 therapy. We observed differences in the IRAEs developed across groups. These associations could be attributed to intrinsic tumor characteristics or differences between anti-PD1 agents. Larger studies are needed to enhance our understanding of these differences.

Legal entity responsible for the study: N. Duma.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**1219P Evaluation of a possible link between immunotherapy (IO) and acute vascular events**


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Background: IO has become one of the major pillars of anti-cancer therapy. A range of immune-related adverse events (IRAE) are recognized within various organs. Acute vascular events (AVE) are generally not considered IRAE. Considering the role of inflammation in acute ischemic cardiovascular events, we assumed such events can be triggered by IO. We aimed to evaluate the frequency and nature of AVEs occurring shortly after the initiation of IO.

Methods: Computerized search of Sheba medical center (SMC) electronic medical records was done for patients (pts) that received IO (any of: pembrolizumab, nivolumab, atezolizumab, ipilimumab). Out of those, we searched for cases with a diagnosis of AVE within 1 month after initiation of IO. Search was for the diagnoses: cerebrovascular accident (CVA), transient ischemic attack (TIA), myocardial infarct (MI), non-STEMI, STEMI, embolic event, pulmonary embol (PE) and deep vein thrombosis (DVT). We excluded cases with AVE within a year prior to the initiation of therapy, concomitant chemotherapy, and cases of a single-site DVT.

Results: Between 1st January 2015 and 14th March 2018, 1396 pts received IO in SMC. 14 pts were identified in the computerized search. Excluded: 4 with a single site DVT, 1 with a prior cardiovascular event within a year prior to initiation of IO, 1 with concomitant chemotherapy, 3 excluded due to AVE not definitely diagnosed, leaving 5 pts not excluded. 8 additional pts were identified by reports of physicians aware of this project, of these 2 were also identified by the computerized search, thus a total of 11 pts fit our study criteria. Events were: multiple CVA (3), PE (2), sudden cardiac death (2), bilateral DVT (1), CVA (1), TIA (1), MI (1). In one pt marantic endocarditis was suspected. 7 pts had diabetes, 7 pts had hypertension, 2 pts had a body temperature > 38.3 were smoking within < 10 years, none had a family history of cardiovascular disease. 9 of the pts were treated in SMC, constituting a frequency of 0.6%. Conclusions: AVEs occur at a low frequency shortly after initiation of IO. Initiation of IO may be the triggering event of those events. Further retrospective studies and analyses of clinical trials data are required to evaluate whether this is a random association or a true IRAE.

Legal entity responsible for the study: Shba Medical Center, Tel Hashomer, Israel.

Funding: Sheba Medical Center.

Disclosure: J. Bar: Consultant fees: Roche, Boehringer Ingelheim, Novartis, BMS, MSD, Pfizer, AstraZeneca, VBL, Takeda; Grant support: Boehringer Ingelheim, Novartis, AstraZeneca, MSD, Pfizer. All other authors have declared no conflicts of interest.

**1220P Real-world experience of pembrolizumab in patients with advanced melanoma: A large retrospective observational study**

F.X. Liu1, W. Ou2, S.J. Diee3, E.D. Whitman4

1COBE, Merck & Co Inc, Kenilworth, NJ, USA, 2COBE, Merck & Co, Inc., Kenilworth, NJ, USA, 3Clinical Oncology, Merck & Co., Inc, Kenilworth, NJ, USA, 4Atlantic Oncology Center, Carol G. Simon Cancer Center, Mornistown, NJ, USA

Background: Pembrolizumab (PEM), a humanized antibody targeting programmed death-1 receptor, has been approved by FDA for the treatment of patients (pts) with advanced melanoma (AM) in the US for over 3 years. The study examined the real-world (RW) use of PEM and associated patient (pt) outcomes in the US Oncology Clinical Practices.

Methods: Flatiron Health longitudinal database was used to identify adult pts with AM who received ≥1 dose of PEM between September 4, 2014 and December 31, 2016. These pts were followed up to December 31, 2017. Pts in clinical trials were excluded. Pt demographic, treatment, and clinical characteristics were described. Time on treatment (ToT) and overall survival (OS) were analyzed using the Kaplan Meier (KM) method, with the first dose of PEM as the starting point.

Conclusions: Among Japanese patients with previously-treated, unresectable, advanced or recurrent NSCLC, nivolumab showed an almost consistent safety profile with clinical trial data except for frequency of IILD. The benefit-risk profiles should consistently be monitored.

**Table: 1218P**

<table>
<thead>
<tr>
<th>IRAEs</th>
<th>Melanoma %</th>
<th>NSCLC %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>19 (28)</td>
<td>7 (7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dermatologic Toxicities</td>
<td>19 (28)</td>
<td>22 (22)</td>
<td>0.62</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>33 (48)</td>
<td>18 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6 (8)</td>
<td>14 (14)</td>
<td>0.007</td>
</tr>
<tr>
<td>Transaminases</td>
<td>14 (21)</td>
<td>9 (9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Immunotherapy was restarted</td>
<td>60 (88)</td>
<td>57 (56)</td>
<td>0.60</td>
</tr>
<tr>
<td>Immunotherapy DC due to toxicity</td>
<td>45 (31)</td>
<td>31 (31)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Conclusions: Liver metastases are a poor prognostic factor in pts treated on IO-based phase 1 clinical trials. These findings should be validated in a larger study. Equal Contribution: MAB, JMS, DJM.

Legal entity responsible for the study: Emory University IRB.

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BioTheranostics, Research funding: Argen, Bristol-Myers Squibb, Vaccines, Boston Biomedical. G.K. Ruchkadkar; Consulting/advisory role: Bristol-Myers Squibb, Novartis, Array BioPharma; Honorary: Bristol-Myers Squibb; Research funding: Merck. B. El-Rayes; Consulting/advisory role: Merrimack, BTG, Bayer, Loxo, RTI Health Solutions; Member of the speakers bureau: Lexicon, Bristol-Myers Squibb; Honorary: from Lexicon, RTI Health Solutions, Bayer; Research funding: Taiho Pharmaceutical, Bristol-Myers Squibb, Biston Biomedical, Cleave Biosciences, Genentech, AVEIO, Pfizer, Novartis, Hoosier Cancer Research Network, Five Prime Therapeutics, PPD Inc., Merck, ICON Clinical Research. S.S. Ramalingam; Consulting/advisory role: Aremen, Boehringer, Ingelheim, Celgane, Genentech/roche, Lilly/Imcclone, Bristol-Myers Squibb, Astrazeneca, Abbvie, Merck, Takeda; Travel accommodations: EMD Serono, Pfizer, AstraZeneca. T. K. Owonikoko; Consulting/advisory role: Novartis, Celgene, Lilly, Sanodz, Abbvie, Eisai, GI Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, Medimmune; Intellectual property of the following: “Overcoming acquired resistance to chemotherapy treatments through suppression of STAT3” and “Selective chemotherapy treatments and diagnostic methods related thereto”; Research funding: Novartis, Astellas Pharma, Celgene, Bayer, Stem Cells, Regeneron, Astrazenca/Medimmune, Abbvie, GI Therapeutics, and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Table: 1221P UVA and MVA of liver metastases with CO

<table>
<thead>
<tr>
<th>MeB (CM)</th>
<th>OS</th>
<th>PFS</th>
<th>CB</th>
<th>UVA</th>
<th>MVA</th>
<th>UVA</th>
<th>MVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No liver</td>
<td></td>
<td></td>
<td></td>
<td>0.42 (0.23-0.78)</td>
<td>0.006*</td>
<td>0.38 (0.17-0.84)</td>
<td>0.017*</td>
</tr>
<tr>
<td>metastases</td>
<td></td>
<td></td>
<td></td>
<td>Median: 21.9 months</td>
<td>12 month survival: 60%</td>
<td>Median: 3.6 months</td>
<td>12 month survival: 13%</td>
</tr>
<tr>
<td>(n = 50)</td>
<td></td>
<td></td>
<td></td>
<td>2.64 (1.11-6.28)</td>
<td>0.028*</td>
<td>1.09 (0.27-4.44)</td>
<td>0.903</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td>0.42 (0.23-0.78)</td>
<td>0.006*</td>
<td>0.38 (0.17-0.84)</td>
<td>0.017*</td>
</tr>
<tr>
<td>metastases</td>
<td></td>
<td></td>
<td></td>
<td>Median: 8.1 months</td>
<td>12 month survival: 19%</td>
<td>Median: 1.8 mos</td>
<td>12 month survival: 5%</td>
</tr>
<tr>
<td>(n = 40)</td>
<td></td>
<td></td>
<td></td>
<td>2.64 (1.11-6.28)</td>
<td>0.028*</td>
<td>1.09 (0.27-4.44)</td>
<td>0.903</td>
</tr>
</tbody>
</table>

*Covariates included in MVA were age, whether IO is indicated for the pts histology, ECOG PS, RMH risk group, number of metastatic sites and histology

*statistically significant PD: Prognostic disease, NE: Not evaluable

References:

Results: Five hundred and thirty-two patients were included in the analysis. Of the 532 patients, 315 in first line (1L), 152 second line (2L), and 63 third line or beyond (3L+). Overall, median age at PEM initiation was 68 years (range, 18-84); most were male (66.4%) and Caucasian (95.5%). 32.9% of pts are confirmed BRAF mutant, 5.6% BRAF wildtype, and 13.3% unknown. When data were available, 21.2% had an elevated lactate dehydrogenase (>ULN), 18.0% had brain metastases, and 23.3% had an ECOG performance status of >1. At the time of analysis, pts were followed for a median of 12.9 months (mo; range, 0.03 – 39.7). The overall median ToT was 4.4 mo (95% CI, 3.5-5.2), with 4.2, 4.7, 4.2 mo in 1L, 2L, and 3L+, respectively. The overall median OS was 21.9 mo (95% CI, 15.3-29.1), not reached for 1L, and 13.3 and 12.5 mo for 2L and 3L+ respectively. The 1-year and 2-year survival, using the KM method was 60.9% (95% CI, 56.5-65.0; 1L; 64.9%, 2L; 55.3%; 3L+; 54.6%) and 48.1% (95% CI, 43.2-52.8; 1L; 53.4%; 2L; 41.5%; 3L+; 39.0%) respectively.

Conclusions: The study reports RW use of PEM in a large cohort of pts with AM in US Oncology Clinical Practices. The study pt population is more heterogeneous than that of clinical trials (KEYNOTE-002 and KEYNOTE-006). The findings of ToT and 2-year OS based on RW clinical decision making were consistent with those reported in PEM clinical trials, supporting the RW effectiveness of PEM in pts with AM.

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

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


Background: Selecting the appropriate pts to receive IO remains a challenge due to the lack of optimal biomarkers. We investigated the association between sites of metastatic disease and CO in pts enrolled on IO-based phase 1 clinical trials.

Methods: We conducted a retrospective review of 90 pts treated on IO-based phase 1 clinical trials at Winship Cancer Institute of Emory University between 2009-2017, including sites of metastasis. Overall survival (OS) and progression-free survival (PFS) were measured from the first dose of IO to date of death or clinical or radiographic progression, respectively. Clinical benefit (CB) was defined as a complete response (CR), partial response (PR), or stable disease (SD). Univariate analysis (UVA) and multivariate analysis (MVA) was carried out using Cox proportional hazard model or logistic regression model.

Results: The median age was 63 years and 53% of pts were men. The most common histologies were melanomas (33%) and gastrointestinal cancers (22%). Sites of metastasis were lymph node (N = 58), liver (N = 40), lung (N = 37), bone (N = 24), and brain (N = 8). Most pts (81%) were Royal Marsden Hospital (RMH) good risk. Liver metastases were associated with significantly shorter OS, PFS, and lower rate of CB (Table).

Table: 1221P UVA and MVA of liver metastases with CO

<table>
<thead>
<tr>
<th>MeB (CM)</th>
<th>OS</th>
<th>PFS</th>
<th>CB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UVA</td>
<td>MVA</td>
<td>UVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No liver</td>
<td>0.42 (0.23-0.78)</td>
<td>0.006*</td>
<td>0.38 (0.17-0.84)</td>
</tr>
<tr>
<td>metastases</td>
<td>Median: 21.9 months</td>
<td>12 month survival: 60%</td>
<td>Median: 3.6 months</td>
</tr>
<tr>
<td>(n = 50)</td>
<td>2.64 (1.11-6.28)</td>
<td>0.028*</td>
<td>1.09 (0.27-4.44)</td>
</tr>
<tr>
<td>Liver</td>
<td>0.42 (0.23-0.78)</td>
<td>0.006*</td>
<td>0.38 (0.17-0.84)</td>
</tr>
<tr>
<td>metastases</td>
<td>Median: 8.1 months</td>
<td>12 month survival: 19%</td>
<td>Median: 1.8 mos</td>
</tr>
<tr>
<td>(n = 40)</td>
<td>2.64 (1.11-6.28)</td>
<td>0.028*</td>
<td>1.09 (0.27-4.44)</td>
</tr>
</tbody>
</table>
was analyzed by KM analysis. Steroid use was captured from its initiation to for IrHep, till their discontinuation.

**Results:** IrHep any grade was identified in 80 (42%) pts (19 (26%) ipi; 24 (33%) anti-PD1; 17 (37%) combo). Median time to highest grade IrHep for pts, anti-PD1, and combo groups was 57.8, 9.6 and 6.13 weeks respectively. IrHep grade 3 occurred in 1 (4%), 2 (3%) and 14 (27%) combo pts respectively. For IrHep grade ≥3 (n = 18), MTR was 5 weeks, median starting systemic steroid dose was 1mg/kg and median duration of steroid treatment was 5 weeks. For irHep grade 2 (n = 22), 32% (n = 7) pts were treated with systemic steroid (2 progressed to grade 3 and 5 resolved), 22.7% (n = 5) pts progres- to grade 3-4 with treatment interruption, 22.7% resolved with treatment interruption and 22.7% resolved without treatment interruption. TTF failure for pts with/ without irHep was 5.1/12.4, 12.9/12.5 and NR/24.7 months with ipi, PD1 and combo pts respectively.

**Conclusions:** In our real-world experience, IrHep was identified more frequently than in past AM and was particularly in pts treated with combo. Pts with grade 3 irHep resolved within 5 weeks with systemic steroids at starting dose of 1mg/kg. Pts with grade 2 irHep, one should not proceed with treatment unless they resolved to grade ≤1.

Legal entity responsible for the study: Neil J Shah MD.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**1223P**

**Impact of immune-checkpoint inhibitors (ICPIs) as treatment of patients (pts) with metastatic primary uveal melanoma (UM): Results of a single-institution database**

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**Background:** Metastatic primary UM (MUM) is a rare cancer with a poor prognosis and a median overall survival (OS) of about 6 months in historical datasets. Despite the significant improvements produced by ICPIs in metastatic cutaneous melanoma, pts with MUM have been excluded from most trials of ICPIs thus causing an almost complete lack of prospective clinical data.

**Methods:** An analysis of all pts with MUM included in our institutional prospectively accrued database of all primary UM pts. OS was calculated from date of first diagnosis of metastatic disease to date of death or last follow up.

**Results:** Out of 169 pts registered between April 2008 and April 2018, 39 pts had MUM. Pts characteristics: males 20 (51%); median age 63 years (range 34-85); median tumour thickness at diagnosis 9mm (range 2-22); tumour location: choroidal 19 (49%) cilio-choroidal 8 (20%), undefined/unknown 12 (31%). Primary therapy (PTx): enucleation 22 (56%), brachytherapy 15 (38%), both 2 (5%). Sites of metastases: liver only 29 (73%), liver + other sites 7 (18%), extra-hepatic only 3 (8%). Median follow-up is 37.9mos. 11 pts had resectable disease at diagnosis and underwent primary metastasectomy; 28 patients underwent: immunotherapy (15), other systemic therapies (5), locoregional Tx (5), best supportive care (5). Median OS is 14.25 mos. At the database lock-out (April 30th 2018), 27 pts (70%) have died of MUM. Pts without hepatic involvement tend to have longer median OS (29.9mos) vs those with liver only disease (16.6mos) or liver + other sites (OS 8.9mos). Overall, 32/39 pts (82%) received ICPIs during the course of their disease: ipilimumab 13 (40%), single agent anti-PD1 5 (16%), sequential/concomitant ipilimumab and anti-PD1 14 (44%). Median OS is 23.7 mos (sequential ipilimumab and anti-PD1) vs single-agent ipilimumab (13.8mos) vs single-agent PD1 (14.7mos).

**Conclusions:** In our single-institution experience of nonresectable MUM pts, sequential/concomitant ICPIs produced a longer median OS than single-agent ipilimumab or anti-PD1 and should be considered the preferred treatment option. A more relevant disease could have contributed to more prolonged OS in a subgroup of pts with hepatic involvement.

Legal entity responsible for the study: St Vincents’ Hospitals, Dublin, Ireland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**1224P**

**Q-TWiST analysis to assess benefit-risk of pembrolizumab in patients with PD-L1-positive advanced or metastatic NSCLC**

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**Background:** Pembrolizumab monotherapy showed significantly longer progression-free survival and overall survival (OS), and fewer treatment-related adverse events (AEs) compared to chemotherapy in patients with metastatic non-small cell lung cancer (mNSCLC) with PD-L1 positive tumours in the first-line setting (KEYNOTE-024 (KN024)) and in those previously treated (KEYNOTE-010 (KN010)). The objective of this analysis is to assess the benefit-risk of pembrolizumab in terms of quality-adjusted survival amongst patients in these trials.

**Methods:** The Quality-adjusted Time without Symptoms of disease progression or Toxicity of treatment (Q-TWiST) analysis was used to compare the trial arms. Survival time of each patient was partitioned into three health states: with toxicity before disease progression, without toxicity before disease progression, and disease progression until death. Toxicities considered were grade 3-4 AEs. Mean utility scores for the three health states were estimated using EQ-5D-3L data collected in the trials. Q-TWiST was calcu- lated as the utility-weighted sum of the mean health state durations. KN024 and KN010 have undergone several interim analyses. Data from each of these analyses were exam- ined. The published criterion [Revicki 2006] for a ‘clearly clinically important’ improvement in Q-TWiST is 15% of mean OS in a study.

**Results:** Based on the most recent analysis of KN024 from July 10, 2017 and KN010 from March 24, 2017, patients randomized to pembrolizumab had 3.25 months (about 20% of mean OS) greater Q-TWiST (P < 0.001) compared to those randomized to platinum-based chemotherapy in KNO24, and 3.11 months (about 25% of mean OS) greater Q-TWiST (P < 0.001), compared to docetaxel in KNO10. Results across KN024 and KN010 trial analyses showed an increase in trend for the Q-TWiST improvement of pembrolizumab over time.

**Conclusions:** Pembrolizumab showed statistically significant and clinically meaningful improvement in quality-adjusted survival using the Q-TWiST analysis compared to chemotherapy in mNSCLC in both previously untreated and treated patients. The ben- efits continued to accrue over the trial follow-up period with extended survival.

Legal entity responsible for the study: Merck & Co Inc.

Funding: Merck & Co Inc.


Legal entity responsible for the study: Merck & Co Inc.


Legal entity responsible for the study: The Authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
1226P

Anti-PD1 inhibitors: Assessment of proper use, efficacy and economic impact in daily practice

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Background: Nivolumab and pembrolizumab have been approved in France in treatment of several metastatic cancers, with an approximate monthly processing cost of €5,550 per patient. The objective of our study was to evaluate efficacy and correct use of these anti-PD1 antibodies in daily practice since its approvals.

Methods: We retrospectively collected data from patients treated with nivolumab or pembrolizumab for solid tumor since July 2015. Data included the correct use of anti-PD1 according to the Summary of Product Characteristics, requiring compliance with indications, a WHO status < 2 and a limit of 20 mg per day of corticosteroids. Progression-free survival (PFS) and overall survival (OS) were analyzed for the global population and according to the correct use of anti-PD1 (C+ group) or not (C- group).

Results: 129 patients were treated with nivolumab or pembrolizumab: 108 (83%) patients for lung cancer, 11 (9%) for clear cell renal cancer and 10 (8%) for melanoma. At the cut-off analysis, with a median follow-up of 9.6 months (0.03 – 31.9), 89 patients (69%) had a progressive disease, 64 patients (50%) were still alive with 18 patients (14%) still receiving anti-PD1, 44 patients (34%) were deceased and 21 patients (16%) were lost to follow-up. The correct use of anti-PD1 was observed in 85 patients (69%), 29 (21%) patients had a WHO status of 2, 7 (5%) patients had a WHO status of 3, and 12 patients received corticosteroids. The poor utilization of treatment for these 44 patients (34%) totaled 338 injections, costing about €740,000 for a total of €3,000,000 of expenditures using this treatment. Median PFS were respectively 6.7 m (CI 95% 3.9 – 11.7) in the C+ group and 2.2 m (33% 1.6- 5.1) in the C- group (p = 0.03). Median OS were respectively 22.8m (CI 95% 13.6- NR) in the C+ group and 8.4 m (CI 95% 5.9-11.8) in the C- group (p < 0.001). Response rate were respectively 34 % in the C+ group and 25% in the C- group.

Conclusions: In our retrospective study, 34% patients were not meeting the SPC criteria with a WHO status, costing for 25% of the total expenditures. These results reflect the willingness of oncologists to give patients access to innovative and promising treatments but should be balanced with the high cost and the poor outcomes in the C- group.

Legal entity responsible for the study: Pitié-Salpêtrière Hospital.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1227P

Immune-related adverse events (irAEs) predict therapeutic efficacy of an anti-PD1 antibody in cancer patients

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Background: In addition to inducing clinical responses, cancer immunotherapy may awaken autoimmune disorders. We have attempted to establish if the incidence of any irAE after Nivolumab used in advanced malignant diseases is associated with anti-PD1 treatment efficacy.

Methods: We studied all advanced cancer patients treated with Nivolumab between January 2016 and September 2017 at our institution. IrAEs were identified according to CTCAE-4.0. Efficacy was evaluated with objective response rate (ORR, immune RECIST criteria) and progression free survival (PFS). Odds Ratio tests were performed to determine the association between irAEs and ORR.

Results: Finally, 64 patients were included. Primary tumor diagnosis were: lung cancer (n = 47), squamous cell carcinoma of head and neck (n = 5), melanoma (n = 4), clear cell renal carcinoma (n = 4), Hodgkiss lymphoma (n = 2), and urothelial bladder carcinoma and gallbladder adenocarcinoma (n = 1, each one). IrAEs were observed in 27 patients (42.2%), and included hypothyroidism (n = 15), nephritis (n = 5) and hyperthyroidism (n = 4) as more frequent. ORR was observed in 28 patients (43.7%). Median PFS was 6 months (1-25). 21 of the 27 patients with irAEs had objective response (77.7%) vs 7 of the 37 cases without irAEs (19%) (OR 15.0, p = 0.000001). PFS in patients with irAEs vs non-irAEs was 7 vs 5 months (HR 2.2, p = 0.016). These results were independent of cancer type, age, sex, histology, ECOG performance status, smoking habit or prior lines of therapy.

Conclusions: In advanced cancer patients treated with an anti-PD1-1 antibody, the incidence of irAEs after Nivolumab is associated with a dramatically improved ORR and PFS. Future studies of anti-PD-1 cancer immunotherapy will need to address this association of toxicity and efficacy in order to reveal the underlying biological mechanisms.

Legal entity responsible for the study: Instituto de Investigación Sanitaria Princesa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1227P Descriptions of patients who developed irAEs

<table>
<thead>
<tr>
<th>irAE Category</th>
<th>TOTAL patients N. (% Total Patients)</th>
<th>irAEs Grade 1-2 N.</th>
<th>irAEs Grade 3-4 N.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>12 (18.9%)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Hypothyroidism + Hypophysitis + Panhypopituitarism + Suprarrenal Insufficiency + Hepatitis + Pneumonitis</td>
<td>1 (1.5%)</td>
<td>1 (Hypophysitis + Panhypopituitarism + Suprarrenal Insufficiency + Hepatitis + Pneumonitis)</td>
<td>1 (Hypothyroidism)</td>
</tr>
<tr>
<td>Hypothyroidism + Hyperthyroidism + Ketoacidos Diabetess</td>
<td>1 (1.5%)</td>
<td>1 (Hypothyroidism + Hyperthyroidism)</td>
<td>1 (Ketoacidos Diabetes)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (1.5%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism + Nephritis</td>
<td>2 (3.2%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis</td>
<td>2 (3.2%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nephritis + Arthritis</td>
<td>1 (1.5%)</td>
<td>1 (Arthritis)</td>
<td>1 (Nephritis)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3.2%)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rash + Encephalitis</td>
<td>1 (1.5%)</td>
<td>1 (Rash)</td>
<td>1 (Encephalitis)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2 (3.2%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1 (1.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total patients irAEs</td>
<td>27 (42.2%)</td>
<td>20 irAEs in grade 1-2</td>
<td>11 irAEs in grade 2-3</td>
</tr>
<tr>
<td>Patients without irAEs</td>
<td>37 (57.8%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
patients (2 CRC, 1 NSCLC) presented a decrease in TGR greater than 15% when given treatment after IT therapy.

### Table: 1228P

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>17</td>
</tr>
<tr>
<td>Median (M) age at diagnosis (range)</td>
<td>55 (31-79)</td>
</tr>
<tr>
<td>M lines prior to IT (range)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Primary tumor Gastrointestinal</td>
<td>19 7 5 4 1 1</td>
</tr>
<tr>
<td>Genitourinary Gynecological NSCLC</td>
<td>15</td>
</tr>
<tr>
<td>Head and neck Breast cancer</td>
<td>15/18/31</td>
</tr>
<tr>
<td>Presence of liver disease (pre/IT/pro)</td>
<td>14/18 0 3/14/21 3/0 13/7</td>
</tr>
<tr>
<td>Other alkylating agents (a)</td>
<td>5/4 1 7/19 1/3 4/1 4/3</td>
</tr>
<tr>
<td>Antimetabolites a Anthracyclics</td>
<td>0/1 0/0 0/0</td>
</tr>
<tr>
<td>Topoisomerase inhibitors (i)</td>
<td>1/0 0/0 0/0</td>
</tr>
<tr>
<td>Antimicrotubules a Antiangiogenic a</td>
<td>2/0 0/0 0/0</td>
</tr>
<tr>
<td>Signal transduction i Immunotherapy</td>
<td>0/0 0/0 0/0</td>
</tr>
<tr>
<td>Others</td>
<td>0/0 0/0 0/0</td>
</tr>
<tr>
<td>Combined/monotherapy during IT</td>
<td>22/15</td>
</tr>
</tbody>
</table>

### Conclusions:
Our data suggest a better outcome on ensuing systemic therapies after IT. Further prospective investigations are needed to select the subset of patients who are more prone to a re-sensitization to CLCT and to understand the mechanisms underlying.

**Legal entity responsible for the study:** Clínica Universidad de Navarra.

**Funding:** Has not received any funding.

**Disclosure:** I. Meler: Advisory: BMS, Roche, AstraZeneca, Gennah, Alligator, Tuak, Bioncotech, Merck/Serono. All other authors have declared no conflicts of interest.

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### Table: 1229P Frequency of adverse events during initial 3 months of treatment

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>IO Cohort (n = 152)</th>
<th>C Cohort (n = 54)</th>
<th>p-value Grades 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (0.7%)</td>
<td>4 (2.6%)</td>
<td>5 (3.9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>1 (0.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0 (0%)</td>
<td>1 (0.7%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>Infectious</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>0 (0%)</td>
<td>1 (0.7%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0.7%)</td>
<td>3 (2.0%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>1 (0.7%)</td>
<td>1 (0.7%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (1.3%)</td>
<td>2 (1.3%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

---

### Background:
Randomized clinical trials (RCTs) in metastatic NSCLC have demonstrated superior responses and lower rates of AEs with 2L IO compared with 2L C. Real-world data (RWD) are lacking to confirm tolerability of IO reported in the controlled environment of RCTs. This study examines RWD on AEs among patients (pts) with metastatic NSCLC receiving either 2L IO or C.

### Methods:
The Cota database electronic health records (EHR) of 55 oncologists at 13 US centers (2 academic; 11 community) were reviewed to identify pts with stage IV NSCLC who received 2L therapy following prior first-line C (March 2015 - December 2017). EHR documented AEs were graded per CTCAE v4 criteria by trained oncology nurses.

### Results:
Of 206 pts identified, 152 received 2L IO and 54 2L C. No differences were noted between cohorts in age (median [years]; IO: 70; C: 65; p = 0.21), sex (IO: 55% male; C: 41%; p = 0.08), or age-adjusted Charlson comorbidity index (IO: 4; C: 4; p = 0.92); more IO pts had squamous cell histology (IO: 23%; C: 9%; p = 0.03). Median duration of 2L therapy [mo (range)] was 2.3 (0-19.1) with IO and 1.7 (0-21.6) with C. AEs of grade 3-4 or any grade resulting in treatment change or discontinuation occurred in 39 (19%) pts; less frequently with IO (13%) vs C (35%; p < 0.01), with 87% of AEs occurring by 3 mo. Cumulative % of pts experiencing AEs by 1, 2, 3, and 4 mo of treatment was significantly lower (p < 0.05) at all time-points with IO vs. C (5.3, 8.6, 10.5, 10.5 vs. 25.9, 25.9, 33.3, 35.2, respectively). Unadjusted survival data were similar.

### Conclusions:
This retrospective study of RWD shows 2L therapy with IO, compared with C, is associated with a lower frequency of AEs of grade 3-4 or any grade leading to treatment discontinuation, over 1 to 4 months of therapy. A limitation is that spontaneous reporting of AEs in RWD likely captures fewer AEs compared with RCTs.

**Legal entity responsible for the study:** Cota.
The efficacy and safety of solid tumors combination therapy with immune checkpoint inhibitor: A systematic review and meta-analysis

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3Clinical Pharmacology and Pharmacometrics, Bristol-Myers Squibb, Princeton, NJ, USA

Background: The combination of immune checkpoint therapy with chemotherapy or target therapy in patients with advanced solid tumors remains unclear. Following the completion of several large phase III clinical trials, the role of combination ICIs therapy in solid tumors should be redefined.

Methods: Pubmed, EMBASE, Cochrane Library and ClinicalTrials.gov website were searched for eligible randomized controlled trials (RCTs). The selection criteria were defined according to the PICOC question: In patients with solid tumors (population), is there any difference in efficacy and safety (outcome) between combination ICIs therapy (intervention) and traditional monotherapy (comparison)?

Results: 17 RCTs with 6,616 patients were included in this meta-analysis. The combination therapy of ICI was significantly associated with improvement of overall response rate (ORR) [HR = 1.56 (95% CI 1.24, 1.96), P < 0.0001], progression-free survival (PFS) (HR = 0.69 (95% CI 0.59, 0.81), P < 0.0001) and overall survival (OS) (HR = 0.76 (95% CI 0.67, 0.87), P < 0.001) in solid tumors. In subgroup analyses, combination ICIs therapy obviously prolonged OS in melanoma patients (HR = 0.64 (95% CI 0.57, 0.72), P < 0.0001), but not in SCCL (HR = 0.94 (95% CI 0.82, 1.08), P = 0.40) and NSCLC (HR = 0.92 (95% CI 0.79, 1.07), P = 0.26) patients. As for toxicity, there was an increased risk of fatigue, rash, diarrhea and increased transaminase with combination ICIs therapy.

Conclusions: In conclusion, our meta-analysis found that combination ICIs therapy showed significant benefits in ORR, PFS and OS for patients with solid tumors. Both of combination of ICI with chemotheroadotherapy and dual ICI were effective and relatively safe. Melanoma patients got definite survival benefit from combination ICI therapy. Combination ICI therapy should be taken into account in clinical practice and future study designs for melanoma patients. There was also a tendency of improvement of survival for SCLC and NSCLC patients. However, the current data of our analyses didn’t support the large-scale clinical application of combination ICI therapy in NSCLC and SCLC patients. Furthermore, numerous RCTs assessing the efficacy and safety of combination therapy with ICI are ongoing.

Legal entity responsible for the study: M. Peng.

Disclosure: All authors have declared no conflicts of interest.

Model-based assessment of benefit-risk profile of nivolumab (NIVO) flat dosing schedules (Q2W and Q4W) across multiple tumor types

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Background: Flat dosing regimens of NIVO 240 mg every 2 weeks (Q2W) and 480 mg every 4 weeks (Q4W) were approved in the US across indications (not including 480 Q4W in MSI-H or dMMR CRC) and the EU across indications (240 mg Q4W) and in melanoma and renal cell carcinoma (480 mg Q4W) to provide flexible and convenient treatment options than the initially approved 3 mg/kg Q2W weight-based regimen. These changes were supported by model-based bridging of available efficacy and safety data.

Methods: NIVO exposures with flat dosing regimens were predicted and compared with 3 mg/kg Q2W dosing for 3817 patients with melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, classical Hodgkin’s lymphoma, small cell lung cancer, hepatocellular carcinoma, colorectal carcinoma, and gastric carcinoma. The impact on differences in time-varying exposure on safety were assessed by time-to-event models of Grade 3–4 treatment-related adverse events (TRAEs) or treatment-related AEs (TRAEs). The impact of differences in early (month 1) exposure on efficacy was assessed by models of tumor growth dynamics and overall survival (OS). Additionally, the potential impact of time-varying exposure on efficacy was assessed by predicting intratumoral programmed death 1 (PD-1) receptor occupancy (RO).

Results: The predicted time-averaged concentration at steady-state for 240 mg Q2W and 480 mg Q4W was similar to 3 mg/kg Q2W (<6% difference), whereas the peak and time-averaged concentration after the first dose were higher with 480 mg Q4W. The predicted cumulative probability of experiencing Grade 2–3 TRAEs or TRAEs with NIVO 240 mg Q2W and 480 mg Q4W were similar to 3 mg/kg Q2W (<4% difference at 2 years). The exposure–response relationship of tumor shrinkage and growth rates were flat. Hazard ratios of OS with NIVO 240 mg Q2W and 480 mg Q4W relative to standard-of-care were predicted to be similar to 3 mg/kg Q2W. The median trough intratumorlal RO at steady state was predicted to be maintained above 90% for all 3 dosing regimens.

Conclusions: The benefit-risk of NIVO 240 mg Q2W and 480 mg Q4W regimens are expected to be similar to 3 mg/kg Q2W, with the added convenience and flexibility for patients and providers.

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


Immunotherapy in clinical practice: Real world multicentric Brazilian experience

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Background: Immunotherapy is a new standard of care for metastatic NSCLC patients. Approval of this therapy was based on randomized phase 3 trials. Clinical trials employ their strict patient selection criteria, and this may not represent the ‘real-world’ population.
Methods: From January 2011 to December 2017, all patients with metastatic NSCLC referred for first oncological evaluation at 4 Hospitals in Brazil were identified by electronic database and included in the analysis. Main eligibility criteria used in first-line phase 3 immunotherapy trials were selected to be evaluated. OS was estimated by Kaplan-Meier curves. Cox proportional hazards model was performed to identify factors associated with survival. All statistical analyses were performed using SAS 9.4.

Results: 537 patients were included in this analysis. Mean age was 62.71 ± 10.47 years, 57.3% male and 67.9% had adenocarcinoma. 352 (63.8%) patients did not meet one or more eligibility criteria. Patients with ECOG PS ≥ 2 and/or active brain metastasis accounted alone for 78.3% of non-eligibility cases. The median OS after the diagnosis of metastatic disease was 7.56 (95% CI: 6.37 to 9.59) months in the non-eligible group and 14.55 (95% CI: 12.16 to 18.23) in the eligible group. Logrank test detected a statistically significant difference between the survival curves in both groups (p = 0.0001).

The hazard ratio (HR) of 1.787 (95% CI: 1.423 – 2.217) to mortality reflects worse prognostic features in non-eligible group. Also, Logrank test detected a statistically significant difference between the survival curves of ECOG 0-1 and ECOG 2-4 (HR 2.313 ± 1.839 – 2.909 p < 0.0001) and histology, with a HR of 1.479 (95% CI: 1.135 – 1.927 p = 0.0036) in favor of adenocarcinoma. Median OS in ECOG 0-1 group was 13.17 months (95% CI: 11.89 – 15.05) and in ECOG 2-4 was 6.05 months (95% CI: 4.67 – 6.77). Median OS in Adenocarcinoma group was 12.48 months (95% CI: 9.63 – 13.81) and in Squamous cell was 6.51 months (95% CI: 5.29 – 11.17).

Conclusions: A significant part of real life Brazilian NSCLC population doesn’t fit the strict selection criteria specified by clinical trials. As soon as the experience and safety with this treatment improves, is desirable that future trials admits patients more representative of real-world NSCLC population.

Legal entity responsible for the study: 1. G. Coelho.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1234P
Correlation, in a real-world setting, between clinical-disease characteristics and compliance with immunotherapy in solid metastatic tumors: First results of an Italian CORE-IMMUNO study

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Background: Nivolumab, Pembrolizumab and Ipilimumab monotherapy has shown survival benefits in patients (pts) with melanoma, kidney, lung and head-neck cancer. The aim of this study is to evaluate safety and treatment compliance in terms of delays in the administration or withdrawal of drugs due to toxicity, according to disease and clinical characteristics of pts in clinical practice.

Methods: In this retrospective study, data were evaluated on pts in the Reggio Emilia Provincial Oncology Network who were treated for solid metastatic tumors with Nivolumab, Pembrolizumab and Ipilimumab monotherapy in clinical practice. The pts included in the study had reached at least 1 dose of therapy by December 2017 and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events (v. 4.1).

Results: A total of 92 pts were analyzed, of which 42 with lung cancer, 35 with melano- noma, 12 with kidney cancer and 3 with head-neck cancer. Sixty-five pts (71%) were treated with Nivolumab, 17% with Pembrolizumab and 12% with Ipilimumab. Overall, 36 pts (39%) experienced an immune-related adverse event (AER) of any grade; 33/92 pts (36%) presented a grade 1-2 AE, while only 7% had a grade 3-4. Out of the 92 pts, the immunotherapy of 17% was delayed due to toxicity, but only 5% of pts discontinued treatment due to AE. No statistically significant differences in PFS (9.5 vs. 5.9 months, p = 0.12) and OS (21.9 vs. 12.2 months, p = 0.15) were found between pts who experienced AEs and those who did not. Cox regression was performed for PFS and OS using sex, performance status (PS), comorbidities, presence of brain metastases, number of previous lines of therapy, number of metastatic sites and age as covariates. For both, only PS (1-2) significantly correlates with poor PFS and OS with respect to PS 0 (p < 0.001).

Conclusions: The data supports the use of immune checkpoint-inhibitors in pts treated in clinical practice with different solid tumors. These treatments are suitable for elderly pts with multiple comorbidities, pts with brain metastases and heavily pretreated pts. However, the use of these drugs should be evaluated with caution in pts with poor PS.

Legal entity responsible for the study: Oncology Unit, AUSL IRCCS Reggio Emilia.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1235P
Safety of immunotherapy in elderly patients: A retrospective analysis of a phase I unit


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Background: Cancer immunotherapy has been used in patients over 70 years old with controversial results. Several age-associated changes including the dysregulation of the immune system could be involved. The main goal of our study is to retrospectively investigate the safety of immunotherapy in elderly patients enrolled in early phase studies regardless tumor type.

Methods: We retrospectively reviewed all cases of patients ≥70 years old enrolled in early phase trials with different immunotherapeutics between January 2016 and March 2018. Eligible patients have received at least one cycle of single agent or a combination of first and/or second generation immune-modulating drugs. The primary aim of the study was to evaluate the safety of such an approach in the elderly population. Toxicity has been graded using the NCI CTCAE v.4.0. Secondary objective was disease control rate (DCR). Fisher test was used to perform the comparison analysis.

Results: We identified 29 patients, of those 21 were eligible and 8 were screening failures. Patients included in the analysis had an ECOG performance status 0-1. Twelve patients were treated with combo regimens (including a backbone of an anti-PD1 in combination with a new generation immune-checkpoint inhibitor) and 9 with monotherapy. Only 2 patients, one treated with combo and one with monotherapy, experienced a grade 3-4 immuno-related toxicity leading to treatment discontinuation: an autoimmune thyroiditis in one case and an autoimmune hepatitis, histologically proven, in the other one. The most common adverse event (AE) was G1-G2 fatigue that occurred in 33% of patients. Immuno-related AEs of any grade were observed in 22% of patients treated with monotherapy compared to 33% in the combo group. Three out of 9 patients treated with monotherapy had a partial response or a stable disease with a DCR of 33%, whereas in the combo group the observed DCR was 66%. Differences were not statistically significant between the two groups for neither toxicity nor efficacy (p value 0.55 and 0.19, respectively). No complete response was observed.

Conclusions: Our results suggest that immunotherapy is an effective and well tolerated treatment for older patients with solid tumors.

Legal entity responsible for the study: The Authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1236TP
The safety and efficacy of durvalumab in combination with paclitaxel for the treatment of metastatic triple negative breast cancer

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Background: Metastatic triple negative breast cancer has poor prognosis and limited treatment options. Immunotherapy with anti-PD-L1 monoclonal antibodies has shown promising results in several types of cancer including triple negative breast cancer. We have initiated a clinical trial to test the safety and efficacy of a combination of the investigational anti-PD-L1 monoclonal antibody durvalumab and paclitaxel for the treatment of metastatic breast cancer. The rationale behind this trial is that treatment with paclitaxel correlates with development of tumor infiltrating lymphocytes (Demaria et al. 2001; Sardella et al. 2006), and the upregulation of PD-L1 on tumor cells. On the other hand, response to targeted anti-PD-L1 therapy correlates with the level of expression of PD-L1 on tumor cells and the pre-existing tumor immunity like CD8+ infiltrating cells and type 1 helper CD4+ activated lymphocytes (Herbst, Soria et al. 2014). In addition, PD-L1 has anti-apoptotic function that it blockade will synergize with the apoptotic effect of chemotherapeutic agents like paclitaxel. Therefore, the combination of these two agents is likely to be synergistic.

Trial design: The treatment is designed to start with one cycle of paclitaxel alone to enhance the immunogenicity and immune cell infiltration followed by the combination of the two agents. Paclitaxel will be delivered weekly on days 1, 8 and 15 of each 28 days cycle while Durvalumab will be given every two weeks (Days 1 and 15 of each cycle). Paclitaxel is given for 6 cycles only while Durvalumab is given until disease progression, or unacceptable toxicity. The primary endpoint of the study is to measure safety and tolerability of the combination while the secondary endpoints include efficacy monitoring.

Legal entity responsible for the study: T. Al-Tweigeri, M.D.

Funding: This clinical trial is an investigator-initiated trial sponsored partially by AstraZeneca as an externally sponsored research (ESR 14 10649).

Disclosure: All authors have declared no conflicts of interest.
A first-in-human phase VII clinical trial assessing novel mRNA-lipopolyplex nanoparticles encoding shared tumor antigens for immunotherapy of malignant melanoma


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Background: Local therapeutic vaccination with tumor antigen-encoding mRNA is being investigated in various clinical trials. We have developed a novel class of RNA-lipopolyplexes (RNA-LP) immunotherapeutics for intravenous administration allowing systemic targeting of antigen-presenting cells (APCs). RNA-LP is a novel nanoparticulate formulation of lipid-complexed mRNA which selectively delivers the functional mRNA to APCs in lymphoid compartments outside of the lymphatic system to induce potent cell-mediated immune responses. Moreover, this formulation has intrinsically strong adjuvant activity, mimics a systemic viral infection, and induces synchronized activation of potent adaptive as well as type I–IFN-mediated innate immune responses (Kranz et al., 2016).

Trial design: The first-in-human phase I dose escalation Lipo-MERIT trial (NCT021070173) is the first clinical trial assessing the intravenous administration of a RNA-based cancer vaccine. The trial assesses the safety and tolerability of systemic RNA-LP2, immunotherapy in patients with stage IIB/C and IV melanoma in four German study centers. Patients are treated with two repeated doses of the tetralvalent Lipo-MERIT vaccine composed of RNA-LP2 products encoding the shared melanoma-associated antigens NY-ESO-1, tyrosinase, MAGE-A3, and TPIE based on the expression of at least one of these antigens in routinely collected patients’ tumor samples. Patients in dose escalation cohorts (classical 3 + 3 design) follow a step-up dosing towards different target doses. Pharmacodynamic activity and immunogenicity of the vaccine is investigated by concerted immune monitoring and correlative biomarker studies. Clinical activity is assessed following imaging according to RECIST 1.1.


Legal entity responsible for the study: BioNTech AG.

Disclosure: None.

Background: Significant survival benefit has been achieved with CIT across multiple tumour types, but only subsets of patients (pts) experience durable responses with CIT monotherapy. Efficacious CIT combinations targeting multiple cancer immune escape mechanisms need to be identified to extend clinical benefit to more pts. The MORpheus platform includes multiple Phase Ib/II trials designed to identify early signals of safety and activity of CIT combinations. Using a randomised trial design, multiple CIT combination arms are compared with a single standard-of-care control arm. We present 7 tumour type-specific MORpheus trials, each evaluating various CIT combinations that simultaneously enhance immune-cell priming and activation, tumour infiltration and/or recognition of tumour cells for elimination.

Trial design: The MORpheus trials described here are global, open-label, randomised, Phase Ib/II trials enrolling pts with 1 of the following cancers: pancreatic ductal adenocarcinoma (PDAC), gastric or gastro-oesophageal junction cancers (GGJG), hormone receptor positive or triple-negative breast cancers (HR+/TNBC), non-small cell lung cancer (NSCLC), or colorectal cancer (CRC) (Table). These trials have the flexibility to open new treatment arms with novel CIT combinations as they become available and to close arms that show minimal activity or unacceptable toxicity. Pts experiencing loss of clinical benefit or unacceptable toxicity may be eligible to switch to a different CIT combination arm. Eligibility requires measurable disease per RECIST v1.1. Further eligibility criteria will be provided. Primary endpoints are safety and investigator assessed ORR per RECIST v1.1. Secondary endpoints include PFS, OS, DCR and DOR. Exploratory biomarkers will also be examined.
 Clinical trial identification: NCT03133266.

Table: 1239TiP

<table>
<thead>
<tr>
<th>Cancer Type</th>
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<th>No. of Experimental Arms</th>
<th>Countries Currently Targeted for Enrolment</th>
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<td>3</td>
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<tr>
<td>GC and GEJ</td>
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<td>2</td>
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<tr>
<td>2L</td>
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<tr>
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<tr>
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<tr>
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<td></td>
<td>2L-4b</td>
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<tr>
<td>CRC</td>
<td>3L</td>
<td>2</td>
<td>Australia, France, South Korea, Spain, United Kingdom, United States</td>
</tr>
</tbody>
</table>

*Not all experimental arms may be open at the same time.

bPatients who have progressed on prior platinum chemotherapy and anti–PD-L1/PD-1 treatment given concurrently or sequentially. CIT, cancer immunotherapy; CRC, colorectal cancer; GC, gastric cancer; GEI, gastro-esophageal junction cancer; HR+, BC, hormone receptor–positive breast cancer; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PDAC, pancreatic ductal adenocarcinoma; PD-L1, programmed death-ligand 1; TNBC, triple-negative breast cancer.

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Background: Avelumab, a human anti–PD-L1 IgG1 monoclonal antibody, is approved for the treatment of metastatic Merkel cell carcinoma in various countries and advanced urothelial carcinoma after progression on platinum therapy in the United States and Canada. Talazoparib is a potent, orally bioavailable PARP inhibitor with a dual mechanism (PARP enzyme inhibition and PARP trapping). Preclinical studies suggest that the combination of an immune checkpoint inhibitor and PARP inhibitor may have additive antitumor activity, and initial clinical studies support evaluation of this combination.

Trial design: JAVELIN PARP Medley (NCT03304055) is an open-label, multicohort, phase 1b/2 trial investigating avelumab plus talazoparib in >336 patients with selected solid tumors. Eligible adult patients have locally advanced (primary/recurrent) or metastatic solid tumors that are not amenable for treatment with curative intent, including non-small cell lung cancer with no EGFR mutations, triple-negative breast cancer, hormone receptor–positive and HER2-negative breast cancer, recurrent platinum-sensitive ovarian cancer, urothelial carcinoma, castration-resistant prostate cancer (CRPC), or advanced solid tumors with BRCA/ATM defects. Requirements for prior antitumor therapy and platinum exposure vary between phases 1b and 2 and between tumor types. Prior treatment with a PARP inhibitor or immunotherapy is not permitted. Different daily oral doses of talazoparib plus avelumab 800 mg IV QW2 will be administered in phase 1b to define the recommended phase 2 dose for the combination before enrolling patients in phase 2. The primary endpoints in phase 1b are first-cycle dose-limiting toxicity, and in phase 2, it is objective response according to RECIST 1.1 (also according to Prostate Cancer Working Group 3 [PCWG3] for patients with CRPC). Other endpoints include duration of response and progression-free survival according to RECIST 1.1 (plus PCWG3 for CRPC), overall survival, adverse events, laboratory abnormalities, pharmacokinetic parameters, and tumor tissue biomarkers. Enrollment in phase 2 of the study is expected to begin in Q3 2018.

Clinical trial identification: NCT03303405

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Legal entity responsible for the study: Pfizer.

Funding: This trial was sponsored by Pfizer and is part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.


1243TiP
Study of TBI-1301 (NY-ESO-1 specific TCR gene transduced autologous T lymphocytes) in patients with solid tumors

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Background: The use of cell based immune therapies involving infusion of autologous T lymphocytes with anti-tumor activity targeting tumor-associated antigens is a rapidly evolving area of research. One approach involves the use of peripheral blood as a source of lymphocytes that are then used in the generation of cytotoxic tumor-specific T cells via introducing a tumor-specific TCR gene into T lymphocytes. NY-ESO-1 is a cancer testis antigen expressed in numerous cancers yet absent in most adult normal tissues except in high expression in adult testes—thereby making it an ideal target for immunotherapy.

Trial design: TBI-1301 is a gene-modified T cell product that contains a NY-ESO-1 specific TCR introduced with the MSII-1-NY-ESO-1-STCR retroviral vector. This vector encodes for TCR a and b chains that recognize an NY-ESO-1 derived epitope (amino acids 157-165: SLLMWDIIG) that is presented to the TCR by HLA-A*02:01 and HLA-A*02:06 molecules. The vector also encodes for siRNA (small interfering RNA) that are homologous to the constant region sequence of the endogenous, but not transduced TCR a and b chain mRNAs—these siRNAs in turn increase expression of the transduced TCR. Pre-clinical murine studies demonstrated safety, persistence, and efficacy of transduced T cells. This study represents a Phase 1b study of TBI-1301 in patients with advanced solid tumors, which express NY-ESO-1 (ovarian carcinoma, melanoma, and melanoma). A pre-conditioning lymphodepletion regimen of cyclophosphamide 750 mg/m2 will be used on Day -3 and Day -2 prior to infusion of product. The objectives of this study include assessing the safety profile of TBI-1301, determining the RP2D dose, and evaluating the efficacy of TBI-1301 via RECIST v1.1.

Clinical trial identification: NCT02869217.

Legal entity responsible for the study: Tumor Immunotherapy Program, Princess Margaret Cancer Centre.

Funding: Takara Bio Inc.

Disclosure: M.O. Butler: Advisory boards: Merck Canada, BMS, Novartis, Immunocore, Immunovaccine, GSK; Research support: Takara Bio Inc. conducting this clinical trial. S. Tanaka: Employee: Takara Bio Inc. N. Hirano: Research support: Takara Bio Inc. All other authors have declared no conflicts of interest.

1244TiP
Phase I study of BI 754111 (anti-LAG-3) plus BI 754091 (anti-PD-1) in patients (pts) with advanced solid cancers, followed by expansion in pts with microsatellite stable metastatic colorectal cancer (mCRC), anti-PD-L1 (pembrolizumab)-pretreated non-small cell lung cancer (NSCLC) and other solid tumors

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Background: Lymphocyte-activation gene 3 (LAG-3) is a negative regulator of immune response implicated in T cell exhaustion and tumor immune escape. Available data demonstrate that tumors-derived T cells frequently co-express the PD-1 and LAG-3 co-inhibitory receptors and that dual blockade of the LAG-3 and PD-1 pathways results in more potent reactivation of T-cell function and anti-tumor immune response than blockade of the individual pathway. BI 754091 and BI 754111 are monoclonal IgG4Pro antibodies (mAbs) against PD-1 and LAG-3, respectively. In this Phase I study, we investigate the safety, tolerability, PK, and preliminary efficacy of the combination of these two mAbs.

Trial design: This 2-part, open-label, non-randomized ongoing study consists of dose escalation in pts with advanced solid cancers followed by expansion cohorts in pts with NSCLC, microsatellite-stable (MSS) mCRC, or any PD-1/PD-L1 pretreated solid tumor with high tumor mutational burden (TMB-H) and/or high microsatellite instability and/or DNA mismatch repair deficiency (MSI-H/MMRd). Dose escalation in pts with solid tumors started at 4mg q3w BI 754111 and was guided by Bayesian Logistic Regression Method. All dose levels of BI 754111 were co-administered with 240 mg q3w BI 754091 (the BI 754091 RIDP selected from 1381.1 phase I [Johnson, et al. ASCO-STTC 2017 abstract 212]). Enrollment in the solid tumor dose escalation portion is nearly complete. The expansion phase will use a combination dose selected from the solid tumor dose escalation. Primary endpoints in the dose escalation are the number of pts with dose-limiting toxicities and the combination MTD. The primary endpoint of the dose expansion portion is the objective response rate.

Clinical trial identification: NCT03156114.

Legal entity responsible for the study: Boehringer Ingelheim Pharmaceuticals, Inc.

Funding: Boehringer Ingelheim Pharmaceuticals, Inc.

Disclosure: M. Elgadi: Employee: Boehringer Ingelheim (Canada) Ltd./Ltee. M. Ge, C. Duffy: Employee: Boehringer Ingelheim Pharmaceuticals, Inc. R. Graeser: Employee: Boehringer Ingelheim Pharma Gmbh & Co. KG. All other authors have declared no conflicts of interest.
MELANOMA AND OTHER SKIN TUMOURS

12440 KEYNOTE-022 Part 3: Phase II randomized study of 1L dabrafenib (D) and trametinib (T) plus pembrolizumab (Pembro) or placebo (PBO) for BRAF-mutant advanced melanoma


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1245PD Intratumoral (IT) injection of the TLR9 agonist tilsotolimod (IMO-2125) in combination with ipilimumab (ipi) triggers durable responses in PD-1 inhibitor refractory metastatic melanoma (rMM): Results from a multicenter, phase I/II study

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Talimogene laherparepvec (T-VEC) treatment increases intratumoral effector T-cell and natural killer (NK) cell density in noninjected tumors in patients (pts) with stage IIIB–IVM1c melanoma: Evidence for systemic effects in a phase II, single-arm study


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Phase II multicenter, single arm, open label study of nivolumab in combination with ipilimumab in untreated patients with metastatic uveal melanoma (GEM1402.NCT02626962)


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1248PD Efficacy of pembrolizumab (Pembro) in patients (Pts) with advanced melanoma with stable brain metastases (BM) at baseline: A pooled retrospective analysis


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1249PD Concomitant radiotherapy in melanoma brain metastases using the propensity score matching within the French cohort, MelBase

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1250P Estimate of long-term relapse-free survival (RFS) and analysis of baseline factors associated with RFS in the COMBI-AD trial


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Background: Adjuvant therapy with dabrafenib plus trametinib (D + T) for 12 months significantly reduced the risk of relapse or death vs placebo (Pbo; HR, 0.47; P < 0.001) in patients (pts) in the COMBI-AD trial with resected BRAF V600–mutant stage III melanoma (NCT01688203), leading to the recent US FDA approval in this indication. We used a cure-rate model to estimate long-term RFS benefit and explore the association of baseline factors with RFS to better characterize pts likely to benefit from adjuvant treatment.

Methods: COMBI-AD randomized pts with completely resected BRAF V600E/K–mutant stage III melanoma to receive adjuvant (D + T) or placebo (Pbo). Estimated 3-year (110 months) survival with the Peto method. Cox regression analysis was performed using a stratified Cox regression model for RFS, with P values calculated using a Weibull cure-rate model. Baseline covariates were analyzed using a stratified Cox regression model for RFS, with P values calculated using a Weibull cure-rate model. Baseline disease characteristics and RFS demonstrated that lower T stage, lesser nodal involvement, and a superficial spreading melanoma subtype were independently associated with better RFS (Table). Conversely, tumor ulceration and the presence of in-transit metastases were not associated with RFS. With respect to baseline patient demographics, an association was observed between female sex and RFS benefit (P = .036).

Results: Eight hundred seventy pts were enrolled (D + T, n = 438; Pbo, n = 432). The median follow-up was 2.8 years. Of the 784 pts alive and disease-free (720 D + T, 64 Pbo), 767 (77.0%) were censored. The estimated 3 years survival was 95.5% (95% CI, 93.2%-97.6%) in the D + T arm vs 88.2% (95% CI, 84.4%-91.7%) in the Pbo arm. Evaluation of the association between baseline disease characteristics and RFS demonstrated that lower T stage, lesser nodal involvement, and a superficial spreading melanoma subtype were independently associated with better RFS (Table). Conversely, tumor ulceration and the presence of in-transit metastases were not associated with RFS. With respect to baseline patient demographics, an association was observed between female sex and RFS benefit (P = .036).

Conclusions: The results of the long-term RFS analysis suggest potential long-term RFS in >50% of pts treated with D + T. Lower T stage and less nodal involvement at baseline were associated with better RFS.

Clinical trial identification: NCT01688203.

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Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Disclosure: R. Dummer: Intermittent, consulting, advisor: Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma outside the submitted work. D. Schadendorf: Personal fees: Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Novartis, Incyte; Regeneron, 45C, AstraZeneca, Bristol-Myers Squibb, MS, Pierre Fabre, Merck-EMD, Pfizer, Philogen, Array; Patients’ fees to institution: MSD, Roche, Novartis, Regeneron, Bristol-Myers Squibb, Medac-EMD, Philogen. A. Hauchsd: Consultancy: Agenon, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provecutus, Regeneron, Roche, Oncosec; Research funding: Agenon, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Pierre Fabre, Provecutus, Regeneron, Roche; Honoraria: Agenon, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Philogen, Pierre Fabre, Provecutus, Roche. V.G. Atkinson: Consulting or advisory role: Bristol-Myers Squibb, MSD, Novartis, Merck Serono, Pierre Fabre; Honoraria: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Merck Serono; Speakers’ bureau: Bristol-Myers Squibb, MSD, Novartis, Roche; Travel, accommodations, expenses: Bristol-Myers Squibb. M. Mandala: Research funding, Honoraria, Speakers bureau: Novartis, Roche. V. Chiarion Sileni: Consultancy: Bristol-Myers Squibb, MSD, Novartis, Pierre-Fabre, Merck Serono. J. Larkin: Consultancy, Honoraria: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Kemah, Pfizer, Novartis, Roche, Genentech, Secarna, Pierre-Fabre, EUSA Pharma; Research funding: Bristol-Myers Squibb, Merck Serono, MSD, Novartis, Pfizer. M.S. Nyakas: Honoraria (institution) for advisory board: Novartis, Incyte. C. Duitiaux: Consultancy: Bristol-Myers Squibb, MSD; Membership on board of directors or advisory committee: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD. Clinical trials investigator: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD, Agenon. A. Hauschild: Consultancy: Amgen, Bristol-Myers Squibb, Medac-EMD, Pfizer, Philogen; Research funding: Agenon, Bristol-Myers Squibb, Medac-EMD, Pfizer, Philogen. V. Chiarion Sileni: Consultancy: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD, Novartis, Roche; Travel, accommodations, expenses: Bristol-Myers Squibb X. Feng, E. de Jong: Employee: Novartis. B. Mookerjee: Employee: Novartis; Stock ownership: Novartis, GlaxoSmithKline, AstraZeneca, R. Kefford: Membership on board of directors or advisory committees: Bristol-Myers Squibb, Amgen, Merck, Novartis, Teva; Conference travel: Bristol-Myers Squibb, Amgen. J.M. Kirkwood: Consultancy: Bristol-Myers Squibb, Novartis, Array Biopharma, Merck, Roche, Amgen, Immunocore, Prothenex; Research funding: Merck. G.V. Long: Consultancy: Amgen, Bristol-Myers Squibb, Merck MSD, Novartis, Roche, Pierre-Fabre, Array; Honoraria: Bristol-Myers Squibb, MSD, Roche, Novartis, Incyte. All other authors have declared no conflicts of interest.

Table: 1250P Stratified Cox regression model for RFS (N/n= 870/845)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Effect Tested</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male/Female</td>
<td></td>
<td>1.25 (1.02-1.53)</td>
<td>.030</td>
</tr>
<tr>
<td>T stage: 1/4 2/4 3/4</td>
<td></td>
<td>0.49 (0.34-0.70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T tumor ulceration: Yes/No</td>
<td></td>
<td>0.94 (0.74-1.20)</td>
<td>.630</td>
</tr>
<tr>
<td>N stage: 1/3 2/3</td>
<td></td>
<td>0.67 (0.49-0.93)</td>
<td>.17.109</td>
</tr>
<tr>
<td>In-transit metastases: Yes/No</td>
<td></td>
<td>1.05 (0.76-1.47)</td>
<td>.753</td>
</tr>
<tr>
<td>Melanoma subtype: Superficial spreading/other Nodular/other</td>
<td></td>
<td>0.73 (0.57-0.93)</td>
<td>.010 321</td>
</tr>
</tbody>
</table>

*N/n= total population/patients with data available for all covariates.*
Clinical results show that most AEs with adjuvant D to T led to a significant improvement in relapse-free survival vs Pbo in its treated BRF600–mutant stage III melanoma supporting recent US FDA approval in this indication. There were no new safety signals; however, a higher rate of permanent discontinuation due to AEs was observed compared to CTCAE v4.0. To assess AEs over time, exposure-adjusted AE rates (no. of occurrences/pt/3-mo exposure) were calculated over 3-mo intervals.

Results: Although most pts in both arms experienced AEs, the majority of AEs were grade 1. The exposure-adjusted AE rate of any event in pts treated with D + T was 6.14 occurrences/pt/3-mo exposure. However, the AE rates declined substantially with increased time on treatment. Results: The table shows the number of adverse events per patient per 3-month exposure for dabrafenib plus trametinib (D + T) and placebo (Pbo) in the COMBI-AD trial.

### Table: 1251P AE occurrences per patient per 3-month exposure

<table>
<thead>
<tr>
<th>Term</th>
<th>Preferred Dabrafenib ± Trametinib (n = 435)</th>
<th>Placebo (n = 432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Conclusion

The results show that most AEs with adjuvant D + T occurred during the first 3 mo of treatment and declined thereafter, indicating the importance of AE management early during treatment to prevent premature discontinuations and allow patients to complete 1 yr of adjuvant treatment.

### Table 1252P Management of melanoma recurrence following adjuvant anti-PD1 therapy

<table>
<thead>
<tr>
<th>Pts subset</th>
<th>Methodology</th>
</tr>
</thead>
</table>
| Patients with resected stage III or IV melanoma who received adjuvant anti-PD1-based therapy (pembrolizumab or nivolumab) at two sites since 2015 and who had a melanoma recurrence included. Disease characteristics prior to adjuvant therapy, adjuvant treatments received, timing and nature of recurrences, and subsequent local and systemic management and their outcomes were examined.

Results: 28 patients (pts) had a melanoma recurrence during or following adjuvant anti-PD1 therapy (including 5 on nivolumab/pembrolizumab combination). Prior to adjuvant therapy, 26 patients had stage III (13 IIIa, 12 IIIb, 1 IIIc), 2 had resected stage IV melanoma, 16 were male, median age 59 years, and 12 were BRAF V600E mutation positive (11 wildtype, 5 unknown). 22 (79%) occurred during adjuvant therapy, 6 occurred following cessation of therapy (1 after completing 12 months, 4 after ceasing early for toxicity, 1 withdrew consent). Median time to recurrence from surgery was 6.8 mo (range 2.8-28.2). 15 recurrences were detected clinically and 13 on 3-monthly imaging. 15 (46%) recurrences were loco-regional only, and 15 distant (2 brain, 16) patients were treated with surgery at recurrence (10 local, 1 brain and 1 lung metastasis) to no evidence of disease, and 6 have subsequently recurred. Data on systemic therapy after recurrence (either 1 relapse or 2nd after surgery salvage) are in the Table. Of 17 patients who declared no conflicts of interest.

### Disclosure

V.G. Atkinson: Consulting or advisory role: Bristol-Myers Squibb, MSD, Novartis, Merck Serono, Pierre Fabre; Honoraria: Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Merck Serono; Speakers’ bureau: Bristol-Myers Squibb, MSD, Novartis, Roche; Travel, accommodations, expenses: Bristol-Myers Squibb, A. Hauschild: Consultancy: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/ Merck, Novartis, Phligen, Pierre Fabre, Provectus, Regeneron, Roche, OncoCeol; Research funding: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Phligen, Pierre Fabre, Provectus, Regeneron, Roche, Honoraria: Amgen, Bristol-Myers Squibb, Merck Serono, MSD/Merck, Novartis, Phligen, Pierre Fabre, Provectus, Roche, M. Mandala: Research funding, Honoraria, Speakers bureau: Novartis, Roche. V. Chiarion Sileni: Consultancy: Bristol-Myers Squibb, MSD, Novartis, Pierre-Fabre, Merck Serono. J. Larkin: Consultancy and honoraria: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Kymab, Pfizer, Novartis, Roche, Genentech, Secarna, Pierre-Fabre, EUSA Pharma, Research funding: Bristol-Myers Squibb, MSD, Novartis, Pfizer. M.S. Nyakas: Honoraria (institution) for advisory board: Novartis, Incyte, C. Dutriaux: Consultancy: Bristol-Myers Squibb, MSD, Membership on board of directors or advisory committees: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD; Clinical trials investigator: Bristol-Myers Squibb, Roche, Novartis, Merck Serono, MSD, Amgen. A. Haydon: Honoraria: Novartis, L. Mortier: Research funding: Novartis; C. Robert: Advisory board: Merck, MSD, Novartis, Roche, J. Schachter: Honoraria: Bristol-Myers Squibb, MSD; Travel, accommodations, expenses: Bristol-Myers Squibb. D. Schindofen: Personal fees: Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Novartis, Incyte, Regeneron, 45C, AstraZeneca, Bristol-Myers Squibb, MS, Pierre Fabre, Merck-EMD, Pfizer, Phligen, Arroy; Patients’ fees to institution: MSD, Roche, Novartis, Regeneron, Bristol-Myers Squibb, MECU-EMD, Phligen, X. Feng, E. de Long, Novartis. B. Moorkerjee: Employment: Novartis; Stock ownership: Novartis, GlaxoSmithKline, AstraZeneca. R. Kefford: Membership on board of directors or advisory committees: Bristol-Myers Squibb, Roche, Merck, Novartis, Teva; Conference travel: Bristol-Myers Squibb, Amgen, K. Dummer: Internment, project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dohme (MSD), Bristol-Myers Squibb, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma outside the submitted work. J. M. Kirkwood: Consultancy: Bristol-Myers Squibb, Roivas, Array Biopharma, Merck, Roche, Amgen, Immunocore, Prometheus; Research funding: Merck. G. V. Long: Consultancy: Amgen, Bristol-Myers Squibb, Merck MSD, Novartis, Roche, Pierre-Fabre, Array, Honoraria: Bristol-Myers Squibb, MSD, Roche, Novartis, Incyte. All other authors have declared no conflicts of interest.
Conclusions: These data are the first to demonstrate the utility of salvage therapy for pts who progress early despite adjuvant anti-PD1. Early data suggest that this is a challenging group, likely to require multimodal treatment. Updated analyses will be presented.

Legal entity responsible for the study: Melanoma Institute Australia.

Funding: Has not received any funding.

Disclosure: M.S. Cañizo: Consultant advisor: Novartis, BMS, Merck MSD, Amgen, Pierre-Fabre; A.M. Menez: Consultant advisor: BMS, Merck MSD, Novartis, Pierre-Fabre, Roche; G.V. Long: Consultant advisor: Amgen, BMS, Merck MSD, Novartis, Pierre-Fabre, Roche. All other authors have declared no conflicts of interest.

Table: 1252P

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Best RECIST response</th>
<th>Not reached first scan</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>PR</td>
</tr>
<tr>
<td>BRAF/MEK</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combination anti-PD1/C-TLA-4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combination anti-PD1/LAG-3</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MEX+CDCA/6i</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>2</td>
<td>4</td>
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Disclosures: V. Franke; Travel grant, Research funding: Amgen. A.C.J. van Akkooi: Honoraria: Amgen, Novartis, MSD/Merck; Travel cost: Amgen, Novartis, MSD/Merck. All other authors have declared no conflicts of interest.

1253P

High response rate with T-VEC in early metastatic melanoma (stage IIIB/C-IVM1a)

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Background: Talimogene laherparepvec (T-VEC) is a modified herpes simplex virus, type 1 (HSV-1), which can be administered intralesionally in patients with stage IIIB/C-IVM1a unresectable melanoma (EMA label). The phase 3 OPTIM registration study showed an overall response rate (ORR) of 26%.

Methods: Since approval of T-VEC in the Netherlands in December 2016, 35 eligible patients started treatment with T-VEC monotherapy at the Netherlands Cancer Institute. The median number of lesions was 5 and 50 lesions. Grade 1-2 AE’s occurred in all patients. Mostly, these consisted of fatigue, influenza-like symptoms and injection site pain. 1 patient had to pause treatment due to grade 3 AE (colitis). Prior treatment was documented: all 23 patients underwent surgical resection, 13 isolated limb perfusion (56.5%), 1 targeted therapy (4.3%), 2 immunotherapy (8.7%), 2 radiotherapy (8.7%). Prior treatment did not influence response or toxicity of T-VEC. PET-CT and biopsies proved to be a clinically useful tool to evaluate treatment response for T-VEC monotherapy, confirming CR or PD to stage IV disease requiring systemic treatment.

Results: The median follow-up was 11.3 months. Of 23 patients, 12 (52.2%) had a complete response (CR) as their best response, all except for one ongoing after stopping treatment. As their best response, 7 (30.4%) patients had a partial response (PR), 2 (8.7%) patients had a mixed response and 2 (8.7%) patients showed progressive disease (PD). ORR for the analyzed cohort was 82.6%. Disease Control Rate (DCR) was 91.3%. At baseline, the mean number of lesions was between 5 and 50 lesions. Grade 1-2 AE’s occurred in all patients. Mostly, these consisted of fatigue, influenza-like symptoms and injection site pain. 1 patient had to pause treatment due to grade 3 AE (colitis). Prior treatment was documented: all 23 patients underwent surgical resection, 13 isolated limb perfusion (56.5%), 1 targeted therapy (4.3%), 2 immunotherapy (8.7%), 2 radiotherapy (8.7%). Prior treatment did not influence response or toxicity of T-VEC. PET-CT and biopsies proved to be a clinically useful tool to evaluate treatment response for T-VEC monotherapy, confirming CR or PD to stage IV disease requiring systemic treatment.

Conclusions: ORR for T-VEC monotherapy at our institute was 82.6% with 52.2% achieving a CR. This prospective study for T-VEC in early metastatic (stage IIIB/C-IVM1a) melanoma demonstrated superior results to the phase 3 OPTIM study and confirms the role of oncolytic immunotherapy for melanoma.

Legal entity responsible for the study: Alexander C.J. van Akkooi.

Funding: Has not received any funding.

Disclosure: V. Franke; Travel grant, Research funding: Amgen. A.C.J. van Akkooi: Honoraria: Amgen, Novartis, MSD/Merck; Travel cost: Amgen, Novartis, MSD/Merck. All other authors have declared no conflicts of interest.

1254P

Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection, REDUCTOR trial

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Background: The aim of this trial is to evaluate the potency of short-term neoadjuvant cytoreductive therapy with dabrafenib and trametinib (BRAF and MEK inhibitor respectively) to allow radical surgical resection in patients with unresectable BRAF-mutated, locally advanced stage III or oligometastatic stage IV melanoma.

Methods: A total of 25 patients with BRAF-mutated, unresectable locally advanced stage III or oligometastatic stage IV (≤3 metastases) melanoma will be treated with dabrafenib and trametinib for 8 weeks. Response evaluation by positron emission tomography/computed tomography (PET/CT) will occur at 2 and 8 weeks. If sufficient downsizing occurs, surgical resection will be performed. Biopsies for translational research will be taken at baseline and 2 weeks. The dissection specimen will be stored at 8 weeks.

Results: Currently 17 patients have been included. Of these, 2 patients showed PD upon treatment and did not proceed to surgery. In 14/15 (93%) patients resection was possible after neoadjuvant treatment, of which 13 (93%) were R0 resections. Median follow-up time is 22 months with a median recurrence free survival of 9 months in patients undergoing surgery. The 1-year overall survival (OS) was 88% and 2-year OS 59%. Median OS was not reached. Metabolic response rate (RR) on PET/CT at 8 weeks were: 4 (24%) CR, 11 (65%) PR, 0 (0%) SD, 2 (12%) PD. Pathologic RR differed: 6 (35%) CR, 5 (29%) PR, 3 (19%) SD, 0 (0%) PD and in 3 patients (18%) no pathologic response was measured, since no resection was performed. Most patients (82%) experienced any toxicity of which the majority (64%) was grade 1 and the most common reported toxicity was fever. Grade 3 toxicity occurred in 2 patients (12%).

Conclusions: Neoadjuvant dabrafenib and trametinib shows to be a potential cytoreductive treatment, allowing radical resection of metastases in 13/17 (76%) patients with prior unresectable locally advanced melanoma. Patients with no recurrence remained disease-free for a prolonged period of time. If there was recurrent disease, this usually occurred within months after surgery and this may present an opportunity for further tailored adjuvant therapy.

Clinical trial identification: EuDraCT: 2013-002616-28

Legal entity responsible for the study: Netherlands Cancer Institute, Amsterdam, The Netherlands.

Funding: Netherlands Cancer Institute and Novartis.

Disclosure: D. Peepers: Research support: BMS, A.C.J. van Akkooi: Consulting or advisory role: Amgen, Novartis, MSD Oncology, Merck Research funding: Amgen, Novartis; Travel, accommodations, expenses: Amgen, Novartis, MSD Oncology, Merck, J.B.A.G. Haanen: Compensation to NKI for advisory roles: BMS, Merck, Roche, Neon Therapeutics, Pfizer, Ipsen; Grants to NKI: BMS, Merck, Novartis, Neon Therapeutics. All other authors have declared no conflicts of interest.

1255P

Impact of intralesional interleukin 2 (IL2) for in-transit melanoma in two Canadian centres

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Background: In-transit (IT) melanoma is a form of metastatic disease that is associated with high morbidity and is often refractory to treatment. Intralesional (IAL) IL2 has been increasingly utilized to obtain loco-regional control. This study utilizes a national
Background: Combination ipilimumab and nivolumab is a highly active systemic ther-
apy for metastatic melanoma but can cause significant toxicity. How best to integrate this combination into clinical practice, in real-world patients, and in the setting of BRAF targeted therapy, is not clear. We sought to explore the safety and efficacy of combination ipilimumab and nivolumab in such a population.

Methods: Consecutive patients with untreated stage IIIC/IV melanoma commenced on ipilimumab plus nivolumab via an early access scheme across 10 tertiary melanoma institutions in Australia were identified retrospectively. Data collected included demo-
graphics, prior and subsequent systemic treatments, toxicity, RECIST response and survival outcomes.

Results: 152 patients were included for analysis, including 60 (39%) treatment-naïve and 33 (22%) who had failed first-line BRAF/MEK inhibitors and then treated with combination therapy second-line. In the whole cohort, most patients had a high AJCC M stage (65% M1c, 26% M1d) and elevated LDH (55%), with similar distribution of adverse features in the treatment naïve and BRAF/MEK failure subgroups. Treatment-related adverse events occurred in 102 (67%) patients, grade 3–5 in 38% (1 death from immune myocarditis). The objective response rate was 41% in the whole cohort, 57% (17% complete) in treatment naïve, and only 21% (3% complete) in BRAF/MEK failure patients. Median progression-free survival was 4.0 months (95% CI, 3.0 to 6.0) in the whole cohort, 11.0 months (95% CI, 6.0 - NR) in treatment-naïve patients, and 20 months (95% CI, 1.4 - 4.6) in BRAF/MEK failure patients.

Conclusions: Combination ipilimumab and nivolumab can be used safely and effec-
tively in a real-world population, including in patients that are heavily pre-treated and those with adverse disease characteristics. While first-line efficacy appears comparable to that seen in trial populations, BRAF-mutant patients who have failed prior BRAF/MEK inhibitors are less likely to respond, supporting first-line use of combination immunotherapy in the majority of newly diagnosed poor prognosis metastatic mel-
noma patients.

Legal entity responsible for the study: A. Menzies.

Funding: Has not received any funding.


Melanoma and other skin tumours

registry to evaluate response and duration of response of standardized IAL therapy at tertiary centres in 2 provinces.

Methods: Patients (pts) receiving IAL IL2 between 2000 and 2017 were included. Data regarding patient demographics, stage, extent of disease, and all treatments were col-
lected. All pts received a median IL2 dose of 12 million IU given as an IAL injection every 2 to 4 weeks repeated 2 to 8 times to complete a session.

Results: A total of 87 pts aged 21 to 94 (mean: 69 yrs) were included. IT disease was located in the following areas: limbs in 68 pts (79%), head and neck in 13 pts (15%) and trunk in 5 pts. One third of pts developed IT within 3 months of primary diagnosis, 69% developed IT after 6 months and 11% after 3 years. IT lesions per individual ranged from 1 to 40; 43% had >10 lesions. Patients had a complete response rate of 32% (28 pts) and a partial response rate of 38% (33 pts). 27 (31%) pts experienced a recurrence after their 1st IL2 session, with a mean of 225 days (median: 204). Of these pts, 15 (56%) pts developed loco-regional recurrences, while 6 (22%) developed distant metastases and 6 (22%) had both distant and loco-regional recurrences. 27 pts (33%) received systemic treatment for metastatic disease. 18 (21%) pts died of disease, while 3% died of other causes while disease was present. 7 (8%) died of other causes with dis-
ease status unknown, and 25 (29%) and 34 (39%) are recorded alive with more than a year (1 to 11 yrs) or less than a year follow up, respectively. No grade 3 or 4 toxicity was experienced by pts who received IL2 therapy. On multi-variant analysis, age, extent of disease and prior systemic therapy did not impact overall response (X2 test, p > 0.05).

Conclusions: IAL IL2 appears to be an effective therapeutic option for pts with untreated advanced melanoma and IT disease, with an overall response rate of 70%. With further long-term follow up of these pts, the impact on overall survival can be determined.

Legal entity responsible for the study: Global Melanoma Research Network.

Funding: Global Melanoma Research Network.

Disclosure: All authors have declared no conflicts of interest.

125P

Combined ipilimumab and nivolumab first-line and after BRAF-
directed targeted therapies in advanced melanoma patients

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Background: Combination ipilimumab and nivolumab is a highly active systemic ther-
apy for metastatic melanoma but can cause significant toxicity. How best to integrate this combination into clinical practice, in real-world patients, and in the setting of BRAF targeted therapy, is not clear. We sought to explore the safety and efficacy of combination ipilimumab and nivolumab in such a population.

Methods: Consecutive patients with untreated stage IIIC/IV melanoma commenced on ipilimumab plus nivolumab via an early access scheme across 10 tertiary melanoma institutions in Australia were identified retrospectively. Data collected included demo-
graphics, prior and subsequent systemic treatments, toxicity, RECIST response and survival outcomes.

Results: 152 patients were included for analysis, including 60 (39%) treatment-naïve and 33 (22%) who had failed first-line BRAF/MEK inhibitors and then treated with combination therapy second-line. In the whole cohort, most patients had a high AJCC M stage (65% M1c, 26% M1d) and elevated LDH (55%), with similar distribution of adverse features in the treatment naïve and BRAF/MEK failure subgroups. Treatment-related adverse events occurred in 102 (67%) patients, grade 3–5 in 38% (1 death from immune myocarditis). The objective response rate was 41% in the whole cohort, 57% (17% complete) in treatment naïve, and only 21% (3% complete) in BRAF/MEK failure patients. Median progression-free survival was 4.0 months (95% CI, 3.0 to 6.0) in the whole cohort, 11.0 months (95% CI, 6.0 - NR) in treatment-naïve patients, and 20 months (95% CI, 1.4 - 4.6) in BRAF/MEK failure patients.

Conclusions: Combination ipilimumab and nivolumab can be used safely and effec-
tively in a real-world population, including in patients that are heavily pre-treated and those with adverse disease characteristics. While first-line efficacy appears comparable to that seen in trial populations, BRAF-mutant patients who have failed prior BRAF/MEK inhibitors are less likely to respond, supporting first-line use of combination immunotherapy in the majority of newly diagnosed poor prognosis metastatic mel-
noma patients.

Legal entity responsible for the study: A. Menzies.

Funding: Has not received any funding.


Annals of Oncology
**Background:** Anti-PD1 Nivolumab (N) or Pembrolizumab (P) are an option for first line treatment in metastatic melanoma (MM) but predictive factors of efficacy are needed to choose between them or other treatment (anti-PD1 + Anti-CTLA4, BRAF + MEK inhibitors (BMEi) for BRAF mutated melanoma). Many studies suggest that LDH, ECOG PS, tumor burden can identify BRAF mutated MM patients (pt) in which BMEi show better outcome. Similar data are not available for N or P in first line. We evaluate pt treated with N or P in first line in order to verify if these factors or other factors can be applied also to anti-PD1.

**Methods:** A retrospective multicenter study was conducted in 13 Italian Oncology Evaluating, MM patients treated with N or P in first line from 2016. Endpoints were OS and PFS, Kaplan Mayer and Cox regression were applied for survival analysis.

**Results:** 236 pt were analyzed (53% treated with N, 47% treated with P). ECOG PS was ≥ 0 in 169 pt, number of metastatic sites (Nu) was less then 3 in 135 pt, in 88 pt there were no visceral metastasis (Vi), LDH was normal in 141 pt, ratio between baseline neutrophil and platelet count (Fr) 48% in pt without favorables factors (p value 0.0029). 18 months-OS was 90% in pt with all four favorables factors vs 72% in pt without any of these factors resulted significantly associated with better OS (all p < 0.0005) and PFS (all p < 0.001). The log rank test was for every pt considering the number of favorable factors present (normal LDH, ECOG PS 0, Fr < 0.7, absent Nu). The factors were confirmed as significantly associated with better PFS and OS (all p < 0.005), with the exception of Nu (p = 0.22) A score was counted for every pt considering the number of favorable baseline factors present (normal LDH, ECOG PS 0, Fr < 0.7). In univariate analysis all these factors were significantly different in PFS then pt with higher Nu (p=0.15). In multivariate analysis all these factors can be applied also to anti-PD1.

**Conclusion:**

**Legal entity responsible for the study:** Italian Melanoma Intergroup I.M.I.

**Funding:** Has not received any funding.

**Disclosure:** R. Marconcini. Consultancy, Advisory board, Honoraria for speaking: BMS, MSD, Novartis, Roche. All other authors have declared no conflicts of interest.

**Annals of Oncology**

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Table: 1260P Baseline demographic and disease characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistics</th>
<th>Total (N = 856)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening (years)</td>
<td>Mean (SD)</td>
<td>58.5 (14.8)</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td>474 (55.4)</td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>382 (44.6)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>382 (44.6)</td>
</tr>
<tr>
<td>ECOG PS scale at screening</td>
<td>0 n (%)</td>
<td>531 (62.0)</td>
</tr>
<tr>
<td>1 n (%)</td>
<td>242 (28.3)</td>
<td></td>
</tr>
<tr>
<td>2 n (%)</td>
<td>69 (8.1)</td>
<td></td>
</tr>
<tr>
<td>3 n (%)</td>
<td>13 (1.5)</td>
<td></td>
</tr>
<tr>
<td>4 n (%)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Stage at screening</td>
<td>II n (%)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>IIIC n (%)</td>
<td>76 (9.1)</td>
<td></td>
</tr>
<tr>
<td>III n (%)</td>
<td>87 (10.2)</td>
<td></td>
</tr>
<tr>
<td>IV n (%)</td>
<td>788 (92.1)</td>
<td></td>
</tr>
<tr>
<td>THM staging at screening (M)</td>
<td>0 n (%)</td>
<td>68 (8.0)</td>
</tr>
<tr>
<td>M1a n (%)</td>
<td>81 (9.5)</td>
<td></td>
</tr>
<tr>
<td>M1b n (%)</td>
<td>88 (10.3)</td>
<td></td>
</tr>
<tr>
<td>M1c n (%)</td>
<td>617 (72.2)</td>
<td></td>
</tr>
<tr>
<td>If M1c, brain metastasis</td>
<td>No n (%)</td>
<td>342 (55.4)</td>
</tr>
<tr>
<td>Yes n (%)</td>
<td>275 (44.6)</td>
<td></td>
</tr>
<tr>
<td>Type of BRAF mutation</td>
<td>E n (%)</td>
<td>727 (84.9)</td>
</tr>
<tr>
<td>K n (%)</td>
<td>93 (10.9)</td>
<td></td>
</tr>
<tr>
<td>Other n (%)</td>
<td>36 (4.2)</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L)</td>
<td>Mean (SD)</td>
<td>377.2 (464.8)</td>
</tr>
<tr>
<td>LDH (IU/L) in classes</td>
<td>≤ 400 n (%)</td>
<td>483 (76.9)</td>
</tr>
<tr>
<td>&gt; 400 n (%)</td>
<td>260 (40.4)</td>
<td></td>
</tr>
<tr>
<td>&gt; 800 n (%)</td>
<td>45 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Sequence of dabrafenib and</td>
<td>1st sequence: patient with no prior systemic anti-cancer treatment</td>
<td>n (%)</td>
</tr>
<tr>
<td>trametinib</td>
<td>2nd sequence: patient with one prior systemic anti-cancer treatment</td>
<td>n (%)</td>
</tr>
<tr>
<td>3rd sequence: patient with two prior systemic anti-cancer treatments</td>
<td>n (%)</td>
<td>88 (10.3)</td>
</tr>
<tr>
<td>&gt;3rd sequence: patient with three or more prior systemic anti-cancer treatments</td>
<td>n (%)</td>
<td>59 (6.9)</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = Performance Status; LDH = Lactate Dehydrogenase; SD = Standard Deviation. Footnotes: a Data was missing for 2 patients. b Percentage based on subjects with M1c stage at screening (N = 617). c Based on patients with known LDH at baseline (N = 628).

Conclusions: This is to date, the largest prospective study worldwide in BRAF V600-mutant cutaneous melanoma patients treated with the D+T combination. It confirms the efficacy and tolerability of D+T in this population, including ps with BM.

Clinical trial identification: NCT02416232.

Editorial acknowledgement: Editorial assistance in the writing of the abstract was provided by Jone Iriondo-Alberdi (PhD) of ITEC Services.

Legal entity responsible for the study: Novartis Pharma S.A.S. (France) Novartis Pharma S.A.S. (France).

Funding: Novartis Pharma S.A.S. (France).

Disclosure: P. Saig: Advisory board: BMS, MSD, Novartis, GSK, Merck, Serono, Roche, Novartis, Pierre Fabre, Amgen. C. Robert: Honoraria, Consulting, Advisory board: Amgen, BMS, Merck, Novartis, Roche, GSK. J.J. Grob: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer, Incyte; Consulting or advisory role: BMS, MSD, Roche, Novartis, Amgen, Merck, Pfizer, Incyte; Research funding (self and institution), Travel, accommodation, expenses: BMS, Roche, MSD. L. Mortier: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Incyte; Consulting or advisory role: BMS, MSD, Roche, Novartis, Amgen, Merck, Pfizer, Incyte; Travel, accommodation, expenses: BMS, Roche, MSD. C. Lebbe: Honoraria: BMS, MSD, Roche, Novartis, Amgen, Merck, Pierre Fabre, Pfizer, Incyte; Consulting or advisory role: BMS, MSD, Roche, Novartis, Amgen, Merck, Pfizer, Incyte; Research funding (self and institution), Travel, accommodation, expenses: BMS, Roche, MSD. S. Mansard: Advisory board, Travel expenses: Novartis, BMS, MSD, Roche. E. M. Neidhardt: Advisory board: Novartis, BMS, T. L. Lesimple: Advisory board: Roche, Novartis, MSD, Incyte; C. Bedane: Advisory board: Novartis, Investigator: Combi 1 study. A. Sirenk, A. Denden: Employee: Novartis. C. Dutiaux: Advisory boards, Investigator: Roche, Amgen, BMS, MSD, Merk Serono, Novartis. All other authors have declared no conflicts of interest.

1261P Loss of HLA class I expression and T-cell infiltration or PD-L1 expression are associated with different response patterns to pembrolizumab in melanoma

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Background: PD-1 blockade monoclonal antibodies, nivolumab and pembrolizumab, increase quality of life and overall survival of metastatic melanoma and are today’s first-line treatment of metastatic melanoma. Nevertheless, only 40% of the patients will respond to anti-PD-1 monotherapy. In the era of personalized medicine, an important stake is to identify the patients who will benefit from these treatments, which are also responsible for scarce but serious side effects. We have tested several biomarkers to discriminate between responders and non-responders.

Methods: We have retrospectively analysed 18 patients treated by pembrolizumab for metastatic melanoma. Immunohistochemical staining was performed on pre-treatment metastatic tissue for antigens such as MELANA, TYR, GP100, PD-L1, CD3, CD8, and HLA class I. Two reviewers assessed the staining independently. For PD-L1 testing, the MEL-score was used. For T-cell infiltration, we have quoted the presence of CD3/CD8 T-cell and their location.

Results: We found that only PD-L1 expression and the presence of T-cell infiltration were associated with a better response to pembrolizumab: PD-L1 expression (p = 0.043), T-cell infiltration (p = 0.025) and T-cell location at the periphery of the tumoral nodules (p = 0.025). PD-L1 expression and the presence of T lymphocytes were also associated with a longer survival. The median overall survival was 31.5 months for the T-cell rich metastasis and PD-L1 high expression versus 4 months for non-T-cell infiltrated tumours and 7 months for PD-L1 negative tumours. Furthermore, 90% of the metastases showed reduced or absent HLA class I expression by the tumour cells. The role of tumoral HLA loss in response and resistance to PD-1 blockade has still to be defined.

Conclusions: Although significant correlations were observed between some biomarkers and the response to anti-PD-1 therapy as described in larger studies, no predictive biomarker has currently been identified in our small series. Recent and future technical progresses will enable new studies aiming to find reliable biomarkers and to clarify the complex mechanisms of response and resistance to immune checkpoint inhibitors.

Legal entity responsible for the study: Cliniques universitaires Saint-Luc.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1262P Soluble PD-L1 as a prognostic factor in advanced acral and mucosal melanoma

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Background: Elevated levels of soluble PD-L1 (sPD-L1) have been associated with worse prognosis in renal cell carcinoma and multiple myeloma. However, the regulatory roles and function of sPD-L1 in advanced melanoma are not fully understood. This study was designed to evaluate the association between circulating sPD-L1 expression and prognosis in patients with advanced acral and mucosal melanoma.

Methods: Totally 102 untreated advanced acral and mucosal melanoma patients from Peking University Cancer Hospital between Jan 2012 and Dec 2015 were enrolled in the present study. Peripheral blood samples were obtained from 40 healthy donors as control. Circulating sPD-L1 expression was tested by enzymelinked immunosorbent assay (ELISA).

Elevated levels of soluble PD-L1 (sPD-L1) have been associated with worse prognosis in renal cell carcinoma and multiple myeloma. However, the regulatory roles and function of sPD-L1 in advanced melanoma are not fully understood. This study was designed to evaluate the association between circulating sPD-L1 expression and prognosis in patients with advanced acral and mucosal melanoma.

Methods: Totally 102 untreated advanced acral and mucosal melanoma patients from Peking University Cancer Hospital between Jan 2012 and Dec 2015 were enrolled in the present study. Peripheral blood samples were obtained from 40 healthy donors as control. Circulating sPD-L1 expression was tested by enzyme-linked immunoassay (ELISA).
Results: The advanced melanoma cohort includes 58 acral melanoma and 44 mucosal melanoma. Concentrations of sPD-L1 (2.91 ng/mL) were elevated in the plasma of patients with metastatic melanoma, in comparison with healthy donors (0.59 ng/mL). The expression of sPD-L1 in skin was found to be highly up-regulated in stage III (38.2%) of 102 cases. The sPD-L1 concentration appeared to be significantly related with subtype (acral 3.14 vs. mucosal 2.60 ng/mL; \( P = 0.004 \)). No significant association was observed between serum sPD-L1 level and other clinicopathological variables as: BRAF mutation, LDH level, tumor burden and peripheral blood CD4+CD8+ (Table 1). There were no associations between sPD-L1 and chemotherapy clinical responses in our cohort. But the overall survival rates were statistically estimated with the expression of sPD-L1. The OS in this cohort with high and low sPD-L1 expression levels was 8.50 months and 11.64 months, respectively (\( P = 0.022 \)).

Conclusions: sPD-L1 was elevated in advanced acral and mucosal melanoma patients and may play an important role in patients prognosis. Legal entity responsible for the study: Peking University Cancer Hospital & Research Institute. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

Methods: Patient and disease characteristics were collected among MM patients treated in a reference oncology center since 2012 with targeted and/or checkpoint inhibitor agents. We defined long-term survivors as patients with survival \( > 2 \) years from MM diagnosis; biological material was collected for genomic analyses. Results: From 130 MM patients treated with BRAF/MEK inhibitors and/or anti-CTLA4, anti-PD1 agents in any line, 25 long-term survivors were identified (19.2%), 15 men/10 women. Long-term survival was characterized by good prognosis features at initial diagnosis: median PS 0, normal LDH (60%), low disease burden (<3 metastatic sites, 88%), median Distant Metastasis Free Interval (DMFI) 3 years (range 0.23-16 years). 16/25 BRAF mutant MM. All long-term survivors had achieved an objective response (complete/partial) to targeted or immune-therapy. Objective response was associated with long-term survival regardless of treatment line. Complete responses to targeted or immunotherapy are still ongoing (2 to immunotherapy >3 years, 2 to BRAF/MEK >5 years). Most patients are alive today (21/25, 84%); 9 patients (36%) survive >5 years from MM diagnosis, with 8 of them (32%) surviving >10 years from new therapy initiation (targeted or immune). The majority of patients (22/25, 88%) survive >3 years from initial MM diagnosis and 76% survive >3 years from therapy initiation (targeted or immune), suggesting that the long-term survival benefit is due to the new therapy. Genomic analysis will complement the clinical characteristics of long-term survival. Conclusions: A significant number of patients with MM treated in a reference center achieved long-term survival with different systemic approaches and genomic characteristics of these long-term survivors can improve our understanding of the biological behaviour of the disease but also assist the optimal choice and use of new therapies. Legal entity responsible for the study: Oncology Department, Metropolitan Hospital, Athens. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.
Background: Upregulation of the receptor tyrosine kinase AXL has been linked with tumour load. Pts were allowed to switch D/T with pembrolizumab and vice versa upon Toxicoderma, Adrenal insufficiency, and Muscle weakness lower limb. Of 27 efficacy patients, BORR by irRC at 24 wks was 7% and disease stability rate was 56%. One patient had PR in injected lesions and systemic lesions also showed the response after 6 induction and duration: 15 mg, q2w; then 30 mg, q2w. C-REV was injected into each tumor (1 x 107 TCID50/mL/dose, up to 5mL); 4 injections q1wk; then up to 15 injections q3wk. Four ipi infusions (3 mg/kg) were administered per CTAEC 4.0. Tumor responses were assessed per irRC and mWHO at 6, 12, 18 and 24 wks. Primary endpoint was Best Overall Response Rate (BORR) by irRC at 24 wks was 7% and disease stability rate was 56%. One patient had PR in injected lesions and systemic lesions also showed the response after 6 of the combo therapy.

Conclusions: The combination of C-REV with ipi did not show the exacerbate ipi toxicity, and had a favorable benefit/risk profile. The encouraging antitumor activity was observed in Japanese pts who had received prior therapies such as PD-1. It is currently well-known that the response to ipi after anti-PD-1 therapy was unsatisfactory and associated with a high frequency of severe irAEs, in particular Asian populations.

From this study, C-REV + ipi therapy has potential to become a new 2nd line treatment for melanoma.

Clinical trial identification: NCT03150885

Legal entity responsible for the study: Takara Bio Inc.

Funding: Takara Bio Inc.

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Background: The IL-2 inducible kinase (ITK) is highly expressed in metastatic melanoma and molecular targeting and/or pharmacologic inhibition of ITK in preclinical melanoma models suppresses cell proliferation without inducing cell death (Cancer CCR 2015). Ibrutinib suppresses proliferation of melanoma cell lines in low mM concentrations (Moschos ASCO 2017, TPS9592). We hypothesized that targeting DMCM with ibrutinib will induce antitumor responses, especially in high ITK-expressing melanomas.

Methods: This is an open-label, single-arm, Simon’s 2-stage design, multicenter, phase II study for patients (pts) with DMCM refractory to or ineligible for PD-1 and/or MAKP inhibitors, if ibrutinib(V600) mutant. Given that the IC50 of ibrutinib for ITK is 10 times that than Bruton’s tyrosine kinase, we administered ibrutinib at 840mg qd. We hypothesized that an ineffective drug will have a ≤ 15% 6-month PFS rate. We present the results of the first stage.

Results: 18 pts (13 males; median age 63.5, range 37-82; 14 with M1c disease; 4 with BRAFV600 mutation; 12 with performance status 1 or 2; 4 with resistance to 4 treatments) were enrolled. Median exposure to ibrutinib was 27.5 days (range 4-155). The most frequent all grade side effects were fatigue (55%), anorexia (50%), gastrointestinal upset (44%), and anemia (39%). 4 grade IV (hypotension, sepsis, cytokine release syndrome, and constipation occurred 6% each) and 3 grade III events (hypotension [1%]; pneumonia, hypertension, anemia, hypalbuminemia, dehydration, lymphopenia occurred 6% each) were seen. No antitumor responses were seen. At a median follow-up of 5 months, all pts had progressed (median PFS was 1.3 months, range 0.2-5.5). 15 pts were discontinued from study due to progression and 14 pts had died from melanoma. Median OS was 5 months (range 0.3-10.4 months) in pts who died.

Conclusions: In this treatment-refractory DMCM, high-dose ibrutinib did not induce any meaningful clinical benefit; therefore the study will not proceed to stage 2. Correlation between PFS and expression of ITK by melanoma cells and density of tumor-infiltrating T- and B-cells in pretreatment tumor specimens will be reported at the time of the meeting.

Clinical trial identification: NCT03427198.

Legal entity responsible for the study: NCI-CTEP.

Funding: NCI-CTEP. Pharmacists.

Disclosure: All authors have declared no conflicts of interest.

1268P

NCI 9922: Phase II study of ibrutinib in treatment-refractory distal metastatic cutaneous melanoma (DMCM)


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Background: The IL-2 inducible kinase (ITK) is highly expressed in metastatic melanoma and molecular targeting and/or pharmacologic inhibition of ITK in preclinical melanoma models suppresses cell proliferation without inducing cell death (Cancer CCR 2015). Ibrutinib suppresses proliferation of melanoma cell lines in low mM concentrations (Moschos ASCO 2017, TPS9592). We hypothesized that targeting DMCM with ibrutinib will induce antitumor responses, especially in high ITK-expressing melanomas.

Methods: This is an open-label, single-arm, Simon’s 2-stage design, multicenter, phase II study for patients (pts) with DMCM refractory to or ineligible for PD-1 and/or MAKP inhibitors, if ITK(V600) mutant. Given that the IC50 of ibrutinib for ITK is 10 times that than Bruton’s tyrosine kinase, we administered ibrutinib at 840mg qd. We hypothesized that an ineffective drug will have a ≤ 15% 6-month PFS rate. We present the results of the first stage.

Results: 18 pts (13 males; median age 63.5, range 37-82; 14 with M1c disease; 4 with BRAFV600 mutation; 12 with performance status 1 or 2; 4 with resistance to 4 treatments) were enrolled. Median exposure to ibrutinib was 27.5 days (range 4-155). The most frequent all grade side effects were fatigue (55%), anorexia (50%), gastrointestinal upset (44%), and anemia (39%). 4 grade IV (hypotension, sepsis, cytokine release syndrome, and constipation occurred 6% each) and 3 grade III events (hypotension [1%]; pneumonia, hypertension, anemia, hypalbuminemia, dehydration, lymphopenia occurred 6% each) were seen. No antitumor responses were seen. At a median follow-up of 5 months, all pts had progressed (median PFS was 1.3 months, range 0.2-5.5). 15 pts were discontinued from study due to progression and 14 pts had died from melanoma. Median OS was 5 months (range 0.3-10.4 months) in pts who died.

Conclusions: In this treatment-refractory DMCM, high-dose ibrutinib did not induce any meaningful clinical benefit; therefore the study will not proceed to stage 2. Correlation between PFS and expression of ITK by melanoma cells and density of tumor-infiltrating T- and B-cells in pretreatment tumor specimens will be reported at the time of the meeting.

Clinical trial identification: NCT03427198.

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Funding: NCI-CTEP. Pharmacists.

Disclosure: All authors have declared no conflicts of interest.

1269P

Initial cohort expansion results of sustained arginine depletion with pegzilarginase in melanoma patients in a phase I advanced solid tumor study

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Background: Tumors with low argininosuccinate synthetase 1 (ASS1) expression have impaired arginine synthesis and are dependent on extracellular arginine for survival. Pegazilarginase (AEB1012) is a pegylated, recombinant, cobalt-substituted human arginase I that depletes plasma arginine. MTD was previously reported as 0.33 mg/kg weekly (AACR 2018). Here we update the preliminary safety and activity of arginase pegylilarginase in uveal (UM) and cutaneous (CM) melanoma cohorts of an ongoing Phase 1 study (NCT02561243).

Methods: Adult patients (pts) with metastatic UM or CM were eligible after prior standard treatments. IV pegazilarginase was administered at the MTD. Primary objective was safety (CTCAE v4.03); additional endpoints included PK, PD, tumor ASS1 expression, and preliminary anti-tumor activity (RECIST 1.1).

Results: At analysis, 16 pts with melanoma (11 UM, 5 CM) received pegazilarginase in cohort expansions. 5 dose-escalation pts with UM (5) or CM (2) were also treated at MTD. For the 21 pts with UM or CM treated at MTD, treatment-related AEs (TRAE) in > 10% pts included fatigue, nausea, diarrhea, vomiting, decreased appetite, diarrhea, gait disturbance, muscular weakness, and tremor. No Grade ≥ 4 TRAEs were observed, and Grade 3 TRAEs were reported by one pt each: asthenia, failure to thrive, and hypophosphatemia. Median weeks on pegazilarginase was 5.9 (range [1 [1 dose] to 17.1 weeks). Pegazilarginase depleted plasma arginine from a median of 98 μM at base-line to a median of 4 μM at 72 hours post-dose (n = 12). In 13 pts with week 8 response assessment, 6 had stable disease. 13 pts with UM or CM had prior IO therapy; 7 had PD as best response to prior therapy. 10/16 tumors showed no or low ASS1 expression. Conclusions: The safety, PD, and activity profile of pegazilarginase at the MTD continues to support weekly administration with a margin for dose adjustment. Given very poor outcomes in pts with advanced UM and CM, pre-clinical data showing enhanced effects of pegazilarginase when combined with PD-1 inhibition, and the observation of stable disease this trial, further development of pegazilarginase in combination with anti-PD-1/L1 therapy is warranted for these tumors.

Clinical trial identification: NCT02561243.

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Legal entity responsible for the study: Aeger Biotherapeutics.

Funding: Aeger Biotherapeutics.

Results: A total of 439 patients were included, 229 with MM (151 treated with immunotherapy and 78 treated with chemotherapy) and 210 with UM (100 treated with chemotherapy and 110 treated with chemotherapy). Objective response rates of MM to anti-CTLA-4 and anti-PD-1 were 3/76 (3.9%, 95%CI=0.0%-8.3%) and 13/75 (17.3%, 95%CI=0.9%-29.1%) respectively, versus 11/78 (14.1%, 95%CI=6.4%-21.8%) in patients treated with chemotherapy (p = 0.047 and p = 0.4). No tumor response was observed in UM patients treated with immunotherapy, versus 4/110 responses (3.6%, 95%CI=0.7%-7.4%) in patients treated with chemotherapy (p = 0.12). The OS of MM patients treated with immunotherapy was longer than that of patients treated with chemotherapy (p = 0.002), with a median OS of 15.7 (IQR: 6.89-27.12) and 6.82 months (IQR:5.2-14.9), respectively. After adjusting for main prognostic factors, the OS of MM patients treated with immunotherapy remained longer than that of patients treated with chemotherapy (HR = 0.61 (1.0; 0.95), p = 0.028). The adjusted and non-adjusted OS of UM patients treated with immunotherapy was not different from that of patients treated with chemotherapy (HR = 1.06 (1.07; 1.61), p = 0.78) with median of 13.38 months [IQR=6.03-29.57] and 11.02 months [IQR=5.8-23.8], respectively.

Conclusion: Anti-PD-1 should be considered for the treatment of patients with advanced MM. The prognosis of metastatic UM remains poor.

Legal entity responsible for the study: P. Joly.

Funding: Bristol-Myers Squibb.

Disclosure: N. Meyer: Consultant or investigator: BMS, MSD, Roche, GSK, Novartis, Aurogen, Pierre Fabre, N. Beneton Benhard. Consultant: BMS, Novartis, Roche, J.P. Arnault: Grant support for Congress: BMS, MSD; Investigator: Novartis. P. Joly: Consultant: BMS. All other authors have declared no conflicts of interest.

1272P Outcome of an active surveillance programme for patients (pts) with uveal melanoma (UM) after primary curative therapy (PTx): Single institution 10-year experience

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Background: About 30% of pts with UM develop metastatic disease (MUM) despite PTx. MUM has poor prognosis and no systemic treatment (STx) has been proven to improve overall survival (OS). The role of active surveillance after PTx is still controversial.

Methods: We performed an outcome analysis of all UM pts prospectively registered onto our active surveillance programme after PTx. All pts had systemic staging at diagnosis and then 6-monthly liver imaging (CT triple-phase, MRI, ultrasound) and clinical review for the first 5 years and 12-monthly afterwards. Progression-free survival (PFS) was calculated from time of first systemic relapse to first disease progression, OS from time of first systemic relapse to death or latest FU.

Results: Out of 169 pts registered between April 2008 and April 2018, 32 (19%) developed MUM during surveillance: 14 pts (44%) relapsed <2 yrs, 14 (44%) >2 and <5 yrs, 4 (12%) >5 yrs from PTx. Median FU 46.8 mos. MUM pts characteristics: males 17 (53%); median age 59yrs (range 15-86); median tumour thickness at diagnosis 9mm (range 3-32); site of metastases liver only 10 (31%), liver + other sites 19 (60%), extra-hepatic only 3 (9%). Relapses were asymptomatic and detected on surveillance imaging in 25 (78%) pts. Median duration to relapse after PTx is 27.4 mos. Eight pts (29%) were upfront resectable (PRx) and underwent radical hepatic metastasectomy, 24 pts (73%) were non-resectable (NRx) and underwent best supportive care (BSC). The OS of MM patients treated with immunotherapy was longer than that of patients treated with chemotherapy (HR = 0.61 (1.0; 0.95), p = 0.028). The adjusted and non-adjusted OS of UM patients treated with immunotherapy was not different from that of patients treated with chemotherapy (HR = 1.06 (1.07; 1.61), p = 0.78) with median of 13.38 months [IQR=6.03-29.57] and 11.02 months [IQR=5.8-23.8], respectively.

Conclusion: Anti-PD-1 should be considered for the treatment of patients with advanced MM. The prognosis of metastatic UM remains poor.

Legal entity responsible for the study: P. Joly.

Funding: Bristol-Myers Squibb.

Disclosure: N. Meyer: Consultant or investigator: BMS, MSD, Roche, GSK, Novartis, Aurogen, Pierre Fabre, N. Beneton Benhard. Consultant: BMS, Novartis, Roche, J.P. Arnault: Grant support for Congress: BMS, MSD; Investigator: Novartis. P. Joly: Consultant: BMS. All other authors have declared no conflicts of interest.

1273P Activation of non-canonical NFkB (NC-NFkB) pathway in inflammatory environment of uveal melanoma

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Background: Uveal melanomas are considered as malignant phenotype having a high density of macrophages, blood vessels, and T-lymphocytes. Presence of epithelial cells with high melanin pigmentation leads to worse patient’s prognosis. Non-canonical NFkB (NC-NFkB) pathway plays an important role in inflammation which promotes cancer initiation and progression. p52 and ReB are the dimeric proteins of the NC-NFkB pathway. The aim of the study is to detect the expression of p52/ReB protein dimer in the inflammatory microenvironment of uveal melanoma and its prognostic significance.

Methods: Evaluation of p52/ReB dimer was assessed by using immunohistochemistry and western blotting in 75 formalin fixed uveal melanoma tissues and transcriptional analysis was done on 58 fresh frozen tissues by real-time PCR. Immunopositive expression of both proteins was taken as a positive expression of the dimer (p52/ ReBþ) and immunonegative of both proteins taken as (p52/ReB-). Non-resectable (NRx) and underwent best supportive care (BSC). The OS of MM patients treated with immunotherapy was longer than that of patients treated with chemotherapy (HR = 0.61 (1.0; 0.95), p = 0.028). The adjusted and non-adjusted OS of UM patients treated with immunotherapy was not different from that of patients treated with chemotherapy (HR = 1.06 (1.07; 1.61), p = 0.78) with median of 13.38 months [IQR=6.03-29.57] and 11.02 months [IQR=5.8-23.8], respectively.

Conclusion: Anti-PD-1 should be considered for the treatment of patients with advanced MM. The prognosis of metastatic UM remains poor.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Abstracts
Background: Melanoma of esophagus (ME) is a rare type of melanoma, accounting for <3% of cases. Patients with advanced melanoma of esophagus origin, tend to have lower response rates on traditional therapies. Thus, we report our experience with 11 patients with advanced esophageal melanoma who received PD-1 inhibitors.

Methods: A retrospective analysis of 77 patients with advanced ME were conducted from the database of Peking University Cancer Hospital between Jan 2008 and Sep 2017. We collected the clinical data and assessed objective response rates (ORR) and progression-free survival (PFS). The data cutoff date was Jan 1st 2018.

Results: We identified the 77 patients were unresectable or metastatic esophageal malena. The Median age was 57, 67.5% being male. 78% patients had history of esophagectomy and 64 patients had received prior systemic therapy. There were 6 (10.4%) patients harbored C-KIT mutations and 5 (6.5%) harbored BRAF. We divided the patients into 3 cohorts according to different treatments: Chemotherapy (C: 8 DTIC+6 TAI+23 FTX, 57 cases), Targeted therapy (T: 6 imatinib/3 vemurafenib, 9 cases) or PD-1 inhibitors (P, 11 cases). The PFS were 3.0 and 4.2 months with limited ORR of 3.7% and 25.0% respectively for C and T cohort. In the P cohort, 7/11 patients (63.6%) achieved PR and other 3 remained SD > 4 months. The PFS for the P cohort was 13.0 ± months. Toxicities were as expected and were usually grade 1 or 2.

Conclusions: Although this cohort of patients was small, it was the largest report for now. To our knowledge this is also the first report of outcomes of PD-1 inhibitors in advanced esophageal melanomas. The dramatic response appears to be an option for patients with advanced esophageal melanomas.

Legal entity responsible for the study: Beijing Cancer Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Mucosal melanomas are rare and an aggressive malignancy with poor response compared with cutaneous melanoma. The prospective trial on immune-checkpoint inhibitors in unresectable or metastatic mucosal melanoma has not been reported except pooled analysis. The aim of this phase II trial was to assess the efficacy and safety of nivolumab monotherapy for unresectable or metastatic mucosal melanomas.

Methods: Eligibility criteria were as follows: histological diagnosis of unresectable or metastatic mucosal melanoma. Patients received nivolumab 2 mg/kg every 3 weeks. The primary endpoint was overall response rate. The secondary endpoints were overall survival, progression-free survival, disease control rate, and toxicity.

Results: A total of 20 patients were enrolled between December 2014 and July 2017. Two patients without measurable lesion were excluded from analysis of efficacy. The RR was 22%, suggesting that the primary endpoint was met. One patient achieved a complete response, three patients achieved partial response, and six patients achieved stable disease as their best response. The median progression-free survival was 1.4 months (95% CI, 1.5 to 5.4). The median overall survival was 12.03 months (95% CI, 3.50 to not reach). The 1-year overall survival data was 52.6% (95% CI, 28.5 to 72.0).

Conclusions: Although this trial met the primary endpoint, the RR was still unsatisfactory. Therefore, the further treatment development is required.

Clinical trial identification: UMIN000015345.

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Disclosure: All authors have declared no conflicts of interest.

Outcomes of anti-PD1 antibodies for advanced melanoma in real-world population


Background: Anti-PD1 antibodies (aPD1) for advanced melanoma have proven their superiority over chemotherapy and platinolom in phase III trials. However, in real-world many patients were not represented in these trials. We report real-world outcomes of aPD1 for advanced melanoma.

Methods: Pts with advanced (non-uveal) melanoma from 2014 to 2016 who received 1st line aPD1 were selected from the Dutch Melanoma Treatment Registry – a population based registry in the Netherlands. Outcomes of pts normally eligible (ELI) for trial participation (ECOG PS of 0-1, no brain metastasis, auto-immune disease, HIV, psoriasis or corticosteroid use) were compared to pts normally non-eligible (N-ELI) for trial participation. Time to event was estimated with Kaplan-Meier method and overall survival (OS) with cox regression analysis.

Results: In total 552 patients with advanced melanoma received 1st line aPD1. Median age was 65yrs (range 21-94). At baseline 28% had elevated LDH, 80% EGOG PS of 0-1, 19% brain metastases, 65% stage IV-M1 disease and 41% had a BRAF mutation. Toxicity grade 3-4 occurred in 68 pts (12.3%). Median follow-up estimated with reverse Kaplan-Meier method was 18.8 mo (95% CI: 18.2-20). 1- and 2-yr OS (95% CI) was 72% (68-76%) and 59% (55-65%) and median OS was not reached. Median time to next treatment (TTNT) for ELI pts was not reached and TTNT for N-ELI pts was 10.6 mo (95% CI: 8.3-14.7). Median time of treatment duration was 8.8 mo (95% CI: 6.9-10.5) for ELI pts and 5.3 mo (95% CI: 3.1-7.6) for N-ELI pts. HR for OS was 1.74 (95% CI: 1.26-2.41). The secondary endpoints were overall survival, progression-free survival, disease control rate, and toxicity.

Conclusions: Real-world outcomes of 1st line aPD1 in patients with advanced melanoma seem to be in accordance to results observed in phase III trials. These data support that N-ELI pts normally not represented in phase III trials may benefit from aPD1 treatment. LDH >500 UI/L and BRAF neg. status were associated with poorer survival.

Legal entity responsible for the study: Authors.

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Stereotactic radiation therapy in melanoma brain metastases: A European, multicentric cohort

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Background: Brain metastases are frequent in patients with melanoma and stereotactic radiotherapy is one of the main treatment options. We report the efficacy and safety of hypofractionated stereotactic radiotherapy (HFSRT) and stereotactic radiosurgery (SRS), and its role in melanoma brain metastasis management.
The EORTC 1325-MG/Keynote 054 trial demonstrated prolonged recurrence-free survival. The primary HRQoL outcome was global health/QoL (GHQ) as measured by the EORTC QLQ-C30. Results from the secondary scales revealed a similar pattern with scores stable over time and treatment differences never reaching the 5 point threshold.

Conclusions: Pembrolizumab maintains health-related quality of life compared to placebo, when given as adjuvant therapy for patients with resected high-risk stage III melanoma.


Legal entity responsible for the study: Merck.

Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.

Methods: On behalf of the French-speaking neuro-oncologist association (ANOCF), we retrospectively collected clinical data of 150 patients and 299 brain metastases from melanoma treated with SRS or HFSRT in 6 radiation oncology departments in France and in Germany. The primary endpoint was the response to the treatment according to RANO criteria. Secondary endpoints were overall survival and HRQoL.

Results: We conducted a Bayesian multivariate logistic regression for treatment response probability. Age, control of disease and stereotactic radiosurgery have a odds ratio (OR) 0.80 (95% CI: 0.10–1.50), 1.61 (95% CI: 1.15–2.24) and 4.33 (95% CI: 1.94–9.37) respectively and a probability of being > 0.5, 94% and 97% respectively. BRAF mutation, time between dosimetric MRI and treatment, Ipilimumab administration, multiple brain metastases and WHO performance status an OR of 0.559 (95% CI: 0.21 – 1.33), (0.79 – 0.94), 0.57 (0.17 – 1.39), 0.91 (0.11 – 1.04) and 0.63 (0.25 – 1.28) respectively and a probability of being < 1% of 90%, 100%, 91%, 97% and 91% respectively. Median OS was 11 months (8–20) and the multivariate Cox analysis estimated a Hazard ratio of 0.37 (p = 0.007) and 0.8 (p = 3.7E-6) for the control of the disease and the brain progression-free survival respectively.

Conclusions: We report the results of one of the largest cohorts of patients treated with SRS and HFSRT for melanoma brain metastases. Our analysis suggests that the age of the patient, the control of the disease and SRS are associated with higher response probability while BRAF mutation, the time between dosimetric MRI and treatment, Ipilimumab administration, multiple brain metastases and poor WHO PS are associated with lower response probability.

Legal entity responsible for the study: Association des neuro-oncologues de langue française (ANOCF).

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Disclosure: All authors have declared no conflicts of interest.

The real-world impact of modern treatments on the survival of patients with metastatic melanoma

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Background: Phase III trials with strict enrolment criteria led to the approval of several new treatments for unresectable or metastatic melanoma (MM) between 2010 and 2015. The impact of modern treatments on the overall survival of the whole “real world” population of MM is unknown.

Methods: The Danish MM database contains data on the entire, unselected population diagnosed with MM within a nationwide area. To evaluate the impact of novel treatments, all MM cases diagnosed in three non-consecutive years marked by major changes in the availability of first-line treatments (2012: i.e. IL-2 and BRAF; 2014: anti-CTLA-4: 2016: anti-PI-3 and MEK)) were retrieved. Patients were grouped into “trial-like” and “trial-excluded” based on seven predefined eligibility criteria used in all MM registration immunotherapy clinical trials, including CNS metastases and PS ≥ 2. The database was locked on February 1st 2018.

Results: We retrieved the data of all 838 patients diagnosed with MM (excluding ocular melanoma) in Denmark during 2012, 2014 and 2016. The baseline characteristics of patients diagnosed in 2012, 2014 and 2016 were similar. In the “trial-like” population (39% of all MM), which met all seven eligibility criteria for trial participation, the median overall survival (OS) was not yet reached in the 2016 group versus 20.1 months in 2014 (hazard ratio [HR] for death 0.57, 95% CI 0.38-0.84; p = 0.0049) and 16.5 months in 2012 (HR 0.47, 95% CI 0.30-0.73; p = 0.0008). No major survival differences were observed in 2014 versus 2012 (HR 0.77, 95% CI 0.55-1.08; p = 0.1354). In the “trial-excluded” population (61% of all MM), 75% of patients had known CNS metastases and/or PS ≥ 2. Here, the median OS was improved to 6.8 months in the 2016 group versus 5.2 months in 2014 (HR 0.67, 95% CI 0.52-0.86; p = 0.0013) and 4.3 months in 2012 (HR 0.67, 95% CI 0.53-0.86; p = 0.0016), with no difference between 2012 and 2014 (p = 0.65).

Conclusions: “Trial-like” patients represent only 39% of the total MM population in the real world. Our data show that the introduction of modern treatments led to an improved survival of real world patients with MM, regardless of their clinical trial eligibility.

Legal entity responsible for the study: Danish Melanoma Oncology Group.

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The real-world impact of modern treatments on the survival of patients with metastatic melanoma


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Background: The EORTC 1325-MG/Keynote 054 trial demonstrated prolonged recurrence-free survival with adjuvant pembrolizumab compared to placebo (hazard ratio = 0.37, p < 0.001). Eggermont et al, NEJM, 2018. Incidence of adverse events grades 3 or higher related to treatment were higher in the pembrolizumab arm (14.7%) than the placebo arm (3.4%). Here we report results from the health-related quality of life (HRQoL) exploratory endpoint.

Methods: A total of 1019 patients with histologically confirmed, cutaneous melanoma metastatic to a lymph node, classified as stage IIIA, IIIB or IIIC were randomized after complete resection to receive 200 mg pembrolizumab (514 patients) or placebo (505 patients). Treatment was administered every 3 weeks for 1 year, or until disease recurrence or unacceptable toxicity. All enrolled patients were required to complete a HRQoL questionnaire at baseline and every 12 randomization. The primary HRQoL outcome was global health QoL (GHQ) as measured by the EORTC QLQ-C30. All other scales from this questionnaire were secondary. Scores were compared according to the average score per patient overall, during treatment and after treatment.

Results: HRQoL compliance was >90% at baseline, >70% during the first year and >60% thereafter for both arms. Data attrition limited the analyses to week 84 (19 months). Baseline GHQ scores were similar between arms at 77 points and remained stable over time. The average GHQ score was 2.0 points (95% CI: 4.30-0.2), 1.1 points (95% CI: 3.2-0.9) and 2.0 points (95% CI: 4.8-0.3) lower in the pembrolizumab arm compared to placebo for the average overall, during and after treatment respectively. These differences are within 5 point clinical relevance threshold for the QLQ-C30. Results from the secondary scales revealed a similar pattern with scores stable over time and treatment differences never reaching the 5 point threshold.

Conclusions: Pembrolizumab maintains health-related quality of life compared to placebo, when given as adjuvant therapy for patients with resected high-risk stage III melanoma.


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Funding: Merck.

Disclosure: All authors have declared no conflicts of interest.
nivolumab 23%, (ipilimumab/nivolumab 21%) but ipilimumab use decreased to 13%. BRAF/MEK use did not change (20-21%) but vemurafenib (2%) was replaced by dabrafenib/trametinib and cobimetinib/vemurafenib (14% and 4%). Cytokine and chemotherapy use declined (43% to 3% and 35% to 7%, respectively). During 2011-17, BRAF/MEK and PD-1/PD-L1 were used more in LOT 1-4 (60% and 25%) than as adjuvant (30% and 2%), whereas cytokines were used as adjuvant only (64%). CPI were used most in NRASMut (85%) and less in BRAFMut, BRAF+/NRASMut, or NRASMut (57-66%). In BRAFMut, CPI use was highest in stage III (62%) than IV (52%) unlike in BRAFwt (52% stage III vs. 90% stage IV). BRAFi were used in 65% of BRAFMut, more in stage IV than III (79% vs. 34%). BRAFMut and NRASMut received less adjuvant therapy than wild-type (20-22% vs. 28-51%) but more LOT (20% and 21%) than other LOT 3, 5% LOT 4. The table compares treatment changes in BRAFMut melanoma between 2011-14 and 2015-16.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>2011-14</th>
<th>2015-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant LOT 1</td>
<td>LOT 2</td>
<td>Adjuvant LOT 1</td>
</tr>
<tr>
<td>BRAF/MEK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>12%</td>
<td>28%</td>
</tr>
<tr>
<td>Dabrafenib/Trametinib</td>
<td>4%</td>
<td>21%</td>
</tr>
<tr>
<td>Cobimetinib/Vemurafenib</td>
<td>0</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>0</td>
<td>4%</td>
</tr>
<tr>
<td>Trametinib</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>CPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>14%</td>
<td>23%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>1%</td>
<td>7%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>0</td>
<td>7%</td>
</tr>
<tr>
<td>Ipilimumab/Nivolumab</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td>Cytokines</td>
<td>60%</td>
<td>7%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Conclusions: Checkpoint inhibitors have replaced other advanced melanoma therapies, providing more treatment options to patients with BRAFMut melanoma.

Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.

Disclosure: L. Raskin: Employee, Stock ownership: Amgen Inc. S. Shah, J. Buchanan, D. Cohain: Employee, Stockholder: Amgen Inc. All other authors have declared no conflicts of interest.

1281P
Assessment of real-world effectiveness of first-line (1L) nivolumab (NIVO) plus ipilimumab (IPI) or NIVO monotherapy for advanced melanoma: A retrospective cohort study

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Background: NIVO + IPI and NIVO are approved for 1L treatment of patients with unresectable or metastatic (advanced) melanoma. This study assessed real-world outcomes (objective response rate [ORR], progression-free survival [PFS], and overall survival [OS]) with NIVO + IPI or NIVO alone in patients with advanced melanoma using the US Flatiron Health electronic health record database from January 2011 to June 2017.

Methods: Eligible patients were aged ≥18 years, diagnosed with advanced melanoma, and treated with 1L NIVO + IPI or NIVO (index date). Outcomes were assessed based on an in-depth review of patient charts. Patients were followed until death, database disconnection, or end of the study period. Factors associated with ORR, PFS, and OS were evaluated using logistic and Cox proportional hazards regression models. An evaluation of safety outcomes is ongoing.

Results: 463 patients were eligible (NIVO + IPI, n = 245; NIVO, n = 218), with a mean follow-up of 9.2 months (range: 0.7-30.1). Of those with data available, 39% of patients had elevated LDH, 35% had ECOG PS 1, and 33% were BRAF mutant. Compared with NIVO patients, NIVO + IPI patients were younger (71 vs 61 years) and a higher proportion were treated in academic centers (7.7% vs 18.9%). For NIVO + IPI and NIVO, ORR was 51% and 41%, median PFS was 12.2 and 5.4 months (1-year PFS rate 51% and 37%), and median OS was not reached and 20.1 months (1-year OS rate 71% and 60%), respectively. After adjusting for patient characteristics, NIVO + IPI patients were twice as likely to respond within 3 months, had a 35% lower likelihood of progression, and had a 35% lower likelihood of death compared with NIVO (Table).

Table: 1281P

<table>
<thead>
<tr>
<th>Factor</th>
<th>Model value vs reference value</th>
<th>Hazard/odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>Treatment NIVO+IPI vs NIVO</td>
<td>0.65 (0.50, 0.83)</td>
<td>0.0006</td>
</tr>
<tr>
<td></td>
<td>LDH ≤ULN vs &gt;ULN</td>
<td>0.56 (0.41, 0.77)</td>
<td>0.0003</td>
</tr>
<tr>
<td>OS</td>
<td>Treatment NIVO+IPI vs NIVO</td>
<td>0.65 (0.47, 0.90)</td>
<td>0.0354</td>
</tr>
<tr>
<td></td>
<td>LDH ≤ULN vs &gt;ULN</td>
<td>0.44 (0.29, 0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>ECOG PS 0−1 vs 2−5</td>
<td>0.48 (0.31, 0.75)</td>
<td>0.0016</td>
</tr>
<tr>
<td>Response</td>
<td>Treatment NIVO+IPI vs NIVO</td>
<td>2.13 (1.27, 3.56)</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

Conclusions: In this real-world clinical practice database, 1L NIVO + IPI was associated with improved efficacy outcomes compared with NIVO alone in patients with advanced melanoma.

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

Funding: Bristol-Myers Squibb.


1282P
Responder analysis based on patient-reported outcomes (PROs) and clinical endpoints (CEPs) in patients (pts) with metastatic Merkel cell carcinoma (mMCC) treated with avelumab

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Background: To better understand the impact of the anti–PD-L1 antibody avelumab, clinical outcomes and PROs in chemotherapy-refractory pts with mMCC enrolled in a single-arm, international phase 2 trial (NCT02155647) were analysed. Here we explore the proportion of pts categorised as responders based on these outcomes.

Methods: PROs were assessed at baseline (BL), at week 7, thereafter Q4W until disease progression, and at end of treatment using EQ-5D, a generic health-related quality of life (HRQoL) tool, and FACT-M, a cancer-specific HRQoL tool. Pts were categorised as meaningfully improved/stable or as meaningfully worsened. HRQoL deterioration-free survival (QFS) was defined as the time from BL to either a meaningful worsening from BL with no further improvement in HRQoL or death. QFS rates of PRO endpoints were computed at specific time points. Responders based on PRO meaningfully improved/stable and QFS analyses were described along with the best overall response (BOR) and progression-free survival (PFS) analyses assessed by IERC per RECIST v1.1.

Results: As of Sept 26, 2017, 88 pts had been followed for a minimum of 24 months (mo; median, 29.2 [range, 24.8–38.1]). The table presents responders based on PROs and CEPs at 6, 12, 18, and 24 mo. In addition, PRO-based, 2-year rates of improved/stable endpoints tended to be higher than the BOR rate of 33%, ranging from 41% for FACT-M physical well-being to 58% for FACT-M melanoma surgery scale.

Table: 1282P

<table>
<thead>
<tr>
<th>Response</th>
<th>Treatment</th>
<th>NIVO+IPI vs NIVO</th>
<th>NIVO vs NIVO</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numerical</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical</td>
<td>0.05</td>
<td>0.05</td>
<td></td>
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</tr>
</tbody>
</table>
Conclusions: The findings show similarity in the proportion of responders based on clinical and PRO endpoints, reiterating the potential association of both outcome measures in this mMCC population. This confirms the interest in using PROs in trials to contribute to the interpretation of objective CEPs.

Clinical trial identification: NCT02155647.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: This trial was sponsored by Merck KGaA, Darmstadt, Germany and is part of an alliance between Pfizer and Merck KGaA, Darmstadt, Germany.


Background: In China, treatment options for late-stage melanoma, particularly for second-line (2L) therapy, are limited. This retrospective, observational study used electronic medical records (EMRs) of patients (pts) with melanoma treated at Beijing Cancer Hospital (BCH) to describe the treatment pattern and real-world clinical outcomes in locally advanced, metastatic melanoma in China.

Methods: All adult pts with unresectable stage III or IV melanoma who initiated treatment between Jan 1, 2014, and Dec 31, 2015, were eligible. Pts were treated and followed up with regular imaging (every 3 mo). Trained researchers performed additional medical chart reviews to supplement data captured in the EMR database. Complete or partial responses were captured as per RECIST v1.1 (patients with advanced melanoma were reclassified as untreated case by case). Survival analysis involved the Kaplan–Meier method, pts were censored at last known date alive before Dec 31, 2017.

Results: Of 248 pts included in the study, 40.7% and 30.6% had acral and mucosal histology, respectively; almost all (95%) had stage IV melanoma; 221 received first-line (1L) therapy and 116 received 2L therapy (89 received both at BCH within the treatment period). The most common 1L regimens were dacarbazine + carboplatin + bevacizumab (22.2%). The most common 2L regimens were paclitaxel albumin + carboplatin + bevacizumab (22.4%), paclitaxel + carboplatin + RHE (15.5%) and paclitaxel albumin + carboplatin + RHE (12.1%). Clinical outcomes in pts with advanced melanoma are summarized in the table and are generally unfavorable: ORR <10%; median PFS <4 months; median OS <1 year. Median DOR was 9.1 mo for 1L and 7.5 mo for 2L therapy.

<table>
<thead>
<tr>
<th>Table: 1282P</th>
<th>Treatment pattern and clinical outcomes of patients with locally advanced and metastatic melanoma in a real-world setting in China</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEPs</strong></td>
<td><strong>PFS rate, %</strong></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
</tr>
<tr>
<td>PRO endpoints</td>
<td>40</td>
</tr>
<tr>
<td>QFS rate, %</td>
<td>52</td>
</tr>
<tr>
<td>FACT-M total</td>
<td>45</td>
</tr>
<tr>
<td>FACT-M physical well-being</td>
<td>44</td>
</tr>
<tr>
<td>FACT-M social/family well-being</td>
<td>40</td>
</tr>
<tr>
<td>FACT-M emotional well-being</td>
<td>45</td>
</tr>
<tr>
<td>FACT-M functional well-being</td>
<td>41</td>
</tr>
<tr>
<td>FACT-M melanoma subscale</td>
<td>53</td>
</tr>
<tr>
<td>FACT-M melanoma surgery scale</td>
<td>46</td>
</tr>
<tr>
<td>FACT-G total</td>
<td>41</td>
</tr>
</tbody>
</table>

Conclusions: The poor outcomes observed in this study suggest a high degree of unmet medical need for advanced melanoma in China in both the 1L and 2L settings.

Editorial acknowledgement: Medical writing and/or editorial assistance was provided by Doyel Mitra, PhD, of the ApheCom pembrolizumab team, Yardley, PA, USA. This assistance was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

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

Funding: Merck & Co., Inc.


Background: Cancer care costs are a major concern for patients and society. We aimed to assess real life costs for the medical management of uMM.

Methods: We performed a retrospective patient chart review collecting data on demographics, disease characteristics and management. A complete registry of patients diagnosed with melanoma at the Antwerp University Hospital between 2007 and 12/2017 was compiled. Eligible for this chart review were all patients with uMM with sufficient data available and who either had an observation period of >1 year at the time of this review or who deceased before December 31, 2017. Direct costs were calculated by multiplying each item of resource use, obtained from each individual patient chart, with its unit cost (2018, €) using the Belgian public health care payer’s perspective (PHCP) and patient’s perspective. A Kaplan–Meier sample average (KMSA) estimator was used to weight expected costs by the probability of survival and to adjust for censored data.

Results: 89 patients fulfilled all eligibility criteria for this chart review. Ten of the patients (11%) are still alive. 9 patients (10%) received best supportive care (BSC) only. 40 patients (45%) received >1 immunotherapy or targeted agent. Mean overall monthly cost/patient for the entire cohort was €7,244, of which €7,153 was covered by the public health care payer. The cost was driven by systemic treatment costs (66% of cost). Median overall survival (OS) was 8.18 months (95% CI 6.0-10.3). Mean monthly overall cost was €8,269 for patients (n = 35) treated with chemotherapy/BSC only. Median OS in this cohort was 13.83 months (95% CI 8.6-19.0). Mean monthly overall cost was €5,398 for patients (n = 16) who had access to anti-CTLA-4 and/or BRAF inhibitor and MEKi; median OS in this cohort was 11.0 months (95% CI 7.5-14.6).

Conclusions: Management of uMM results in considerable costs for the PHCP, mainly driven by systemic treatment costs. Also in a real-life setting, the introduction of immunotherapy and targeted agents substantially improved survival. However, mean monthly cost has nearly tripled.

Legal entity responsible for the study: Antwerp University Hospital.

Table: 1283P | 1L Therapy (N = 221) | 2L Therapy (N = 116) |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td><strong>CR, n</strong></td>
<td><strong>PR, n</strong></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>6.3% (3.5-10.4)</td>
<td>3.4% (0.9-8.6)</td>
</tr>
<tr>
<td>Median DOR (range, months)</td>
<td>9.1 (7.2-28.4)</td>
<td>7.5 (4.6-24.2)</td>
</tr>
<tr>
<td>Median PFS (95% CI, months)</td>
<td>3.5 (2.9-4.2)</td>
<td>2.3 (2.0-3.0)</td>
</tr>
<tr>
<td>12-month PFS rate</td>
<td>10.6%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>171 (77.4)</td>
<td>101 (87.1)</td>
</tr>
<tr>
<td>Median OS (95% CI, months)</td>
<td>10.5 (9.2-12.1)</td>
<td>7.5 (6.5-8.7)</td>
</tr>
<tr>
<td>12-month OS rate</td>
<td>43.5%</td>
<td>30.5%</td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; DOR, duration of response; 1L, first-line therapy; 2L, second-line therapy; ORR, objective response rate; OS, overall survival; PR, partial response; PFS, progression-free survival.
1285P

Drug treatment in melanoma: A real-world analysis across Europe and Japan

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Background: Incidence/prevalence of melanoma in Asia are both 3% of that in Europe. However, westernization of the Asian population (increase in UV exposure and sun-seeking), is impacting these traditionally low figures. Local drug regulatory agencies have anticipated a shift in treatment from standard to novel molecular targeted and immunotherapeutic products. This study examines treatment differences in melanoma patients in EU5 and Japan, considering dissimilarities between populations.

Methods: A large sample of 4,269 drug treated melanoma cases were collected January 2017–March 2018 through a cross sectional survey in EU5 (France, Germany, Spain, Italy, UK), and Japan. Testing for genetic mutations and drug use were analysed for 5,997 advanced/metastatic (adv/met) patients.

Results: When specified, Acral Lentiginous Melanoma (ALM) and Nodular Melanoma were the most common histology in Japan (25%) during the investigated period, while being only 4% in EU5, where nodular melanoma (23%) and superficial spreading melanoma (21%) were the most frequent. Anti PD1/PD-L1 play an important role in adv/met melanoma setting in EU5 (58%), followed by BRAF (35%) and MEK inhibitor (19%). In Japan, although anti PD1/PD-L1 play an important role in adv/met melanoma (57%), BRAF and MEK inhibitors are uncommon (up to 2% use) and other standard drugs (Interferons, Anthracyclines, Platinum-based, other chemotherapy) which are uncommon in EU5 (4% use at most), are used in up to 21% of Japanese patients. BRAF mutations were tested in 96% in EU5 vs. 32% in Japan for adv/met patients, with 48% and 26% positive rates respectively. PD1 testing was higher in Japan (40%), also presenting a larger PD1 positive population (17%) than the European counterpart.

Conclusions: We have demonstrated penetration of novel immunno-oncology drugs both in Europe and Japan. Existing differences in melanoma treatment between both regions provide insights on Asian populations, which are not well documented. Although these might be influenced by ethnic and genetic factors, maturity of the region should be considered and further analyses would provide an interesting observation on the trend of both regions.

Legal entity responsible for the study: IQVIA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1286P

EUMelaReg: A European platform for outcome research on real-world treatment data of patients with advanced melanoma


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Background: During the past ten years several fundamental breakthroughs have radically changed the treatment options in metastatic melanoma. Both targeted therapies (TT) and immunotherapies (IT) randomized clinical trials have shown significant benefit in relapse free and overall survival. Since the underlying clinical trials represent selected patient populations who had to meet several inclusion and exclusion criteria, the EUMelaReg consortium sought to evaluate “real world” melanoma cases presenting for initial treatment decision with stage IV or unresectable stage III disease.

Methods: Data sources from Denmark (Danish metastatic melanoma database), Germany (ADOKeg Registry) or The Netherlands (Dutch Melanoma Treatment Registry) were merged in a stepwise procedure into a standardized data representation format. The harmonized database for the current analysis included subgroups of patients presenting in 2014 for treatment of non-resectable stage III or metastatic stage IV disease on a regular basis. Criteria used to validate the process of data harmonization contained primary demographic data as well as data concerning the advanced disease status (ECOG status, serum LDH, and baseline tumor burden including the presence of brain metastasis), and the different treatment strategies and their reported outcomes.

Results: It could be shown that more than 30% of the cases included would not have qualified for common inclusion and/or exclusion criteria of clinical phase III trials in advanced melanoma. Moreover, the distribution of prognostic and predictive factors varied substantially between the real-world populations and published study populations.

Conclusions: Final endpoints of the ongoing data collection and analysis will contain among other parameters progression-free survival, overall survival, and tolerability of treatment. Collaboration is sought to a range of other European registries and countries.

Legal entity responsible for the study: The EUMelaReg Consortium (European Melanoma Registries Network).

Funding: BMS, MSD, Roche, Novartis.


1287P

Advanced melanoma treatment patterns in the modern era: United Kingdom (UK) real world retrospective chart review study


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Background: In 2016, all licensed single agent and combination BRAF-targeted therapies (BT) and checkpoint inhibitors (CI) were approved for advanced melanoma in the UK. An evaluation of treatment choices in routine clinical practice was undertaken.

Methods: A retrospective chart review was conducted in 7 UK cancer centres, which included patients ≥18 years old with advanced melanoma who started 1st-line (1L) therapy and received at least 1 dose between July 2016 and June 2017. Patients taking part in clinical trials were not eligible. Patient demographics, disease characteristics, and 1L and subsequent therapy lines were recorded. Interim analyses were descriptive.

Results: 280 patients were followed for median 9 (range: <1-19) months; 80%, 19%, and 1% patients received 1, 2, or 3 therapy lines. 92% of patients had BRAF testing, 26% had NRAS testing, and <1% of tumours were tested for PD-L1. BRAF and NRAS mutation rates were 41% and 7%, respectively. 73% of patients received CI 1L: 46% pembrolizumab (Pem), 26% nivolumab + ipilimumab (N+I), 1% nivolumab (N), <1% nivolumab (N), 27% patients received BT 1L: 20% dabrafenib + trametinib (D+T), 7% dabrafenib (D). 38% of BRAF mutant patients received 1L CI. Most common reasons for therapy selection were biomarker status (42%) and perceived benefit (27%). Two-thirds of patients discontinued 1L therapy (BT: 76%, CI: 63%), 79% within 6 months of starting. Most common reasons for stopping were adverse events for N (15%) and progressive disease for BT and PEM (34% each). 40% of patients who discontinued BT received 2nd line (2L) therapy (BT: 76%, CI: 63%), 29% Pem, 0% vemurafenib. 17% of patients who discontinued Pem received 2L therapy: 57% Ipi, 21% BT (7% D+T, 14% D), 14% other, and 7% trial agents. 41% of patients who discontinued N received 2L therapy: 63% BT (58% D+T, 5% D), 21% Pem, 8% other, and 8% trial agents.

Conclusions: The most common 1L therapy was CI. BRAF mutation status, however, influenced treatment choice, with two-thirds of BRAF mutant melanoma patients receiving BT 1L. More than double the number of patients receiving BT and N 1L received 2L therapy compared with patients receiving Pem 1L. Further exploration of these data will be presented.

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

Funding: Bristol-Myers Squibb.

Disclosure: J.J. Sacco: Lead investigator: Clatterbridge hospital which is a site participating in this chart review study which received funding from BMS. P.G. Corrie: Lead investigator from Addenbrooke’s hospital which is a site participating in this chart review study which received funding from BMS. O. Oladipo: Lead investigator from Belfast City hospital which is a site participating in this chart review study which received funding from BMS. M. Payne: Lead investigator from Churchill hospital which is a site participating in this chart review study which received funding from BMS. J. Larkin, T. Talbot: Lead investigator from Royal Marsden hospital which is a site participating in this chart review study which received funding from BMS. J. Wagstaff: Lead investigator from Singleton hospital which is a site participating in this chart review study which received funding from BMS. S. Cheetham: Data manager from Addenbrooke’s hospital which is a site participating in this chart review study which received funding from BMS. D. Stein, M. Soni, C. Coombs: Employee of Evidera. S. Cheetham received funding from BMS for development of this abstract. A. Amadi, M. Wang, I. Ellis: Employee of BMS.
Assessment of quality of life in patients with metastatic melanoma in real clinical practice in France

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Background: Significant advances were recently observed in the treatment of metastatic melanoma (MM). With 60% of patients now reaching a second line of treatment (trt) and a significant improvement in survival, the assessment of quality of life (QoL) during whole disease is necessary. The objective of this work is to describe the evolution of QoL of patients (pts) over trt lines until death.

Methods: QoL is collected through MultiBases, a prospective French multi-centric cohort dedicated to the follow-up of aunts with MM. It is assessed using the EQ-5D (score range 0-1) and the FACT-M (score range 0-172) questionnaires, at inclusion (i.e. at MM diagnosis) and then every 3 months or at each trt change, until death. Evolution of QoL as compared to the beginning of the 1st line is described at the beginning of the 3rd line. The objective of this work is to describe the evolution of QoL of patients (pts) over trt lines until death.

Results: QoL is assessed on 1183 pts included between 2013 and 2017. Median follow-up is 12 months and 605 patients died during follow-up. At inclusion, the mean score is 0.71 and 0.81 for the FACT-M and EQ-5D, respectively. Evolution of QoL. During the progression and one month before death.

Conclusion: The avelumab EAP provides an alternative treatment option for pts with mMCC, with PD on/after chemotherapy or who are ineligible for either chemotherapy or participation in clinical trials. In contrast to JAVELIN Merkel 200, pts could have ECOG PS ≥ 2, treated brain metastases, or immunosuppressive conditions. Pts received a 5-mo supply of avelumab (administered 10 mg/kg IV Q2W until PD or unacceptable toxicity); resupply was allowed for pts with complete response (CR), partial response (PR), stable disease, or clinical benefit per physician assessment. No central imaging was obtained. Results: As of April 30, 2018, of 521 requests for avelumab across 37 countries, 434 were received in Europe: 305 were approved (including 20 for immunocompromised [IC] pts), 29 were medically rejected, and 9 were withdrawn. Most requests were from France (n = 96) and Italy (n = 87). 275 European pts received avelumab. Median age was 73 y (range, 28-95 y); 69% of pts were male. Of 290 pts on treatment > 3 mo, 145 (50%) had an unexpected tumor or no data reported (including 11 IC pts). Of 105 evaluable pts, physician-assessed objective responses were observed in 54.3% (57 pts, including 3 CR pts [2 CR and 1 PR] with 25.7% CR [27 pts] and 28.6% PR [30 pts]. Median duration of treatment in pts with response was 193d (range, 30-570d). The disease control rate in evaluable pts was 79%. No new safety signals were reported. The EAP is ongoing but closing in 2018 as required postapproval.

Conclusions: The avelumab EAP provides an alternative treatment option for pts with mMCC, with PD on/after chemotherapy or who are ineligible for either chemotherapy or clinical trials. In a real-world setting, avelumab showed efficacy and safety consistent with JAVELIN Merkel 200.

Clinical trial identification: Trial Protocol Number: NCT03089658.

Editorial acknowledgement: Medical writing support was provided by ClinicaIThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: Funding was provided by Merck, KGaA, Darmstadt, Germany in alliance with Pfizer, Inc.

Disclosure: P. Nathan: Honoraria: AstraZeneca, Bristol-Myers Squibb, Novartis, Immunocore, Roche, Pfizer; Membership on any entity’s Board of Directors or Consultant: Amgen, Celgene, Merck, MSD, Pfizer, Roche, Sanofi.

Legal entity responsible for the study: IACF-IIPEP.

Funding: None.

Disclosure: None.
Cost-effectiveness (CE) of avelumab vs standard care (SC) for the treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC)

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Background: mMCC is a rare, aggressive skin cancer with limited response to chemotherapy and a poor prognosis. Avelumab, an anti–PD-L1 IgG1 monoclonal antibody, provides a new treatment option with demonstrated durable responses and promising survival outcomes in the only registration-grade, prospective study of mMCC. JAVELIN Merkel 200 (JM 200; NCT02155647). This analysis assesses the CE of avelumab vs SC in pts with mMCC.

Methods: A 3-state partitioned-survival model was generated to assess the lifetime costs and effects of avelumab and SC from a UK National Health Service (NHS) perspective. Survival and health-related quality-of-life data were taken from JM 200 and observational studies to inform estimates of life-years (LYs) and quality-adjusted LYs (QALYs). Published literature and NHS reference costs were sought to quantify costs within the model, with other parameters sourced from JM 200, literature, or clinical opinion. Overall costs and QALYs were used to calculate the incremental CE ratio (ICEC [cost per QALY gained]). Treatment-experienced (TE) pts had a minimum follow-up of 24 months, while data were extrapolated using hazard ratios for treatment-naïve (TN) pts due to data immaturity.

Results: When costs and QALYs were discounted at 3.5% per annum, avelumab was associated with ICERs of £32,612 (TE) and £36,635 (TN) per QALY gained. Probabilistic sensitivity analysis demonstrated that avelumab was associated with a 9.3% (TE) and 76.4% (TN) probability of being CE at a willingness-to-pay threshold of £50,000 per QALY gained.

Conclusions: This CE analysis from JM 200 demonstrates that avelumab is a CE treatment option for pts with mMCC vs SC. The UK National Institute for Health and Care Excellence recommended avelumab for TE and TN pts; hence, an effective treatment is now available to all UK pts with mMCC. A confirmatory analysis will be conducted with more-mature TN data.

Clinical trial identification: Clinical Trial Number: NCT02155647.

Editorial acknowledgement: Medical writing support was provided by ClinicalThinking Inc., Hamilton, NJ, USA.

Legal entity responsible for the study: Merck KGaA, Darmstadt, Germany.

Funding: This trial was sponsored by Merck KGaA, Darmstadt, Germany, and is part of an alliance between Pfizer, Inc. and Merck KGaA, Darmstadt, Germany.


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Table 129P

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<td>TN</td>
<td>2.11</td>
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Disclosures: None.

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Table 129P

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TK. Owonikoko: Fees for consulting or advisory, Novartis, Celgene, Lilly, Sandoz, Abbvie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, MedImmune, A. K. Salama: Fees for consulting or advisory, Speakers’ bureau: Bristol-Myers Squibb, Roche-Genentech, Array, Novartis, A. Engleberg: Employee: Pfizer Pharma GmbH, S. Harihan: Employee, Equity ownership: Pfizer. C. Lebhe: Financial interest: Roche, BMS, Novartis, Amgen, MSD. All other authors have declared no conflicts of interest.
Cetuximab in patients with unresectable cutaneous squamous cell carcinoma is safe and effective: A real-life analysis

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1Medical Oncology, Centre Anticancer Antoine Lacassagne, Nice, France, 2Unit of Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 3Dermatology, CHU de Caen, France, 4Dermatology, CHU de Rouen, Rouen, France, 5Dermatology, CHU de Caen, France, 6Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 7Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 8Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 9Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 10Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 11Dermatology, CHU de Caen, France, 12Dermatology Venerology, AP-HP BICHAT, Paris, France, 13Dermatology, Centre Hospitalier Lyon Sud, Pierre Bénite, France, 14Dermatology, Université Paris Descartes, Hôpital Saint-Antoine, Paris, France, 15Dermatology, Université Paris Descartes, Hôpital Saint-Antoine, Paris, France

Background: Approximately 20–30% of non-melanoma skin cancers are squamous cell carcinomas of the skin (SCCS). SCCS incidence is increasing and they often occur in elderly or immunosuppressed patients (pts). SCCS can progress to stages impossible to treat by surgical excision or radiotherapy. Cisplatin-based combinations show efficacy but are toxic for elderly pts. Cetuximab (C) demonstrates 69% disease control rate (DCR) at 6 weeks in a few, highly selected pts. This study aims to evaluate the efficacy of C in non-selected pts with SCCS.

Methods: This retrospective study included pts with relapsing unresectable or metastatic SCCS treated with C monotherapy (weekly loading dose 400 and 250 mg/m2). The primary objective was DCR at 6 weeks. 60 pts (38 male) with local relapses of metastatic SCCS (100%), were treated between 30/03/2007 and 07/04/2017 in 13 centers. Median age was 83.1 yrs (min 47.4, max 96.1 yrs). Two-thirds of pts had one or two comorbidities, including 13% (n = 8) with immune disorder. 54% had local relapse. Main metastatic locations were nodules (n = 15), lung (n = 8) and skin (n = 5). 90% were chemotherapy-naïve, 57% had previous radiotherapy, and all were primarily resected. Median time between previous treatment and C was 20.1 months (min 0, max 300). Mean C injection number was 24.8 (min 4, max 60).

Results: Complete response, partial response, stabilization (S) and progression were 7%, 48%, 32% and 13%, respectively, at 6 weeks and 2%, 42%, 29% and 27% at 3 months. 90% of pts experienced at least a disease 5 as best overall response. C was discontinued in 1 patient after first injection due to grade III infusion-related toxicity. All other grade III toxicities were cutaneous (n = 8) with 5 discontinuations. No toxic deaths were reported. Median follow-up, progression-free survival and overall survival were 11.7 months [95% CI: 9.6-30.1], 9.7 months [95% CI: 4.8-43.4] and 17.5 months [95% CI: 9.4-43.1] respectively.

Conclusions: Cetuximab is a safe and efficient treatment for patients, even very old, with SCCS. The toxicity profile of C compares very favorably with cisplatin-based protocols. These results indicate that C is a promising platform to test new combinations.

Legal entity responsible for the study: Centre Antoine Lacassagne

Funding: Merck KGaA

Disclosure: F. Peyrade: Board member: Merck KGaA. All other authors have declared no conflicts of interest.

Sonidegib preplanned subgroups analyses of objective response rates: Final 42-month results from the BOLT study

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Background: Based on results of the phase 2 BOLT study (NCT01327053), sonidegib 200 mg once daily (QD) was approved in the US for patients with locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiotherapy and in Switzerland and Australia also for metastatic BCC (mBCC). Here we report the final 42-month results—the longest follow-up data available from a hedgehog inhibitor (HHI) clinical trial—for a preplanned sonidegib subgroup analysis for the primary endpoint, the objective response rate (ORR), in patients receiving 200 mg.

Methods: BOLT was a double-blind phase 2 study where HHI treatment-naïve patients with laBCC not amenable to curative surgery/ radiotherapy, or with metastatic BCC (mBCC) were randomized 1:2 to sonidegib 200 or 800 mg QD, respectively. The primary endpoint was ORR. Analyses were performed at 12, 30, and 42 months after the last patient was randomized.

Results: For prespecified groups at 42 months, the ORRs for 200 mg QD were consistent for laBCC aggressive (59.5%; n = 37) and laBCC nonaggressive (31.7%; n = 29) histologies; male (43.8%; n = 48) and female (54.8%; n = 31); patients aged <65 years (59.4%; n = 32) and those aged ≥65 years (40.4%; n = 47); while (49.3%; n = 71) and nonwhite patients (37.5%; n = 8); and for patients not receiving (51.8%; n = 56) and those receiving (39.1%; n = 23) gastric pH agents. Subgroup analyses by disease strata (laBCC [56.1%; n = 66] vs mBCC [7.7%; n = 13]) and Eastern Cooperative Oncology Group performance status (0 [60.9%; n = 50] vs 1 [25.4%; n = 3]) were not significant. The safety/tolerability profile was consistent across 42 months with no new AEs emerging.

Conclusions: These results confirmed the consistency of treatment effect for sonidegib 200 mg QD at 42 months across several prespecified subgroups, including age, disease histology, gender, race, and use of gastric pH agents.

Editorial acknowledgement: Leonard Lionnet, PhD, CMP of Ley Medical Communications provided medical writing support for this abstract.

Legal entity responsible for the study: Sun Pharmaceuticals Ltd.


Treatment of advanced basal cell carcinoma with sonidegib: Duration of response and quality of life evaluation from BOLT

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Background: For patients with advanced basal cell carcinoma (BCC), including those with locally advanced BCC (laBCC) and metastatic BCC (mBCC), hedgehog pathway inhibitors (HPIs) are a treatment option. Sonidegib is an HPI approved for use in patients with advanced BCC (Switzerland and Australia) and laBCC (USA and EU), based on data from the BOLT study (NCT01327053). Here we report the duration of response (DOR) at 42 months and quality of life (QoL) results at the 12- and 30-month analyses from BOLT.

Methods: BOLT was a multicenter, randomized, double-blind, phase 2 trial that evaluated sonidegib in treatment-naïve patients with mBCC (n = 36) or laBCC (n = 194) who were not amenable to curative surgery or radiotherapy. Patients were randomized 1:2 to either 200 mg or 800 mg QD, and data analyses were performed at 6, 12, 18, 30, and 42 months. The primary endpoint was objective response rate (ORR) and a key secondary endpoint included DOR as assessed by central review. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the associated Head and Neck Cancer Module 35 (EORTC H&N35).

Results: At the 42-month analyses, the median DOR was 26.1 months in laBCC patients treated with sonidegib 200 mg vs 23.3 months in patients treated with 800 mg. The ORR was higher in the 200 mg group vs the 800 mg group (Table). In mBCC patients, the median DOR was 24 months for sonidegib 200 mg and not estimable for the 800 mg group. The ORR was lower in the 200 mg group vs the 800 mg group (Table). During the course of treatment, the QoL for these patients was analyzed, and the majority of patients in both dosage groups had maintenance of or improvement in QoL relative to baseline.

Table: 1295P ORR in sonidegib-treated patients with advanced BCC

<table>
<thead>
<tr>
<th></th>
<th>laBCC</th>
<th>mBCC</th>
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<tbody>
<tr>
<td>200 mg</td>
<td>n = 66</td>
<td>200 mg</td>
</tr>
<tr>
<td>800 mg</td>
<td>n = 128</td>
<td>800 mg</td>
</tr>
<tr>
<td>ORR %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>56 (3.4)</td>
<td>6 (46)</td>
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<tr>
<td>Partial Response, n (%)</td>
<td>34 (5.1)</td>
<td>57 (44.5)</td>
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<tr>
<td>1295P</td>
<td>(7.7)</td>
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</table>

Conclusions: Data from the 42-month analysis demonstrated that patients receiving sonidegib had a long duration of response. Results from the 12- and 30-month analyses show maintenance and improvement in QoL consistent with that of the primary data observed in BOLT.

Clinical trial identification: NCT01327053 CLDE225A2201.

Editorial acknowledgement: Medical writing support provided by Adriana Vela, PhD, Medical Exchange International, LLC, New York, NY.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

1296P

Discovery of novel germline genetic biomarkers of melanoma recurrence impacting exonic and long non-coding RNA (IncRNA) transcripts


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Background: One challenge in clinical management of cutaneous melanoma (CM) is the limited predictability of recurrence and hence the progression to advanced stages that associate with less favorable outcomes. Aggressive follow-up care and novel adjuvant therapy strategies in early-stage patients with high-risk of recurrence would likely improve CM-specific survival and reduce mortality. We developed a genome-wide approach to identify germline genetic determinants of melanoma prognosis as putative personalized biomarkers for patients at risk of CM recurrence.

Methods: Exploring both the coding and non-coding transcribed genome we formed germline whole genome sequencing (WGS) and tumor RNA-seq on 96 CM patients with tumor/blood matched specimens. All patients were of primary stages I-IIA and of Ashkenazi Jewish ancestry to reduce genetic heterogeneity. We compared 48 patients that recurred in ≤ 5 years versus 48 patients with recurrence in >6 years. Univariate and multivariate logistic regression, gene-burden analysis (SKAT), and differential expression analyses of both mRNA and IncRNAs were used to identify germline regions associated with melanoma recurrence.

Results: Several gene regions were associated with melanoma recurrence, with NEGR1 and MGVST both passing SKAT levels of significance (p < 1e-05), and logistic regression analysis on common WGS variants found over 100 variants with significance p < 1e-05. In addition, we found 200 differentially expressed putative IncRNAs (p < 0.05). The analysis of germline WGS found rs19981892, a 1bp insertion previously associated with both NEGR1 and IncRNA LINC00366, among our top 3 most significant regression results (OR = 9.107 ± 2.31e-05).

Conclusions: This initial phase of our large scale whole genome scan has uncovered germline variants in several coding loci and putative IncRNAs that associate with melanoma recurrence. Most notably, we identified germline variation in a IncRNA near NEGR1, a putative tumor suppressor that has been shown to be under-expressed in advanced cancers, indicating its putative role in cancer progression to metastatic stages. We are currently expanding the patient cohorts and validating these results.

Legal entity responsible for the study: Tomas Kirchhoff.

Funding: NIH.

Disclosure: All authors have declared no conflicts of interest.

1297P

Pilot study: Localizing target lymph node using a magnetic marker allows reliable and representative judgement of pathological stage III melanoma

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Background: The outcome of high risk stage III melanoma patients (pts) is poor, with a 5-year overall survival (OS) rate of ≤ 50%. Adjuvant (ad) high dose IPI, ad NIVO and pembrolizumab improved RFS. Neo-adjuvant (neoad) treatment may be an even more favorable approach as immune checkpoint inhibition is of greatest value at the moment of ICR triggering and therefore dependent on the amount of antigen present. In our previous phase Ib OpACIN study the pathological RR (pRR) was 78% in the neoad arm, and to date after 25 months of follow-up none of the responders has relapsed. This raises the question whether such pts need to undergo complete lymph node dissection (CLND). A prerequisite for such an approach would be an analysis method that reliably indicates pathological response within the whole lymph node bed, without the need for CLND.

Methods: To address this question an in-house developed magnetic marker was placed ultrasonography-guided at baseline into the largest regional lymph node metastasis of pts participating in OpACIN-neo, (NCT02977052), a phase 2 trial aiming at identification of the optimal neoad combination scheme of IPI and NIVO in stage IIIb/C melanoma pts followed by CLND.

Results: So far, 11 pts participated in this side trial of OpACIN-neo. No complications from marker placement were observed, and all magnetic markers were retrieved during the CLND after 6 weeks of neoad IPI + NIVO. 10/11 marked lymph-nodes (LN) were representative in their response for the whole CLND specimen, i.e. index node showed a complete or partial response (PR), all others on CLND showed the same or better responses. Only 1 case was incongruent, as the index LN had 60% vital tumor (no response) compared to another LN (40% vital tumor, PR).

Conclusions: Our early exploratory data from this pilot study indicate that marked LN in stage III melanoma could serve as response indicators for the outcome of the whole CLND after neoad IPI + NIVO. If confirmed, our findings may open the path towards response-driven extent of lymph-node dissection in macroscopic stage III melanoma.

Clinical trial identification: NCT02977052.

Legal entity responsible for the study: Alexander C.J. van Akkooi.

Funding: Has not received any funding.

Disclosure: A.C.I. van Akkooi: Consulting or advising: Amgen, Novartis, MSD Oncology, Merck; Travel, accommodations, expenses: Amgen, Roche, Novartis, Research funding: Amgen, Novartis. C.U. Blank: Personal fees, Advisory role: MSD, BMS, Roche, GSK, Novartis, Pfizer, Lilly, Grants: BMS, Novartis, outside the submitted work. All other authors have declared no conflicts of interest.

1298P

Discovery of KIRREL as a biomarker for prognostic stratification of patients with thin melanoma

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Background: There is a great unmet clinical need to identify patients with thin primary cutaneous melanomas (<1mm, Breslow thickness ≤ 1 mm) who have a high risk for tumor recurrence and death from melanoma. Kin of IRRE-like protein 1 (KIRREL/NEPH1) is expressed in podocytes and involved in glomerular filtration, but its expression in human cancer has not yet been reported. Screening in the Human Protein Atlas portal revealed a particularly high expression of KIRREL in melanoma, both at the mRNA and protein levels. In this study, we followed up on these findings and examined the prognostic value of KIRREL in a population-based cohort of melanoma.

Methods: Immunohistochemical analysis of KIRREL was performed on tissue microarrays with a subset of primary tumors and paired lymph node metastases from an original cohort of 268 incident cases of melanoma in the Malmö Diet and Cancer study. Kaplan Meier analysis and Cox proportional hazard modelling were used to assess the relationship between KIRREL expression and time to recurrence (TTR) and melanoma-specific survival (MSS).

Results: Membranous/cytoplasmic expression of KIRREL was detected in 158/185 (85.4%) primary tumours and 18/19 (94.7%) metastases, in various fractions and intensities. High expression of KIRREL was significantly associated with several unfavourable clinicopathological factors. KIRREL expression was not prognostic in tumours >1 mm thickness, but in T1 tumours (n = 106, median thickness 0.38, range 0.08-1.00), high expression of KIRREL was significantly associated with a reduced TTR, independent of and outperforming absolute thickness in mm and ulceration (HR = 4.54, 95% CI 1.01-20.45), and borderline significantly associated with MSS. High mRNA levels of KIRREL were associated with a significantly reduced overall survival in the TCGA (p = 0.028).

Conclusions: KIRREL is not only a novel potential diagnostic marker for melanoma, but may also be a useful prognostic biomarker for improved stratification of patients with thin melanoma. These findings may be of high clinical relevance and therefore merit further validation.

Legal entity responsible for the study: Lund University.

Funding: Swedish Cancer Society, the Swedish Research Council, the Swedish Government Grant for Clinical Research, the Mrs Berta Kamprad Foundation, Lund University Faculty of Medicine and University Hospital Research Grants.

Disclosure: All authors have declared no conflicts of interest.

1299P

BRAF V600E mutation in melanoma sustains IFN-gamma inducible PD-L1 expression by coactivating STAT1 and increasing protein translation

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Background: Approximately 40-40% of melanoma patients have activating BRAF mutations. Targeting BRAF inhibits proliferation of melanoma cells and increases their immunogenicity. PD-1 immune checkpoint blockade is another breakthrough in melanoma therapy, shown to effectively restore T cell function. These observations indicate that combinatorial use of BRAF inhibitors and immunotherapy might be a rational therapeutic strategy. Herein, we studied the role of BRAF V600E in regulating the expression of PD-L1 in melanoma cells.

Methods: C7274 gene transcript abundance and PD-L1 protein level was measured with qPCR, Western blot and FACS. Identification of signalling pathways responsible for regulation of PD-L1 expression was performed using western blot, FACS and
Results: BRAF-mutant melanoma cell lines exhibited low basal expression of PD-L1 that was markedly induced by IFN-γ, pointing to an adaptive mechanism of PD-L1 expression. BRAF-inhibiting significantly reduced IFN-γ-induced PD-L1 levels in cell lines treated with IFN-γ, vemurafenib decreased STAT1 S727 phosphorylation and expression of PD-L1, suggesting direct regulation of STAT1 by ERK. In A375 cells with constitutively active MEK kinase, vemurafenib had no effect on STAT1 phosphorylation and CD274 transcript level. These results indicate that RAS/RAF/MEK/ERK axis is crucial for maintaining IFN-γ-induced CD274 gene transcription. In addition, vemur- afenib decreased activity of proteins responsible for translation regulation (p6e, PEl, BP1), suggesting that inhibition of protein synthesis could be another mechanisms leading to PD-L1 decrease. To test this hypothesis, we measured de novo PD-L1 synthe- sis following BRAF inhibition, and found markedly reduced PD-L1 translation. Importantly, we also noted decreased translation of other immunoregulatory proteins, such as galectin-1.

Conclusions: BRAF mutations influence PD-L1 expression by modulating its tran- scription and translation. BRAF inhibition has a potential immunomodulatory effect, at least in part by decreasing IFN-γ-induced PD-L1 production.

Legal entity responsible for the study: Institute of Hematology and Transfusion Medicine.

Funding: Polish National Science Center.

Disclosure: All authors have declared no conflicts of interest.

A randomized phase II feasibility study of intermittent versus continuous dosing of targeted therapy in patients with BRAFV600 mutant advanced melanoma (INTERIM)

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Background: BRAF and MEK inhibitor (BRAF+MEK) combination therapy has helped extend median life expectancy of BRAF mutant advanced melanoma patients to over 2 years. Acquired resistance limits duration of benefit and treatment-related toxic- ity can be a problem. Clinical reports suggest that intermittent dosing to manage side- effects does not compromise efficacy and can help patients to remain on treatment long- er. In a mouse model, tumour cells resistant to the BRAF inhibitor vemurafenib appear to suffer a fitness deficit in the absence of drug, so that intermittent dosing could delay or prevent the emergence of resistant tumours. We hypothesise that intermittent dosing with BRAF+MEK will sustain patients on treatment for longer, delay disease progression and improve quality of life (Qol.). However, patient and investigator acceptance of intermittent dosing and compliance with less treatment is uncertain.

Trial design: INTERIM is a UK national portfolio multi-centre feasibility trial devel- oped by the NCRIF Skin Cancer Clinical Studies Group. Patients with BRAF+1000 mutant stage III unresectable or metastatic melanoma will be randomised to receive dabrafenib (150mg bid) and trametinib (2mg od) either continuously or intermittently (dabrafenib days 1-21 and trametinib days 1-14) on a 28-day cycle. Concomitant immunotherapy is not allowed. Randomisation is stratified by brain metastases, FN, stage and lactate dehydrogenase level. We will recruit 150 patients (75 patients per arm) in 18 months at 20 UK sites to provide reliable information on recruitment, treatment compliance, progression-free survival and overall Qol. (composite primary endpoint). Secondary endpoints include safety, health-economic evaluation, patient reported outcomes focusing on skin toxicity and patient experience. In addition we will explore cDNA as a predictive biomarker and in tracking evolution of patients’ tumours. Pharmacokinetic sampling will be per- formed in a subset of patients to help refine the intermittent schedule. From November 2017 until April 2018, 11 patients have been randomised at 9 sites.


Legal entity responsible for the study: Cambridge University Hospital NHS Foundation Trust.

Funding: National Institute for Health Research (NIHR) Research for Patient Benefit Grant.

Disclosure: P. Corrie: Honoraria: Merck Sharp & Dohme (MSD), Novartis, Bristol Myers Squibb (BMS); Consultancy/ advisory role: Celgene, Incyte, BMS, Novartis, MSD, Pierre Fabre; Speakers’ bureau: Novartis, MSD; Travel, accommodation, expenses: MSD, BMS, Research funding (institution): Celgene. R.N. Matin: Consultancy/advisory role: Simon-Kucher and Partners, Healthcare Partners

Institution; Research funding: Barco NV, Skin MD Now, Inc. A. Gupta: Travel, accommodation, expenses: Bristol-Myers Squibb. C. Mather: Immediate family member employed: Argerion and Cardiome in last 2 years; Immediate family member holds stock: Agerion and Cardiome. M.R. McDermott: Honoraria: Amgen, Roche, Consultancy: Merck, CytoImmune, Therapeutics, RogenTec, BMS, NewLink Genetics, Novartis; Expenses: Merck; Institution funding: Immunocore, Novartis, AstraZeneca, Roche, Amgen, Millennium, BMS, Vertex, Merck, Pfizer, RogenTec, Replimune, Array Biopharma, TCI Biopharma, Regnusat. All other authors have declared no conflicts of interest.

1A phase I/II study of concurrent intravenous (IV) and intrathecal (IT) nivolumab (Nivo) for melanoma patients (pts) with leptomeningeal disease (LMD)


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Background: Although advances in treatment with immune checkpoint inhibitors (ICI) have greatly improved the survival for pts with metastatic melanoma (MMM), many still progress and ultimately die from this disease. Metastases to the Central Nervous System (CNS) are one of the most common and devastating complications of MM, occurring in up to 60% of pts and those with LMD have the worst prognosis (overall survival only weeks) and limited treatment options. Our program has demonstr- ated that IT administration of interleukin-2 (IL2) induces durable disease control and prolonged survival in pts with LMD, with 1, 2, 5-year survival rates of 36%, 26%, and 15% respectively. Given the favorable clinical activity and safety compared to sys- temic IL2 and supported by pre-clinical data, we hypothesize that IT administration of nivo is safe and will induce CNS immune responses in pts with LMD.

Trial design: This single center Phase I/II trial (NCT03025256) will treat MMM LMD pts with concurrent IT (via Omnyxs) and IV nivo. The initial dose escalation phase (up to 18pts) will determine the safety and recommended dose (primary objective) followed by an expansion cohort (12 pts) at the recommended dose to assess overall survival (secondary objective). Cycle 1 will consist of IT nivo only at a starting flat dose of 5mg. In subsequent cycles, IT nivo will be followed the next day by IV nivo 240mg Q2W. Pts will be hospitalized overnight for the IT dosing and monitored for neurotoxicity, including signs of elevated intracranial pressure. We will use the Bayesian mTPI method to determine the recommended dose. Pts must have radiographic and/or CSF cytopathologic (CSF) confirmed LMD. Prior therapy with systemic CPI and steroid use (≤ 4 mg/24 hs of dexamethasone or equivalent) to control CNS symptoms is allowed.

Exploratory objectives include the evaluation of immunological effects of this treat- ment on immune cells in the CSF versus peripheral blood and non-LMD tumors. This is the first in human study for LMD pts to receive CPI via IT and systemic administration concurrently. This approach has great potential to be a safe and more efficacious therapy in MM patients with LMD for which there is an urgent unmet need.

Clinical trial identification: NCT03025256.

Legal entity responsible for the study: University of Texas MD Anderson Cancer Center.

Funding: Bristol-Myers Squibb.

Disclosure: J.C. Glitza: Research trial funding: BMS. W-J. Hwu: Research grant: BMS. M. Wong: Advisory board: EMS-Parento, Pfizer, Merck, R. Arman: Research trial funding, BMS. H. Tawbi: Consulting/participated advisory boards: Merck, BMS, Genentech, Novartis; Research funding (institution): Merck, GSK, BMS, Genentech. Celgene. M. Davies: Advisory board, BMS. All other authors have declared no conflicts of interest.

CA224-047: A randomized, double-blind, phase II/III study of relatlimab (anti–LAG-3) in combination with nivolumab (anti–PD-1) versus nivolumab alone in previously untreated metastatic or unresectable melanoma


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Background: Immune checkpoint inhibitors targeting the programmed death recep- tor 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4) pathways have provided sig- nificant clinical benefit for patients with unresectable or metastatic melanoma.

However, a proportion of patients may not respond or may progress with current

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therapies. Lynphocyte reactivation gene 3 (LAG3) is an additional immune checkpoint pathway that negatively regulates effector T-cell function and is a marker of T-cell exhaustion. Dual checkpoint inhibition of the LAG3 and PD1 pathways, by relatimat and nivolumab, respectively, showed clinical activity in patients with previously treated metastatic or unresectable melanoma whose disease progressed during prior anti-PD-1/L1 therapy, with a safety profile similar to nivolumab monotherapy (Ascierto P, et al. Presented at the ESMO 2017 Congress; September 8–12, 2017, Madrid, Spain. Oral LBA18). CA24847 will assess the clinical efficacy and safety of relatimat in combina-
tion with nivolumab versus nivolumab alone in previously untreated metastatic or unresectable melanoma.

Trial design: This is a randomized, multicenter, doubleblind, phase 2/3 study of relatimi-

 Randomized phase III study comparing a non-myeloblastic lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma

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

Funding: Bristol-Myers Squibb.


Background: Less than a decade ago, the prognosis of advanced melanoma was extremely poor, with a 5-year overall survival (OS) of only 9-28%. Introduction of targeted therapies and immunotherapies have significantly improved the outcome of these patients. Ipilimumab, an anti-CTLA-4 antibody, was the first to show clinical benefit in advanced melanoma patients and 20% achieved long-term survival. The PD-1 inhibitor pembrolizumab showed similar activity in metastatic melanoma and further increased objective response rates (ORR) up to 40% and are now often used as first-line therapy. However, a large group of patients still does not benefit from this treatment. Adoptive cell therapy with tumor infiltrating lymphocytes (TIL) has shown promising activity. Among 452 patients with advanced melanoma in several phase I/II trials, with durable responses in a substantial group of patients. TIL treatment consists of infusion of ex vivo expanded tumor resident T cells following non-myeloblastic (NMA) chemotherapy and subse-

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Background: A randomized, open-label, phase II open platform study evaluating the efficacy and safety of novel spartalizumab (PDR001) combinations in previously treated unresectable or metastatic melanoma (PLATforM)


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Background: Significant advancements, including development of immune check-
point inhibitors and targeted therapies, have transformed outcomes for patients (pts) with unresectable or metastatic melanoma. However, pts who do not respond or who progress while receiving these regimens have limited options. Spartalizumab (PDR001) is a high-affinity, humanized monoclonal antibody blocking the programmed cell death 1 (PD-1) receptor. This study is evaluating combinations of spartalizumab with novel compounds to restore antitumor T-cell activity in pts with melanoma progressing after prior PD-1 blockade therapy.

Trial design: This randomized, open-label, 2-part, multicenter, open platform, phase II study (NCT03484923; PLATforM) will evaluate safety and efficacy of spartalizumab combination treatment in pts with unresectable or metastatic melanoma progressing after prior anti-PD-1/L1 therapy and a BRAF inhibitor if the tumor harbors a BRAF V600 mutation. The primary endpoint will be objective response rate per RECIST v1.1, with duration of response and assessment of paired tumor biopsies for biomarkers of antitumor T-cell activity as part of the secondary endpoints. The first “selection” part will begin with 3 combination arms (1) spartalizumab + LAG325 (LAG-3 antibody), (2) spartalizumab + capmatinib (c-MET inhibitor), and (3) spartalizumab + canakinumab (IL-1b antagonist). For the selection part, the PLATforM study uses an adaptive design that, during the selection phase, allows dropping arms for futility, adding new arms, and selecting 1 or multiple arms for further expansion. Bayesian methodology is used with specific probability criteria for futility and efficacy assessments at each interim analysis. Prop(H): at least 50% will be stratified by baseline LDH, maximum of 15 doses). The primary endpoint is progression free survival at 6 months. Secondary endpoints are ORR, complete response rate, OS and safety. Enrollment started in September 2014.

Clinical trial identification: NCT03484923.

Disclosure: T.H. Borich: Travel support: Roche; Travel support, Speaker’s fee: Bristol-

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Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.
Clinical trial identification: NCT03291002.

Legal entity responsible for the study: CureVac AG, Paul-Ehrlich-Str. 15, 72076 Tübingen, Germany.

Disclosure: P. Terheyden: Honoraria; Novartis; Travel expenses: Novartis, Merck, Roche, BMS, Biofrontera; Advisory board: Roche, BMS, Sanofi Novartis; Merck. L. Heinerling: Consultant: CureVac AG PI in clinical study at site Erlangen. P. Mohr: Consultant or advisory role: Merck, Roche. GSK, BMS, Novartis, Scalpay, LEO; Honoraria: GSK, Merck, Roche, Merck, BMS, Novartis, LEO, Scilboase; Research funding: Merck. F. Kiecker: Payments, Travel grants for symposia, Advisory boards, Meetings: Amgen, BMS, Merck-Serono, MSD, Novartis, Pierre-Fabre, Regeneron, Roche. C. Becker: Speaker honoraria: Amgen, MerckSerono and Pfizer; Advisory board honoraria: Amgen, CureVac, eTheRNA, Lytx, MerckSerono, Novartis, Rigontec, Takeda; Research funding: Boehringer Ingelheim, BMS, MerckSerono. U. Gnad-Vogt: Stock, Other ownership interests: Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

Trial design: This is a randomized phase 3 global, multi-center, open-label comparison of ipi (3 mg/kg) +/- intratumoral tilsotolimod (8mg) in subjects with advanced cutaneous or mucosal melanoma with disease progression while on anti-PD-1 therapy. Eligible subjects are age ≥ 18 years with histologically confirmed Stage III or IV melanoma, ≥ 1 measurable lesion accessible for injection, ECOG ≤ 1, adequate organ function, and excluding those with previous TLR agonist treatment, prior ipi (except adjuvant), or CNS disease other than stable (≤ 2 cm) brain metastases. Subjects will be randomized 1:1 to either ipi alone (Arm A) or tilsotolimod + ipi (Arm B) and stratified on the duration of prior anti-PD-1 therapy (≥ 12 weeks/ < 12 weeks), stage (M1c/other), BRAF status and prior targeted therapy (TT) (BRAF wt/BRAF mut + with /TT/BRAD mut - no TT). Primary endpoints comprise RECIST v1.1 or ORR by independent central review and OS. Secondary endpoints include DRR, TTR, PFS, PRO, and safety. Treatment duration is 10 weeks (4 ipi doses) in subjects for Arm A and 24 weeks (9 tilsotolimod + 4 ipi doses) in Arm B. Final analysis (ORR and OS) will occur when 219 death events have occurred, estimated at 36 months after the first randomization. After 110 deaths, an interim analysis will be done for OS. Enrollment is planned at 308 subjects at around 80 centers in 10 countries. It is currently recruiting in the US and Australia with study initiation ongoing in EU and Canada.

Clinical trial identification: NCT03445533.

Legal entity responsible for the study: Idera Pharmaceuticals, Inc.

Funding: Idera Pharmaceuticals, Inc.

Disclosure: J. Gieb, S. Rahmanian, S. Swan: Employees: Idera Pharmaceuticals. A. Diab: Advisory board: Idera Pharmaceuticals. All other authors have declared no conflicts of interest.
Efficacy of lenvatinib in patients with advanced pancreatic (panNETs) and gastrointestinal (gNETs) grade 1/2 (G1/G2) neuroendocrine tumors: Results of the international phase II TALENT trial (GETNET 1509)


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Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NETs) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx)


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Efficacy and safety of PD-1 blockade with JS001 in patients with advanced neuroendocrine neoplasms: A non-randomized, open-label, phase Ib trial

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Prospective genome and transcriptome sequencing in advanced-stage neuroendocrine neoplasms


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Abstracts

1311PD
Health-related quality of life (HRQoL) for octreotide long-acting (oct-LA) vs. placebo (PBO) in patients (pts) with metastatic midgut neuroendocrine tumors (mmNETs) in the phase IIIb PROMID trial

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1312PD
Everolimus after transarterial liver therapy of metastases from gastrointestinal neuroendocrine tumors: The FFCD 1104-EVACEL-GTE phase II study

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1313PD
A phase II study of everolimus in patients with unresectable pancreatic neuroendocrine carcinoma refractory or intolerant to platinum-containing chemotherapy

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Efficacy and safety of telotristat ethyl (TE) in combination with lanreotide (LAN) in patients with a neuroendocrine tumour and carcinoid syndrome (CS) diarrhoea (CSD): Meta-analysis of phase III double-blind placebo (PBO)-controlled TELESTAR and TELECAST studies


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Background: LAN 120 mg, a somatostatin analogue (SSA), is approved in the EU and recently in the USA for CS. In two phase 3 trials in CS, TE 250 mg or 500 mg three-times daily (tid) combined with SSA therapy (LAN or octreotide) demonstrated reduced bowel movement (BM) frequency and urinary 5-hydroxyindole acetic acid (u5-HIAA) levels vs. PBO. TE 250 mg is approved by the FDA and EMA for CSD inadequately controlled by SSAs. This post hoc meta-analysis used patient-level data from the two phase 3 studies to further examine the efficacy and safety of TE + LAN.

Methods: In the TELESTAR (NCT01677910) and TELECAST (NCT02063659) studies, patients using and continuing stable-dose SSAs were randomly assigned 1:1:1 to PBO, TE 250 mg or TE 500 mg tid for a 12-week double-blind (DB) period. Here, only data for patients using LAN during the run-in periods were included. Endpoints included descriptive changes from baseline in 24-hour u5-HIAA, BMs/day, flushing episodes and incidence of adverse events (AEs).

Results: Of 211 patients in the studies, 54 receiving LAN were included in the analysis (44% women, mean [SD] age 61.8 [10.5] years, mean [SD] BMI 25.7 [5.0] kg/m²; 63% used LAN 4-weekly, 20% 3-weekly). One patient received octreotide instead of LAN during the DB period. Randomization of this cohort is shown with efficacy and safety data in the table.

<table>
<thead>
<tr>
<th></th>
<th>PBO tid</th>
<th>TE 250 mg tid</th>
<th>TE 500 mg tid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of LAN patients randomly allocated</td>
<td>n = 29</td>
<td>n = 10</td>
<td>n = 15</td>
</tr>
<tr>
<td>u5-HIAA (mg/24 hour)</td>
<td>24.9 [12.2; 80.9]</td>
<td>57.6 [12.9; 159.8]</td>
<td>31.0 [9.0; 259.2]</td>
</tr>
<tr>
<td>Patients with levels &gt; upper limit of normal (at randomization): n (%)</td>
<td>15 (51.7)</td>
<td>6 (60.0)</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Baseline: median [95% CI]</td>
<td>1.6 [-6.7; 5.0]</td>
<td>-12.4 [-86.4; 77.2]</td>
<td>-24.6 [-134.6; -10.0]</td>
</tr>
<tr>
<td>Week-12 change from baseline: median [95% CI]</td>
<td>3.5 [2.4; 4.4]</td>
<td>3.1 [1.3; 5.6]</td>
<td>5.3 [3.6; 6.1]</td>
</tr>
<tr>
<td>BMs/day: median [95% CI]</td>
<td>3.5 [1.5; 5.1]</td>
<td>2.8 [0.5; 4.9]</td>
<td>2.9 [0.8; 4.3]</td>
</tr>
<tr>
<td>Week-12 change from baseline: median [95% CI]</td>
<td>0.00 [-1.1; 0.4]</td>
<td>-0.5 [-1.2; 0.7]</td>
<td>-0.5 [-2.0; 0.4]</td>
</tr>
<tr>
<td>Flushing (counts/day): median [95% CI]</td>
<td>3.5 [1.5; 5.1]</td>
<td>2.8 [0.5; 4.9]</td>
<td>2.9 [0.8; 4.3]</td>
</tr>
<tr>
<td>Safety: n (%) patients</td>
<td>26 (90)</td>
<td>9 (90)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Any AE</td>
<td>8 (28)</td>
<td>6 (60)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>3 (10)</td>
<td>1 (10)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Treatment-related serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Background: Treatment with somatostatin analogue (SSA) in monotherapy is the most attractive first-line option for patients with well-differentiated stage IV unmetastatic gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The objective is to develop and internally validate tool for predicting progression-free survival (PFS) during treatment with SSA.

Methods: The GETNE-TRASGU study is a subsanalysis of the Spanish Group of NETs registry (R-GETNE). The cohort contains 399 patients treated between 2000-2017 with SSA in the first-line of advanced disease. PFS data were evaluated using Cox proportional risk regression and graphically represented as a nomogram. Missing data were controlled by multiple imputation. Bootstrap Harrell’s c-index with 150 replications was used to assess discrimination.

Results: The median PFS was 25.5 months (95% CI, 20.8-30.8). The nomogram contains 6 covariates significantly associated with PFS: Ki67 index, neurophil-lymphocyte ratio (NLR), extranodal metastases, liver tumor burden and primary tumor location. The median PFS was 3.7% (95% CI, 2.5-9.9) in metastatic disease, 8.8% (95% CI, 6.0-30.0) in intermediate-bad, 18.4% (95% CI, 14.3-26.6) in intermediate-good, and 37.1% (95% CI, 30.8-53.5) in good prognosis group. Ki67% (continuous variable) predicted PFS with HR 1.03 (95% CI, 1.01-1.06), RNA (continuous variable) with HR 1.08 (95% CI, 1.01-1.16), extranodal metastases with HR 1.70 (95% CI, 1.23-2.32), liver tumor burden > 30% with HR 2.07 (95% CI, 1.28-3.54), compared with intestinal (reference), pancreatic with HR 2.18 (95% CI, 1.56-3.04), rectal with HR 1.99 (95% CI, 1.11-3.58), unknown origin with HR 1.71 (95% CI, 1.02-2.85), and other tumors with HR 2.58 (95% CI, 1.22-5.34). This model shows adequate calibration, with acceptable discrimination capability (c-index of 0.641 (95% CI, 0.60-0.68).

Conclusions: The GETNE-TRASGU nomogram allows stratification of patients with advanced and well-differentiated GEP-NETs into four prognostic groups, with potential implications for treatment selection.

Legal entity responsible for the study: Advanced Accelerator Applications, a Novartis company.

Funding: Advanced Accelerator Applications, a Novartis company.

Disclosure: B. Polack, B. He, D. Barton, P. Santaro: Employment: Advanced Accelerator Applications. All other authors have declared no conflicts of interest.

Impact of liver tumor burden on therapeutic effect of 177Lu-dotatate treatment in NETTER-1 study population

Conclusions: The NETTER-1 study population.

Legal entity responsible for the study: Grupo Espa±ol de Tumores Endocrinos y Neuroendocrinos (GETNE).

Funding: Grupo Espa±ol de Tumores Endocrinos y Neuroendocrinos (GETNE).

Disclosure: All authors have declared no conflicts of interest.

Treatment outcomes for well differentiated grade 3 neuroendocrine tumors (NET G3)

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Carboplatin (CB) combined with oral or intravenous (IV) etoposide (ET) for advanced extra-pulmonary (EP) poorly differentiated (PD) neuroendocrine carcinoma (NEC): Real-world findings from two European neuroendocrine tumour society centres of excellence

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Background: Carboplatin–Etoposide is a 1st-line (1L) option for patients (pts) with advanced EP-PD-NEC. Schedules with oral or IV ET are used in clinical practice. Data from randomised trials are lacking.

Methods: Records of pts diagnosed with advanced EP-PD-NEC and treated with CB/oral ET and CB/IV-ET were reviewed retrospectively (99/96-02/17). First-line survival/activity/toxicity data are reported.

Results: One-hundred-thirteen pts were included: median (med) follow-up was 11.5 months (m); med age was 65.8 years (range 24-88); male=64%; ECOG performance status 0-1=88%; no/mild comorbidities=41%+; gastro-entero-pancreatic origin=54%; stage IV=90% (93% liver metastases). Median Ki-67=70% (95%CI 60-80%); Ki-67=55%±=59%. A total of 123 courses of CB-ET were administered: 106 (86%) 1L, 13 (13%) 2nd-line (2L) and 11 (1%) 3rd-line (3L); med cycles-line=4-oral ET 45%, IV ET 35%. Median CB-ET dose-intensity (available for 82 courses) 96% (1L), 90% (2L). Median 1L-progression free survival (PFS) was 5.9m (95%CI 5.0-7.1); median ET 6.5m, IV-ET 6.2m, hazard ratio (HR) =0.76 (95%CI 0.51-1.14). Median 1L-overall survival (OS) was 11.5m (95%CI 8.9-13.6); oral-ET 8.9m, IV-ET 12.1m, HR =0.68 (95%CI 0.45-1.03), p =0.07. Radiological response (assessed for 95 pts), 1L-disease control rate was 75.8% (95%CI 67.1-84.6); oral-ET 69.8% (95%CI 55.5-84.1); IV-ET 80.8% (95%CI 69.7-91.8). Liver metastases were the only independent factor related to worse 1L-PFS on multivariable analysis, HR =1.71 (95%CI 1.11-2.62). Commonest 1L-grade 3-4 adverse event (AE) was myelosuppression (47.2%); no significant differences between oral ET and IV ET AEs, except for venous thromboembolism; oral ET 12.5%, IV-ET 1.7% (p =0.04).

Conclusions: This is one of the largest series of pts with advanced PD-NEC treated with CB-ET in the current literature. Oral-ET and IV-ET schedules are associated with comparable 1L-PFS/activity/toxicity data. There is a trend towards better 1L-OS for IV-ET schedules; this, however, may be driven by differences in patient selection between the two subgroups.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Surgical resection of primary tumor is prolonged survival in metastatic pancreatic neuroendocrine carcinoma

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Background: Most of pancreatic neuroendocrine carcinoma (PanNEC) present with distant metastases. Removal of the primary tumor is not recommended for metastatic PanNEC patients considering the limited survival benefit compared to well-differentiated grade patients. However, published data to support these recommendations regarding PanNEC are scarce. The aim of this study was to assess whether resection of the primary tumor in patients with stage IV PanNEC has an impact on survival.

Methods: Patients with stage IV PanNEC registered in the Surveillance, Epidemiology, and End Results database between 1973 and 2014 were identified. The specific criteria and other authors have declared no conflicts of interest.

Legal entity responsible for the study: Fengting Feng.

Funding: Has not received any funding.

Disclosure: C. Thirlwell: Advisory board, Speaker honoraria: Ipsen. C. Toumpanaki: Speaker honoraria: Ipsen. Novartis and AAA. M. Caplin: Advisory Board, Speaker honoraria: Novartis, Ipsen, AAA, Lexicon. All other authors have declared no conflicts of interest.

Results: We identified 461 patients with metastatic PanNEC and survival data. 15.8% (73/461) of patients had surgical removal of their primary tumor. Median survival of patients undergoing primary tumor resection was 28 (95% CI 4.751-51.249) versus 6 (95% CI 4.672-7.328) months for those without resection (p < 0.0001). Patients undergoing primary tumor resection showed a significant benefit in both OS (HR of death =0.296, 95% CI 0.206-0.424, p < 0.001) and CSS (HR of death =0.329, 95% CI 0.219-0.493, p < 0.001) in an unadjusted multivariate Cox regression analysis; the benefit persisted after propensity score adjustment.

Conclusions: The recent recommendations judging resection of the primary as inadvisable and the accompanying trend towards fewer palliative resections of the primary tumor in IV stage PanNEC have to be contested.

Legal entity responsible for the study: Fengting Feng.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

**Background:** DIPNECH is considered a rare condition and the natural history is poorly described. Its prevalence is likely underestimated given the absence of routine reporting on histopathology and often insufficient background lung parenchyma in the setting of lung biopsy. It is thought to give rise to pulmonary carcinoids (PCs) (>3 mm) or tumourlets (<5 mm). We aimed to assess the prevalence and characteristics of DIPNECH in the PC population and to investigate predictors of progression-free (PFS) and overall survival (OS).

**Methods:** We identified patients with PCs plus histologically-proven DIPNECH and/or high suspicion of DIPNECH on imaging. The relationship between baseline characteristics and PFS and OS was analysed using the Kaplan-Meier method and curves were compared using the logrank test.

**Results:** 46/233 (20%) patients with well-differentiated PCs and DIPNECH were identified (91% female, 52% never smokers, 50% cough and/or dyspnoea at time of diagnosis, 76% typical carcinoids (TC), 24% atypical carcinoids (AC)) who received at least 1 cycle of PRRT at 18-37 mo (range 2-138 mo). Multicentric carcinoids were demonstrated in 11 (24%) patients on histopathology and a further 26 (57%) patients had synchronous carcinoids suggested on enhanced CT (multiple nodules >5 mm). Median PFS was 10.4 years. Six (13%) patients developed regional or distant metastases after a median of 25 months (95% CI 18-35) and most patients had higher proliferative indices on biopsy of metastases compared to histopathology at diagnosis. Atypical carcinoid morphotype (PFS p-value 0.006, OS p-value 0.01) and carcinoid TNM stage (PFS p-value <0.001, OS p-value 0.04) was associated with shorter PFS and poorer OS. Of the entire cohort, ten year survival rate was 87%. Median OS was not reached.

**Conclusions:** DIPNECH may be more prevalent in the PC population than previously appreciated, especially in women. Whilst our results confirm DIPNECH is predominantly an indolent disease associated with TCs, up to one quarter of patients may develop ACs and these patients may warrant closer observation. Median PFS is long and lifelong follow-up is recommended.

**Legal entity responsible for the study:** Aimees Hayes.

**Disclosure:** A. Grossman. Lecture fees: Novartis, Ipsen, HRA Pharma, Pfizer, but none for the past 12 months. C. Toumpanakis: Speaker honoraria: Ipsen, Novartis, AAA. M. Caplin: Advisory board and speaker honoraria: Novartis, Ipsen, AAA, Lexicon. All other authors have declared no conflicts of interest.

**Funding:** Has not received any funding.

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**Background:** The NETTER-1 trial has recently shown the efficacy of 
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**1324P**

**The role of modulation of somatostatin analogues (SSAs) in association to peptide receptor radionuclide therapy (PRRT) after SSAs progression disease (PD) in advanced well-differentiated (WD) entero-pancreatic neuroendocrine tumours (EP-NETs)**


**Medical Oncology Department, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy**

**Background:** The NETTER-1 trial has recently shown the efficacy of 

**Methods:** Out of 107 WD EP-NETs, treated with PRRT (177Lu-DOTATOC/DOTATATE and/or 90Y-DOTATOC/DOTATATE) at the Istituto Nazionale Tumori of Milan, from 2008 to 2017, 69 patients (pts) treated with the combination of PRRT and SSA (OCT or Lanreotide, LAN) after SSA treatment failure, were evaluated for present analysis. We identified 2 groups: S1, pts who kept the same SSA treatment beyond first PD; S2, pts who switched the SSA with another SSA after first PD. Median Progression Free Survival (mPFS) (from the start of first SSA) and Overall Survival (OS) have been evaluated using the Kaplan-Meier method.

**Results:** In S1 (n = 47) and S2 (n = 22) groups median age and sex were 58 yrs (range 29-78) and 59.3% males vs 52.5 yrs (range 35-78) and 45.4% males, respectively. We had a P-NETs percentage of 34% vs 40.9% in the S1 vs S2 groups, respectively. The most of pts (82.9% in S1 and 86.3% in S2) received PRRT with alternate radionuclides (177Lu). Overall the median number of PRRT cycles was 4.2 in S1 and 4.8 in S2 (p = 0.09). In the S1 (SSA beyond PD) group PRRT was associated with OCT in 74.3% and LAN in 25.5% of pts. In the S2 group (SSA switched with other SSA) PRRT was associated with OCT in 27.3% and LAN in 72.7% of pts. In the overall population the mPFS and OS were 70 (95% CI 58.8-87.1) and 82 (95% CI 67.9-97.2) months (mo), respectively. The difference on mPFS was 53 and 127 mo in S1 and S2, respectively (p = 0.001; HR: 0.31; CI95% 0.15-0.63). In S1 group the OS was 69 mo vs 150 mo in S2 (p = 0.004; HR: 0.32; CI95% 0.14-0.71).

**Conclusions:** Despite the retrospective nature of the analysis and the low number of pts, we found a significant difference on mPFS and OS between S1 and S2 groups. In pts with advanced WD EP-NETs treated with PRRT plus SSA after SSA failure, the “switch” strategy of SSA after PD, might improve PFS and/or OS. Legal entity responsible for the study: Sara Pusceddu.

**Funding:** Has not received any funding.

**Disclosure:** N. Pritzl: Iliadfarmaco, Novartis: Consultancies. G. Lo Russo: AttraZeneca, IMS, MSPI: Consultancies. S. Pusceddu: Novartis, Ipsen, Iliadfarmaco, Pfizer and advanced accelerator applications (AAAL). All other authors have declared no conflicts of interest.

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**Conclusions:** Prognostic importance of lymph node (LN) yield after curative resection of gastroenteropancreatic neuroendocrine tumours (GEP NETs)


**Background:** Surgery is the mainstay of treatment for GEP NETs, but there is no consensus on optimal number of resected LNs. The effect of LN status and yield on relapse-free (RFS) and overall survival (OS) in patients (pts) with resected GEP NETs were evaluated.

**Methods:** On pts who underwent curative resection for GEP NETs (Jan 02-Mar 17) were retrospectively analysed. Grade III tumours (Klo7>20%) were excluded. Kaplan-Meier and univariate/multivariable Cox-proportional hazard analyses were performed. Cut-point analysis was attempted to distinguish a binary categorisation of total LNs retrieved associated with RFS. **Results:** Of 217 pts, median (med) (age) was 59 yrs: 51% male. Primary tumour sites: small bowel (42%), pancreas (25%), appendix (18%), rectum (7%), colon (3%), gastric (2%), others (2%). Med follow up times for all pts were 41 months (95% CI 36-51) and 71 months (95% CI 63-76) for RFS and OS respectively. On univariate analysis, there was no effect of LN ratio (number involved/number retrieved) on RFS: p = 0.1 or OS: p = 0.75. On univariate analysis, tumour necrosis (p = 0.021) and perineural infiltration (p = 0.016) were the only two variables significantly associated with OS; G (p < 0.05), TNM staging (p = 0.19) and surgical margin (p = 0.69) were not significantly associated with OS. Multivariable analysis for RFS included 4 variables of interest: perineural infiltration, LNs retrieved, positive LNs and localisation (Table).

**Legal entity responsible for the study:** The Christie Hospital NHS Trust, Manchester, UK.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Table: 1325P**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>Perineural infiltration</td>
<td>1.46 (0.74 - 2.69)</td>
<td>0.277</td>
</tr>
<tr>
<td>≥8 lymph nodes retrieved</td>
<td>2.70 (1.07 - 6.84)</td>
<td>0.036</td>
</tr>
<tr>
<td>Any lymph nodes positive</td>
<td>2.71 (1.08 - 8.30)</td>
<td>0.081</td>
</tr>
<tr>
<td>Pancreas (relative to ‘other’)</td>
<td>37.33</td>
<td>(2.54 - 294.08)</td>
</tr>
<tr>
<td>Small Bowel (relative to ‘other’)</td>
<td>32.44</td>
<td>(2.92 - 360.58)</td>
</tr>
</tbody>
</table>

**Conclusions:** Removal of ≥ 8 LNs is associated with greater risk of relapse in G1 & G2 GEP NETs; localisation also has a significant association with RFS, necessitating stricter surveillance. Larger prospective studies are required to validate these findings.

Legal entity responsible for the study: The Christie Hospital NHS Trust, Manchester, UK.
Evaluation of the safety and efficacy of everolimus as a first-line treatment in newly diagnosed patients with advanced gastroenteropancreatic neuroendocrine tumors


Background: The purpose of this study was to explore the efficacy and safety of everolimus administered as first-line treatment in newly diagnosed patients (pts) with metastatic or inoperable gastroenteropancreatic neuroendocrine tumors (GEPNETs).

Methods: This phase II, multicenter, single-arm clinical trial, included pts with advanced GEPNET of well or moderate differentiation and a Ki67<20%. Everolimus (10mg/day) was administered until disease progression. All pts’ tumors were non-functional. 18 pts (72%) received concomitantly octreotide long-acting release (LAR) 30mg/month. Endpoints of the study included progression-free survival (PFS), objective response to treatment (RECIST 1.1) and safety.

Results: After a median follow-up of 53 months, twenty-five pts (G1:11 pts, G2:14 pts; Ki67: <11% pts, Ki67: 11-14% pts, Ki67 >14% pts) received a median of 4 treatment cycles per patient. Centrally assessed radiographic responses in 23 evaluable patients included 43% PR, 48% SD and 9% PD. Of the 18 pts receiving octreotide LAR and everolimus, 9 patients had SD and 9 PR. The median PFS was 14.6 months, while the 15-months PFS rate was 48%. No fatal reaction occurred. Twenty-three grade 3-4 events were recorded (14 pts; 56%). Among them, 19 events were assessed as related to treatment and included stomatitis (G3: 3 pts; 12%), diarrhea (G3: 2 pts; 8%), CPK increase (2 pts; 8%), GGT increase (2 pts; 8%), hypokalemia/hypomagnesemia (1 pt; 4%), neutropenia (G3: 1 pt; 4%), anemia (G3: 1 pt; 4%), and hyperglycemia (G3:1 pt; 4%). Baseline cholestasis (G3: 4 pts; 16%), GGT increase (2 pts; 8%), GPT increase (1 pt; 4%), bile duct obstruction (1 pt; 4%), and CPK increase (1 pt; 4%) and G4 (1 pt; 4%). Baseline cholestasis (G3: 4 pts; 16%), GGT increase (2 pts; 8%), GPT increase (1 pt; 4%), bile duct obstruction (1 pt; 4%) and CPK increase (1 pt; 4%) and G4 (1 pt; 4%). Baseline cholestasis (G3: 4 pts; 16%), GGT increase (2 pts; 8%), GPT increase (1 pt; 4%), bile duct obstruction (1 pt; 4%) and CPK increase (1 pt; 4%) and G4 (1 pt; 4%). Baseline cholestasis (G3: 4 pts; 16%), GGT increase (2 pts; 8%), GPT increase (1 pt; 4%), bile duct obstruction (1 pt; 4%) and CPK increase (1 pt; 4%) and G4 (1 pt; 4%). Baseline cholestasis (G3: 4 pts; 16%), GGT increase (2 pts; 8%), GPT increase (1 pt; 4%), bile duct obstruction (1 pt; 4%) and CPK increase (1 pt; 4%) and G4 (1 pt; 4%).

Conclusion: This prospective phase II study confirms everolimus’ efficacy as upfront therapy and provides for the first time high rates of partial responses in advanced GEPNETs attributed to the combined effect of everolimus and octreotide LAR.

Clinical trial identification: NCT01644865.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group, Novartis.

Disclosure: A. Koumarianou, D.G. Pectasides, G.A. Kaltsas, E. Samantas, G. Pentheroudakis: Honoraria for advisory board: Novartis. All other authors have declared no conflicts of interest.

Improved quality of life in patients with GEP-NETs treated with 177Lu-dotatate

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Background: The incidence of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has been increasing over recent decades. Lutetium therapy is now established as a treatment with benefit towards progression-free survival (PFS) in patients with metastatic GEP-NETs with median PFS of up to 36 months. However, the effect of 177Lu-DOTATATE on quality of life (QoL) is not yet well understood with few studies evaluating the impact on symptom control and patient function. Our study sought to evaluate the change in QoL for patients with progressive GEP-NETs treated with 177Lu-DOTATATE.

Methods: Our study was conducted as a part of the Phase II open label clinical trial at the Cross Cancer Institute in Edmonton. Patient enrollment started in March of 2014 and is ongoing. Treatment consisted of induction phase of 5.5 5QG administered at four treatments, 10 weeks apart. For patients without toxicity or progression on treatment, a maintenance phase was entered consisting of 2.78 5QG every 6 months up to 4 years and maximum of 12 total treatments. QoL over 177Lu-DOTATATE treatment was assessed with EORTC-QLQ-C30 and QLQ-GI-NET 21 QoL questionnaire at baseline and subsequent to each treatment. Planned interim analysis of QoL was completed in all patients having completed induction therapy. Repeated measures ANOVA was performed. A p value of ≤ 0.05 was considered to be clinically significant.

Results: In total 85 patients met inclusion criteria for interim analysis: tumor of gastroenteropancreatic origin and completion of four 177Lu-DOTATATE treatments. Primary analysis revealed statistically significant change and clinically significant improvement in mean insomnia (36.43 to 25.58), endocrine symptom (20.37 to 14.81) and GI symptom scores (22.28 to 16.67) from baseline to post fourth treatment. Overall global health status was maintained over treatment course with no improve but also no statistically significant deterioration in QoL.

Conclusions: 177Lu-DOTATATE is not only effective in improving PFS for patients with metastatic GEP-NETs but also maintains overall quality of life and importantly provides patients with improvement in specific symptoms such as insomnia, endocrine and GI symptoms.

Clinical trial identification: NCT01876771.

Legal entity responsible for the study: Alberta Health Services.

Funding: Alberta Cancer Foundation, Alberta Heritage Foundation for Medical Research, Canadian Institutes of Health Research, Canada Foundation for Innovation.

Disclosure: All authors have declared no conflicts of interest.
**Efficacy and safety of vandetanib for patients with advanced and progressive medullary thyroid cancer (MTC) as systemic treatment beyond first-line therapy**

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**Background:** Vandetanib has demonstrated efficacy in advanced MTC in a large phase III trial (ZETA trial, JCO 2012). However, the study had several limitations that impact in the daily clinical practice, such as the efficacy in patients (pts) with documented disease progression or beyond first-line therapy who have a worse prognosis.

**Methods:** Pts with advanced unresectable MTC with previous radiologically documented disease progression were included in the Spanish National Database of the Rare Cancer Working Group (GETH). Pts started treatment with vandetanib 300mg qd as initial dose, with dose reductions allowed as per toxicity. Baseline characteristics, progression free survival (PFS), response rate (RR), correlation with biomarkers and toxicity data were reviewed retrospectively in first, second and third line setting. The program was validated by regulatory authorities and all patients signed and informed consent form.

**Results:** 59 pts (med age:48y; male 61%) were included. 14% had RET mutations. Vandetanib was given as first line in 61%, second line in 22% and third-line therapy in 17% of pts. RR and median PFS in first, second and third lines were 47%, 33% and 40% (p 0.035) and 16.8, 13.6 and 11.5 months (p 0.94) respectively. No correlation was found between calcitonin or CEA reduction and RR. However, CEA level decrease was 42% (p 0.85%) and 16.8, 13.6 and 11.5 months (p 0.94). PFS in the daily clinical practice, such as the efficacy in patients (pts) with documented disease progression or beyond first-line therapy who have a worse prognosis.

**Conclusions:** Probability of tumor shrinkage with vandetanib is maintained through-out treatment lines despite of a trend of reduced benefit in PFS beyond first-line in a cohort of pts with a worse prognosis. CEA reduction may predict longer PFS. Safety is maintained regardless prognosis and prior therapies.

**Legal entity responsible for the study:** Spanish Rare Cancer Working Group (GETH).

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**Development and validation of neuroendocrine tumor marker panel in small biopsies using multiplexed mass spectrometry**

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**Background:** Neuroendocrine tumors (NET) occur throughout the body but are not commonly suspected in breasts, prostate or colorectal tumors. Morphologic evidence of neuroendocrine differentiation may prompt testing for neuroendocrine markers, but such testing is not routine. Now that NET-specific therapies can increase patient survival, distinction of NET from non-NET is essential. We developed a multiplexed mass-spectrometry-based screening tool to measure tumor expression of 3 common neuroendocrine (NE) markers. We tested and validated this NET panel in clinical biopsies of NET and non-NET.

**Methods:** Formalin-fixed-paraffin-embedded (FFPE) NET were microdissected and solubilized to tryptic peptides for mass spectrometric analysis using selected reaction monitoring. Synthetic versions of chromogranin A (CHGA), synaptophysin (SYP) and CD56 peptides were used to develop the assay. Using mass spectrometry with stable isotope labeled internal standards, these 3 NE proteins were quantitated in FFPE tumor biopsies of NET and non-NET.

**Results:** In the test set, 20 of 20 previously diagnosed NET (of the lung and gastroenteropancreatic tract) expressed ≥2 of the 3 NE protein markers (positive predictive value =100%), and 47 of 50 non-NET (non-small cell lung cancer) expressed none of the markers, with only one sample expressing ≥2 markers (negative predictive value =98%). NET positivity was therefore defined as expression of ≥2 markers. In a validation set of 16 NET, the proteomic panel confirmed 13 cases. Of the 3 discordant cases, one of these was a small-cell lung cancer with mixed NE and squamous histology. When used to screen 614 consecutive clinical samples of multiple tumor types, the panel found 16 tumors that unexpectedly expressed ≥2 NE markers. Upon pathology review, 3 of these were confirmed as NET, thus revealing new treatment options for 5 patients.

**Conclusions:** A mass spectrometry-based screening tool can identify NET with sensitivity and specificity similar to that of immunohistochemistry. Such proteomic testing can identify NE proteins simultaneously with dozens of other clinically relevant bio-markers (eg, HER2, EGFR) to inform treatment decision making without the need for additional FFPE sections.

**Legal entity responsible for the study:** NantOmics.

**Funding:** NantOmics.

**Disclosure:** S. Thyparambil, E. An, S. Sellappan, E.R. Wertheimer, F. Cecchi, R. Heaton, T. Hembrough: Employee: NantOmics. All other authors have declared no conflicts of interest.
Conclusions: Effectiveness was encouraging in this small selected population. TGR suggested tumour regression during LAN–PRRT. Despite low baseline TGR, 35% pts had RECIST PR on central assessment.

Clinical trial identification: PRELUDE: NCT02788578.

Editorial acknowledgement: Writing and editorial/submission support provided by Tom Vizard, PhD, and Richard McDonald (Watermeadow Medical), funded by Ipsen.

Legal entity responsible for the study: Ipsen.

Funding: Ipsen.


Table: 1331P

<table>
<thead>
<tr>
<th>Patients with GEP-NETS (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (tange) LAN exposure, mOva</td>
</tr>
<tr>
<td>Median (range) LAN exposure, mOva</td>
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<td>Median (range) LAN exposure, mOva</td>
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<td>Median (range) LAN exposure, mOva</td>
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<tr>
<td>Median (range) LAN exposure, mOva</td>
</tr>
<tr>
<td>Mean (95% CI) TGR Prebaseline/baseline</td>
</tr>
<tr>
<td>Median (range) LAN exposure, mOva</td>
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<td>Median (range) LAN exposure, mOva</td>
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<td>Median (range) LAN exposure, mOva</td>
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<tr>
<td>Median (range) LAN exposure, mOva</td>
</tr>
</tbody>
</table>

Conclusions: We provide evidence for the presence of ctDNA in patients with a metastatic PNET. Non-metastatic cases were ctDNA-negative. An increase in VAF and genetic instability were found in the follow-up sample of one of the metastatic cases, suggesting potential for ctDNA as follow-up marker. Furthermore, CNAs in primary tumor and plasma sample were significantly correlated, proposing ctDNA as an alternative for molecular profiling of tissue in metastatic patients.

Legal entity responsible for the study: Antwerp University Hospital.

Funding: Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society; Research Foundation – Flanders (FWO).

Disclosure: All authors have declared no conflicts of interest.

1333TP CAPTEM or FOLFIRI as second-line therapy in neuroendocrine carcinomas and exploratory analysis of predictive role of PET imaging and biological markers (SENECA study)

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Background: Patients with metastatic or locally advanced, non-resectable, grade 3 neuroendocrine carcinoma (NEC) of the lung or gastroenteropancreatic system (GEP NEC) are usually treated with first-line platinum-based chemotherapy. There is no standard second-line treatment when progression occurs. Different second-line chemotherapy combinations have been evaluated retrospectively, but with poor results.

FOLFIRI was evaluated in a retrospective monocentric study, showing a disease control rate (DCR) of 62%. In another retrospective study, temozolomide-based chemotherapy obtained a DCR of 71%. There is growing evidence that the current grading system for NECs has a number of inconsistencies, highlighting the need for more accurate biomarkers to better understand the natural history of this very aggressive disease.

Trial design: SENECA study is a randomized, non-comparative, multicenter phase II trial designed to evaluate the efficacy and safety of FOLFIRI or capcitabine plus temozolomide (CAPTEM) after failure of first-line treatment in lung and GEP NECs. Primary aim is to assess DCR of the regimens, with safety as a co-primary. Secondary aims are the evaluation of overall survival (OS), progression-free survival (PFS) and quality of life. It is also planned to assess Gallium-PET/CT and tissue and circulating biomarkers as prognostic and predictive factors. Eligibility criteria are age ≥18 years, metastatic or locally advanced, non-resectable, lung or GEP NEC, and documented evidence of progressive disease during or after first-line platinum-based chemotherapy (cisplatin/carboplatin and etoposide; FOLFOX4 or CAPOX). Each patient is randomized to receive FOLFIRI or CAPTEM, considering Ki-67 (25–55 vs >55%) and primary tumor site (lung vs GEP) as stratification factors.

Randomized study design allows for two active treatments to be evaluated in a comparable patient population. Analysis will be performed for each regimen separately. 56 patients will be enrolled in each arm of the study (total of 112 patients). Sixteen centers are taking part in the study and recruitment is ongoing. The first patient was randomized on March 6, 2017.

Clinical trial identification: IRB/100.22
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Background: Neuroendocrine tumours (NET) associated with the gastrointestinal tract are frequently indolent but problematic as a result of potential endocrine secretory properties and metastasis often to the liver. Metastases (mNET) located in the midgut and liver often secrete vasoactive products, giving rise to the “carcinoid Syndrome,”; flushing, diarrhoea, wheezing, abdominal cramps and peripheral oedema. Treatment options for mNET include surgical resection, chemoablation, and use somatostatin analogues (e.g. octreotide, lanreotide) or radio-labelled analogues (e.g. Lutate/Lutathera, 177Lu-DOTA-octreotate). However there is a need for additional options for mNET patients. There has been a paradigm shift in anti-cancer therapy over the last decade with the introduction of immunotherapy treatments. Intrallesional rose bengal disodium (PV-10) is undergoing clinical development as an oncolytic immunotherapy and is the subject of this phase 1 study examining potential use of PV-10 for treatment of symptomatic mNET of the liver (NCT02963067).

Trial design: This phase 1 study is evaluating the safety, tolerability and reduction of biochemical markers and symptoms resulting from image guided percutaneous administration of PV-10 in up to 12 participants with mNET of the liver not amenable to resection or other potentially curative therapy. The Target Lesion(s) as defined by the interventional radiologist must be a uni-dimensionally measurable lesion with longest diameter between 1.0cm and 3.9cm as measured. The primary endpoint is safety. Secondary endpoints include objective response rate (ORR), target lesion SSTR and biochemical response. ORR is assessed by contrast enhanced CT and 68Ga-DOTATATE PET standardized uptake value (SUV) allows SSTR expression to be used as a surrogate for tumour viability. In addition to characterizing direct effect of PV-10 in injected lesions, response of un.injected bystander lesions is evaluated by CT and PET to characterize potential systemic benefit. Integration of patient-reported outcome (QLQ-GI.NET21), serum biomarker (CgA) and objective response (PET) data will allow testing of concordance between independent indicators of clinical benefit.

Clinical trial identification: NCT02693067.

Legal entity responsible for the study: Provectus Biopharmaceuticals.
This study suggests that evaluation of BI-RADS 4 or 5 breast lesions with contrast-enhanced ultrasound (CEUS) can improve the precision of BI-RADS assignment. The diagnostic performance of CEUS-based BI-RADS evaluation classified 287/1060 (27.08%) lesions into category 3, 195 (18.40%) into category 4A, 124 (11.7%) into category 4B, and 144 (13.58%) into category 4C. The cancer-to-biopsy yield was 60.16% with CEUS-based BI-RADS 4A or 5 selected as the biopsy threshold compared with 43.86% otherwise, while the biopsy rate was only 72.92% compared with 100% otherwise (Figure 2). Overall, only 1.94% of invasive cancers were misdiagnosed as BI-RADS 3.  

Conclusion: This study suggests that evaluation of BI-RADS 4 or 5 breast lesions with CEUS result in reduced biopsy rates and increased cancer-to-biopsy yields. 


Legal entity responsible for the study: Ultrasound Department of Sichuan Provincial People’s Hospital. 

Funding: Has not received any funding. 

Disclosure: All authors have declared no conflicts of interest.

13360 Unbiased genomewide screening of circulating plasma DNA for cancer detection

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1337P Predictive models for CEUS of the breast: is it feasible in improved performance of BI-RADS evaluation of critical breast lesions?

L. Luan1, Q. Chen1, L. Tang1, L. Yang1, E. Han1, Y. Chen1, L. Yuan1

1Ultrasound Department, Sichuan Provincial People’s Hospital, Chengdu, China.

Background: This prospective study is to determine whether predictive model for contrast-enhanced ultrasound (CEUS) of the breast can improve the precision of BI-RADS.

Methods: A total of 1060 breast lesions classified as BI-RADS 4 or 5 on ultrasound were evaluated. CEUS was performed before core needle biopsy or surgical resection and a revised BI-RADS classification was assigned based on 6 predictive models for CEUS. The diagnostic performance of CEUS-based BI-RADS was assessed. 

Results: The CEUS-based BI-RADS evaluation classified 287/1060 (27.08%) lesions into category 3, 195 (18.40%) into category 4A, 124 (11.7%) into category 4B, and 144 (13.58%) into category 4C. The cancer-to-biopsy yield was 60.16% with CEUS-based BI-RADS 4A or 5 selected as the biopsy threshold compared with 43.86% otherwise, while the biopsy rate was only 72.92% compared with 100% otherwise (Figure 2). Overall, only 1.94% of invasive cancers were misdiagnosed as BI-RADS 3.  

Conclusion: This study suggests that evaluation of BI-RADS 4 or 5 breast lesions with CEUS result in reduced biopsy rates and increased cancer-to-biopsy yields. 


Legal entity responsible for the study: Ultrasound Department of Sichuan Provincial People’s Hospital. 

Funding: Has not received any funding. 

Disclosure: All authors have declared no conflicts of interest.

1338P Tracking VSV-IFN-J-NIS oncolytic virus (OV) activity in patients (pts) with advanced solid tumors: The iodide symporter gene (NIS) is a pharmacodynamic (PD) marker using SPECT/CT imaging of OV therapy


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Background: VSV-IFN-J-NIS (Voyager V1, VV1) is a VSV-derived OV with low human seroreactivity. In addition to its tumor-selective and immune-stimulatory properties, V1 encodes the human thyroidal sodium iodide symporter NIS to allow imaging of virus-infected tumors with IV 124mI and 123I. 

Methods: Single photon emission computerized tomography (SPECT/CT) is used to assess virus replication and spread. In a phase 1 study, VV1 is intratumorally injected into target lesion on Day 1 (D1). SPECT/CT imaging is performed 45 minutes after 20 mCi IV 124mI at baseline and D3. If there is uptake in injected tumor on D3, SPECT/CT is repeated on D8 and D15. Imaging requirements include: gamma camera, low energy high resolution collimators with standard acquisition protocols and iterative image reconstruction. All images are read locally and centrally.

Results: SPECT/CT has been performed on 12 patients at 4 VV1 dose levels (DL). 124mI uptake was not detected at the first 2 DLs but was seen in injected lesions of 2/4 pts at DL 3 (37 TCID50) in pts with metastatic colorectal and pancreas cancer, and 1/2 at DL 4. PD analysis revealed SPECT/CT-positive pts had peak uptake in injected lesions between D3 and D8. Tumor biopsy samples are being analyzed to correlate SPECT/CT with viral RNA. Spread to un.injected lesions was not yet visualized, but viral RNA was recovered in cystic fluid from the lesion with the strongest signal in a pancreas cancer pt. 

Conclusions: This novel therapeutic and diagnostic approach allows PD visualization of the investigational oncolytic virus therapy, VV1, replicating within the injected lesion. Positive images at dose levels 3–4 indicate we have reached a viral dose that allows sufficient viral replication for potential clinical activity. Further objectives include correlation of SPECT/CT positivity with clinical response, viremia, immune infiltrates, and genetic markers of susceptibility to OV therapy. 

Clinical trial identification: NCT02923466. 

Legal entity responsible for the study: Vyriad.

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mRNA expression of ER, PR, HER2 and Ki67 are concordant to central IHC and predict clinical outcome: A validation study from the ABCSG-6 biomarker cohort

M. Filipits1, M. Rudas1, C. Singer1, Z. Bago-Horvath1, R. Greil1, M. Balic2, S.F. Lax1, N. Wu3, S. Zhao3, J. Weider2, M. Bates1, D. Hlauschek2, M. Grani1, P. Dubsky1. 1Department of Medicine I, Comprehensive Cancer Center, Institute of Cancer Research, Medical University of Vienna, Vienna, Austria, 2Department of Pathology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, 3Department of Pathology, Comprehensive Cancer Research Institute, Cancer Cluster Salzburg, Paracelsus Medical University Salzburg, Salzburg, Austria, 4Department of Internal Medicine, Division of Oncology, Medical University Graz, Graz, Austria, 5Department of Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria, 6Department of Surgery, and Development, Oncology, Cepheid, Sunnyvale, CA, USA, 8Data Management and IHC, (HR 0.35, P tested by STRAT4 were all significantly associated with DRFI whereas neither ER by (HR 2.62, P 0.48, P Excelled by central IHC and PGR with DRFI. Concordance (overall percent agreement) between STRAT4 and IHC for each marker was the predetermined primary objective. The effect of binary parameters (positive vs negative) obtained by IHC and by STRAT4 on distant recurrence free interval (DRFI) was analyzed by Cox models and described by hazard ratios (HR).

Results: In this study, concordance between STRAT4 and IHC was 98.6% for ER, 92.6% for PR, 98.4% for HER2, and 88.7% for Ki67 (excluding intermediate IHC 10-21%). In univariate Cox regression analyses, PR (HR 0.9, P < 0.001), HER2 (HR 2.62, P = 0.005), and Ki67 (HR 3.45, P = 0.001) tested by central IHC and PGR (HR 0.48, P = 0.007), ERBB2 (HR 2.29, P = 0.037) and MKI67 (HR 3.87, P < 0.001) tested by STRAT4 were all significantly associated with DRFI whereas neither ER by IHC, (HR 0.85, P = 0.07), nor ER by STRAT4 (HR 0.73, P = 0.597), was associated with DRFI.

Conclusions: We demonstrate high concordance between centrally assessed IHC and mRNA measurements of the four main biomarkers routinely assessed in early breast cancer. This was corroborated by the similar prognostic values observed for protein versus mRNA assessments for each marker. Future investigations of the clinical utility of mRNA based measurements by STRAT4 in breast cancer cohorts are warranted.

Legal entity responsible for the study: ABCSG Austrian Breast and Colorectal Cancer Study Group.

Funding: Cepheid. Disclosure: M. Filipits: Personal fees: AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Roche, Roche Ltd outside the submitted work. M. Rudas: Funding: Cepheid/Danaher to ABCSG. R. Greil: Grants and personal fees: Roche, Celgene, Merck, AstraZeneca, Novartis, Amgen, Abbvie, BMS, MSD, Takeda, Honoraria, Consultant, advisory role, research funding, travel accommodations and expenses outside the submitted work: Sandor. N. Wu, S. Zhao, J. Weider, M. Bates: N. Employment and stock ownership: Cepheid (during the conduct of the study and outside the submitted work). D. Hlauschek: Employee: ABCSG which receives study funding from Cepheid. M. Grani: Grants: AstraZeneca, Novartis, Pfizer and Roche; Personal for: Accessions, Amgen, AstraZeneca, Celgene, Eli Lilly, Ipsen, NanoString Technologies, Novartis, Pfizer, Roche, P. Dubsky: Funding: Cepheid/Danaher to ABCSG. All other authors have declared no conflicts of interest.
resistance mechanisms (EGFR, MET and HER2 amplifications) in 24% (53/226) samples affecting an additional 33% (70/226) patients on top of those harboring mutation-based resistance mechanisms. RAP and MEK inhibitor indications were identified in 12% (28/226) and 3% (8/226), and BRAFV600E blockades in 8% (19/226) and 7% (19/226) of tissue and liquid biopsy tests, respectively.

**Conclusions:** Although liquid biopsy tests are able to identify a large proportion of lung cancer patients with indications for targeted therapy, tissue-based testing outperforms liquid biopsy for most therapeutic indications. Inclusion of CNS analysis could potentially increase the detection rate in liquid biopsies.

**Legal entity responsible for the study:** ACT Genomics Co., Ltd.

**Funding:** ACT Genomics Co., Ltd.


### Table: 1343P Sensitivities of whole-body and dedicated breast PET according to histology

<table>
<thead>
<tr>
<th>N</th>
<th>Sensitivity (%)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td><strong>WbPET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>435</td>
<td>339 (74.5)</td>
</tr>
<tr>
<td>Noninvasive carcinoma</td>
<td>82</td>
<td>34 (41.5)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>72</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>8</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td><strong>DbPET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microinvasive carcinoma</td>
<td>18</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Invasive carcinoma of no special type</td>
<td>305</td>
<td>256 (83.9)</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>9</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Others</td>
<td>41</td>
<td>32 (78.0)</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>19</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>5</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Carcinoma with apocrine differentiation</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Invasive micropapillary carcinoma</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>6 (85.7)</td>
</tr>
</tbody>
</table>

**Conclusions:** Breast cancers with the specific histological subtypes are hard to detect on WbPET. DbPET can overcome the factors for weak WbPET detectability, such as tumor size and histology, and might prevent the overdiagnosis of lobular carcinoma in situ.

**Legal entity responsible for the study:** Hiroshima University.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

### 1343P Histology and detectability on ring-type dedicated breast PET in breast cancer


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**Background:** Although dedicated breast PET (DbPET) visualizes sub-centimeter breast cancer lesions and intratumoral heterogeneity, the impact on histology of the detectability of DbPET remains unknown.

**Methods:** This study included 455 patients with breast cancer, who underwent whole-body PET (WbPET) and ring-type DbPET between January 2016 and March 2018. The relationship of histology and sensitivities of WbPET and DbPET for breast cancer was assessed.

**Results:** The median patient age was 57 years and histology was as follows: 82 (18.0%) noninvasive carcinoma, 18 (4.0%) microinvasive carcinoma, 305 (67.0%) invasive carcinoma in special type, 9 (2.0%) invasive lobular carcinoma, and 41 (9.0%) other types. The sensitivity of WbPET and DbPET was 74.5% and 93.2%, respectively. The sensitivities of each histology on WbPET/DbPET were 41.5%/78.0%, 72.2%/100%, 83.9%/96.7%, 44.4%/88.9%, and 78.0%/95.1%, respectively (Table). The sensitivity was low on WbPET in noninvasive, microinvasive, invasive lobular, mucinous and tubular carcinomas. Lobular carcinoma in situ had low sensitivity on both WbPET and DbPET imaging. In the multivariate analysis, undetectable tumor factors on WbPET were sub-centimeter tumor size (Odds ratio [OR] = 6.04, P < 0.001) and histology (OR = 1.69, P = 0.08) for DbPET. Ki-67 labeling index was an undetectable tumor factor (OR = 4.32, P = 0.039).

**Funding:** ACT Genomics Co., Ltd.


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both were more than 85.0%). Comparing HC to LCP, we calculated OR obtaining 10 parameters over than 10, showing a high positive association between clinical parameters and DSC results.

Conclusions: High positive association between clinical groups and TLB parameters offers advantages over current diagnosis techniques (CT imaging), providing a powerful diagnostic approach with a minimally-invasive, low-risk, low-cost clinical test for LCP. Future promising applications, such as screening programs, could be developed from TLB.

Legal entity responsible for the study: Instituto Investigación de Aragón (IIS).

Funding: Instituto Carlos III (Spain).

Disclosure: All authors have declared no conflicts of interest.

1345P
Data-mining of 110,172 electronic patient records with the ConSoRe tool: An analysis of second primary cancer in a comprehensive cancer center

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Background: We report a data-mining analysis of 110,172 electronic patient records (EPR) of the Leon Bérard Comprehensive Cancer Center (LBCC) over a 10 years period to identify characteristics of second primary cancers (SPC).

Methods: ConSoRe is a new generation data analytics solution using natural language processing to search aggregated data and perform advanced data mining. It was used for data extraction from EPR of 110,172 patients (pts), 47,257 men (M) and 62,915 women (W), treated at the CLBB from 2007 to 2017. Patient characteristics, treatments and survival were extracted.

Results: Data extraction identified 86,622 pts with at least one cancer. Among them 7,430 (8.4%) had a SPC: 9% (3,475/38,554) in M and 7.9% (3,955/50,068) in W (p = 3.10^-9). Of interest, only 4,296 SPC (57%) were already documented manually by the physicians in the dedicated forms. Mean age at diagnosis of first cancer (FC) is 55.1 years (yr) in M and 51.8 yr in W. Mean interval (ME) from diagnosis of FC to SPC is 5.3 years (yr) in M, 6.1 yr in W; T test p = 4.10^-7). Proportions of SPC among specific localization FC are: For M, head & neck cancer (n = 484/5,277, MI: 3.4 yr), lymphoma (n = 336/3,631, MI: 5.1 yr), prostate cancer (n = 334/4,643, MI: 6.1 yr); for W, breast cancer (n = 1,502/1,447, MI: 8.6 yr), soft tissue sarcoma (n = 321/3,683, MI: 4.5 yr), lymphoma (n = 293/4,432, MI: 6.3 yr). Time to SPC differ significantly depending on FC (ANOVA p = 2.10^-6). Pts with SPC were more likely to have received chemotherapy (31.1%) for their FC treatment compared to pts without SPC (20.8%; p = 1.60^-6). Also, pts with SPC treated by chemotherapy for their FC had shorter MI than pts who did not (3.2 y versus 5.6 y). In multivariate analysis, time from diagnosis of FC to SPC is significantly linked to FC site and shorter when FC was treated with chemotherapy. SPC was significantly correlated to a worth survival: 19% of death with FC at the time of analysis, versus 27.6% of those with SPC (p = 9.7 10^-7).

Conclusions: Seven over 100,000 EPR with ConSoRe enabled to retrieve SPC more exhaustively than the physicians forms. ConSoRe will be validated in a broader series of 300,000 EPR and used to study SPC risk factors to enable prevention and early detection.

Legal entity responsible for the study: Lyon Bérard Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1346P
Real world cfDNA collection in EGFR-mutant NSCLC

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Background: Plasma cell-free DNA (cfDNA) assays are increasingly used in clinic. Despite their rapid adoption, best practices for use and interpretation need better definition. We assessed key clinically-relevant questions using a prospectively collected cohort of EGFR-mutant pts.

Methods: Starting in 2015, serial cfDNA testing via Guardant360 NGS was obtained from MGH pts with advanced EGFR-mutant NSCLC across multiple lines of therapy in an IRB-approved project. Medical records were analyzed retrospectively, tissue was genotyped by institutional NGS (SNPshot), scans were assessed by RECIST. Correlations were tested by Wilcoxon Rank-Sum.

Results: 372 plasma samples were collected from 89 pts, covering 150 therapy regimens including 26 drugs (targeted, immune, cytotoxic). To assess genotype correlation, we examined matched cfDNA and tissue biopsies at clinical progression for 60 regimens (51 pts). cfDNA-tissue concordance was 73% for founder EGFR mutations (n = 60), 72% for T790M (n = 60) and 89% for MET amp (n = 53). Excluding 15 samples without detectable founder mutation (presumed “non-shedders”), concordance for T790M=89% and MET=90%. To assess if relative change in cfDNA allelic fraction (AF) correlates with radiographic response, we examined 21 regimens (19 pts) with cfDNA samples at baseline and ≤ 30 days, and 3 aspects of the Guardant360 report. 12/21 regimens yielded PR by scans. Decrease in cfDNA AF in the 1st month of therapy correlated with ultimate PR whether assessing the change in AF of founder EGFR (p = 0.03), largest AF regardless of gene (p = 0.02) or sum of all detected AFs (p = 0.02).

Conclusions: Commercial cfDNA assays are readily available, facilitate serial AF monitoring and provide clinically-relevant data at minimal cost. Among EGFR pts, we found real world cfDNA tissue-correlation of founder mutations and T790M was high and resistance mutation (T790M, MET) results in cfDNA may be most reliable when founder EGFR mutations are detected. Importantly, MET amp had high cfDNA-tissue concordance, which was unexpected. Early AF-decrease (within 1st month of therapy) significantly correlates with radiographic response regardless of which aspect of the Guardant360 report is considered. Further investigation is needed to inform optimal use of interpretation cfDNA assays.

Legal entity responsible for the study: MGH Cancer Center.

Funding: Guardant Healthcare, Lungevity.


1347TIP
Proof-of-concept study evaluating a new tool for standardising radiological assessment of tumour response to treatment in routine clinical practice

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Background: Accurate and timely radiological assessment of solid tumour response to treatment is essential to optimise patient outcomes in oncology. Evaluation of tumour response according to Response Evaluation Criteria In Solid Tumors (RECIST) is currently performed in clinical trials and more occasionally in routine clinical practice.

Radiological reporting is not usually standardised. MIRO (ONCO/HUB), a newly developed tool, streamlines interactions between oncologists and radiologists to optimise and ease response evaluation according to RECIST in routine practice. It applies to reading computed tomography scans and magnetic resonance imaging, and allows switching between evaluation criteria (RECIST 1.1, IRIS/2014 and modified RECIST). MIRO also provides a standardised radiological report, improving communication between oncology and radiology teams to guide treatment decisions. An ongoing proof-of-concept study is evaluating the feasibility of using MIRO to assess tumour response according to RECIST in routine clinical practice and identify the benefits it may provide to clinical oncology teams and patients.

Trial design: Oncologists specialised in sarcomas, breast, lung, colorectal and head and neck cancers, plus radiologists, will use MIRO to assess tumour assessments at baseline and tumour response according to RECIST for all new patients seen at Centre Léon Bérard, Lyon, France during the study period. Approximately 80 patients in clinical trials and 320 patients in routine clinical practice will be included. Study duration will be 6 months, with the first patients included in March 2018. All investigators will receive training on MIRO before including patients in the study. A sample of 20 patient records will be peer-reviewed to determine if MIRO can improve concordance of assessments made by the radiologist and the oncologist. Other outcome measures include assessments of the quality of data in radiology reports with MIRO versus standard practice, user satisfaction, integration of MIRO tool into routine practice and improvements in therapeutic follow-up for patients.

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Legal entity responsible for the study: DeepLink Medical.

Funding: WeHealth by Servier.

Disclosure: C. Manter, C. de la Foucauldrière: Medical consulting: DeepLink Medical. All other authors have declared no conflicts of interest.

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1348PD Genomic landscape and its correlation with TMB, CD8 TILs and PD-L1 expression in Chinese lung squamous cell carcinoma

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1349PD Gene expression signature of DNA damage response to predict the prognosis of early stage lung adenocarcinoma

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1351P Impact of the 8th edition AJCC classification in early stage lung cancer

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Background: Lung cancer is the main cause of cancer death worldwide. Even in early stages the cancer-specific survival is poor due to disease relapse. The TNM classification is the strongest prognostic tool. The 8th AJCC edition has changed the cutpoints for stage, leading to a "stage shift" or a "stage decrease", mainly reflecting changes in the prognostic score attributed to the tumor diameter. We have reviewed a cohort of patients that were treated before the benefit of adjuvant chemotherapy was proved, in order to corroborate which of the two classifications represents better the risk of recurrence.

Methods: Retrospective analysis of a cohort of 182 patients with lung cancer treated with complete resection and no adjuvant chemotherapy, between 1999 and 2006. Evaluation criteria: overall survival.

Results: 1. Patient characteristics: median diagnostic age 68 years (39–86), 90% males, 48% current and 42% former smokers, 37% diagnosed of COPD. 2. Tumor characteristics:
   - Histology: squamous 57%, adenocarcinoma 36%.
   - Grade: 47% moderately differentiated, 33% undifferentiated.
   - Pathological staging by TNM edition.

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3. median OS in our cohort of patients = 79 months (IC95% = 58-100) log Rank test p=NS me OS by pathological stage defined by 8th ed. AJCC: IA1 97 m (IC95% 37-158) IA2 108 m (IC95% 34-162) IA3 139 m (IC95% 45-96) IIA 35 m (IC95% 19-51) IIB 62 m (IC95% 34-90) IIA 56 m (IC95% 0-141) 4. OS stage I vs II by 7th edition: 93 vs 66 m, log Rank test, p = 0.016 - by 8th edition: 97 vs 70 m, log Rank test, p = 0.026 5. COPD as an adverse prognostic factor: meOS = 111 vs 55 months, log Rank test, p = 0.002

Conclusions: In our cohort of patients, the 8th edition of AJCC classification identifies better than the previous edition a group of patients with worse prognosis regarding to a higher size of the tumour and shifting their pathological stage. Due to the small sample, we couldn’t prove a more accurate prognostic information for the new stage I.
A serum miRNA biomarker panel for the detection of early stage non-small cell lung cancer

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Background: Non-small cell lung cancer is the most prevalent cancer and leading cause of cancer death worldwide. Low-dose spiral computed tomography (LDCT) scan is being considered as a screening test for smokers in the US. However, the poor specificity of LDCT has raised significant concerns about its high chance of false positive results. This study aimed to develop a blood miRNA based molecular diagnostic test for the detection of early stage lung cancer.

Methods: The three-phase study was designed with a total of 948 cancer-free controls, and 768 patients with NSCLC. In the discovery phase, more than 400 miRNAs were profiled with MIRXES’s qPCR based high throughput assay platform through a highly defined Chinese male smoker case-control cohort (n = 424) where the cases were collected from Zhejiang Cancer Hospital and the controls were collected form the LDCT screening program in Zhejiang province, China. Differentially expressed miRNAs were further validated in another Chinese case-control cohort (n = 432) collected from similar sources and a white case-control cohort (n = 218) collected from the EU and US. Finally, the identified miRNAs were further assessed in three additional Asian cohorts: a Chinese cohort collected from the similar sources (n = 237), a Chinese cohort collected from independent sources (n = 340), and a Singaporean cohort (Chinese, Malay and Indian population) (n = 65).

Results: 29 miRNA biomarkers with p-value (FDR) < 0.01 and more than one z-score (standard deviation) difference were identified in the discovery phase. With multiple time of two-fold cross-validation, 5 miRNAs were found to be minimally required to form the biomarker panel for the accurate prediction of early stage lung cancer and the panel gives 0.936 (95% CI, 0.912-0.957) AUC for the Chinese validation cohort and 0.970 (95% CI, 0.939-0.986) AUC for the white validation cohort. The 5-miRNA biomarker panel were then further validated in three additional Asian cohorts, giving 0.973 (95% CI, 0.950-0.986) AUC for similarly sourced Chinese cohort, 0.916 (95% CI, 0.852-0.949) AUC for the independently sourced Chinese cohort, and 0.911 (95% CI, 0.882-0.963) AUC for the Singaporean cohort, respectively.

Conclusions: The five-miRNA panel in serum may serve as a potential non-invasive biomarker in detecting early stage NSCLC.

Legal entity responsible for the study: Zhejiang Cancer Hospital & Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology of Zhejiang Province.

Disclosure: Has not received any funding.

Legal entity responsible for the study: Zhejiang Cancer Hospital & Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology of Zhejiang Province.

Disclosure: Has not received any funding.

Conclusions: This study comparing a matched cohort, revealed no clinical significant differences in Qol following either SBRT or surgery for an early stage NSCLC.

Legal entity responsible for the study: Leonie Alberts and Harold Wolff.

Funding: Has not received any funding.

Disclosure: H. B. Wolff, V. M. H. Coupe: Research funding: Novartis. Novartis Pharma B.V. was not involved in the data collection, data analysis, or reporting. F. J. Lagerwaard: Honoraria, Speaker’s bureau. Viewray inc: USA. S. Y. El Sharouni: Consulting/advisory role company: Lilly Oncology, AstraZeneca; Research funding: Varian Medical systems. All other authors have declared no conflicts of interest.

Split-lobe resections versus lobectomy for stage IA-IB peripheral non-small cell lung cancer

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Background: To compare left-upper, right and left inferior split-lobe procedures with the same lobectomies for surgical treatment of peripheral non-small cell lung cancer of stage IA-IB, originating from the large pulmonary lobe.

Methods: We analysed the results of the treatment of 116 patients, who underwent surgical procedures for clinical stage IA-IB non-small cell lung cancer. Patients were divided into two groups, based on the type of procedure performed. Lobectomies were performed in 78 (67.2%) patients, split-lobe resections of the large pulmonary lobes in 38 (32.8%) in patients with left upper lobe, and 76 in 14 patients, resection of the lingu show a significant differences between lobectomy and split-lobe group (7,7% vs. 5,3%, p<0.05). RR was registered in 9 patients in the lobectomy group vs 7 patients from split-lobe group (11,5% vs 18,4%, p<0.05). Regional recurrence in hilar lymph nodes was confirmed only in one patient from split-lobe group 28 months after right anatomical segmentectomy. Survival analysis did not show significant differences between lobectomy and split-lobe groups. Overall 5-year survival was 82,0% (95% confidence interval, 70,3-93,7) in lobectomy group versus 74,8% (95% confidence interval, 75,5-97,1) in split-lobe group (p = 0,369). Relapse-free 5-year survival was 85,2% (95% confidence interval, 76,8-94,6) in lobectomy group versus 76,2% (95% confidence interval, 99,6-96,8)% in split-lobe group (p = 0,353). Cox regression analysis with multiple factors demonstrated statistical significance for overall (p = 0,05) and relapse-free (p = 0,025) survival only for F11-T2 tumour descriptors.

Conclusions: Split-lobe procedures and lobectomy have equivalent in-hospital morbidity and long-term results for patients with clinical stage IA-IB peripheral non-small cell LC. In the future split-lobe resection can be recommended as a standard procedure for early stage peripheral non-small cell LC.

Legal entity responsible for the study: City Clinical Hospital no. 40.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

miR-200s in operated NSCLC: Main drivers of epithelial to mesenchymal transition and independent prognostic factors

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Background: Epithelial-to-mesenchymal transition (EMT) plays essential roles in non-small cell lung cancer (NSCLC) progression and was related to TWIST1 reactivation. Among regulators of EMT, microRNAs are extensively studied. This work aimed at identifying microRNAs that might be important regulators of TWIST1 and EMT in NSCLC.

Methods: We performed miRseq in a series of EGFR-mutated lung adenocarcinomas (n = 24, series A) and identified a set of miRNAs (n = 12) associated to TWIST1 reactivation. These miRNAs and additional EMT-related miRNAs selected from the

Categories in the 8th edition. COPD is confirmed in our serie as an adverse prognostic clinical factor.

Legal entity responsible for the study: IDS.

Funding: IDS.

Disclosure: All authors have declared no conflicts of interest.
Background: Natural killer (NK) cells are innate effector lymphocytes involved in cancer immunosurveillance. Here we investigated the distribution, function and prognostic role of circulating NK cell subsets in non-small cell lung cancer (NSCLC).

Methods: Blood samples from 176 NSCLC patients were collected before any treatment and from 41 healthy donors (HD) as control. The phenotype and cytotoxic functions of NK cells were performed by multicolor flow cytometry. Kaplan–Meier method was used to estimate survival.

Results: NSCLC patients exhibited distinct NK cell subsets in blood such as CD56dimCD16+, CD56dimCD16-, and CD56bright NK cells. However, a lower rate of CD56dimCD16+ NK cells and a higher rate of CD56dimCD16- NK cells were found in patients as compared to HD. Unsupervised clustering analysis of activating receptors expression such as NKp46, NKp30, NKp44, and NKp46 identified four groups of patients with distinct circulating NK cell profiles. We showed that the rate of circulating NKp46- NK cells was inversely correlated with overall survival (OS). Consistently, the median OS in high versus low level NKp46+ NK cell group was 16 and 27 months respectively (p = 0.04). This effect was mainly driven by NKp46+ CD56dimCD16+ NK cell subset (p = 0.02). Finally, blocking NKp46 receptor in vitro was able to restore antitumor T cell immunity suggesting an inhibitory role of NKp46+ NK cells.

Conclusions: Altogether, our results show a distinct pattern of circulating NK cell subsets in NSCLC and also support the immune regulatory property of NKp46+ NK cell subsets as potential prognostic factor in lung cancer.

Legal entity responsible for the study: Olivier Adotevi.

Disclosure: All authors have declared no conflicts of interest.

1356P The level of circulating NKp46+ CD56dim CD16+ natural killer cells predicts distinct survival in non-small cell lung cancer

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Oncolog were seen in the 1st cohort (1 Pembro treatment, 3 wks later surgery). Out of 3 pts on delay of surgery. DLT period was defined as 30 days post-surgery.

Toxicities (DLT) were defined as significant surgical complications (bleeding, delayed wound healing, acute respiratory distress syndrome, prolonged air-leak) or a significant to the negative values as reference.

Results: The median age was 66 years (IQR 60-75), 135 men and 35 women. Eighty-eight per cent of them were smokers. The median follow-up was 64 months (range 1-163). The distribution by stages was: 51% of pathological stage IA, 31% of IB stage and 18% corresponded to stage II with pT3N0. Regarding histology there were 57% adenocar cinomas, 34% squamous cell carcinomas and 7% large cell carcinomas. PD-L1 expression was detected in 28.8% of the cases. 19.8% of the adenocarcinoma tumours and 41.3% of the squamous subtypes. The percentage of patients with PD-L1 expression was greater than 5% in 24.7% of cases and 11.8% of the total showed a PD-L1 expression ≥ 50%. The median DFS was 59.6 months (IQR 27-85) and OS 64.2 months (IQR 39.9-94.9). A statistically significant association was observed between expression of PD-L1 and younger age (inverse relationship, p = 0.033) and histologic subtype (lower expression in squamous type, p = 0.029). Kaplan-Meier analysis showed no DFS in positive PD-L1 patients. No significant differences were observed in relation to overall survival.

Conclusions: The expression of PD-L1-L1 is associated with morphological data of greater aggressiveness and is a risk factor for relapse in NSCLC in early stages without positive ganglia.

Legal entity responsible for the study: Hospital General de Alicante.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1360P Neoadjuvant pembrolizumab (Pembro) for early stage non-small cell lung cancer (NSCLC): Initial report of a phase I study, MK3475-223
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Background: NSCLC is the most common cause of cancer-related death. Even clinical stage I or II tumours that are completely resected harbor a 5-year survival of only 30-50%. Immunotherapy is being investigated now as adjuvant therapy and might improve those results. We hypothesize that neo-adjuvant immunotherapy is a safe, effective treatment for early stage NSCLC.

Methods: MK3475-223 is a phase I study, testing neoadjuvant Pembro for stage I and II NSCLC. Study design is based on a classical 3 + 3 cohort, but the differences between cohorts are not drug dose but number of treatments (1st cohort 1 treatment, 2nd and 3rd cohorts 2 treatments with a 3 weeks (wk) interval between them) prior to surgery, and interval from last dose to surgery (1st cohort 3 wks, 2nd cohort 2 wks, 3rd cohort 1 wk). All Pembro treatments are 200mg. Primary objectives are to determine safety, recommended phase 2 dose/schedule, pathological and radiological response. Dose limiting toxicities (DLT) were defined as significant surgical complications (bleeding, delayed wound healing, acute respiratory distress syndrome, prolonged air-leak) or a significant delay of surgery. DLT period was defined as 30 days post-surgery.

Results: To date, two cohorts (6 patients (pts)) have been fully recruited and completed the DLT period. No DLT has occurred. Adverse events (AEs) are within the recognized AE profile of Pembro and of thoracic surgical procedures. No significant responses were seen in the 1st cohort (1 Pembro treatment, 3 wks later surgery). Out of 3 pts on the 2nd cohort (2 Pembro treatments, 2 wks later surgery), 2 pts (66.6%) demonstrate near complete pathologic response, with less than 1% of tumor cells left estimated. The study is ongoing and continuing to recruit, currently recruiting the final cohort (2 pembro treatments, 1 wk later surgery), to be followed by an expansion cohort.

Conclusions: Neoadjuvant Pembro is a promising option for early stage NSCLC. Initial data suggest the safety of this approach. The trial will provide initial evidence as well as correlative studies regarding the efficacy of this approach.

Legal entity responsible for the study: Sheba Medical Center.

Funding: MSD.

Disclosure: I. Bar: Consultant fees: Roche, Boehringer Ingelheim, Novartis, BMS, MSD, Pfizer, AstraZeneca, Takada, Abbvie, VBL, Grant support: Boehringer Ingelheim, AstraZeneca, MSD. All other authors have declared no conflicts of interest.

1361P Neoadjuvant chemotherapy with bevacizumab followed by surgery for clinical stage II/IIIA non-squamous non-small cell lung cancer: Survival results from a phase II feasibility study (NAVAL)
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Background: We previously reported that neoadjuvant cisplatin, pemetrexed, and bevacizumab followed by surgery is safe and feasible in patients with clinical stage II/IIIA non-squamous non-small cell lung cancer (NSCLC) (NAVAL study). The purpose of this study is to evaluate survival results, which are secondary endpoints of NAVAl study.

Methods: In a phase II feasibility study of neoadjuvant chemotherapy with cisplatin (75 mg/m²), pemetrexed (500 mg/m²), and bevacizumab (15 mg/kg), followed by sur gery for resectable clinical stage II/IIIA non-squamous NSCLC, progression-free survival (PFS) and overall survival (OS) were analyzed. Patients who had less than 33% residual viable primary tumor after neoadjuvant chemotherapy were defined as patho logical responders. Others were defined as non-responders.

Results: Among all 30 patients, 25 underwent surgical resection after 3 cycle of neoad juvant chemotherapy with bevacizumab, and 3 underwent off protocol surgical resec tion. Two-year PFS rate and 5-year PFS rate were 41.5% and 34.6%, respectively. Two year OS rate and 5-year OS rate were 70.0% and 60.0%, respectively. Six (20%) patients were classified as pathologic responders, whereas 24 (80%) as non-responders. There was significant difference in PFS between pathologic responders (5-year PFS rate, 100%) and non-responders (5-year PFS rate, 17.5%; P = 0.002). Also, there was significant difference in OS between pathologic responders (5-year OS rate, 100%) and non-responders (5-year OS rate, 43.5%; P = 0.006).

Conclusions: Neoadjuvant cisplatin, pemetrexed, and bevacizumab followed by surgery is effective for clinical stage II/IIIA non-squamous NSCLC. Long-term survival after surgery is expected for pathologic responders, whereas additional therapy will be needed for non-responders.

Clinical trial identification: UM1100004278, 2010/10/01.

Legal entity responsible for the study: Morihito Okada.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1362P Clinical outcomes and treatment strategies of sarcomatoid carcinoma of the lung
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Background: Sarcomatoid carcinoma of the lung is characterized by worse prognosis, and generally felt to be chemo-refractory compared with other non-small cell lung cancer. We conduct this retrospective study to investigate the clinical characteristics of patients with sarcomatoid carcinoma of the lung and determine the optimal treatment strategies.

Methods: We reviewed the medical records of 8176 patients with resected lung cancer in a single high-volume institution between 2008 and 2015. All patients with pathologi cally diagnosed sarcomatoid carcinoma were evaluated. Clinicopathologic data were analyzed using Kaplan-Meier analysis and Cox regression analysis. Subgroups stratified by pathological stage were analysed to determine the optimal treatment modality. We also conducted subgroup analysis of overall survival among pulmonary sarcomatoid carcinoma and other NSCLC patients.

Results: Kaplan-Meier and Cox regression analyses showed pathological stage (6th edition) is the independent prognostic factor (P = 0.001, prognostic factor (P = 0.001, HR = 2.601, 95%CI (1.447- 4.075)) for pulmonary sarcomatoid carcinoma. Overall survival favored other NSCLC over PSC across subgroups. Male (HR = 0.695, 95%CI(0.505-0.955)), age above 60...
years (HR = 0.622, 95%CI(0.417-0.928)), never-smoker (HR = 0.583, 95%CI(0.383-0.888)), patients who had no alcohol abuse history (HR = 0.597, 95%CI(0.416-0.856)), tumor size >5cm (HR = 0.700, 95%CI(0.492-0.995)), tumor stage T1 (HR = 0.383, 95%CI(0.167-0.877)), tumor location in peripheral (HR = 0.577, 95%CI(0.367-0.906)), or in both peripheral and central (HR = 0.626, 95%CI(0.424-0.923)), node stage N0 (HR = 0.599, 95%CI(0.403-0.891)), stage Ia (HR = 0.362, 95%CI(0.131-1.000)), stage Ib (HR = 0.430, 95%CI(0.278-0.729)), surgery alone (HR = 0.712, 95%CI(0.507-0.999)).

**Conclusions:** Pathological stage (8th edition) is independent prognostic factor for sarcomatoid carcinoma of the lung. Surgery followed by adjuvant chemotherapy should be considered for stage I pulmonary sarcomatoid carcinoma. Further prospective studies are needed to confirm these results.

**Legal entity responsible for the study:** The Fourth Hospital of Hebei Medical University.

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NSCLC, LOCALLY ADVANCED

13630 Efficacy and safety evaluation based on time from completion of radiotherapy to randomization with durvalumab or placebo in pts from PACIFIC


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1364PD Cardiac events in stage III non-small cell lung cancer (NSCLC) treated in daily clinical practice: Is it time for cardiovascular screening and follow-up?

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1365PD Screening for brain metastases (BM) in patients (pts) with stage III non-small cell lung cancer (NSCLC), magnetic resonance imaging (MRI) or dedicated contrast-enhanced computed tomography (dCE-CT)? A prospective observational study

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In the new 8th TNM classification, stage III non-small cell lung cancer (NSCLC) is divided into three subgroups. Stage IIIA includes T4 N0 M0 and T3/4 N1 M0 tumours as well as T1/T2 N2 M0 tumours. Stage IIIB includes T3/T4 N2 M0 or T1/T2 N3 M0. Stage IIIC involves T3/T4 N3 M0 tumours. Beside new IIIC stage, the greatest change is reclassification of T category based on dimension. Tumours larger than 7 cm that were previously T3 are now staged T4. The anatomic extent of disease is the base of the TNM classification with impact on survival. The aim of this analysis was to determine applicability of the new 8th TNM edition on survival of stage III NSCLC treated with combined radiochemotherapy between 2005 and 2010 in our institution.

Methods: A total of 101 patient with stage III NSCLC treated between September 2005 and November 2010 with induction chemotherapy and radiochemotherapy were included in long term survival analysis of TNM staging. Results of survival are presented for the 2nd and 8th edition in view of the revised T stage.

Results: After a median follow up of 117.5 months, median overall survival (mOS) of stage IIIA patients according to the 7th TNM classification was significantly longer than those of stage IIIB patients (30.8 months and 19.0 months, \( p = 0.003 \)).

Redefinition of the stages according to the new 8th TNM classification showed similar mOS for patients in stage IIIA and stage IIIB (21.6 months and 24.9 months), but much shorter mOS for stage IIIC patients with 6.6 months (\( p = 0.085 \)). Of 101 patient 13 were up-graded from T3 to T4 according to new TNM classification. In the 7th TNM classification T3N2 was in stage IIIA and T4N2 in stage IIIB, while in 8th TNM classification both are in stage IIIC. According to 7th TNM classification, mOS of patients in stage T3N2 was significantly longer with 60.0 months than in stage T4N2 with 19.2 months (\( p = 0.004 \)). After the revision there is no difference, mOS of patients with T3N2 was 28.4 months and with T4N2 was 31.4 months (\( p = 0.478 \)).

Conclusions: The statistical difference in survival between subgroups of stage III shown in the old TNM classification did not appear in the new classification. Other factors could affect prognosis that are patient, tumour and treatment related.

Legal entity responsible for the study: Martina Vrankar.

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Disclosure: All authors have declared no conflicts of interest.

Background: Tobacco smoking is the major risk factor for lung cancer. However, approximately 10% of patients diagnosed with lung cancer have never smoked and knowledge of their characteristics and survival remain limited. Specific genetic alterations, e.g. ALK (anaplastic lymphoma kinase) rearrangements and EGFR (epidermal growth factor receptor) mutations, are more common in never-smoking lung cancer patients than in current or former smokers. We aimed to investigate characteristics of patients with different smoking history and estimate their lung cancer-specific survival.

Methods: This study was based on data from the Lung Cancer Database Sweden generated by record linkage between the Swedish National Lung Cancer Register and other population-based registers. Patients diagnosed with primary non-small cell lung cancer between 2002 and 2016 were included. The Kaplan-Meier method was used to estimate lung cancer-specific survival by smoking history (never-smokers, former smokers, and current smokers).

Results: In total, 41,262 patients with lung cancer were included. Of those 4,624 (11.2%) had never smoked. Never-smokers were older at time of the diagnosis (median: 73 years, Inter Quartile Range (IQR)=63-80) than current smokers (median: 67 years, IQR=61-73) and former smokers (median: 72 years, IQR=66-78). Women were over-represented among never-smokers (66%) and among current (49%) and former smokers (43%). Adenocarcinoma was the most frequent histological subtype in all groups, but was proportionally more frequent in never-smokers (77%) compared to current smokers (52%) and former smokers (57%). The estimated overall (all stages) 2-year specific lung cancer survival was higher in never-smokers (35.6%, 95% CI 34.4 - 37.5) than among current smokers (29.4%, 95% CI 28.7 - 30.2) and former smokers (30.7%, 95% CI 30.0-31.4).

Conclusions: The observed longer survival and the difference in histopathology suggest that tumours in never-smokers have a different pathogenesis and a different behaviour than tobacco-associated lung cancer. In further analyses, we will examine observed differences in outcomes in more detail, including the modifying role of other prognostic factors.

Legal entity responsible for the study: Regional Oncologic Centre Uppsala-Orebro and Karolinska Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare subtype of lung cancer that is less reported and not well understood around the world. Specific genetic alterations have been described and associated with PLELC patients. PLELC is preferentially associated with the young (<60 years old), nonsmokers (72.9%), without significant difference in gender. The median follow-up time was 15 months (1-37 months) for the whole group and most patients were in the early stage with opportunity of operation (36.6%). For the advanced stage group, patients mainly received chemotherapies and radiotherapies, the 0.5-year and 1.5-year PFS rates were 63% and 29%, respectively. The TNM stage (\( P = 0.014 \)) and performance status (PS) (\( P = 0.040 \)) were associated with PFS significantly in the univariate analysis, while TNM stage was a significant independent prognostic factor in multivariate analysis (\( P = 0.026 \)).

In the subtype analysis, patients in the advanced stage receiving Gemcitabine plus platinum (GP group) or Paclitaxel plus platinum (TP group) had better PFS than Pemetrexed plus platinum (PP group) (\( P = 0.005 \)).

Conclusions: PLELC had a better prognosis compared with other types of non-small cell lung cancer (NSCLC) and was sensitive to radiotherapy and chemotherapy. The current results recommended that the GP and TP should be used as first-line treatment of PLELC. The TNM stage and PS were predictive in prognosis of PLELC patients.
Meta-analysis of prognostic factors of completely resected pathologic N2 stage IIa non-small cell lung cancer including 11,384 patients

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Background: Patients with IIIA-pN2 non-small cell lung cancer (NSCLC) are a heterogeneous group. So this meta-analysis aimed to determine prognostic factors and compare different postoperative adjuvant therapies on survival.

Methods: MEDLINE, Embase, Web of Science were searched to identify relevant trials up to May 2017. Data of univariate and multivariate analyses of prognostic factors for overall survival (OS) were extracted and calculated by hazard ratios (HR) and 95% confidence intervals (95% CI). Pooled survival curves were constructed by Engauge Digitizer and RStudio.

Results: Overall 26 trials comprising 11,384 patients were included. The subgroup analysis for OS indicated that increased age (HR 1.02, 95% CI 1.02-1.02, P < 0.0001), male (HR 1.37, 95% CI 1.25–1.49, P < 0.0001), increased pathologic T stage (HR 1.27, 95% CI 1.12–1.45, P = 0.0001), multiple N2 metastases (HR 1.53, 95% CI 1.34–1.74, P < 0.0001), presence of skip metastasis (HR 107.89, 95% CI 1.25–3.42, P = 0.001), involvement of N1 nodal station (HR 1.42, 95% CI 1.35–1.70, P = 0.001), pneumonectomy (HR 1.42, 95% CI 1.16–1.73, P = 0.0001), increasing clinical T classification (HR 1.48, 95% CI 1.08–2.02, P = 0.01), increasing clinical N classification (HR 1.75, 95% CI 1.23–3.51, P = 0.002) were significantly associated with poor OS and N downstaging (HR 0.46, 95% CI 0.37–0.68, P = 0.001), PORT (HR 0.76, 95% CI 0.64–0.72, P = 0.004), adjuvant chemotherapy (HR 0.69, 95% CI 0.56–0.85, P = 0.007) were significantly associated with better OS. The 5-year disease-free survival rate was 38.9% in postoperative chemotherapy group and 29.5% in postoperative chemotherapy group (p = 0.001). Survival was improved in patients with pN2 disease who received postoperative radiotherapy, both in the chemotherapy (5-year survival rate, 65.3% vs. 49.3%) and observation arm (5-year survival rate, 53.3% vs. 32.3%).

Conclusions: The main prognostic factors were age, gender, clinical T stage, pathologic T stage, operation procedure, clinical N status, involved N2 stations, N1 nodes involved, N2 skip metastasis, N downstaging, postoperative radiotherapy as well as adjuvant chemotherapy. And these should be considered as stratification factors for further trials.

Legal entity responsible for the study: Key Laboratory of Cancer Proteomics of Chinese Ministry of Health, Xiangya Hospital, Central South University.

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Disclosure: All authors have declared no conflicts of interest.

The results of treatment of non-small cell lung cancer stage III with a preoperative vinorelbine/carboplatin and personalized adjuvant chemotherapy

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Background: Individual chemotherapy based on the determination of molecular biomarkers of chemosensitivity is a new way to treat patients with NSCLC. Promising markers for chemosensitivity are monoresistance genes such as BRCA1, RRMI, ERCC1, TOP1, TOP2a, TUBB3, TMY5, and ABCG2.

Methods: We enrolled and analyzed 62 patients with stage III NSCLC. All the patients have received 2 courses of neoadjuvant chemotherapy vinorelbine/carboplatin and surgery. Then patients were randomly assigned (1:1 ratio) to either the personalized adjuvant chemotherapy arm (main group) or the adjuvant chemotherapy vinorelbine/ carboplatin arm (control group). In the main group, carboplatin-containing doublets were assigned based on monoresistance gene expression levels ABCG2, RRMI, ERCC1, BRCA1, TOP1, TOP2a, TUBB3, TMY5, and ABCG2.

Results: The follow-up period was 4 - 76 months. In the main group, the disease progression was observed in 6 patients (19.4%), in the control group - 15 patients (48.4%). Three-year disease-free survival in the main group was 80.7% (median DFS not achieved), in the control group - 51.6%, median DFS - 34 months (HR: 2.56, 95% CI: 1.09 - 6.03), differences are statistically significant. Log-Rank test z2 =4.196, p = 0.041.

Legal entity responsible for the study: Yu. Qin.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.
Background: Treatment with an immune checkpoint inhibitor (ICI) on completion of concurrent thoracic radiotherapy, in pts with inoperable stage III NSCLC showed a significantly prolongs the PFS; however the best chemotherapy regimen in CCRT has not been established. This study compared the efficacy and safety of docetaxel/cisplatin (DP) with concurrent thoracic radiotherapy for locally advanced NSCLC using an ultra-sensitive next-generation sequencing (NGS) assay.

Methods: Pts with inoperable stage III NSCLC were randomized to SP (54 mg/m2 bid on days 1-14 and 29-42 plus cisplatin 75 mg/m2 on days 1 and 29) or DP (docetaxel 50 mg/m2 and cisplatin 80 mg/m2 on days 1 and 29), with concurrent radiotherapy beginning on day 1 (60 Gy/30 fr) followed by two additional cycles of the chemotherapy regimen with prolonged follow-up has been awaited. Primary endpoint was 2-year OS rate, and secondary endpoints included OS, PFS and safety.

Results: Among 110 pts enrolled, 106 (53 in each arm) were evaluable, with male/female 56/50; median age 65 (range 42-74); performance status 0/1 59/41; ECOG/WHO 0/1 55/45. With a median follow-up of 48.1 months, 2-year survival and median OS were 79% (95% CI 68-90%) and 53.2 months in the SP and 69% (95% CI 57-82%) and 50.8 months in the DP arm, respectively. 5-year PFS rates in SP and DP arms were 23.2 (95% CI: 68-90%) and 33.8(95% CI: 13-56), and 5-year OS rates were 48.8 (95% CI: 34-64) and 42.3% (95% CI: 24-61), respectively. Hematological and non-hematological toxicities were less in the SP arm. Relapsed site in the RT field and in the CNS were similar between the two arms. Post-treatment chemotherapy for pts with progression was delivered in 52.9% and 71.1% pts in SP and DP arms, respectively.

Conclusions: Because of favorable 2-year OS with less toxicity, we choose SP in CCRT as a future reference regimen. High 5-year PFS and OS rates shown here should be considered in designing further studies where CCRT is followed by ICI.

Legal entity responsible for the study: NPO Thoracic Oncology Research Group (TORG).

Funding: Has not received any funding.


Methods: Treatment naive tumor and longitudinally collected plasma specimens were analyzed using a 197-gene NGS assay (AVENIO ctDNA Surveillance Kit and AVENIO Tumor Tissue Surveillance Kit prototype, Research Use Only). Mutations detected in pre-chemotheraphy tumor specimens and in pre-chemotherapy or pre-radiation therapy plasma specimens were monitored in post-treatment plasma samples by measuring the number of Mutant Molecules Per Milliliter-of-plasma (MMPM). MMPM values were correlated with disease control (as evaluated by RECIST 1.1). Kaplan-Meier curves and Cox proportional hazards models were used to assess association of tumor burden with subject survival.

Results: We sequenced 36 tumor and 160 plasma specimens from 40 subjects. At least one mutation reporter was identified in 92% (n = 27/33) of tumor and in 100% (n = 31/31) of pre-chemo or 100% (n = 37/37) of pre-radiation plasma specimens. The best predictive performance of the assay was observed using tumor pre-treatment reporters and MMPM cutoff of 8 in plasma samples collected at completion of the scheduled chemoradiation regimen. Sensitivity of MMMP below the cutoff had a mean overall survival (OS) benefit of 18.5 months (n = 27, Tumor p-value = 0.013, HR = 3.73, 95%CI = 1.35-10.12). A similar trend was observed using plasma pre-chemo reporters (n = 31, Tumor p-value = 0.024, HR = 2.08, 95%CI = 0.91-4.74).

Conclusions: Circulating tumor DNA monitoring with an ultra-sensitive NGS-based assay identifies subjects with a locally advanced NSCLC who will have a more favorable outcome when treated with a stand-of-care chemoradiation therapy.

Legal entity responsible for the study: Roche.

Funding: Roche.


Results: Eighteen cases out of 68 developed radiation pneumonitis, 50 of 68 cases have no radiation pneumonitis, 50 of 68 cases have no radiation pneumonitis. There was no significant change of Ape1/Ref-1 concentration in serum after radiotherapy between radiation pneumonitis group and non-radiation pneumonitis group (P < 0.05). There was no significant change of Ape1/Ref-1 concentration in serum after radiotherapy between radiation pneumonitis group and non-radiation pneumonitis group (P < 0.05). Compared with before radiotherapy, upregulation degree of ICAM-1 level in radiation pneumonitis group was higher than that in non-radiation pneumonitis group (P < 0.05). There was no significant change of IL-17A concentration before and after radiotherapy in radiation pneumonitis group, but after radiotherapy IL-17A concentration in serum were higher than that in non-radiation pneumonitis group (P < 0.05). Correlation analysis found that the change of ICAM-1 before and after radiotherapy has no obvious correlation with the incidence of radiation pneumonitis, and IL-17A change has obvious correlation with the incidence of radiation pneumonitis.

Conclusions: IL-17A in serum could be the predictive factors of radiation pneumonitis for local advanced NSCLC patients with concurrent chemoradiotherapy.

Legal entity responsible for the study: Department of radiology, affiliated Cancer Hospital, Zhengzhou University.

Funding: National Natural Science Foundation of China (No.81372436).

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Programmed cell death ligand 1 expression and CD8+ lymphocytes in stage III non-small cell lung cancer after neo adjuvant concurrent chemoradiotherapy and their relation with prognosis

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Background: Previous studies in non-small cell lung cancer (NSCLC) on programmed cell death ligand 1 (PD-L1) expression and CD8+ lymphocyte density improved OS. Because this study was performed with small number of patients, prognostic value of PD-L1 in this group is unknown. The impact of PD-L1 expression on OS in stage III NSCLC patients treated with neo adjuvant CCRT followed by surgery with curative aim.

Methods: We retrospectively enrolled 43 patients with stage III NSCLC treated with neo adjuvant CCRT followed by surgery at Yonsei Cancer Center Severance hospital, between June 2008 and October 2010. Immunohistochemistry (IHC) was performed on tissue sections of PD-L1 expression and presence of stromal CD8+ lymphocytes in NSCLC specimens. Weekly standard chemotherapy based on platinum was included in CCRT.

Results: The median age of patients at diagnosis was 62 years. Thirty patients (70%) were males and 13 patients (30%) were females. Never smokers were 17 patients (40%). Twenty-five patients had squamous cell carcinoma (58%). The post-CCRT PD-L1-positive group exhibited a tendency of poorer recurrence free survival (RFS) compared to post CCRT PD-L1-negative group (p = 0.108). The overall survival (OS) also showed a similar trend (p = 0.215). In the survival analysis with pre-CCRT specimens, both RFS and OS analyses showed no statistically significant differences (p = 0.423). Although it was not statistically significant, in a group showed increase in PD-L1 expression after CCRT resulted in the steepest curve in OS analysis (p = 0.220).

Conclusions: Increase in CD8+ lymphocyte density improved OS. Because this study was performed with small number of patients, prognostic value of PD-L1 in this group of patients should be considered for future treatment planning or study design although it was not statistically significant in this study.

Legal entity responsible for the study: Yonsei Cancer Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

The standard of care for stage III NSCLC in the era of immunotherapy: An Italian national survey on the current pattern of care among Italian thoracic oncologists

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Background: Concurrent Chemo-Radiotherapy (cCRT) is standard treatment in “fit patients” (pts) affected with locally advanced (LA) NSCLC, with surgery limited to few selected cases. Despite some improvements, outcomes are still unsatisfactory, with only 15-25% of pts alive at 5 years. Recently, encouraging results were obtained with the addition of immunotherapy (IT) to cCRT. Survey was conducted to evaluate the pattern of care of LA-NSCLC treatment among Italian Thoracic Oncologists (TO) involving pneumologists, thoracic surgeons, radiation and medical oncologists.

Methods: In February 2018, all Italian TO were invited to participate to a “web-based” survey consisting in 15 multiple-choice questions about staging procedures and most appropriate multimodal approach to manage LA-NSCLC. Questions were also focused on diagnostic imaging and histopathological modalities.

Results: 421 responses were analyzed. 69% of responders had more than 5 years experience in thoracic oncology. 72% of Centers, TO regularly attend a weekly multidisciplinary Team (MDT) meeting, while in 28% MDT is not regularly planned. About pathology, cytological/histological morphologic diagnosis of malignancy were considered enough to define a therapeutic approach in 63% of responders. In N2, Stage IIIA, “minimal” pts upfront surgery was considered the preferred option from 43% of responders, while in N2, multi-nodal and/or bulky pts cCRT was recommended. For this latter group (“unsectable”) only 54% considered cCRT the most appropriate choice, while 46% preferred a sequential chemo-RT, even in fit pts due to better pts compliance and lower toxicity profiles.

Conclusions: Our analysis showed an inhomogeneous scenario between different specialists regarding the appropriate therapeutic choices for LA-NSCLC treatment. Additionally, some discrepancies were found about a correct selection of pts fit for cCRT. Many efforts have to be put towards the increase of a true multidisciplinarity, since in many Institutions lack of MDT was described. Future investigations and trials are necessary to optimize treatment approaches in LA-NSCLC, in particular considering recent clinical results on combination of cCRT and IT.

Legal entity responsible for the study: Alessio Brunì.

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.
Phase II study of tepotinib + gefitinib (TEP+GEF) in MET-positive (MET+)
epidermal growth factor receptor (EGFR)-mutant (MT) non-small cell lung cancer (NSCLC)

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ARCTIC: Durvalumab + tremelimumab and durvalumab monotherapy vs SoC in ≥3L advanced NSCLC treatment


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Impact of the EML4-ALK variant on the efficacy of alectinib (ALC) in untreated ALK+ advanced NSCLC (aNSCLC) in the global phase III ALEX study


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Efficacy of lorlatinib in patients (pts) with ROS1-positive advanced non-small cell lung cancer (NSCLC) and ROS1 kinase domain mutations

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Gefitinib with or without pemetrexed in nonsquamous (NS) non-small cell lung cancer (NSCLC) with EGFR mutation (mut): Final overall survival (OS) results from a randomized phase II study


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Phase III study of gefitinib (G) versus gefitinib+carboplatin+pemetrexed (GCP) as first-line treatment for patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009)

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An open-label, multicenter, phase I study of ABBV-399 (telisotuzumab vedotin, teliso-V) as monotherapy (T) and in combination with erlotinib (T+E) in non-small cell lung cancer (NSCLC)

R. Camidge\textsuperscript{1}, R.S. Heist\textsuperscript{2}, J. Goldman\textsuperscript{3}, E. Angevin\textsuperscript{4}, J. Strickler\textsuperscript{5}, D. Morgensztern\textsuperscript{6}, M. Barve\textsuperscript{7}, T.M. Bauer\textsuperscript{8}, E.E. Vokes\textsuperscript{9}, T. Yi\textsuperscript{10}, M. Motwani\textsuperscript{11}, A. Parikh\textsuperscript{12}, J. Wu\textsuperscript{13}, K. Kelly\textsuperscript{14}

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Pembrolizumab in performance status 2 patients with non-small cell lung cancer (NSCLC): Results of the PePS2 trial


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A randomised phase III trial evaluating the addition of denosumab to standard first-line treatment in advanced NSCLC: The ETOP and EORTC SPLENDOUR trial


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Annals of Oncology

IMpower150: Clinical safety, tolerability and immune-related adverse events in a phase III study of atezolizumab (atezo) + chemotherapy (chemo) vs bevacizumab (bev) vs chemo + bev in 1L nonsquamous NSCLC


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Background: In the primary analysis of this study (EudraCT: 2007-005792-34), D dosed to a 12.0-g/dL Hb ceiling was noninferior to P for overall survival (OS) and progression-free survival (PFS) and superior to P for transfusion (TN) or Hb £ 8.0 g/dL in anemic pts with advanced NSCLC (screening Hb £ 11.0 g/dL).

Methods: Adults with stage IV NSCLC expected to receive 6 cycles of myelosuppressive chemotherapy, life expectancy > 6 mos, ECOG 0–1, and Hb £ 11.0 g/dL were randomized 2:1 to D (500 µg SC) or P Q3W. Pts were stratified by region, histology, and Hb. This ad hoc analysis assessed key study endpoints in pts with baseline Hb £ 10.0 g/dL and in subgroups with Hb 9.0–10.0 and < 9.0 g/dL. Primary endpoint of the parent study was OS; a Cox proportional hazards model, stratified by randomization factors, was used to evaluate noninferiority (upper confidence limit for hazard ratio [HR] < 1.15). Secondary endpoints were PFS (noninferiority) and incidence of TN or Hb £ 8.0 g/dL from wk 5 to end of efficacy treatment period (EOETP).

Results: Of 2549 pts enrolled in the trial, 1183 had baseline Hb £ 10.0 g/dL (735, Hb 9.0–10.0 g/dL). Pts were well matched between arms for sex, race, and age. Among pts with Hb £ 10.0 g/dL, the HRs for OS and PFS were close to 1.0; results were consistent in the subgroups. Odds ratios for TN or Hb £ 8.0 g/dL from wk 5 to EOETP were < 1.0 and were consistent in the subgroups (Table). TN was more frequent in pts with lower baseline Hb. Safety findings were consistent with previous studies; thrombovascular events were more frequent with D than P (Table).

Conclusions: The results presented here appear mostly consistent with the primary study results, but this ad hoc analysis was not powered to demonstrate noninferiority or superiority, so the results should be interpreted in that context.

Clinical trial identification: NCT00858364; July 17, 2009.

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Legal entity responsible for the study: Amgen Inc.

Funding: Amgen Inc.


Table: 1387P

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hb &lt; 9.0 g/dL</th>
<th>Hb 9.0–10.0 g/dL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (death), n/N (%)</td>
<td>D</td>
<td>P</td>
<td>D</td>
</tr>
<tr>
<td>126/157 (80.3)</td>
<td>370/486 (76.1)</td>
<td>197/249 (79.1)</td>
<td>590/777 (75.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.05 (0.83–1.32)</td>
<td>0.96 (0.80–1.15)</td>
<td>0.98 (0.85–1.13)</td>
</tr>
<tr>
<td>PFS (progression or death), n/N (%)</td>
<td>D</td>
<td>P</td>
<td>D</td>
</tr>
<tr>
<td>141/154 (91.6)</td>
<td>222/246 (90.2)</td>
<td>272/307 (88.9)</td>
<td>670/837 (80.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.89 (0.79–1.24)</td>
<td>0.89 (0.75–1.05)</td>
<td>0.93 (0.81–1.06)</td>
</tr>
<tr>
<td>TN or Hb £ 8.0 g/dL from wk 5 to EOETP, n/N (%)</td>
<td>D</td>
<td>P</td>
<td>D</td>
</tr>
<tr>
<td>71/137 (51.8)</td>
<td>76/233 (32.6)</td>
<td>230/693 (33.2)</td>
<td>147/170 (39.7)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.77 (0.54–1.09)</td>
<td>0.75 (0.57–0.98)</td>
</tr>
</tbody>
</table>

Safety

| n | D | P | D | P | D | P |
| 292 | 229 | 126 | 285 | 141 | 246 | 590 |
| All treatment-emergent AEs, % | 90.1 | 90.4 | 86.0 | 86.7 | 87.5 | 88.1 |
| Serious AEs, % | 41.8 | 44.6 | 34.1 | 31.5 | 37.0 | 36.5 |
| Fatal AEs, % | 15.1 | 14.6 | 14.6 | 13.7 | 14.8 | 14.1 |
| AEs leading to discontinuation of blinded drug, % | 2.4 | 3.1 | 3.5 | 3.2 | 3.1 | 4.0 |
| Arterial embolic and thrombotic events, % | 1.7 | 0.6 | 0.6 | 0.4 | 1.0 | 0.5 |
| Venous embolic and thrombotic events, % | 4.5 | 3.8 | 3.5 | 2.0 | 3.9 | 2.7 |

*Standardized MedDRA query.

AEs, adverse events; CI, confidence interval; HR, hazard ratio; OR, odds ratio.
Incidence of cardiac toxicities in patients with advanced non-small cell lung cancer treated with osimertinib: A combined analysis of two phase III randomized controlled trials

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Background: Osimertinib is an oral, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). In both EGFR-TKI sensitizing and EGFR T790M resistant mutations in advanced non-small-cell lung cancer (NSCLC), osimertinib has shown to improve survival. Nevertheless, cardiac toxicities remain a safety concern. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the incidence of cardiac toxicities.

Methods: MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018 were queried. Phase III RCTs that mentioned cardiac failure (CF), decrease in ejection fraction (EF) and ECG QT prolongation as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) and absolute risk difference (RD) with 95% confidence interval (CI). A fixed effects model was applied.

Results: 971 patients with advanced NSCLC from two phase III RCTs were included. Studies compared osimertinib vs carboplatin/paclitaxin + pemetrexed or osimertinib vs gefitinib/erlotinib. The I² statistic for heterogeneity was 0, and the heterogeneity X² statistics for anlotinib (0.7%) and placebo (1.45%) in control group. The RR for CF was 2.719 (95% CI: 1.094 – 6.735, P = 0.031) and RD was 0.026 (95% CI: 0.006 – 0.046, P = 0.012). The decrease in EF was noted in 16 (2.867%) in study arm vs 5 (1.211%) in control arm. The RR for decrease in EF was 2.502 (95% CI: 0.927 – 6.753, P = 0.070) and RD was 0.019 (95% CI: - 0.001 – 0.037, P = 0.37). The QT prolongation was reported in 35 (2.272%) vs 12 (2.906%) in control group with the RR of 2.623 (95% CI: 1.374 – 5.007, P = 0.003) and RD of 0.04 (95% CI: -0.017 – 0.071, P = 0.082).

Conclusions: Chemotherapy-induced cardiotoxicity, a major cause of morbidity and mortality, is one of the most feared complications and affects patients’ quality of life and adds financial burden. Our study showed that osimertinib notably increased the risk of cardiac toxicities with a RR of 2.71 for CF and 2.62 for QT prolongation. Prompt monitoring and early intervention is warranted.

Legal entity responsible for the study: Kyaw Zin Thein/ Texas Tech University Health Sciences Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Impact of early steroids use on clinical outcomes of patients with advanced NSCLC treated with immune checkpoint inhibitors

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Background: In advanced non-small cell lung cancer (NSCLC), immune checkpoint inhibitors (ICIs) significantly improved patients’ (pts) prognosis, even if many factors could impair their efficacy. The impact of steroids (well below the immunosuppressant dose) on ICIs outcomes is debatable, although a quite number of pts starts immunotherapy while on, or early recurs to steroids as supportive care medications or for mild AEs. Here, we aimed at assessing the impact of early steroids use on clinical outcomes of ICIs treatment in a series of pts with advanced NSCLC.

Methods: All consecutive pts with advanced NSCLC who started ICIs at our institution from Apr 2013 to Dec 2017 were retrospectively reviewed. Pts with at least one instrumental response assessment were included. Early use of steroids was defined as the use of a daily prednisone-equivalent dose > 10 mg for at least 1 day within 28 days from ICIs initiation. Chi-square test or Fisher’s exact test were used to test the association of early use of steroids with pts’ characteristics. The Kaplan-Meier method and the Cox proportional-hazards model were used for survival analyses.

Results: Out of 151 pts included, 35 (23%) made early use of steroids. Most of the pts (96%) received single agent anti PD-1/PD-L1, while 6 pts (4%) received combinatorial PD-L1 + CTLA-4 blockade. Early use of steroids was negatively associated with disease control rate (OR 0.32, 95% CI 0.14-0.71, P = 0.006) and positively associated with ≥ 2 metastatic sites (OR 3.08, 95% CI 1.33-7.89, P = 0.01) and ECOG PS ≥ 2 (OR 4.57, 95% CI 1.10-20.37, P = 0.03). With a median follow-up of 32.7 months, early use of steroids conferred a worse median progression-free survival (PFS) (1.98 vs 3.94 months; HR 1.80, 95% CI 1.02-3.28; P = 0.03). In the multivariable model including other covariates, steroids significantly associated with PFS (i.e. ECOG PS and PD-L1 status), the early use of steroids was confirmed to be independently associated with poorer PFS (HR 1.88, 95% CI 1.08-3.28; P = 0.03).

Conclusions: We found that the early use of steroids independently affects clinical outcomes in patients with advanced NSCLC treated with ICIs. If those findings will be further validated, such use in this setting should be carefully evaluated and avoided when not strictly needed.

Legal entity responsible for the study: Giovanni Fucik.

Funding: Has not received any funding.

Disclosure: D. Signorelli: Consultancies: AstraZeneca, Boehringer Ingelheim, BMS. M.C. Garassino: Consultancies: MSD, BMS, AstraZeneca, Eli Lilly. C. Proto: Consultancies: MSD, BMS. All other authors have declared no conflicts of interest.

Dose modification and therapy interruption due to adverse events in treatment with anlotinib for refractory advanced NSCLC: Data from ALTER0303

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Background: Anlotinib is an oral tyrosine kinase inhibitor targeting VEGFR, FGFR, PDGFR and c-kit. Anlotinib showed significantly improvement in overall survival in ALTER0303 trial for refractory NSCLC, a randomized, double-blind, placebo-controlled phase III trial in China. This study reported the tolerance of anlotinib in the ALTER0303.

Methods: The adverse events (AEs), dose modification, and therapy interruption were collected from anlotinib group (n = 294) and placebo group (n = 145) that were enrolled in ALTER0303. AEs were graded using Common Terminology Criteria.

Results: The anlotinib related grade ≥ 3 AEs reported in ≥ 1% patients were hypertension (13.3%), hypotension (4.8%), hand-foot syndrome (HFS) (3.7%), hemoptysis (3.1%), GGT elevation (2.7%), hyperglycemia (2.4%), QT interval prolongation (2.4%), lipase elevation (2.4%), proteinuria (2.4%), oral mucositis (1.6%), diarrhea (1.0%), and hyperbilirubinemia (1.0%). Grade ≥ 3 hypertension, HFS, and hyperglycemia were significantly more frequent in the anlotinib group than in the control group. Dose reduction and drug interruption were required in 24 (8.16%) (Table) and 31 (10.54%) patients in anlotinib group, respectively. The most common anlotinib-related AEs causing interruption were hemoptysis (2.3%), venous thromboembolism (0.7%), proteinuria (0.7%), and interstitial lung disease (0.7%).

Conclusions: It was important to manage hand-foot syndrome, hypertension, diathea and hemoptysis, so that patients could benefit from anlotinib.

Table: 1390P Dose modification due to anlotinib-related adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. (%)</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome</td>
<td>7 (2.3)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1.0)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (1.2)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.3)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>1 (1.2)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (1.2)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>2 (1.2)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Arthrythmia</td>
<td>2 (1.2)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.3)</td>
<td>12mg—10mg</td>
</tr>
<tr>
<td>Dyspnnea</td>
<td>1 (0.3)</td>
<td>12mg—10mg</td>
</tr>
</tbody>
</table>

NCT02388919.
Background: Immune-related adverse events (irAEs) are a new standard of care in first and second line treatment of advanced NSCLC. Immune related adverse events (irAEs) have been proposed as an indicator of treatment efficacy.

Methods: Retrospective analysis of mNSCLC patients treated with anti PD-1/anti-PD-L1 with or without anti-CTLA4 therapy. Electronic patient records were reviewed; irAEs were identified and graded according to CTC AE v4.03 criteria. The association with survival was evaluated in univ- (UV) and multivariable (MV) Cox-regression models.

Results: 64 pts were identified; 41 (64.1%) were adenocarcinomas and 27 (42.2%) received immunotherapy in first-line. 44 pts (68.8%) received antiPD1/PDL1 monotherapy, and 20 pts (31.2%) received antiPD1 + antiCTLA4. 15 pts (25%) developed irAEs: gastrointestinal (17.6%), endocrine (11.8%), cutaneous (17.6%), other (33.3%). Treatment was interrupted in 8 (33.3%) and suspended in 5 (33.3%) pts. 7 (50%) pts received high dose corticosteroids. No toxic deaths occurred. IrAEs were not significantly increased in pts receiving combination therapy (30% vs 20%, p = 0.377). Median OS was 6.5 mo (95%CI 0.24-12.7). Pts experiencing irAEs had a significantly higher OS (HR: 0.82, 95%CI 0.07-0.8; p = 0.005) in UV analysis, and was independent of other prognostic factors in MV analysis (Table).

Conclusions: The development of irAEs may identify pts with a higher likelihood of benefiting from immunotherapy in NSCLC. These findings will require prospective validation in well-designed clinical trials.

Disclosure: All authors have declared no conflicts of interest.

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Dose-determination results from a phase Ib/II study of carboplatin (CER) + ribociclib (RIB) in ALK-positive (ALK+) non-small cell lung cancer (NSCLC)

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Background: Preclinical data suggest cyclin-dependent kinase 4/6 inhibitors (CDK4/6) may improve ALK inhibitor (ALKI) efficacy in ALK+ NSCLC. A Phase Ib/II study (NCT02292530) is assessing CER (ALK+ > RIB (CDK4/6) in patients (pts) with ALK+ NSCLC; here we report data from the Phase Ib dose-escalation.

Methods: Pts with Stage IIIB/IV ALK+ NSCLC (≥1 prior therapy for advanced NSCLC; no prior CDK4/6) received escalating doses of CER (starting dose 300 mg once daily [QD]; continuous [cont]) + RIB (starting dose 100 mg QD, 3 weeks [wks] on/1 wk off) under fed conditions. Primary objective: maximum tolerated dose (MTD) and secondary objectives: safety, pharmacokinetics, and efficacy.

Results: As of Jan 8, 2018, 27 pts were enrolled into 5 dose cohorts (Table); 8 were ALK+ naive, 14 had prior crizotinib, 5 had prior 3rd-generation (gen) ALKi. Treatment was ongoing in n = 4; the most common reason for discontinuation was disease progression (n=10/27). One dose-limiting toxicity occurred (CER 450 mg + RIB 100 mg; Grade 2 increased blood creatinine for ≥7 consecutive days); RP2D was CER 300 mg QD (cont) + RIB 200 mg QD (3 wks on/1 wk off). At steady state, CER and RIB exposure (AUC) each increased by ~1.5–2 fold compared with CER and RIB single-agent exposures under fasting conditions, with considerable variability in the setting of limited pts number. G3/4 treatment-related adverse events occurred in 15 pts; the most common (≥10% of pts) were decreased neutrophil count, increased ALT, and

Disclosure: All authors have declared no conflicts of interest.

Table: 1392P

<table>
<thead>
<tr>
<th>CER 300 mg + RIB 100 mg</th>
<th>CER 450 mg + RIB 100 mg</th>
<th>CER 300 mg + RIB 200 mg</th>
<th>CER 450 mg + RIB 200 mg</th>
<th>CER 450 mg + RIB 300 mg</th>
<th>All</th>
</tr>
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<tbody>
<tr>
<td>Enrolled (n)</td>
<td>4</td>
<td>7</td>
<td>4</td>
<td>7</td>
<td>5</td>
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<tr>
<td>Prior antineoplastic therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ALKi naive</td>
<td>3 (75.0)</td>
<td>2 (28.6)</td>
<td>1 (25.0)</td>
<td>1 (14.3)</td>
<td>1 (20.0)</td>
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<tr>
<td>Prior crizotinib‡</td>
<td>1 (25.0)</td>
<td>4 (57.1)</td>
<td>2 (50.0)</td>
<td>5 (71.4)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Prior 3rd-gen ALKi§</td>
<td>0</td>
<td>1 (14.3)</td>
<td>1 (25.0)</td>
<td>1 (14.3)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Treatment ongoing, n (%)</td>
<td>2 (50.0)</td>
<td>1 (14.3)</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Discontinuation due to disease progression, n (%)</td>
<td>2 (50.0)</td>
<td>1 (14.3)</td>
<td>1 (25.0)</td>
<td>3 (42.9)</td>
<td>3 (60.0)</td>
</tr>
</tbody>
</table>

Most common Grade 3/4 treatment-related adverse events (≥10% of all pts, n (%)

| Complete response       | 1 (25.0)               | 0                      | 0                      | 0                      | 1 (3.7) |
| Partial response         | 1 (25.0)               | 4 (57.1)               | 2 (50.0)               | 3 (42.9)               | 2 (40.0) |
| Stable disease           | 2 (50.0)               | 2 (28.6)               | 1 (25.0)               | 2 (28.6)               | 2 (40.0) |
| Progressive disease      | 0                      | 0                      | 0                      | 1 (20.0)               | 1 (3.7) |

| ORR‡ in % (90% CI)       | 2 (50.0) [0.10–0.90]   | 4 (57.1) [0.22–0.87]   | 2 (50.0) [0.10–0.90]   | 3 (42.9) [0.13–0.77]   | 2 (40.0) [0.08–0.81] |

‡These 4 pts discontinued study treatment prior to completing their first tumor evaluation; pts received prior crizotinib only;
§Pts received prior 3rd-gen ALK only (n = 2) or prior 3rd-gen ALK and crizotinib (n = 3); ORR = complete response + partial response.
A multicenter study of mutational profiling of Chinese ALK+ non-small cell lung cancer patients with acquired resistance to crizotinib using next generation sequencing

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Background: Anaplastic lymphoma kinase (ALK) rearrangements define a distinct molecular subtype of non-small-cell lung cancer. Recently, the therapeutic landscape for advanced ALK+ NSCLC has been transformed by the development of increasingly potent and selective ALK inhibitors. Crizotinib was the first ALK inhibitor to enter clinical development. The mechanism of acquired resistance to crizotinib for the patients with ALK+ NSCLC is not yet fully identified. In this study, we performed mutational profiling in a cohort of 42 ALK+ NSCLC patients at diagnosis and following acquired resistance to crizotinib using targeted NGS.

Methods: A total of 42 patients with stage IIIB-IV ALK+ NSCLC underwent tumor biopsies or blood withdrawal by the time of acquiring resistance to crizotinib, including 19 formalin-fixed paraffin-embedded (FFPE) samples, 12 serum samples and 11 serum effusions. We used targeted NGS to detect the gene status of patients.

Results: In total, we identified 92 genetic alterations with a median of 2.2 mutations per patient. 83% of patients still exhibit fusions, and 29% of patients acquired ALK point mutations. Besides other known resistance mechanisms, we identified KRAS mutations in 14% of patients, and EGR8 mutations in 12%. Interestingly, we also observed IGF1R, GPR133, CDH18 and HSD17B3 mutations in ALK point mutation-negative patients, which were restricted to crizotinib resistance.

Conclusions: Our study uncovered mutational profiles of ALK+ NSCLC patients with crizotinib resistance with potential therapeutic implications, and this study also comprehensively depicted the genetic landscape in a Chinese ALK+ NSCLC population resistant to crizotinib. Our analysis demonstrates new perspectives for further study of resistance and suggests corresponding relevant tactics against the challenge of disease progression.

Legal entity responsible for the study: Chunwei Xu.

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Lung cancers carrying distinct ALK fusion variants demonstrate similar responsiveness to ALK tyrosine kinase inhibitors

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Background: Multiple laboratory evidences indicate that distinct variants of ALK translocations differ in their biochemical properties and responsiveness to ALK tyrosine kinase inhibitors (ALK TKI). These data are supported by some Asian clinical studies, which showed improved responses to crizotinib in non-small cell lung cancer (NSCLC) patients carrying particular variants of ALK translocation.

Methods: This study retrospectively considered 64 Russian patients with ALK-rearranged NSCLC, who were treated by crizotinib (n = 23), ceritinib (n = 39) or alectinib (n = 2). ALK fusion variants were genotyped by PCR. Results: Median progression-free survival (PFS) approached to 18 and 21 months in subjects with “short” (v.34a, v.3a/b) vs. “long” (TAPE-domain containing) fusion variants (p = 0.783), respectively; similar data were obtained while comparing EML4/ALK variant 1 vs. other ALK translocations (19 and 21 months, respectively; p = 0.604). Objective response rates were also strikingly similar in the above groups (“short”: 80%, “long”: 77%; p = 0.479; variant 1: 76%, other translocations: 81%, p = 0.733). Furthermore, ALK variant did not influence the disease outcomes when patients treated by crizotinib and ceritinib were analyzed separately. Overall, PFS on ALK TKI did not depend on whether the drug was administered upfront or after chemotherapy. Ceritinib produced significantly longer PFS than crizotinib (p = 0.022).

Conclusions: This is the first non-Asian study evaluating the relationship between ALK fusion variants and response to ALK TKI. Although being larger in size as compared to published data sets, it failed to confirm the role of the type of ALK translocation in determining the treatment outcome.

Legal entity responsible for the study: Evgeny Imyanitov.

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Safety profile and effectiveness of alectinib in the real-world surveillance study of 1251 Japanese patients with ALK-positive non-small cell lung cancer

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Background: Alectinib is a CNS penetrant and highly selective ALK inhibitor. The Japanese Risk Management Plan based on the phase II/III studies highlighted interstitial lung disease (ILD), liver function disorder, decreased neutrophil cell and white blood cell counts as identified risk in Japanese patients (pts). To investigate the safety and effectiveness of alectinib, including adverse drug reactions (ADR) of particular concern in the real-world setting, a large scale surveillance funded by Chugai Pharmaceuticals has been implemented. This study is registered with the UMIN, number UMIN000014989.

Methods: From Sep 2014 to June 2015 all pts with ALK-positive recurrent/advanced NSCLC treated with alectinib, were enrolled in the study. The observation period was 18 months, ADR were collected. Overall survival (OS) was also assessed.

Results: By Jun 2015, a total of 1251 pts were registered. We analysed 1221 pts as the safety population. Baseline characteristics included: female (54% of population), median age (62 years), ECOG PS 3.4 (n = 89) (7%), pts who received first line (18%), second line (32%) or third line or more (50%) treatments, pts who received crizotinib (63%), brain metastases (41%). The overall incidence of ADRs was 53.6% (modally grade 1/2), the most common were laboratory tests abnormality (27.7%). ILD events were reported in 47 pts (3.8% of population), including grade 3 events in 8 pts and grade 4 events in 1 pt, in which the rate of recovery or improvement was 92%. Events of liver function disorder were reported in 242 pts (19.8%), including grade 3 events in 24 pts, and events of neutrophil cell and white blood cell decrease were reported in 93 pts (7.6%), including grade 3 events in 12 pts and grade 4 events in 2 pts, in which the rates of recovery or improvement were 83% and 93%, respectively. Median OS was not reached. Overall survival rate at 12 months and 18 months were 82.4% and 76.2%, respectively.

Conclusions: These final data from this study in Japanese ALK-positive NSCLC pts provide an acceptable safety and effectiveness profile in the real-world setting. Alectinib was primarily chosen as the effective therapies for the treatment of ALK-positive NSCLC.

Legal entity responsible for the study: Chugai Pharmaceutical Co., LTD.

Funding: Chugai Pharmaceutical Co., LTD.

Efficacy and safety of crizotinib in previously treated patients (Pts) with ALK+ advanced non-small cell lung cancer (NSCLC) aged ≥65 years (y)

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Background: Crizotinib is an oral tyrosine kinase inhibitor (TKI) approved for treatment of ALK+ advanced NSCLC. We report efficacy and safety from subgroups of pts aged ≥65 y included in PROFILE 1005, the largest clinical trial to date of an ALK TKI in ALK+ NSCLC.

Methods: PROFILE 1005 (NCT019932451) was a multicenter, single-arm phase 2 trial of crizotinib (250 mg twice daily; continuously) in pts with ALK+ NSCLC who had failed ≥1 line of systemic treatment for advanced/metastatic disease. Co-primary endpoints were objective response rate (ORR) per RECIST v1.1 and adverse events (AEs). Other efficacy endpoints included duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Results: Of 1066 treated pts, 93 (54 female/39 male) and 79 pts (49 female/30 male) were aged 65–70 y, respectively, at baseline (overall safety population). 908 out of 1066 pts, including 74 pts in the 65–70 y subgroup and 57 in the >70 y subgroup, were ALK+ by central FISH testing, all were evaluable for response. The table shows investiga- tor-assessed efficacy endpoints for these pts. Most common TRAEs in the 65–70 (n = 93) and >70 (n = 79) subgroups, respectively, were vision disorder (34.8% & 45.6%), nausea (50.6% & 57.0%), edema (43.0% & 57.0%), and diarrhea (39.8 & 48.1%), mostly Grade 1/2, comparable to the safety profile of the overall safety population (n = 1066), but with some higher frequencies seen in the >70 y subgroup. In the 65–70 y and >70 y subgroups, respectively, 24.7% and 27.8% of pts had TRAEs leading to dose reductions (overall safety population, 18.3%), and 9.7% and 13.9% had TRAEs requiring permanent treatment discontinuation (overall safety population, 5.6%).

Conclusions: Efficacy and safety profiles in ALK+ NSCLC pts aged 65–70 or >70 y were comparable to those previously reported for PROFILE 1005, with some TRAEs occurring at higher frequencies in pts >70 y.

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Disclosure: D. Moro-Sibilot: Membership of an advisory board or board of directors: MSD, BMS, Takeda, Roche, AstraZenea, Ariad, Abbvie, Novartis, Pfizer, Lilly, Boehringer Ingelheim. Corporate sponsored research: Pfizer, Boehringer Ingelheim. M-J. Ahn: Membership of an advisory board or board of directors: AstraZeneca, Lilly, Lyra. B. Halmo: Membership of an advisory board or board of directors: Pfizer, Novartis, Takeda, AstraZenea, Boehringer Ingelheim, Genentech, Ignyta. Corporate sponsored research: Merck, Pfizer, Mirati, Boehringer Ingelheim, AstraZeneca, Takeda, Novartis, Eli Lilly; Other: Foundation Medicine, Guardant Health 360, Eli Lilly, Merck. G.J. Rely: Speakers or advisory board: Genentech; Grant/research support: Novartis, Roche/Genentech, Millenium, GlaxoSmithKline, Pfizer, Infinity Pharmaceuticals, Ariad. A.T. Shaw: Membership of an advisory board or board of directors: Blueprint Medicine, ECOG Theraapeutics; Consulting or honoraria: Pfizer, Novartis, Genentech, Roche, Takeda, Ariad, Ignyta, Luo. Brazil, Blueprint, Natera, Foundation Medicine, EMD Serono. S. Lanzzione, A. Polli, K.D. Winer: Stock ownership and employment: Pfizer. J. De Castro Carpe: Advisory board: Roche, Takeda, Pfizer. All other authors have declared no conflicts of interest.

Table: 1396P

<table>
<thead>
<tr>
<th>Patients With ALK+ NSCLC by Central FISH Testing</th>
<th>65–70 y (n = 74)</th>
<th>&gt;70 y (n = 57)</th>
<th>PROFILE 1005 Total (n = 908)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>67 (65–70)</td>
<td>76 (71–84)</td>
<td>52 (19–84)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>54.1 (42.1, 65.7)</td>
<td>47.4 (34.0, 61.0)</td>
<td>541 (50.8, 57.4)</td>
</tr>
<tr>
<td>Median DOR (Kaplan–Meier), months (95% CI)</td>
<td>11.4 (8.3, 16.6)</td>
<td>12.4 (9.6, 14.1)</td>
<td>11.8 (10.4, 12.8)</td>
</tr>
<tr>
<td>Median PFS (Kaplan–Meier), months (95% CI)</td>
<td>9.6 (5.5, 16.8)</td>
<td>11.6 (6.9, 15.1)</td>
<td>84 (7.1, 9.7)</td>
</tr>
<tr>
<td>Median PFS (Kaplan–Meier), months (95% CI)</td>
<td>23.2 (17.6, 31.3)</td>
<td>17.0 (12.2, 22.4)</td>
<td>21.8 (19.4, 24.0)</td>
</tr>
</tbody>
</table>

aCalculated using the exact method based on the F distribution

Long-term safety of crizotinib in previously treated patients (pts) with ALK-positive advanced/metastatic non-small cell lung cancer (NSCLC)


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Background: The oral tyrosine kinase inhibitor (TKI) crizotinib is approved for the treatment of pts with anaplastic lymphoma kinase (ALK+) advanced NSCLC. Here we report safety results for pts who were treated with crizotinib for longer than 1 year (y) in PROFILE 1005, the largest clinical trial to date of an ALK TKI in ALK+ advanced NSCLC.

Methods: The PROFILE 1005 study (NCT00932451) was a single-arm phase 2 trial of crizotinib (250 mg twice daily; continuously) conducted at multiple centers. The study enrolled pts with ALK+ NSCLC who had failed ≥1 line of systemic treatment for locally advanced/metastatic disease. Co-primary endpoints were safety and objective response rate.

Results: A total of 1066 pts were treated; 240 and 248 pts were treated for 1–2 y and >2 y, respectively. Treatment-related adverse events (TRAEs) are summarized by treatment duration subgroup in the table. Most common TRAEs of any grade in the 1–2 y and >2 y subgroups, respectively, were vision disorder (65.8% and 69.4%), nausea (57.5% and 58.1%), diarrhea (54.2% and 61.3%), vomiting (49.6% and 46.4%) and edema (47.1% and 60.1%). The most common grade 3/4 TRAE in both subgroups was neutropenia (17.1% and 23.0%). Two grade 5 TRAEs (interstitial lung disease [n = 1] and cardiac arrest [n = 1; for which other factors could not be excluded]) were reported in the 1–2 y subgroup; no grade 5 TRAEs were reported in the >2 y subgroup. Selected TRAEs of interest based on prior experience with crizotinib included the following, reported in the 1–2 y and >2 y subgroups, respectively: elevated transaminases (35.4% and 37.4%), hepatotoxicity (1.3% and 1.2%), interstitial lung disease (2.1% and 2.4%), EGQ QT prolonged (2.5% and 4.8%), bradycardia (13.3% and 16.5%), and renal cysts (2.1% and 7.7%).
Conclusions: No new major safety signals were observed. The long-term safety profile was consistent with the known safety profile of crizotinib.

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Real-world progression-free survival of patients on anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) for ALK+ non-small cell lung cancer (NSCLC)

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Background: Patients with NSCLC characterized by ALK rearrangements may benefit from ALK TKI therapies. Although ALK TKIs have shown improved efficacy relative to conventional chemotherapy, the prognosis for patients with ALK + NSCLC remains suboptimal. The present study uses real-world evidence to examine progression-free survival (PFS) among patients with ALK + NSCLC treated with an ALK TKI.

Methods: Patients with advanced ALK + NSCLC diagnosed and treated with an ALK TKI in 2011-2017 were identified from the Flatiron Health Electronic Health Record (EHR) -derived database. Real-world PFS (rwPFS) was estimated as the time from treatment start to progression or death, where progression was abstracted from clinician notes and radiology/pathology reports by trained medical reviewers. Analyses examined rwPFS following the patient’s first line containing ALK TKI. For patients who received crizotinib as their first TKI followed by a second ALK TKI, a similar analysis examined rwPFS following their second ALK TKI line. Data were censored at end of follow-up for patients without progression or death. The median and 95% confidence interval (CI) of rwPFS following first and second ALK TKI were obtained from Kaplan-Meier methods.

Results: Of 409 ALK TKI-treated patients with advanced ALK + NSCLC, mean age was 60.4 years and 51.6% were female. Most patients (n = 379; 92.7%) received crizotinib as their first ALK TKI, of these 180 (47.5%) were later treated with a second ALK TKI (e.g. ceritinib, alectinib). Median (95% CI) rwPFS was 7.5 (6.6-8.6) months following first ALK TKI and 6.4 (5.2-8.2) months following second ALK TKI post-crizotinib (including 6.3 [4.3-8.4] months for ceritinib in (n=99) and 7.6 [5.2-13.6] months for alectinib (n = 641)).

Conclusions: In this real-world analysis of patients with advanced ALK + NSCLC treated with earlier approved ALK TKIs, rwPFS remains short, indicating a clear need for more effective treatments of ALK + NSCLC.

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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

Impact of lorlatinib on patient-reported outcomes (PROs) in patients (Pts) with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC)


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Background: Lorlatinib is a selective, potent, brain-penetrant, third-generation ALK/ ROS1 tyrosine kinase inhibitor with robust clinical activity in pts with ALK+ (ALK+) or ROS1-positive (ROS1+) advanced NSCLC. The phase 1/2 study (NCT019790865) assessed lorlatinib in pts with ALK+ or ROS1+ NSCLC based on prior treatment phase. 2 efficacy/safety was previously reported. Here, we present PRO results.

Methods: In this ongoing open-label, multicenter study, pts received lorlatinib 100 mg once daily. Global quality of life (QoL), pt functioning and symptoms were assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30/36 (baseline [BL]) and on day 1 of each cycle. Higher scores indicated better functioning/ QoL, or greater symptom severity. Change from BL (ABL) was summarized: 10-point ABL (improved or worsened) was considered clinically meaningful. An average of mean ABL was calculated for each pt across cycles to determine the proportion of pts with a clinically meaningful change.

Results: Median treatment duration was 8.3 months. Interim PRO data were analysed through cycle 24, the completion rate was ≥94%. Clinically meaningful improvements from BL were seen for global QoL, most pts had improved (45%) or stable (neither improved nor worsened) scores (40%). Clinically meaningful improvements occurred in functioning domains and symptoms; further details will be presented. The highest proportion of pts improved in emotional (38%), role (38%) and social (34%) functioning domains. Proportions of pts with improved/stable/worse cognitive functioning were 24%/51%/24%. Most pts had improved or stable symptom scores; the greatest proportions of pts improved for symptoms of fatigue (49%), insomnia (45%) and appetite loss (42%) on QLQ-C30 and cough (44%), pain in other parts (33%) and pain in chest (30%) on QLQ-LC13. The symptom with the greatest proportion of pts with clinically meaningful worsening was peripheral neuropathy (38%).

Conclusions: Lorlatinib showed favorable clinical benefit and improvements in global QoL, functioning and key NSCLC symptoms in pts with ALK+ or ROS1+ NSCLC. Clinical trial identification: Clinical trial registration: NCT019790865.

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Legal entity responsible for the study: Pfizer

Funding: Pfizer.

Disclosure: S. Peters: Consulting or advisory role: Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Roche, AstraZeneca, Speakers’ bureau: AstraZeneca, Roche, Bristol-Myers Squibb, MSD, Boehringer Ingelheim. A.T. Shaw: Speakers or advisory board: Pfizer, Novartis, Genentech, Roche, Aria, Takeda, Ignyta, Blueprint, Loxo, Daichi Sankyo, EMD Serono, Taiho Pharmaceutical, Natera; Honorary: Pfizer, Novartis, Roche/Genentech, Foundation Medicine, Takeda; Research funding: Pfizer; Novartis, Roche/Genentech. B. Bese: Travel, accommodations, expenses: Roche, Pfizer, Bristol-Myers Squibb/Medarex, Novartis, Pierre Fabre. Institutional: Research funding: AstraZeneca, Roche/Genentech, Pfizer, Boehringer Ingelheim, Lilly, Servier, Oncoz, Bristol-Myers Squibb, Ose Pharma, Innata, Novartis. F. Felip: Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, GuardantHealth, MSD, Novartis, Pfizer, Roche, Takeda, Merck; Speakers’ bureau: AstraZeneca, Boehringer Ingelheim, BMS, MSD, Novartis, Pfizer, Roche. B.J. Solomon: Honorary: Bristol-Myers Squibb, AstraZeneca, Royalties, IP Rights/Patient Holder: Veristat (Biodiesa); Travel, accommodations, expenses: AstraZeneca, Roche, Merck, Bristol-Myers Squibb, Novartis; Institutional: Speakers or advisory board: AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Genentech, Taiho Pharmaceutical; Honorary: AstraZeneca, Roche/Genentech, Novartis, Research funding: Pfizer, R.A. Soo: Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Novartis, Pfizer, Roche/Genentech; Research funding: AstraZeneca. A. Beaz: Speakers’ bureau: MSD, Roche, BMS, Pfizer, Takeda, Eli-Lilly, Novartis; Consultant: MSD, Roche, BMS, Pfizer, Takeda, Eli-Lilly, Novartis. S.M. Gadgeel: Consulting or advisory role: Pfizer, Genentech/Roche, Aria, AstraZeneca, Bristol-Myers Squibb; Speakers’ bureau: AstraZeneca, Travel, accommodations, expenses: Ariad/Takeda, Genentech/Roche; Institutional: Research funding: Pfizer, Clovis Oncology, Merck, Genentech/Roche, Incyte, Millennium, AstraZeneca/MedImmune, Bristol-Myers Squibb.
**1401P** The efficacy and safety of crizotinib in patients with ROS1 positive advanced stage NSCLC: The real-world experience from Turkey

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**Background:** ROS1 mutation occurs in approximately 1-2% of patients with NSCLC. There are limited data on the efficacy of crizotinib treatment in the real-world experience of patients with ROS1-positive advanced stage NSCLC. The survival results of two studies evaluating the efficacy of crizotinib in these patients are contradictory. In the study, we aimed to evaluate real-life data of the patients with ROS1-positive advanced stage NSCLC treated with crizotinib in Turkey.

**Methods:** In this multicenter study, patients with ROS1-positive NSCLC treated with crizotinib were retrospectively analyzed. Clinical and demographic characteristics of the disease, response rates median PFS and side effects with crizotinib were evaluated in 42 patients.

**Results:** Twenty-two of the patients (52.4%) were female, and 23 (54.8%) were non-smoker. The median age at the time of diagnosis was 51 (20-80) years. The most common histology was adenocarcinoma (n=26). At baseline, 12 (28.6%) patients had pleural effusion, 11 (26.2%) had brain metastasis, and 17 (40.9%) had bone metastasis. The baseline ECOG performance score was 0 in 28.6% and 1 in 64.3%. Crizotinib was used in 45% of patients at the first line, 42.9% at the second line, and 12.0% in the next steps. The most common side effect was fatigue (43%). In 4 patients vascular event developed (3 thromboemboli, 1 acute MI). Brain metastasis developed in 31% of the patients at the follow-up. The overall response rate with crizotinib was 99.0% with 9.5% complete remission and 50.0% partial remission. The disease control rate was 85.3%. The median PFS was 13.2 months and the 12-month PFS was 25%. Thirty-six percent of patients did not received additional treatment. At the time of data cut off, 11 patients had received another treatment.

**Conclusions:** In 2 published studies, median PFS in patients with ROS1-positive NSCLC with treated crizotinib were reported as 9.1 and 19.2 months independently of the treatment step. In our study, the median PFS was 13.2 months in patients as a result of real-life data of patients in Turkey. The clinical features of the disease are compatible with the literature.

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Legal entity responsible for the study: Turkish Oncology Group, Lung Cancer Subgroup.

**Funding:** Has not received any funding.

**Disclosure:** S. Kilickap: Pfizer. All other authors have declared no conflicts of interest.
Background: The addition of bevacizumab (B) to platinum doublets prolongs the survival for non-squamous (NSQ) NSCLC. The role of monotherapy with B is unclear for elderly NSQ NSCLC patients (pts). We presented the comparable efficacy data in a previous meeting. Here, we present the survival and quality of life analyses of TORG1323.

Methods: Pts were pathologically diagnosed untreated elderly (≥75 years old) NSQ NSCLC, who were stage IIIb, IV, or recurrent disease, and P8:0.61. EGFR mutation or ALK rearrangement were allowed in B monotherapy arm. B plus cisplatin or carboplatin plus docetaxel (CB) were allocated in randomization. Pts were randomized in a 1:1:1 ratio to receive either docetaxel (D) or pemetrexed (P) with B. The primary endpoint was progression-free survival (PFS) assessed by independent review committee. B was administered 15 mg/kg, D was 50 mg/m², or P was 500 mg/m² every 3 weeks until disease progression or unacceptable toxicity based on our previous studies. Selection design was adopted for this study. The planned sample size was 120 pts to evaluate if the point estimate of hazard ratio (HR) for PFS was 1.20.

Results: Enrollment was terminated early at the end of March 2017 because of slow accrual. A total of 103 pts (DB/PB=51/52 pts) were enrolled and 99 pts (49/50 pts) comprised the full analysis set. Pts characteristics were well balanced between the two arms. Median age was 78 (range: 75-88) in DB and 79 (75-94) in PB. EGFR mutation or ALK rearrangement were detected in 9.7% and 18.8% of patients, respectively. The addition of bevacizumab (B) to platinum doublets prolongs the survival for non-squamous (NSQ) NSCLC. The role of monotherapy with B is unclear for elderly NSQ NSCLC patients (pts). We presented the comparable efficacy data in a previous meeting. Here, we present the survival and quality of life analyses of TORG1323.

Conclusions: PB results in less deterioration of QoL. The efficacy is comparable between the two arms for elderly (≥75 years old) advanced NSQ NSCLC.

Clinical trial identification: UMIN000012786 01-Jan-2014.

Legal entity responsible for the study: Thoracic Oncology Research Group.

Funding: Chugai Pharmaceutical Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

**Disclosure:** All authors have declared no conflicts of interest.

**Funding:** Clinical trial identification: UMIN000012786 01-Jan-2014.

**Legal entity responsible for the study:** Thoracic Oncology Research Group.

**Funding:** Chugai Pharmaceutical Co., Ltd.

**Disclosure:** All authors have declared no conflicts of interest.

**Background:** The SENECA trial, a phase IIb, open-label, multicentre study, aimed to investigate in the real-life efficacy and safety of nintedanib plus docetaxel, used weekly (T1) or q2wk (T2), in pretreated non-small cell lung cancer patients, stratified for eligibility (within or over 3 months from end of first-line therapy). Preliminary efficacy data have been previously presented: no difference in median Progression Free-Survival and a similar trend in Overall Survival between T1 and T2 were showed. Weekly docetaxel has better tolerability than q2wk administration: aim of this study is to evaluate two different docetaxel schedules combined with nintedanib, in order to potentially maximize their use.

**Methods:** Baseline characteristics have been already presented. Incidence and severity of treatment-related Adverse Events (AEs) were evaluated from beginning of treatment until 28 days after its completion, according to Common Terminology Criteria for Adverse Events (CTCAE) version 3, in 167 patients (receiving at least one dose of study drugs) enrolled in 18 Italian oncologic centres, between January 2016 and March 2018.

**Results:** Incidence of any grade AEs was numerically higher in T2 compared to T1 (454 vs 450 events, respectively). A complete overview of AEs (≥ 5% incidence in either group) is reassembled in Table. Docetaxel was reduced in 14.4% patients, more frequently in T2 vs T1 (18.8% vs 9.7%). Nintedanib reduction was needed in 19.8% of patients. 23.2% in T1 and 15.5% in T2, mainly due to diarrhea. Thirty-one (18.9%) patients permanently discontinued study drugs (11 in T1 vs 20 in T2) due to hypersensitivity reactions and pain.

**Table: 1404P Main AEs observed in the SENECA trial according to docetaxel schedule and CTCAE grade**

<table>
<thead>
<tr>
<th>AEs</th>
<th>T1</th>
<th>T2</th>
<th>p-value</th>
<th>T1</th>
<th>T2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grades</td>
<td>(N = 82)</td>
<td>(N = 85)</td>
<td></td>
<td>(N = 82)</td>
<td>(N = 85)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>44 (52.4%)</td>
<td>35 (41.2%)</td>
<td>0.10</td>
<td>5 (6.1%)</td>
<td>10 (11.9%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>41 (50.0%)</td>
<td>40 (46.5%)</td>
<td>0.70</td>
<td>4 (4.8%)</td>
<td>4 (4.7%)</td>
<td>0.95</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>24 (29.3%)</td>
<td>17 (20.0%)</td>
<td>0.16</td>
<td>4 (4.8%)</td>
<td>5 (5.9%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Afebrile Neutropenia</td>
<td>11 (13.4%)</td>
<td>45 (52.9%)</td>
<td>&lt;0.0001</td>
<td>3 (3.6%)</td>
<td>12 (14.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain</td>
<td>19 (22.6%)</td>
<td>21 (24.7%)</td>
<td>0.81</td>
<td>3 (3.6%)</td>
<td>2 (2.4%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Anemia</td>
<td>18 (21.9%)</td>
<td>16 (18.8%)</td>
<td>0.61</td>
<td>1 (1.2%)</td>
<td>2 (2.3%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (20.7%)</td>
<td>14 (16.5%)</td>
<td>0.47</td>
<td>3 (3.6%)</td>
<td>3 (3.5%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16 (19.5%)</td>
<td>18 (21.2%)</td>
<td>0.78</td>
<td>2 (2.4%)</td>
<td>2 (2.3%)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fever</td>
<td>15 (18.3%)</td>
<td>9 (10.6%)</td>
<td>0.15</td>
<td>2 (2.4%)</td>
<td>0.00</td>
<td>0.14</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (15.8%)</td>
<td>14 (16.5%)</td>
<td>0.91</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NE</td>
</tr>
<tr>
<td>Decreased Platelets</td>
<td>11 (13.4%)</td>
<td>2 (2.3%)</td>
<td>0.00</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NE</td>
</tr>
<tr>
<td>Skin Toxicity</td>
<td>11 (13.4%)</td>
<td>9 (10.6%)</td>
<td>0.57</td>
<td>0 (0%)</td>
<td>1 (1.2%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Oral Mucositis</td>
<td>10 (12.2%)</td>
<td>19 (22.3%)</td>
<td>0.08</td>
<td>3 (3.6%)</td>
<td>1 (1.2%)</td>
<td>0.29</td>
</tr>
<tr>
<td>GGT elevation</td>
<td>9 (11.0%)</td>
<td>10 (11.8%)</td>
<td>0.87</td>
<td>3 (3.6%)</td>
<td>5 (5.9%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (8.5%)</td>
<td>15 (17.6%)</td>
<td>0.08</td>
<td>0 (0%)</td>
<td>1 (1.2%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
<td>6 (7.3%)</td>
<td>6 (7.0%)</td>
<td>0.94</td>
<td>2 (2.4%)</td>
<td>1 (1.2%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6 (7.3%)</td>
<td>5 (5.9%)</td>
<td>0.70</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NE</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4 (4.9%)</td>
<td>11 (13.2%)</td>
<td>0.38</td>
<td>7 (8.5%)</td>
<td>0.00</td>
<td>0.97</td>
</tr>
</tbody>
</table>

**ALT:** alanine aminotransferase; **NE:** not evaluable; **AS1:** aspartate aminotransferase; **GGT:** gamma-glutamyltransferase.
Conclusions: Preliminary safety data of SENECA trial show statistically significant differences only in a few of the items explored (particularly alfibrol neutropenia), but underline a clear trend of higher tolerability for weekly docetaxel combination treatment in second line nNSCLC patients.


Legal entity responsible for the study: Department of Oncology, University of Turin.

Funding: Department of Oncology, University of Turin.

Disclosure: A. Morabito: Honoraria: Roche, AstraZeneca, Boehringer Ingelheim, Pfizer, MSD, BMS. F. Grossi: Advisory boards and lectures: Boehringer Ingelheim, MSD, BMS, AstraZeneca; Lectures: Lilly, Celgene, Amgen, Roche. V. Scotti: Advisory boards and speak-er’s fee: B. S. Novello: Speakers’ bureau: BL, AstraZeneca, Roche, MSD, BMS, Ely Lilly, Takeda, Pfizer. All other authors have declared no conflicts of interest.

1406P Final results of the concordance analysis of PD-L1 immunohistochemistry (IHC) assays and polymersene chain reaction (PCR) in non-small lung cancer (NSCLC) patients

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Background: The goal of the CLOVER study is to perform a pairwise comparison of 4 tests based on the same patient population: 3 validated PD-L1 IHC assays (Ventana SP142 (axéllumina), Ventana SP263 (durvalumab), Dako 22C3 (pembrolizumab)) and one PCR test.

Methods: 473 NSCLC samples (including 81 EGFR +, 6 ALK +, 131 squamous cell carcinoma) were stained with PD-L1 IHC assays. Four pathologists independently evaluated the percentages of tumor (TC) and tumor infiltrating immune cells (IC) staining positive at any intensity. PD-L1 transcripts were quantified by Taqman RT-PCR assay using SDHA as a gene-referee; dCT = 2 was chosen as a threshold between positive and negative RNA expression. The concordance analysis was performed to assess (1) correlation of IC and TC between different assays, (2) the predictive properties of one test of another. One test-specific cutoff rule for each assay was pre-specified as: for first-line TC or IC ≥ 5% for SP142, TC ≥ 25% for SP263, TC ≥ 50% for 22C3, and for second-line TC ≥ 50% or IC ≥ 10% for SP142, TC ≥ 25% for SP263, TC ≥ 1% for 22C3.

Results: Pearson Correlation Coefficients (PCC) for TC were: 0.71, 0.87 and 0.75 between SP142/22C3, SP263/22C3 and SP142/SP263, respectively. PCC for IC were: 0.45, 0.61 and 0.68 for the same pairs. Low correlation was observed between PCR test and any of the IHC assays for TC and IC. Table represents how well one assay can predict the same outcome (positivity or negativity) of another assay using recommended individual cutoffs for each test. Among patients who were negative by PCR, 42-99% of the patients were negative by any of the three IHC assays using corresponding recommended cutoff. Among patients who were positive by PCR, 9-45% of them were positive by IHC assays.

<table>
<thead>
<tr>
<th>Test A</th>
<th>Test B</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP142</td>
<td>SP263</td>
</tr>
<tr>
<td>First-line</td>
<td>Second-line</td>
</tr>
<tr>
<td>SP142 -</td>
<td>92% 85%</td>
</tr>
<tr>
<td>SP263 91%</td>
<td>98% -</td>
</tr>
<tr>
<td>22C3 88%</td>
<td>99% 99% -</td>
</tr>
<tr>
<td>Probability of Positive Test B, given Positive Test A</td>
<td></td>
</tr>
<tr>
<td>SP142 -</td>
<td>65% 76%</td>
</tr>
<tr>
<td>SP263 68%</td>
<td>28% -</td>
</tr>
<tr>
<td>22C3 82%</td>
<td>17% 93%</td>
</tr>
</tbody>
</table>

Conclusions: PCR should not be recommended as a substitute for a PD-L1 IHC assay due to high probability of false positive prediction and low PCC. 22C3 could be considered as a substitute for SP263 in first-line.

Legal entity responsible for the study: Russian Society of Clinical Oncology.

Funding: AstraZeneca, BMS, MSD, Roche.

Disclosure: All authors have declared no conflicts of interest.
### Table: 1407P

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65</td>
<td>0.98</td>
<td>0.79-1.21</td>
</tr>
<tr>
<td>Gender Male</td>
<td>0.92</td>
<td>0.72-1.18</td>
</tr>
<tr>
<td>Smoking Former/current smoker</td>
<td>0.56</td>
<td>0.38-0.84</td>
</tr>
<tr>
<td>Histology Squamous</td>
<td>1.25</td>
<td>0.98-1.60</td>
</tr>
<tr>
<td>NF1 mutation (in ICI treated)</td>
<td>0.88</td>
<td>0.70-1.09</td>
</tr>
<tr>
<td>NF1 mutation (not in ICI treated)</td>
<td>1.56</td>
<td>1.26-1.94</td>
</tr>
<tr>
<td>Performance status &gt;2</td>
<td>1.73</td>
<td>0.29-2.31</td>
</tr>
<tr>
<td>dNLR monitoring Intermediate Poor</td>
<td>2.24</td>
<td>1.62-2.23</td>
</tr>
</tbody>
</table>

## 1408P

### Prognostic factors in non-small cell lung cancer (NSCLC) patients (pts) with brain metastases (BM) treated with immune checkpoint inhibitors (ICI)

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline &amp; cycle 2 dNLR &gt;1.24</td>
<td>1.15</td>
</tr>
<tr>
<td>Gender Male</td>
<td>1.05</td>
</tr>
<tr>
<td>Smoking history</td>
<td>0.49</td>
</tr>
<tr>
<td>Histology Squamous</td>
<td>1.13</td>
</tr>
<tr>
<td>NF1 mutation (in ICI treated)</td>
<td>0.93</td>
</tr>
<tr>
<td>NF1 mutation (not in ICI treated)</td>
<td>1.70</td>
</tr>
<tr>
<td>Performance status &gt;2</td>
<td>2.05</td>
</tr>
<tr>
<td>dNLR monitoring Intermediate Poor</td>
<td>1.23</td>
</tr>
</tbody>
</table>

**Background:** Brain metastases (BM) are frequent in NSCLC. Unfortunately, pts with (untreated) BM are often excluded from ICI trials and prognostic factors in ICI treated BM pts are largely unknown.

**Methods:** Retrospective data collection of all consecutive advanced ICI treated NSCLC pts in 6 centers (5 French, 1 Dutch) (nov 2012 – Mar 2018). All BM pts were selected; (intracranial) overall response rate (investigator assessed), progression free survival (PFS), overall survival (OS) data were collected. Active BM, non-irradiated new and/or growing lesions on brain imaging ≤ 6 weeks before ICI start.

**Results:** 241/945 (26%) pts had BM: 61% male, 76% WHO PS 0-1, median age 61 years, 79% nonsquamous, 4% driver mutation, 31% known PD-L1 (61% ≥1% expression). ICI treatment was median 2nd line (range 1-8), 93% had monotherapy ICI.

Median time BM diagnosis till ICI start: 184 days. >5 BM: 30%, active BM: 40%, symptomatic: 14%, steroid use: 26%, known disease specific Graded Prognostic Assessment (ds-GPA) at start of ICI: 34% 0-1, 58% 1-2, 5% 3-4. Previous cranial radiotherapy (RT): 68% (56% stereotactic, 44% whole brain), median time RT to ICI start: 109 days. Median follow-up: 14 months. 78% had PD on ICI: 12% BM only: 28% extracranial, 50% both, 10% no imaging (clinical PD). At PD, 23% of BM only PD pts had extracranial response and 21% of extracranial only PD pts had cranial response.

Median (95% CI) PFS and OS were 2 (1-2) and 9 (7-13) months, respectively. In multivariate analysis, >2 metastatic organs and symptomatic BM at ICI start were associated with a worse PFS and OS; higher ds-GPA with superior PFS and OS (Table). In univariate analysis, active BM vs stable BM and brain RT vs no brain RT were not associated with outcome (HR PFS 0.98 (p = 0.66)/ HR OS 0.93 (p = 0.92) and HR PFS 0.82 (p = 0.19) / HR OS 0.82 (p = 0.27).

**Conclusions:** Number of metastatic organs, symptomatic BM and ds-GPA are associated with outcome in BM pts treated with ICI.

**Legal entity responsible for the study:** Gustave Roussy.

**Funding:** L. Hendriks: Grant: DUERTECC/eurocon.

**Disclosure:** L. Hendriks: Outside the current abstract: Research funding: Roche; Advisory board: Boehringer Ingelheim, BMS; Travel reimbursement: Roche, BMS. C. Le Pechoux: Outside the current abstract: Advisory board: Astrazeneca, A-M.C. Dingemans: Outside the current abstract: Advisory board: BMS, MSD, Roche. B. Besse: Outside the current abstract: Institutional grants for clinical and translational research: AstraZeneca, BMS, Boehringer Ingelheim, Lilly, Pfizer, Roche; Genentech, Sanofi-Aventis, Servier, Onexco, OncoMed, Invivra, Ose Pharma, Loxo. All other authors have declared no conflicts of interest.
Annals of Oncology abstracts

1409P Association of efficacy and immune-related adverse events (irAEs) in patients with NSCLC receiving immune-checkpoint inhibitors (ICIs) to predict efficacy of immune-checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC)

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Background: ICIs are standard treatment in advanced NSCLC. However, ICIs can induce irAEs that may interrupt treatment. Here we report the incidence of irAEs and its correlation with efficacy.

Methods: We retrospectively analyzed 101 patients (pts) with advanced NSCLC receiving ICIs in our institution from March 2014 to January 2018. IrAEs were graded following CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survival (OS). Analyses were performed using SPSS v24 package.

Results: Median age was 66.4 [37.85] years, 74.3% were male. 35 (33.2%) pts presented squamous and 68 (67.3%) non-squamous histology. Most frequent ICIs were nivolumab (50%), pembrolizumab (31%) and atezolizumab (16%), used as monotherapy (79.2%) or in combination with chemotherapy (20.8%). Median duration of treatment was 2.7 [0.6-26.2] months. 61 (60.6%) pts developed 166 irAEs, with a mean of 1.02 (0-4) irAEs/pts. Most frequent irAEs were rash (24.5%), pruritus (22.6%), diarrhea (21%), thyroid dysfunction (10.5%), arthritis (8.5%), hepatitis (2.9%) and pneumonitis (2%). 8 (7.9%) patients experienced grade (G) 3-4 irAEs. 1 G3 pneumonitis, 4 G3 diarrhea, 1 G3 mucositis, 1 G3 nephritis and 1 G3 haemolytic anemia. There was one treatment-related death due to pneumonitis. 47 (46.5%) pts received systemic corticosteroids during immunotherapy, 29.8% for irAEs management. 11 (10.9%) pts discontinued treatment due to irAEs. At the time of data analysis, 86.8% of irAEs had improved. With a median follow-up of 8.9 [0-48.2] months, median OS was superior in pts experiencing irAEs: not reached vs 9.9 months (p = 0.0011). Similarly, PFS was significantly longer: 6.2 [95%CI: 2.3-10.1] vs 2.7 [95%CI: 1.8-3.5] months (p < 0.0001). OS was higher in pts who didn’t receive steroids during ICIs: NR vs 9.9 [95%CI: 6.4-13.0] months (p = 0.024). No association was found between efficacy and the use of antibiotics in the 3 months before first ICIs injection or during treatment.

Conclusions: Development of irAEs was associated with efficacy of ICIs in pts with advanced NSCLC. A negative correlation between the use of systemic corticosteroids and outcomes was found.

Legal entity responsible for the study: Medical Oncology Department, Hospital de la Santa Creu i Sant Pau.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1410P Tumor mutation burden (TMB) estimation using small-sized targeted next-generation sequencing (NGS) to predict efficacy of immune-checkpoint inhibitors (ICIs) for non-small cell lung cancer (NSCLC)

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Background: TMB is promising as a biomarker for the treatment with ICIs. However, because it is difficult to apply whole exom-based TMB analysis into the current practice, clinically-applicable simple methods for estimating TMB are needed. The aim of this study was to evaluate TMB based on a small-sized targeted NGS as a biomarker for ICIs.

Methods: Since March 2015 to April 2017, a total of 2243 NSCLC patients (pts) from 244 institutions were enrolled in our large-scale nationwide genome screening network (LC-SCRUM-Japan). Tumor samples were subjected to a 260 kb-sized NGS assay, Oncomine Comprehensive Assay (OCA) ver.1, targeting 143 cancer-related genes. TMB, number of somatic mutations/Mb, was assessed from the results of OCA ver.1 assay, and a cut-off point of TMB to predict response to ICIs was determined by ROC curve. Clinico-genomic database of LC-SCRUM-Japan was utilized for this analysis.

Results: 470 NSCLCs, consisting of 359 adenocarcinomas, 73 squamous cell carci- mas and 38 others, were evaluated in this study. The median number of mutations was 15.3/Mb (range, 0.130-6.8Mb). We defined number of mutations ≥15.4 Mb as high TMB and <15.4/ Mb as low TMB. High TMB was observed 34.3% (123/359) in adenocarcinoma and 41.1% (30/73) in squamous cell carcinoma. The response rate was higher in pts with high TMB than in those with low TMB (13.3% [29/217] vs. 5.7% [7/ 201], p = 0.0059). The durable clinical benefit (DCB; complete response, partial response or stable disease that lasted >6 months) rate also tended to be higher in pts with high TMB than in those with low TMB (17.3% [38/217] vs. 11.4% [35/297], p = 0.0980). The progression-free survival (PFS) was not significantly different between the high and low TMB pts (median PFS, 4.4 vs. 3.3 months, p = 0.1401).

Conclusions: TMB estimated by OCA ver.1 seemed to be correlated with response rate and DCB but not PFS in NSCLC pts treated with ICIs, suggesting a limitation of TMB estimation by this small-sized targeted NGS as a biomarker of ICIs. Optimal TMB estimation to predict the efficacy of ICIs are warranted.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1411P Identification of genomic markers of sensitivity and resistance to checkpoint inhibitors in non-small cell lung cancer in a real world clinico-genomic database

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Background: Treatment of non-small cell lung cancer (NSCLC) with checkpoint inhibitors (CI) that block the PD-L1 pathway has resulted in profound responses but only in a subset of patients. Our aim was to examine biomarkers associated with response and resistance to CI in advanced NSCLC to help inform patient stratification.

Table: 1408P

<table>
<thead>
<tr>
<th>Factor</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
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<td>Smoking yes vs no</td>
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<td>Histology squamous vs adenocarcinoma</td>
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<td>Number of organs with metastases &gt; 2 vs ≤ 2</td>
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<td>Immuno line &gt; 2 vs ≤ 2</td>
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<tr>
<td>Use of corticosteroids at ICI start yes vs no</td>
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<td>0.19</td>
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<tr>
<td>BM symptomatic at start yes vs no</td>
<td>0.61 (0.3-0.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Ds-GPA 1.5-2.5 vs 0-1 | 0.061 \(0.29-0.66\) | 0.05 | 0.21-1.21 | 0.0003 |
HLA-Orb1 heterozygosity and early auto-antibody rise predict prolonged survival in metastatic NSCLC patients undergoing PD-1 blockade

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Background: PD-1/PDL1 blockade by nivolumab is a promising and efficacious treatment for mNSCLC patients who showed early rise (within thirty days) of one (score 1, HR 0.235, 95%CI: 0.081-0.624, P = 0.001). Finally, Cox analysis revealed a predictive role for treatment-related early increase in eosinophil cell counts (OS, HR 0.68, 95% CI: 0.57-0.81, P = 0.031).

Conclusions: Heterozygosity in the HLA-Orb1 locus and early rise in patient response (DCR > 90%) associated with prolonged survival period (OS). Patients with a high level of eosinophil cell counts had a better survival outcome. These results offer a strong rationale to design future immunotherapy trials in NSCLC patients.

Legal entity responsible for the study: Grande Ospedale Metropolitano “Bianchi-Melacrino-Morelli”, Reggio Calabria, Italy.

Disclosure: All authors have declared no conflicts of interest.

Methods: We examined 820 lung adenocarcinoma (LUAD) samples that had matched PD-L1 staining and received genomic profiling to measure tumor mutational burden (TMB) and genomic alterations in 315 genes (FM cohort). We also examined progression-free survival (PFS) of 1310 CI-treated patients in a HIPAA compliant, real-world clinogenomic database (CGDB). These patients received the FoundationOne assay as part of routine care and had electronic health record data available in the Flatiron Health Database (Singal, ASCO 2017).

Results: In the CGDB, we observed known associations between likelihood of PFS and TMB, loss of STK11. TMB correlated with median PFS in months (mPFS): TMB > 20 mutations per Mb (N = 164) – 6 mo vs TMB ≤ 20 (N = 1146) – 2.8 mo, P = 0.007. Patients with STK11 loss had reduced mPFS (wt 3.1 mo vs mut 2.5 mo, P = 0.001). We also analyzed PDL1 negative staining (FM cohort: P = 0.6-3.5) and the EGFR cohort had reduced mPFS (CGDB: wt 3.5 mo vs mut 2.4 mo, P = 0.003). Samples with MET exon 14 skipping mutations were enriched for PDL1 high positive staining (FM: P = 2.3e-5), but the MET cohort had similar mPFS (CGDB: wt 3.5 mo vs mut 2.7 mo, P = 0.8). Samples with BRAF alterations trended towards both PDL1 high positive staining (FM: P = 0.06) and increased mPFS (CGDB: wt 2.9 mo vs mut 4.6 mo, P = 0.2).

Conclusions: We examined PFS of NSCLC patients on CI therapies in a clinogenomic database and observed known associations with TMB, STK11 and EGFR alterations. We were not able to find a correlation between TMB and PFS or other marker, possibly due to the small size of the patients who did not have enhanced mPFS despite increased PDL1 expression levels, suggesting dual or targeted therapies. Real-world datasets such as the CGDB hold promise in prioritizing therapies and identifying biomarkers that work in parallel.

Legal entity responsible for the study: Foundation Medicine Inc., Cambridge, Massachusetts, United States of America.

Funding: Foundation Medicine Inc., Cambridge, Massachusetts, United States of America.

**Annals of Oncology**


**1415P** Association between early immune-related adverse events and clinical outcomes in patients with advanced non-small cell lung cancer treated with pembrolizumab as first-line therapy: A retrospective multicenter cohort study


**Background:** Previous studies have shown that early immune-related adverse events (irAEs) are associated with better outcomes in patients with advanced non-small cell lung cancer (NSCLC) who received nivolumab, and the associations differ among various types of early irAEs. However, these previous studies included patients regardless of their PD-1 status and lines of therapy.

**Methods:** We retrospectively analyzed patients with advanced NSCLC and PD-L1 TPS of ≥ 50% who received pembrolizumab as the first-line therapy at 10 institutions between February 2017 and January 2018. Patients were excluded if they were treated with systemic glucocorticoids or other immunosuppressive agents. Early irAEs were defined as irAEs that occurred within 3 weeks after commencing pembrolizumab with systemic glucocorticoids or other immunosuppressive agents. Early irAEs were defined as irAEs that occurred within 3 weeks after commencing pembrolizumab therapy.

**Results:** In total, 145 patients were included; their median age was 71 (range: 39-87) years. Of the 145 patients, 122 (84%) were men, 119 (82%) had PS 0-1, and 5 (3%) had their PD-1 status and lines of therapy.

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**Conclusion:** Early development of rash and pyrexia was strongly associated with better clinical outcomes.

**Clinical trial identification:** UMIN000032470

**Legal entity responsible for the study:** Hanshin Oncology clinical Problem Evaluation group (HOPE).

**Funding:** Has not received any funding.

**Disclosure:** D. Fujimoto, M. Tamizu, A. Tamizah, K. Hirao: Speaking fees: MSD; T. Yokoyama: Speaking fees: MSD. All other authors have declared no conflicts of interest.

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**1416P** Immunoensenseness (ÎSeness) correlates with disease progression in advanced non-small cell lung cancer (aNSCLC) patients treated with PD-L1 inhibitors (iO)


**Background:** Previous studies have shown that early immune-related adverse events (irAEs) are associated with better outcomes in patients with advanced non-small cell lung cancer (NSCLC) who received nivolumab, and the associations differ among various types of early irAEs. However, these previous studies included patients regardless of their PD-1 status and lines of therapy.

**Results:** In total, 145 patients were included; their median age was 71 (range: 39-87) years. Of the 145 patients, 122 (84%) were men, 119 (82%) had PS 0-1, and 5 (3%) had their PD-1 status and lines of therapy.

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**Legal entity responsible for the study:** Hanshin Oncology clinical Problem Evaluation group (HOPE).

**Funding:** Has not received any funding.

**Disclosure:** D. Fujimoto, M. Tamizu, A. Tamizah, K. Hirao: Speaking fees: MSD; T. Yokoyama: Speaking fees: MSD. All other authors have declared no conflicts of interest.

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**1417P** Preliminary results of PRINCIpe (predictors of resistance to Immunotherapy with nivolumab [NIv]) study in advanced pretreated non-small cell lung cancer (APNCC) investigating the role of an immune genomic signature (IGS) including JAK2, JAK3, PIAS4, PTNP2, STAT3, IFNAR2 alterations


**Background:** Although immunotherapy impressively improved the outcome of APNCC, many patients (pt) rapidly progress. The mechanism of resistance may be influenced by genomic abnormalities in immune-scape/editing genes.

**Methods:** DFKE tumor-blocks of APNCC pts undergone Niv were retrospectively sequenced for Somatic Mutations/Copy Number Variations (SM/CNV) (Ampliseq 17 genes customized panel: APLNR, RIM, IFNAR1, IFNAR2, JAK3, JAK2/STAT3 SM (2 pts, 8.3%) were the most frequent abnormalities. Pts (12) with JAK5, PIAS4, PTNP2, STAT3, IFNAR2 SM and/or JAK2/3 CNV (IGS+) had a significantly lower OS/PFS than those without (IGS-). At multivariate analysis, IGS+ was independently associated with shorter OS (HR 4.90, 95% CI 1.40-16.5, p = 0.01) and PFS (HR 6.10, 95% CI 2.0-18.7, p = 0.001), the (previous) surgery was significantly associated
Progress in immunotherapy has led to new therapeutic guidelines. We
Conclusions: The derived IGS appears to identify APNSCLC pts with a lower chance to benefit from NIV, supporting intrinsic resistance. Given the small sample, a prospective larger and external validation is ongoing.
Legal entity responsible for the study: Emilio Bria.
Funding: University of Verona.
Disclosure: All authors have declared no conflicts of interest.

The need of re-biopsy: Increase in PD-L1 expression from initial stage to recurrence of non-small cell lung cancer

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Background: Non-small cell lung cancer (NSCLC) has the highest mortality rate of all cancers worldwide. Developments in oncological therapy have led to new therapeutic guidelines including immunotherapy such as PD-1/PD-L1 inhibitors. However, PD-L1 expression in tumor cells might be a dynamic process explaining variability in PD-L1 expression. To test the hypothesis of PD-L1 conversion in patients presenting with NSCLC we evaluated PD-L1 expression in initial tumor samples as well as at recurrence.

Methods: We retrospectively examined PD-L1 expression in resected specimens of patients with NSCLC as well as in biopsies at recurrence by immunohistochemistry (IHC). Patients presenting NSCLC recurrence after adjuvant chemotherapy and with no adjuvant chemotherapy were included. IHC score was defined as the proportion of tumor cells with stained cell membrane. Migration of IHC group was considered as a significant change in PD-L1. Four IHC score groups were defined: TCO < 1%, TCO ≥ 1% < 5%, TC2 ≥ 5% and TC3 ≥ 50%.

Results: In total, 36 patients were included. All patients presented adenocarcinoma. 20 patients (56%) underwent adjuvant chemotherapy after surgical resection and 16 patients (44%) had no adjuvant chemotherapy. Initial PD-L1 expression was present in 10 out of 36 patients corresponding to 28%. Out of 20 patients receiving adjuvant chemotherapy 7 patients (35%) showed significant upregulation in PD-L1 expression at recurrence. In comparison to patients with no adjuvant therapy, where only 2 out of 16 (12.5%) showed significant change in PD-L1 expression. Furthermore, 6 out of 36 patients (17%) were PD-L1 negative and had become positive at NSCLC recurrence.

Conclusions: Progress in immunotherapy has led to new therapeutic guidelines. We demonstrated that chemotherapy might increase PD-L1 expression in NSCLC specimens. These findings suggest that chemotherapy in combination with immunotherapy might constitute a new therapeutic strategy for locally advanced NSCLC. Furthermore, in about 17% of our patients, the initial tumor sample proved PD-L1 negative, but a significant change in PD-L1 expression at tumor recurrence was demonstrated. This might suggest the use of PD-L1 inhibitors in first line therapy, even if PD-L1 expression is not present at time of diagnosis.

Legal entity responsible for the study: Alessandra Curioni-Fontecedro.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

Basal lymphopenia as a potential predictor of benefit from immunotherapy in metastatic non-small cell lung cancer

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Background: Immunotherapy (IO) is an established treatment (tx) option for metastatic non-small cell lung cancer (mNSCLC). Nonetheless, as only a minority of pts shows tumor response, research is focusing on identification of predictive factors to improve pts’ selection. The potential role of blood cell count alterations has been proposed, but evidence is contradictory. We aimed at studying the role of lymphopenia in a cohort of mNSCLC pts treated with IO.

Methods: We retrospectively collected data about all mNSCLC pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, from 04/2013 to 02/2018. Basal lymphopenia (L) was defined as a lymphocyte count (LC) <900/mL at the first administration of IO and was considered as a categorical variable. Survival was estimated with Kaplan-Meier method; log-rank test was used to compare curves. Multivariate analyses were performed with Cox proportional model.

Results: We identified 150 pts, with a median age of 66.5 years. IO was an anti-PD1 in 64.0% of cases, an anti-PD-L1 in 31.3% of cases, and a combination anti-PD-L1/CTLA4 in 4.7% of cases. IO was administered as a first line in 23 pts, as a second line in 66 cases, as a more advanced line of tx in 61 cases. Median progression free survival (PFS) and overall survival (OS) of the global population were 3.2 and 11.2 months (mos), respectively. Though non-statistically significant, there was a tendency towards a lower response rate (RR) for cases with basal L (0.10 vs 0.25%, p=0.881), disease control rate (DCR) for the same group was significantly worse (30.0% vs 38.4%, p=0.074) than for cases without L. Pts with L also showed shorter PFS and OS than cases with normal LC (PFS 1.9 vs 3.0 mos, p=0.011; OS 4.4 vs 13.3 mos, p<0.001). The impact of LC on OS retained significance after correction for the effects of performance status, which was the only other variable influencing this endpoint.

Conclusions: The presence of L at the beginning of IO was related to inferior disease control and shorter survival in the analyzed cohort. Given the limitations of a retrospective study, these results need confirmation in larger case series. Nonetheless, the suggestion that L may predict poor benefit from IO in mNSCLC warrants further investigation.

Legal entity responsible for the study: Istituto Nazionale dei Tumori.
Funding: Has not received any funding.
1421P Clinical characterization of rare EGFR mutations in non-small cell lung cancer and in silico prediction of drug sensitivity

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Background: Recent genome scale characterization of cancers identified overwhelming numbers of novel, rare and uncharacterized somatic mutations, variance of unknown significance (VUS), in non-small cell lung cancer (NSCLC). In order to make these VUS data clinically useful, further functional and biological characterization of each mutation is mandatory. In addition, development of novel strategies to overcome mutation diversity of lung cancer is needed.

Methods: Using the large-scale prospective cohort data of the LC-SCRC-Japan, nationwide lung cancer clinical and the genomic characterization network in Japan, we characterized the frequency and distribution of rare EGFR mutations in NSCLC and the clinical course of the patients harboring these mutations. In addition, to perform functional and biological characterization of each mutation, we created a Ba/F3 EGFR minor mutation library. Furthermore, the in silico sensitivity prediction model has been developed to demonstrate binding affinity of protein and drug compound and applied to EGFR tyrosine kinase inhibitor with mutated EGFR.

Results: Of the 2164 NSCLC patients examined by LC-SCRC-Japan, 113 (5.2%) harbored rare EGFR mutations. We found the diverse distribution of EGFR mutations throughout the gene, the most frequent group included EGFR exon 20 insertion mutations (52 cases). We clarified the sensitivity profile of the VUS to EGFR tyrosine kinase inhibitors. Binding affinities calculated by in the silico sensitivity prediction model showed statistically significant correlation (R2 = 0.7425, p < 0.005) with the IC50 values.

Conclusions: These data may help in choosing or predicting the appropriate inhibitor for lung cancer with VUS in EGFR, thereby contributing to the further development of precision medicine. Here, we clarified the diversity of VUS in EGFR and provide novel insights, via supercomputer utilized drug sensitivity prediction, in the cancer field.

Legal entity responsible for the study: Keio University School of Medicine.

Disclosure: All authors have declared no conflicts of interest.

1422P Evolution and clinical impact of EGFR mutations in circulating free DNA in the BELEIF trial

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Background: BELEIF, a single-arm, phase 2 trial, showed a median (md) progression-free survival (PFS) of 13.2 months (m) with erlotinib and bevacizumab in patients (pts) with advanced EGFR mutated NSCLC (Rosell et al 2017). We prospectively and longitudinally examined the evolution of sensitizing EGFR and p 7970M mutations, in circulating free DNA (cfDNA).

Methods: Blood samples were collected at baseline (BaS), at time of response (4w) and at progression (PD) and sent to a central laboratory. cfDNA was purified, and EGFR mutations were analyzed with real-time PCR assay. The fully validated assay is highly specific (>99%) and sensitive (76%) for EGFR sensitizing mutations.

Results: As of 12 March 2018, at a med follow-up of 47m (IQR: 42, 59), 2 pts (2%) are still on full protocol treatment, while 95 PFS events (87%) and 76 deaths (64%) have occurred. The med PFS is 13.2m (95% CI: 10.3, 15.5), the med overall survival (OS) is 30.2m (95% CI: 23.1, 39.6) and the 2-year OS is 58.4% (95% CI: 48.2-67.2%). cfDNA are available at BaS for 91 pts, at 4w for 72 pts and at PD for 58 pts. EGFR mutations identified in blood were also originally found in tissue. 69 pts had cfDNA assessment both at BaS and 4w. Med PFS was 19 for 24 pts without EGFR mutations in cfDNA at BaS and at 4w, versus 12.6m for 43 pts with EGFR mutations detected in cfDNA at BaS, but not at 4w (p = 0.019). 46 pts had the 3- pronged assessments (BaS, 4w, PD). The med PFS for the BaS negative group that remained negative at PD was 17.4m (12 pts), while for the BaS positive group that converted to negative at 4w and remained negative at PD was 13.1m (7pts; p = 0.72). For those BaS positive who converted to negative at 4w, but later became positive again at PD, the med PFS was 16.0m (p = 0.20). At PD, 41% of pts harbored T790M. For pts with EGFR mutations at BaS, the med PFS was 13.4m (16 pts) in those without T790M, and 9m (17 pts) for the T790M mutated at PD (p = 0.14).

Conclusions: These data suggest the absence of sensitizing EGFR mutations in cfDNA at BaS confers significantly better PFS and OS. The diversity of VUS in EGFR and a trend of shorter PFS is seen in the subgroup of pts with BaS EGFR mutant cfDNA, from whom, at PD, EGFR mutations were again detected. EGFR mutant cfDNA could be an indicator for on-going oncogenic events and the use of cfDNA exome platforms should be encouraged.

Clinical trial identification: NCT01626028.

Legal entity responsible for the study: European Thoracic Oncology Platform (ETOP).

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1423P Pre-treatment EGFR-T790M subclones in lung adenocarcinoma harboring activating mutation of EGFR: A positive prognostic factor for survival?

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Background: In lung adenocarcinoma, activating mutation of EGFR (aEGFR) and EGFR-T790M can coexist. T790M confers resistance to 1st and 2nd generation TKIs, the standard 1st line treatment. T790M may also be observed at diagnosis (preT790M) in 0.3-3% cases using standard techniques and up to 30% with highly sensitive techniques. FDA and EMA approved osimertinib, a 3rd generation TKI overcoming T790M resistance, for 2nd line in patients T790M +. Recently it was proved that T790M is not always a marker of a true preT790M & wild-type for T790M (WT), detecting T790M with a highly sensitive technique.

Methods: We selected aEGFR + lung adenocarcinoma who received 1st or 2nd generation TKI in 1st line treatment in our Institution. We reanalyzed the tumor samples of the diagnosis with RainDrop Digital PCR. For statistical analysis we used Kaplan-Meier method and log-rank test.

Results: We analyzed tumor samples of 28 subjects. At diagnosis, all were wild-type for T790M with standard techniques. With RainDrop Digital PCR, preT790M + were 28,6% (n = 8). In ≥ 2 preT790M + and 30% of WT received osimertinib,
The plasma ctDNA monitoring during epidemiological growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in patients with EGFR mutant non-small cell lung cancer (JP-CLEAR trial)

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Background: The EGFR mutations are a target for treatment of non-small cell lung cancer (NSCLC). The detection of EGFR mutations in tumor tissues and plasma ctDNA is important for selecting patients who can benefit from EGFR-TKIs. The aim of this study was to evaluate the clinical usefulness of plasma monitoring using ctDNA during the EGFR-TKI treatment.

Methods: A total of 1291 plasma samples from 121 patients were analyzed for EGFR mutations using the i-densyTM genetic testing platform. All patients received gefitinib (50 mg). The primary endpoint was median progression-free survival (PFS) and the secondary endpoint was overall survival (OS).

Results: The ORR for low-dose gefitinib in the 48 patients was 62.5% (CR/PR/SD/PD cases were 701/737/590, p = 0.241). Median PFS was 10.4 months for preT790M and 13.3 months for WT (p = 0.721). In the re-biopsied materials from the patients who participated in this trial, T790M was detected in 14 patients (19.0%). The clinical benefit of gefitinib treatment was significantly higher in patients with preT790M (89% vs. 100% for WT, p = 0.098).

Conclusions: The ctDNA monitoring during the EGFR-TKI treatment is useful for selecting patients who can benefit from EGFR-TKI treatment.

Legal entity responsible for the study: University of Pisa, Italy.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1425P

ABC1 genetic polymorphism and pharmacokinetic analysis of low-dose erlotinib in frail patients with EGFR mutation (mt)-positive, non-small cell lung cancer: TORIG1425

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Background: We conducted a trial evaluating the efficacy of low-dose erlotinib (ERL) in frail patients with EGFR-mt small non-cell lung cancer (NSCLC). The primary endpoint was the objective response rate (ORR) of 60% (2018 ASCO Abstr. 904). Previously, it has been reported that ABC1 genetic polymorphisms affect pharmacokinetics (PK) of ERL and associated adverse events. We investigated ERL plasma concentration and efficacy, as well as the effects of ABC1 genetic polymorphisms in the patients who participated in this trial.

Methods: Frail patients with EGFR-mt NSCLC who had not undergone chemotherapy were enrolled and administered 50 mg of ERL. Blood samples were collected prior to treatment for ABC1 genetic polymorphism testing and at 15 days (+7 days) after initiating ERL administration to measure steady-state trough values. The samples were analyzed at the central laboratory. Plasma concentration was measured with a high-performance liquid chromatography tandem mass spectrometry and ABC1 gene polymorphism analysis using the i-denstYTM testing platform.

Results: Of the patients who participated in the study (n = 48) from October 2017 to April 2018 (n = 80), ERL plasma concentration could be measured in 48 patients (males: females 17:31; median age 81 (range 49-90); PS 0-1:2-3: 4-5;7/6) and genetic analysis in 45 patients. The ORR for low-dose ERL in the 48 patients was 62.5% (CR/PR/SD/PD cases were 701/737/590, p = 0.435. Genetic polymorphisms were not correlated with ERL PK, nor were they associated with diarrhea (p = 0.202) or rash (p = 0.29) by Mann-Whitney test.

Conclusions: In this trial, no clear correlation was observed between ERL PK and efficacy. In frail patients, low-dose ERL administration of 50 mg is effective and safe, regardless of ABC1 genetic polymorphisms.

Clinical trial identification: UMIN000015949, release date: 2014/12/15

Legal entity responsible for the study: NPO Thoracic Oncology Research Group.

Funding: Has not received any funding.

Disclosure: T. Toktiko: Chugai Pharmaceutical (research funding), AstraZeneca (research funding), MSD (research funding). A. Besho: Chugai Pharmaceutical Co. (honoraria), H. Tanaka: AstraZeneca (research funding, honoraria), Ono Pharmaceutical (research funding, honoraria), Chugai Pharma (research funding, honoraria), Boehringer Ingelheim (honoraria), MSD (research funding, honoraria), Lilly (research funding, honoraria), Taiho Pharmaceutical (research funding, honoraria), Bristol-Myers Squibb Japan (research funding, honoraria), Pfizer (research funding, honoraria), Novartis (honoraria), Takeda (research funding), Astellas Pharma (research funding), Merck Serono (research funding). T. Fukui: AstraZeneca K.K. (honoraria), Boehringer-Ingehelm Japan Inc. (honoraria), Chugai Pharmaceutical Co. Ltd. (honoraria), Novartis Pharma K.K. (honoraria), Ono Pharmaceutical Co. Ltd. (honoraria), Pfizer Japan Inc. (honoraria), Taiho Pharmaceutical Co. Ltd. (honoraria), Y. Hosomi: AstraZeneca (honoraria), Taiho Pharmaceutical (honoraria), Lilly Japan (honoraria), Chugai Pharma Onco Pharmaceutical (honoraria), Bristol-Myers Squibb Japan (honoraria), MSD (honoraria). K. Yamada: Pfizer Japan (honoraria), Chugai Pharmaceutical (honoraria), EL Lilly Japan (honoraria), Astarea Zeneca (honoraria), Ono (honoraria). H. Okamoto: Takeda (research funding), MSD (research funding), Ono (research funding), AstraZeneca (research funding), Merck (research funding), Chugai (research funding), Taiho (research funding), Bristol-Myers Squibb (research funding), EL Lilly (research funding), Daich Sankeyo (research funding). All other authors have declared no conflicts of interest.
1426P Longitudinal plasma monitoring of subjects treated with EGFR-TKIs allows better understanding of evolution of acquired resistance and can inform optimal treatment strategies


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Background: Targeted therapy (EGFR tyrosine kinase inhibitors, EGFR-TKIs) has been proven effective in NSCLC patients with activating EGFR mutations. Despite the initial response, most patients progress. Several acquired-resistance mutations have been described, including the EGFR T790M mutation. Here we use longitudinal plasma monitoring to identify different mechanisms of acquired resistance to EGFR-TKIs and demonstrate that tumor heterogeneity and clonal evolution may play a role in the outcome of subjects treated with osimertinib.

Methods: Tumor and plasma were collected from 13 subjects with metastatic lung adenocarcinoma treated with erlotinib followed by osimertinib, upon the development of resistance (T790M positive). Overall, 10 FFPE tumor and 115 longitudinally collected plasma specimens were analyzed with either the FDA-approved cobas® EGFR Mutation Test v2 or a 197-gene NGS assay (AVENIO ctDNA Surveillance Kit and Hospital, Hangzhou, China, 3Key Laboratory on Diagnosis and Treatment Technology, Zhejiang Cancer Hospital, Hangzhou, China, 4Clinical Science, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, 5Clinical, Roche Sequencing Solutions, Inc., Pleasanton, CA, USA, 6Biometrics, Roche Sequencing Solutions, Inc., Potsdam, Germany, 7Biomarcs, Roche Sequencing Solutions, Inc., Potsdam, Germany, 8Clinical Operations, Roche Sequencing Solutions, Inc., Potsdam, Germany, 9Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, 10Clinical-Biochemistry, Aarhus University Hospital, Aarhus, Denmark

Results: The concordance of EGFR mutations (L858R, T790M, Ex19Del) detected by EGFR and non-EGFR mutations were correlated with disease control (evaluated by RECIST 1.1).

Legal entity responsible for the study: Roche.

Funding: Roche.

Disclosure: J. Palma, N. Tkok, L. Xi, S. Young, E. Kwek, A. Lovejoy, P. Vitazka, A. Balasubramaniam, K. Probst, P. Meldgaard, P. Sorensen, M. Meldgaard. This study was supported by Roche Sequencing Solutions, Inc., Pleasanton, CA, USA.

1427P Applicability of lung-molGPA index in non-small cell lung cancer patients with various gene alterations and brain metastases

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Background: The Lung-molGPA index is based on the original Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) by incorporating recently reported gene alteration data for non-small cell lung cancer (NSCLC) patients with brain metastases (BM). Hence, the prognostic prediction value of DS-GPA and Lung-molGPA model remains undetermined, especially in patients with different molecular types.

Methods: A total of 1184 NSCLC patients with BM analyses for clinical factors and outcomes were identified at Zhejiang Cancer Hospital, China. All prognostic factors were weighted for significance by hazard ratios. The applicability of DS-GPA and Lung-molGPA were reappraised in NSCLC patients with BM and various genetic profiles. Additionally, a modified Lung-molGPA, was newly developed for mutant NSCLC patients.

Results: The NSCLC patients in the present study had a median survival of 14.0 months from the time of BM diagnosis. Both DS-GPA and Lung-molGPA models could predict the outcomes (P < 0.001), while Lung-molGPA model appeared to exhibit better accuracy. Furthermore, Lung-molGPA scores exhibited a discrimination capability in patients with gene variations (5.3-4.0 vs 2.5-3.0 vs 1.5-2.0 vs 0.1-0.0 > 62.0 vs 32.0 vs 17.7 vs 13.2 months, P < 0.001). However, no significant difference was reached in wild-type patients (P = 0.133). Regarding the oncopositive NSCLC patients with BM, a modified Lung-molGPA index had been established derived from the prognostic factors with the C-index of 0.73 (95% CI: 0.73-0.80) to accurately calculate the survival probability (P < 0.001).

Conclusions: In an era of precision medicine, the Lung-molGPA could precisely predict the prognosis of mutant NSCLC patients with BM, while not working in wild-type patients.

Legal entity responsible for the study: Yun Fan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1428P Testing for and frequency of molecular alterations in patients with advanced NSCLC in Germany. Results from the prospective German registry CRISP (AIO-TRK-0315)

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Background: Several therapies targeting molecular alterations in subgroups of NSCLC patients (pts) have been approved and require pts to be tested for these targets. Through knowledge of the diagnostic and therapeutic algorithm in routine practice is crucial to evaluate and improve the quality of care.

Methods: The prospective, national clinical research platform CRISP recruits pts in currently 149 representative cancer centres in all therapeutic sectors in Germany. Up to 8000 pts will be recruited and followed until death or up to a maximum of 3 years, respectively. Data from 823 pts recruited by 89 centers by June 30th, 2017 was analysed regarding molecular testing. An update with data cut June 30th, 2018 including at least 2,000 pts by 130 centres will be presented at the conference.

Results: Median age was 67 years and 61% of pts were male. 12% of pts were never smokers. 79% of pts had non-squamous carcinoma (nsqc), 21% squamous carcinoma (scc). Overall 84% (nsqc 92%, scc 52%) of pts were tested with at least one test method at the start of treatment. Median turn around time was 2 weeks for next generation sequencing (NGS), 10 days for FISH and one week for other sequencing and IHC. In pts with nsqc (n = 633) 32% of pts were tested by NGS, 45% by other sequencing and 4% by IHC and 38% by FISH. Molecular test rates for EGFR, ALK, and ROS-1 were 73%, 70%, and 53% respectively. In pts with scc (n = 170) 12% of pts were tested by NGS, 11% by other sequencing, 34% by IHC and 10% by FISH. Molecular test rates for EGFR, ALK, and ROS-1 were 23%, 21%, and 15%, respectively. Test rates for PD-L1 increased from 23% in 2016 to 48% in the first half of 2017. For pts with nsqc for whom test results were available at time of analysis, an EGFR alteration was detected in 15% (n = 71), an ALK alteration in 8% (n = 37), and a ROS-1 alteration in 3% (n = 10) of pts. 24% (n = 65) of pts for whom PD-L1 tumour proportion score (TPS) results were available had a TPS ≥50%.

Conclusions: CRISP presents current real life data on molecular testing from all treatment sectors in Germany. Pts are frequently tested for molecular alterations. NGS is used in one third of nsqc pts. Reasons for testing / non-testing and changes over time will be discussed based on the 2018 data cut.

Clinical trial identification: NCT02622581.

Legal entity responsible for the study: AIO-Studien gGmbH.

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Disclosure: All authors have declared no conflicts of interest.
Cell-free circulating tumour DNA (ctDNA) in the management of patients with non-small-cell lung cancer (NSCLC)

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Background: Cell-free circulating tumour DNA (ctDNA) is a non-invasive and quick method of guiding personalised medicine. We assessed the utility of ctDNA in routine clinical practice when tumour biopsy was impossible to obtain, tissue insufficient or clinically contraindicated.

Methods: 71-gene panel using ctDNA NGS (Guardian; 800V) was offered to consecutive stage IV NSCLC patients - results were discussed in our Genomics Review Board to assess potential actionable alterations and enrolment into clinical trials.

Results: 50 pts (37F:13M; median 64 yrs) participated. ctDNA was obtained in 6 treatment (TX) have patients (pts), in 22pts post 1st-line, in 7pts post 2nd-line, in 5 pts post 3rd-line (range 1-94 months). New EGFR mutations were found in 3 pts with unknown EGFR status at Dx. ctDNA testing confirmed EGFRmt in 14 pts. In 9 pts with previously EGFR-mutant ctDNA without T790M mutation, 7 pts showed partial response after 6-16 weeks of osimertinib, 1 pt had complete response to osimertinib. EGFR T790M mutation was present in 6 pts (12/60; 20%). Overall response, complete response, progression-free survival were calculated by bivariable analyses. EGFR T790M mutation and MET amplification were also identified in two patients who showed primary resistance to osimertinib. The WES of osimertinib-resistant PDC revealed amplification of GLI1, CD9, and CD261D. The osimertinib-resistant PDC harboring PIK3CA H1047R mutation and MET amplification were established, and PIK3CA and MET inhibitors will be tested. The RNA-seq analysis showed upregulation of epithelial-mesenchymal transition signatures in P9-CGR-AR cells compared to P9-CGR cells that are potentially epigenetic resistance mechanisms.

Conclusions: Our multi-layered molecular analysis of osimertinib-resistant patients’ clinical samples and patient-derived cancer models demonstrates a diverse spectrum of osimertinib resistance mechanisms.

Legal entity responsible for the study: Byung Chul Choo.

Funding: Astrazeneca.

Disclosure: J.C. Barrett, D. Stetson, J. Chmielicki, A. Markovets: Employee: AstraZeneca. All other authors have declared no conflicts of interest.

Cell-free circulating tumour DNA (ctDNA) in the management of patients with non-biopsiable advanced non-small cell lung cancer (NSCLC)

M. Kushnir1, H. Winter2, C. Murias1, P. Bains3, Z. Abbas1, D. Papadatos-Pastos2, T. Newsome-Davis3, T. Ahmed2, C. Swanton5, M.D. Forster6, D. Moore7, P. Bennett8, M. Kushnir1, H. Winter2, C. Murias1, P. Bains3, Z. Abbas1, D. Papadatos-Pastos2, T. Newsome-Davis3, T. Ahmed2, C. Swanton5, M.D. Forster6, D. Moore7, P. Bennett8, J.R. Fischer1, S. Reiken1, F. Lasitschka2, H. Bischoff1, P. Schirmacher2, M. Thomas1, J. Christopoulos1, M. Kirchner2, F. Bozorgmehr1, V. Endris2, M. Elsayed1, N. Magios1, A. T. Voepel1, R. Perell1, J.F. Herr1, C.P. Heussel2, H. Winter2, T. Muley1, M. Masters4, J.R. Fischer1, S. Reiken1, F. Lasitschka2, H. Bischoff1, P. Schirmacher2, M. Thomas1, J. Christopoulos1, M. Kirchner2, F. Bozorgmehr1, V. Endris2, M. Elsayed1, N. Magios1, A. T. Voepel1, R. Perell1, J.F. Herr1, C.P. Heussel2, H. Winter2, T. Muley1, M. Masters4

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Background: Cell-free circulating tumour DNA (ctDNA) is a non-invasive and quick method of guiding personalised medicine. We assessed the utility of ctDNA in routine clinical practice when tumour biopsy was impossible to obtain, tissue insufficient or clinically contraindicated.

Methods: 71-gene panel using ctDNA NGS (Guardian; 800V) was offered to consecutive stage IV NSCLC patients - results were discussed in our Genomics Review Board to assess potential actionable alterations and enrolment into clinical trials.

Results: 50 pts (37F:13M; median 64 yrs) participated. ctDNA was obtained in 6 treatment (TX) have patients (pts), in 22pts post 1st-line, in 7pts post 2nd-line, in 5 pts post 3rd-line (range 1-94 months). New EGFR mutations were found in 3 pts with unknown EGFR status at Dx. ctDNA testing confirmed EGFRmt in 14 pts. In 9 pts with previously EGFR-mutant ctDNA without T790M mutation, 7 pts showed partial response after 6-16 weeks of osimertinib, 1 pt had complete response to osimertinib. EGFR T790M mutation was present in 6 pts (12/60; 20%). Overall response, complete response, progression-free survival were calculated by bivariable analyses. EGFR T790M mutation and MET amplification were also identified in two patients who showed primary resistance to osimertinib. The WES of osimertinib-resistant PDC revealed amplification of GLI1, CD9, and CD261D. The osimertinib-resistant PDC harboring PIK3CA H1047R mutation and MET amplification were established, and PIK3CA and MET inhibitors will be tested. The RNA-seq analysis showed upregulation of epithelial-mesenchymal transition signatures in P9-CGR-AR cells compared to P9-CGR cells that are potentially epigenetic resistance mechanisms.

Conclusions: Our multi-layered molecular analysis of osimertinib-resistant patients’ clinical samples and patient-derived cancer models demonstrates a diverse spectrum of osimertinib resistance mechanisms.

Legal entity responsible for the study: Byung Chul Choo.

Funding: Astrazeneca.

Disclosure: J.C. Barrett, D. Stetson, J. Chmielicki, A. Markovets: Employee: AstraZeneca. All other authors have declared no conflicts of interest.
Hybrid capture NGS reliably detects a spectrum of clinically significant genetic aberrations in both, primary diagnostics and the relapse scenario

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Background: The purpose of this study was to analyze the frequency and type of genetic alterations in tyrosine kinase inhibitor (TKI)-naïve vs. TKI-treated NSCLC patients. We report a spectrum of resistance mechanisms upon TKI treatment in liquid biopsies using a comprehensive hybrid-capture NGS test (HC-NGS).

Methods: We retrospectively collected mutational data of 200 solid NSCLC biopsies of treatment-naïve patients that were routinely tested for clinically relevant mutations by HC-NGS at our institution. In addition, we analyzed mutational data from 367 liquid biopsies of NSCLC patients whose disease progressed under treatment. Solid tumor biopsies and liquid biopsies were tested using a 39-gene HC-NGS panel including 39 clinically relevant genes (NEOselect, LOD 3.0%; NEOliquid, LOD 0.1%; NEO New Oncology GmbH, Cologne).

Results: Primary HC-NGS diagnostics in TKI-naïve patients revealed 12% (24/200) TKI-sensitive EGFR mutations, 5.0% (10/200) Alk/RON/RET translocations, 0.5% (1/200) BRAF V600E, and in one patient a MET Exon 14 skipping mutation (0.5%, 1/200). Further, a variety of clinically relevant mutations were detected, among others, prognostically relevant TP53 mutations at a frequency of 52.0% (104/200). In addition, we tested 367 liquid biopsies from relapse patients. 30.9% (113/367) pts had an activating EGFR mutation and therefore presumably received EGFR TKI treatment. Of the 113 pts, 39.8% (45/113) developed a T790M resistance mutation and 1.8% (2/113) an additional MET amplification.

Conclusions: HC-NGS allows for comprehensive analysis of somatic tumor aberrations in the primary diagnostic setting as well as in the relapse scenario. Mechanisms of primary oncogenic activation as well as mechanisms of resistance are heterogeneous and include point mutations, translocations and gene amplifications. Therefore, HC-NGS should be used for diagnosis in both, the primary and the relapse setting.

Legal entity responsible for the study: Hematopathology Hamburg.

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Prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in advanced non-small cell lung cancer

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Background: Metastatic non-small cell lung cancer (NSCLC) represents one of the biggest therapeutic challenges. Palliative chemotherapy (CT) is the first-choice treatment in patients without targetable mutations. Unfortunately, reliable markers predicting response to CT have not been found yet. Most of NSCLC cases arise and develop in a background of smoking-related chronic inflammation. Since neutrophils are the most prevalent immune cell type in NSCLC microenvironment we hypothesized that the nivicator of the inflammatory process such as the neutrophil to lymphocyte ratio (NLR) could have a prognostic or predictive value.

Methods: To evaluate the predictive and prognostic value of pretreatment NLR in NSCLC we analyzed data of the group of consecutive patients treated systemically for NSCLC at two institutions between January 2011 and December 2014. NLR was retrospectively calculated from the peripheral blood counts collected before therapy.

Multivariate Cox logistic regression was used to assess the relationship between NLR and treatment results after adjusting for age, gender, ECOG, and cigarette smoking. Based on available data we chose NLR $\geq 3$ as the cut-off level discriminating high (NLR $\geq 3$) vs low NLR.

Results: In the whole cohort (N = 204) with 184 patients (90%) being current or former smokers, 131 (64%) were male, 188 (92%) had a performance status (PS) 0 to 1, 93 patients (46%) had squamous cell cancer, 85 (42%) adenocarcinoma, and 26 (12%) other subtypes. Median age at diagnosis was 65 years (range 41 to 71.7 years). Platinum-based CT was administered in 92% of patients: cisplatin in 155 (76%), and carboplatin in 33 (16%) patients. NLR ranged from 2.04 to 4.62 (median = 3.02). Study groups created according to the NLR value were well balanced. There were 54 objective responses (26.5%) including 2 complete remissions. NLR was a significant and independent factor predicting response to treatment (OR 0.048, 95% CI 0.015–0.152, p < 0.001). Median survival in all patients was 12 months: 9.6 vs 13.2 months, respectively in NLR=3 vs NLR$\leq 3$ (p<0.001).

Conclusions: NLR$>3$ was correlated with worse outcomes, therefore might be useful for identifying patients unlikely to benefit from CT.

Legal entity responsible for the study: Renata Zaucha.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Bevacizumab as first-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC) in patients aged over 65 years in France: Final results of the AVANTAGE study


Funding: Roche S.A.S.


Background: NSCLC is frequent in elderly patients (pts), however there is limited information on the treatment of this population. This study describes the first-line treatment with bevacizumab (bev) of NSCLC elderly pts in real life in France.

Methods: AVANTAGE is a non-interventional, prospective, multicenter French study conducted in pts with advanced NSCLC, starting first-line chemotherapy (CT) with bev. It includes 2 cohorts, pts aged 65-70 (C1), or ≥ 70 (C2) . Data were collected at inclusion and every 3 months subsequently for 18 months. The primary objective was to describe CT used with bev in first-line in routine clinical practice.

Results: A total of 249 pts were eligible (277 included) in 68 centers: 108 (43%) in C1 & 141 (57%) in C2. They were predominantly men (75%), ECOG PS 0-1 (85%) PS 2 (15%), G8 questionnaire score ≥14 (35%), stage IV (96%), Charlson comorbidity index unadjusted ≤2 (63%), and brain metastases identified in 18% of pts overall, 20% of pts in C2. Platinum-based doublet CT and pemetrexed (pem) was the most used combination with bev in 186 (75%) pts overall - 81% of pts in C1 (62% cisplatin-pem and 18% carboplatin-pem) - 79% of pts in C2 (26% cisplatin-pem and 44% carboplatin-pem). The initial dose of bev with CT was 7.5 mg/kg/3wks in 79 pts of overall. Overall, maintenance treatment was administered to 61% pts, including 53% with bev (24% in monotherapy and 29% with pem). Maintenance was 64% in C1 and 62% in C2. Median PFS was 7.1 months, and median OS was 12.3 months (14.9 months in C1, 11.3 months in C2). Overall, 92% of pts presented at least 1 AE. Pts with grade ≥ 3 AEs related to bev were 12% in C1 and 24% in C2. In the safety population (260), 148 pts died during the study. pts (all in C2) died due to SAEs related to treatment (intestinal perforation, febrile neutropenia/septic shock/ thrombocytopenia; unknown cause).

Conclusions: AVANTAGE is the 1st prospective cohort conducted in routine clinical practice in France in elderly pts eligible for 1st-line CT with bev. The most frequently used treatment was the combination of platinum-pem doublet (75% of pts). Bev effectiveness as 1st line treatment in NSCLC was consistent with the efficacy observed in clinical trials in the elderly as was the safety profile.

Clinical trial identification: Clinical Trial Gov: NCT01893260.

Editorial acknowledgement: Dr Samia Rahal from ELTIM (French medical writing company).

Legal entity responsible for the study: Roche S.A.S.


Randomized phase II study comparing cisplatin + pemetrexed + bevacizumab with carboplatin + paclitaxel + bevacizumab in treatment-naïve advanced non-squamous non-small cell lung cancer (CLEAR study)

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Background: Bevacizumab (Bev) combined with platinum-based chemotherapy is a standard treatment for advanced non-squamous non-small cell lung cancer (non-Sq NSCLC). Cisplatin + pemetrexed (CisPem) is suggested as the most promising chemotherapy regimen combined with Bev. However, no study has been conducted to evaluate the efficacy and safety of CisPemBev compared with carboplatin + paclitaxel + bevacizumab (CarPacBev) for advanced non-Sq NSCLC.

Methods: Treatment-naïve patients with advanced or recurrent EGFR/ALK-negative non-Sq NSCLC from 55 sites across Japan were randomly assigned in a 2:1 ratio to either CisPemBev (4 cycles of Cis [75 mg/m²] + Pem [500 mg/m²] + Bev [15 mg/kg] q3wk, followed by maintenance Pem + Bev q3wk until progression) or CarPacBev (4 cycles of Car [AUC 6] + Pam [200 mg/m²] + Bev q3wk, followed by maintenance Bev q3wk until progression). The primary endpoint was progression-free survival (PFS) by central review. The secondary endpoints were overall survival (OS), overall response rate (ORR) and safety profile. The target numbers of patients and events were determined to be 210 and 170, respectively, to observe a point estimate of HR for PFS (CisPemBev/CarPacBev) < 0.83 with a high probability (80%) when the true HR was 0.72. The data were cutoff in July, 2017. OS data were updated for this presentation in April, 2018.

Results: Between May 2014 and May 2016, 199 patients were randomly assigned to receive CisPemBev (N = 132) or CarPacBev (N = 67). In the primary analysis, PFS events occurred in 171 patients. The HR for PFS by central review (CisPemBev/ CarPacBev) was 0.825 (95% CI 0.600-1.134, median PFS, 7.6 vs 7.0 months), and the ORR was 37% for CisPemBev and 55% for CarPacBev. OS events occurred in 119 patients. The median survival follow-up duration was 28.3 months. The median OS was 23.4 months for CisPemBev and 21.6 months for CarPacBev (HR 0.845, 95% CI 0.583-1.242).

Conclusions: PFS was prolonged with CisPemBev compared with CarPacBev. However, there was no difference in OS between two arms. CisPem is the most effective chemotherapy regimen combined with Bev for advanced non-Sq NSCLC.

Legal entity responsible for the study: National Cancer Center Hospital East.

Funding: Chugai Pharmaceutical.


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Annals of Oncology
Phase I dose expansion data for M6620 (formerly VX-970), a first-in-class ATR inhibitor, combined with gemcitabine (Gem) in patients (pts) with advanced non-small cell lung cancer (NSCLC) by R. Plummer1, N. Cook2, T. Arkenau3, J. Meletis4, C. Redfern4, A.I. Spira5, K. Chung5, T. Haddad1, S.S. Ramalingam5, R. Wesolowski5, E. Dean1, T. Goddemeier5, M. Falk5, G. Shapiro5 1Northwestern Center for Cancer Care, Freeman Hospital, Newcastle Upon Tyne, UK; 2Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; 3Medical Oncology, Sarah Cannon Research Institute, London, UK; 4Medical Oncology, Texas Oncology, Midtown, Austin, TX, USA; 5Clinical Oncology Research, Sharp Memorial Hospital, San Diego, CA, USA; 6Virginia Cancer Specialist, Fairfax, VA, USA; 7Hematology/Oncology, Greenville Health System, Greenville, SC, USA; 8Mayo Clinic, Rochester, MN, USA; 9Department of Hematology and Medical Oncology, Emory University Winship Cancer Institute, Atlanta, GA, USA; 10Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; 11Medical Oncology, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; 12Department of Medical Oncology, Darmstadt, Germany; 13Global Research & Development, Merck Germany, Darmstadt, Germany; 14Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background: Ataxia telangiectasia and Rad3-related protein (ATR) is an essential DNA damage response regulator, and is required for proliferating cell survival. DNA-damaging agents often induce replicative stress leading to activation and reliance on ATR; inhibition of ATR signals is an attractive strategy to sensitize tumors to DNA-damaging chemotherapy. M6620 is a potent, selective inhibitor of ATR with preclinical anticancer activity in combination with DNA-damaging chemotherapy. Here, we report dose expansion cohort data for a phase I trial of M6620 plus Gem in pts with advanced NSCLC (NCT02157792).

Methods: Eligible pts had measurable (RECIST 1.1) advanced NSCLC with up to 2 lines of prior therapy, with one including a platinum analog. Of 40 pts planned for enrollment, ≥20 had to have a TP53 mutation (TP53+) ≥10% (≥10/9 time loss of expression (ATM)) and ≥40 had to have a TP53+ or ATM+ status. Safety was assessed by fresh or archival tissue. Pts received Gem 1000 mg/m2 on days 1–8 and M6620 210 mg/m2 on days 2–9 of each 21-day cycle. Pharmacokinetics was assessed on day 2 of cycle 1. Primary endpoints were safety and overall response rate (ORR).

Results: The safety set included 33 pts who received combination therapy (median age, 62.0 years [range 36–76]; TP53+, 19; WHO PS 0/1, 9/25). 31/33 pts had a treatment-emergent adverse event (TEAE), with 19 (57.5%) having grade ≥3 TEAEs: fatigue (6), neutropenia (4), anemia (3), thrombocytopenia (3), malaise (2), vomiting (2), ALT increase (2), AST increase (2), pneumonia (2), sepsis (2) (grade 5/2 TEAEs occurring ≥2 pts). Of the 24 treated pts with baseline and on-treatment assessments, 3 pts had a partial response (PR; ORR 12.5%) and 18 pts (75%) had stable disease (SD). Four pts had PR or SD ≥6 months (clinical benefit rate 16.7%). Updated efficacy and PK data will be presented from an upcoming analysis.

Conclusions: The ATR inhibitor M6620 combined with Gem showed signs of activity in advanced NSCLC; tolerability was acceptable.

Clinical trial identification: NCT02157792

Disclosure: R. Plummer: Clinical trial costs to institution to conduct the trial; Personal honoraria: Verastem Pharmaceuticals for advisory board; C. Redfern: Stock holdings; P. J. Spira: Research funding (to institution); Merck for study. T. Haddad: Research funding (institution): Takeda Oncology; Consulting: TerSera Therapeutics (fee donated to institution). S.S. Ramalingam: Consultant: Amgen, Abbvie, AstraZeneca, BMS, Lilly, Genentech/Roche, Loxo, Nektar and Merck. E. Dean: Commercial income to institution for the conduct on the study; Employment and owns stock: AstraZeneca. T. Goddemeier: M. Falk: Employee: Merck KGaA. G. Shapiro: Research funding: Merck/EMD Serono, Lilly, Pfizer; Advisory Board: Roche, Merck/EMD Serono, Lilly, Pfizer; Gen Therapecutics. All other authors have declared no conflicts of interest.

A multicenter single-arm phase II study of nab-paclitaxel/carboplatin for non-small cell lung cancer patients with interstitial lung disease by V. Yamauchi1, K. Morii2, A. Ono3, K. Yoh4, T. Baba5, Y. Fujisawa6, D. Yamaguchi7, R. Ko8, H. Okamoto9, N. Yamamoto1, T. Nishimura1, T. Ogura2, T. Kato1 1Department of Thoracic Oncology, National Cancer Center Hospital East, Kawasaki, Japan; 2Division of Thoracic Oncology, Shiga University of Medical Science, Shiga, Japan; 3Clinical Trial Coordination Office, Biostatistics, Shizuoka Cancer Center Hospital, Nagasaku, Japan; 4Department of Thoracic Oncology, National Cancer Center Hospital East, Kawasaki, Japan; 5Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan; 6Developmental Therapeutics, National Cancer Center Hospital East, Tokyo, Japan; 7Department of Respiratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan; 8Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; 9Department of Respiratory Medicine and Medical Oncology, Okayama Municipal Citizen’s Hospital, Okayama, Japan; 10Third Department of Internal Medicine, Waseda Medical University, Waseda, Japan; 11Department of Respiratory Medicine and Allergy, Okayama University, Okayama, Japan; 12Division of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan

Background: The prognosis of non-small cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) has been reported to be poor, and 10–20% of those receiving chemotherapy experienced exacerbation of ILD induced by chemotherapy. To evaluate the safety and efficacy of nab-paclitaxel (nab-P)/carboplatin (C) for NSCLC patients with ILD, this multicenter phase II study was conducted.

Methods: Chemotherapy-naïve patients with pathologically confirmed advanced NSCLC and ILD received 4 cycles of nab-P (100 mg/m2; d1, 8, 15) + C (AUC=6 d1) every 3 weeks. ILDs were diagnosed based on the fibrosing ILD criteria and categorized to three patterns by investigators; usual interstitial pneumonia (UIP), possible UIP, and inconsistent UIP. Primary endpoint was exacerbation-free rate (EFR) of ILD at 28 days after protocol treatment. Secondary endpoints were response rate, progression-free survival (PFS), overall survival (OS), EFR of ILD, toxicities.

Results: From 06/2014 to 12/2016, 94 patients were enrolled in this study, and 92 pts received protocol treatment. The overall response rate (ORR) was 35.5% (26/73), and 38/73 pts were PR or SD. EFR was 73.6% (49/67), with 58% having no severe ILD exacerbation. The 1-year OS, 73.7% (52/71), and median PFS were 7.6 months (95%CI: 5.3–11.0). There were 9 deaths due to ILD-related causes, which accounted for 3% (2/67) of grade ≥3 AEs. ILD exacerbation of any grade occurred in 21 pts (26%) during the treatment period.

Conclusions: This study demonstrated that nab-P/C was well tolerated in NSCLC patients with ILD in terms of safety including risk of exacerbation of ILD, even if of UIP pattern. Although this study was a single arm, nab-P/C might be more effective compared with other regimens of previous reports.


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

Conclusions: The study discontinued early due to treatment landscape changes, including unacceptable toxicity in long-term follow-up. Primary objectives were PEGPH20 docetaxel safety and tolerability were acceptable. Given the introduction of immune checkpoint inhibitors and in standard care for NSCLC, docetaxel became later-line therapy. Thus, RP2D was not determined but the highest tolerated dose was 2.2 g/kg. Prior to discontinuation, 15 pts were treated (1.6 g/kg n = 7; 3.0 g/kg n = 4; 2.2 g/kg n = 4). Most were female (66.7%) and had adenocarcinoma (66.7%); mean age was 62.6 years. ECOG PS was 0 or 1 in 46.7% and 53.3% of pts, respectively. Safety findings are summarized in the table. All TEs and all but one MSE were considered related to PEGPH20.

Methods: The study was planned as dose escalation (standard 3+3 design) and dose expansion (in HA high patients). During dose escalation, eligible pts received PEGPH20 (1.6, 3.0 and 2.2 g/kg) as an IV infusion on D1 and docetaxel 75 mg/m² IV on D2 of each 21-day cycle. Pts continued study treatment until disease progression or unacceptable toxicity in long-term follow-up. Primary objectives were PEGPH20 + docetaxel safety and tolerability and determination of the RP2D of PEGPH20. Secondary objectives included PEGPH20 + docetaxel efficacy and pharmacokinetics.

Results: The study discontinued early due to treatment landscape changes, including the introduction of immune checkpoint inhibitors and in standard care for NSCLC, ie docetaxel became later-line therapy. Thus, RP2D was not determined but the highest tolerated dose was 2.2 g/kg. Prior to discontinuation, 15 pts were treated (1.6 g/kg n = 7; 3.0 g/kg n = 4; 2.2 g/kg n = 4). Most were female (66.7%) and had adenocarcinoma (66.7%); mean age was 62.6 years. ECOG PS was 0 or 1 in 46.7% and 53.3% of pts, respectively. Safety findings are summarized in the table. All TEs and all but one MSE were considered related to PEGPH20.

Conclusions: PEGPH20 + docetaxel safety and tolerability were acceptable. Given the observed rates of TEs and MSEs, more effective methods for management of these AEs should be explored in future studies.

Clinical trial identification: NCT0346370.

Editorial acknowledgement: Medical writing assistance provided by Deborah Cantu at Paragon, Knutsford, UK.

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

Funding: Halozyme Therapeutics, Inc.


1440F

Table: 1439P

<table>
<thead>
<tr>
<th>AE category</th>
<th>PEGPH20 1.6 µg/kg + docetaxel (n = 7)</th>
<th>PEGPH20 3.0 µg/kg + docetaxel (n = 4)</th>
<th>PEGPH20 2.2 µg/kg + docetaxel (n = 4)</th>
<th>Total (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>7 (100)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Any Grade ≥ 3 AE, n (%)</td>
<td>5 (71.4)</td>
<td>4 (100)</td>
<td>3 (75.0)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Serious AEs (SAEs), n (%)</td>
<td>3 (42.9)</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>AEs leading to discontinuation, n (%)</td>
<td>1 (14.3)</td>
<td>1 (25.0)</td>
<td>2 (50.0)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>AEs with outcome of death, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AEs (≥50% of the total population), n (%)</td>
<td>6 (85.7)</td>
<td>3 (75.0)</td>
<td>4 (100)</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>4 (57.1)</td>
<td>2 (50.0)</td>
<td>3 (75.0)</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (57.1)</td>
<td>3 (75.0)</td>
<td>1 (25.0)</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Thromboembolic events (TEs), n (%)</td>
<td>0 (0)</td>
<td>1 (25.0)</td>
<td>3 (75.0)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Musculoskeletal events (MSEs), n (%)</td>
<td>6 (85.7)</td>
<td>4 (100)</td>
<td>4 (100)</td>
<td>14 (93.3)</td>
</tr>
</tbody>
</table>

With the exception of two Grade 4 SAEs (gastroenteritis/Escherichia coli sepsis), and one Grade 2 SAE, most SAEs were Grade 3.

1One event of Grade 2 myalgia was also considered a SAE;
2All thromboembolic events were considered related to PEGPH20;
3One event of Grade 3 deep vein thrombosis was also considered to be a SAE.
1.8% vs 3.6%, septic shock 0 vs 1.8%. Grade 1-2 related alopecia (8.8% vs 21.4%). One toxic death in each arm. Biological toxicities of grade 3-4 neutropenia 43.9%/37.5%, anaemia 17.5%/10.7%, thrombocytopenia 1.8%/10.7%. Full results to be presented at the meeting.

Conclusions: This study confirms efficacy, safety of OV + P in sq NSCLC with a trend for a better median survival for OV + P.


Legal entity responsible for the study: Pierre Fabre Médicament.

Funding: Pierre Fabre Médicament.


All other authors have declared no conflicts of interest.

1441P Phase III study comparing bevacizumab plus erlotinib (BE) to erlotinib (E) in patients (pts) with untreated NSCLC harboring EGFR mutations: NEJ026


Background: Combinations of EGFR-TKIs and VEGF inhibitors are one of the candidates for next strategy for EGFR-mutated lung cancer. We conducted a phase III study comparing BE to E in pts with untreated non-small-cell lung cancer (NSCLC). This study includes the pts with central nervous system (CNS) metastases (mets).

Methods: Chemotherapy-naïve pts with advanced non-squamous NSCLC harboring EGFR-mutation were randomly assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily). Pts with asymptomatic stable CNS mets that did not require corticosteroids were allowed to enroll. The primary endpoint was PFS. Secondary endpoints were OS, RR, disease control rate (DCR), and manageable.

Results are consistent with those previously reported for LL8. Updated results are to be presented at the meeting.

Conclusions: BE significantly improved PFS compared with E in pts with untreated non-squamous NSCLC harboring EGFR-mutation. OS, RR, and manageable.

Legal entity responsible for the study: Lung Cancer Research Committee, Japan Clinical Oncology Society.

Funding: AstraZeneca, MSD, Ono, Bristol-Myers.


Legal entity responsible for the study: North East Japan Study Group (NEJSG).

Funding: Chugai Pharmaceutical.


Legal entity responsible for the study: Roche, AstraZeneca.
A randomized phase II trial of erlotinib or erlotinib and bevacizumab in patients with advanced EGFR mutant non-small cell lung cancer (NSCLC)


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Background: A retrospective subset analysis from a phase 3 trial, and preclinical data supported prospective study of erlotinib and bevacizumab in patients (pts) with EGFR mutant NSCLC.

Methods: Pts were required to have an EGFR exon 19 deletion or exon 21 L858R mutation based on local testing. Pts were assigned to erlotinib 150 mg daily (E) or erlotinib 150 mg daily and bevacizumab 15 mg/kg IV every 3 weeks (EB). The primary objective was progression-free survival (PFS); secondary objectives were objective response rate (ORR), and overall survival (OS). The study was powered to detect a median PFS of 10.5 months in the EB arm, based on a median PFS of 9.3 months in the DCO arm of a phase 3 study. The primary endpoint was the HR of PFS from the EB arm to the E arm.

Results: From 11/2012 to 8/2016 88 pts were enrolled. The median age was 63 years (range 31-94), the majority were women (71%), there was a history of never smoking (55%), performance status (PS) of 1 (51%), and EGFR exon 19 deletion (67%). With a median follow-up of 23 months, 69 PFS events have been observed. A statistically significant difference in PFS in pts assigned to EB compared to E was not observed (HR of 0.87, 95% CI 0.54–1.43; p = 0.59; median PFS 17.9 and 13.5 months, respectively). The ORR in the EB and E arms were 83% vs 81% (p = 0.1). 33 OS events have been observed. The OS analysis of pts assigned to EB compared to E revealed a HR of 1.54, 95% CI 0.74–3.19, p = 0.25; median OS 29 months in the EB arm and not evaluable, respectively. Grade 3 or more adverse events (rate ≥ 10%) in the EB and E arms were: rash (26% and 18%), diarrhea (9% and 13%), hypertension (40% and 22%), and proteinuria (12% and 9%). In EB and E arms 23 and 21 pts received subsequent therapies; in the EB and E arms osimertinib was a subsequent therapy in 10 and 13 pts, respectively. cDNA were available for 36/69 pts with progressive disease; exon 19 deletion or exon 21 L858R detected in 12 samples and 79/90 in 5 samples

Conclusions: Treatment with EB compared to E did not result in a statistically significant improvement in PFS in pts with EGFR mutant NSCLC. OS data are immature. A review of subsequent therapies and additional cDNA analyses are ongoing.

Clinical trial identification: NCT02474355

Legal entity responsible for the study: AstaZenaeca

Funding: AstaZenaeca

Disclosure: All authors have declared no conflicts of interest.
1446P Management of leptomeningeal metastases in EGFR mutated non-small cell lung cancer: Analysis of tyrosine kinase inhibitors sequence

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Background: Non-small cell lung carcinomas (NSCLC) with leptomeningeal metastasis are associated with poor outcomes. Tyrosine kinase inhibitors (TKI) in EGFR-mutated (EGFRm) tumors might have substantial activity. Impact of TKI sequence on survival and clinical benefit is unknown.

Methods: Consecutive patients (pts) from 2 institutions with EGFRm NSCLC and LM were included. Retrospective collection of clinical, pathological and radiological data was performed. Overall survival (OS), Progression-free survival (PFS), clinical response rate (CRR) and disease control rate (DCR, stable disease > 2 months or clinical response) were assessed. Evaluation of TKI sequence and dose modifications in pts who had LM progression with first-line TKI was performed.

Results: Seventy pts were enrolled from Apr. 2003 to Feb. 2018. Median age was 54 [26-79], 73% were female and 85% non-smokers. Median time from initial diagnosis to LM onset was 17.5 months (m) [0-106], and pts received a median of 2 [1-7] prior therapies before LM onset. Median OS from LM onset was 7m [95% CI 6-9]. After LM diagnosis, pts received a median of 2 [1-6] lines of systemic therapy. Forty pts received 2nd-line TKI after LM progression under TKI, with a 2nd-line median PFS of 3m [95% CI 2-not reached]. In pts who switched treatment at LM progression (N = 36), 21 switched from any TKI to erlotinib (“E”, 33%), 10 maintained erlotinib with either dose increase or concurrent bevacizumab (“HD-E”, 22%), 2 switched from gefitinib to alimta or gefitinib (“AG”, 6%), and 4 with T790M mutation switched from any TKI to osimertinib (“O”, 11%). Pts with E had 6 months PFS of 41%, median OS of 6 months [95% CI 3-7], and DCR of 62%. Both pts with AG had absolute OS > 2m. Pts with HD-E had a median OS of 3 months [2-6] and a DCR of 80%. In T790M-mutated pts, O provided a median OS of 10 months [6-10] and a DCR of 100%.

Conclusions: TKIs in LM from EGFRm NSCLC provide disease control in most pts. Switch from alimta/gefitinib to erlotinib provided extended survival for patients who progressed with first-line TKI. A higher dose of erlotinib might rescue resistance to erlotinib in subsets of pts. Legal entity responsible for the study: Gustave Roussy. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

1447P Risk of not receiving second-line therapy is high in EGFR mt + pts: Real world data of certified lung cancer centers on treatment sequence in EGFR mt + pts


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Background: Recently FLAURA study demonstrated significant PFS and numeric OS benefit for Osimertinib 1st line vs. 1st gen. TKI’s Erlotinib/Gefitinib. The number of pts switching from 1st gen. to 3rd gen. TKI (30%) appeared to be low and it is questionable whether these data represent real world sequencing treatment patterns. Therefore, we investigated the sequence pattern, i.e. the percentage of 2nd line therapy in EGFR mt + pts in 3 certified lung cancer centers in Germany.

Methods: Data of 912 of 1477 pts tested for EGFR mutations were analyzed between 2009-2017. 140/144 pts with an activating EGFR mt + (16%) and treated with systemic therapy (4 pts received no therapy) were identified and their treatments were captured as well as their outcome. 36 pts were treated before accessibility to 3rd generation TKI and 104 pts after accessibility to 3rd generation TKI.

Results: 130/140 pts were treated with 1st line TKI and 10 received 1st line chemother- apy: 17 pts are still on 1st line TKI, 8 pts were lost to follow-up, 3 pts died while on 1st line TKI. 112 pts were candidates for 2nd line therapy. 34/112 (30%) of these pts did not receive 2nd line therapy. Causes for not receiving 2nd line therapy were pts refusal (n = 2), bad PS (n = 26) frequently due to CNS metastases, fast progression and death (n = 6). After accessibility of 3rd gen. TKI, 20 died of 30 (66%) pts did not receive 2nd line therapy. Median OS of the overall cohort was 27 months (m) (n = 140), median OS of pts receiving 2nd line (n = 78) vs. no 2nd line (n = 62) was 36 vs. 14 m (p < 0.0001). After accessibility of 3rd gen. TKI 30/104 pts (29%) receive a 3rd gen. TKI after 1st line therapy. 10 pts (9.6%) received a 2nd line therapy. Median OS of pts of receiving (n = 30) and not receiving 3rd gen. TKI (n = 110) was 55 months vs. 22 months (p < 0.0001).

Conclusions: In real world, a significant number of pts treated with 1st or 2nd gen. TKI do not reach 2nd line therapy even when 3rd gen. TKI were accessible. Reasons for not receiving 2nd line therapy are in most cases deterioration of PS and lack of possibility to test for T790M in the minority of cases (n = 28/66, 42%) were not tested. These data, although favorable for the small and very selected cohort of pts treated with Osimertinib, might argue for the most effective therapy in 1st line for pts with EGFR mt + tumors.

Legal entity responsible for the study: Carl von Ossietzky University Oldenburg Department of Internal Medicine-Oncology.

Funding: Has not received any funding.

Disclosure: J. Reuer: Advisory boards: Roche, Boehringer Ingelheim. M. Falk: Advisory boards: Boehringer Ingelheim, Pfizer, Roche. M. Tiemann: Advisory boards: Novartis. S. Schatz: Scientific support: Novartis. F. Griesinger: Advisory boards: Astra, AstaRoneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Roche; Travel support: Astra, AstaRoneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, oche; Scientific support: Astra, AstaRoneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis, Lilly, Merck-Sharp-Dome, Novartis, Pfizer, Roche. All other authors have declared no conflicts of interest.

1448P Patterns of recurrence to Osimertinib in T790M positive NSCLC: A Swiss cohort study

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Background: Osimertinib (Osi) is an EGFR-TKI that potently inhibits both EGFR-sensitizing and EGFR T790M resistance mutations in non-small cell lung cancer (NSCLC). Identification of oligo-progression (PD) on Osi may allow local treatment and cessation of Osi. Metastatic patterns at the time of acquired resistance to Osi are poorly understood.

Methods: We retrospectively analyzed 50 pre-treated T790M + NSCLC patients who received Osi at 7 Swiss centers. Oligo-PD was defined as PD in ≤ 5 lesions. Archived pre-treatment and fresh biopsies at PD were analyzed for mutational profiling.

Disclosure: All authors have declared no conflicts of interest.

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Efficacy of afatinib in the clinical practice: First results of the GIDEON trial: A prospective non-interventional study (NIS) in EGFR mutated NSCLC in Germany


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Background: Afatinib is an irreversible ErbB family blocker, which is approved as monotherapy for the treatment of advanced non-small cell lung cancer (NSCLC) patients with activating EGFR mutations. Here we report the first interim analysis of the NIS GIDEON, which was initiated to investigate the efficacy and tolerability of Afatinib in first line treatment in the daily clinical routine in Germany.

Methods: EGFR-mutated NSCLC patients were treated with Afatinib according to label until progression, death or discontinuation due to patients’ physicians’ decision. Efficacy (objective response rate, ORR, disease control rate, DCR and progression-free survival, PFS) was prospectively assessed by investigators and additional data about tolerability under everyday treatment conditions were documented.

Results: A total of 151 pat. were enrolled in the study and received Afatinib treatment. EGFR mutations comprised exon 19 deletions (Del19, 56.6 %), L858R exon 21 mutation (24%), and concomitant exon 18 exon 20 mutation (2%). Before Osir start, T790M was detected in 28% or tumour tissue (72%). Median follow-up was 15.3 (IQR: 8.6-21.6) months. Overall response rate was 83%, median progression-free survival 15.1 months (IQR: 9.4-20.1), median overall survival 25.1 months (IQR: 16.7-29.7 reached (NR) and median treatment duration 18.1 months (IQR: 10.1-23.5). At data cut off, PD had occurred in 26 patients (52%). There were 73% oligo- vs. 27% systemic PD. Median treatment duration in patients with oligo-PD was 19.6 vs 6.5 months if systemic PD. The number of progressive lesions in oligo-PD patients were 1 (32%), 2 (37%), 3 (26%), and 5 (5%). Main sites of PD were lung (n = 14), bone (n = 10), lymph nodes (n = 6), liver and pleura (n = 3 each), and brain (n = 4). 12 patients with oligo-PD continued treatment with Osir beyond progression, ten of them after local therapy (e.g radiation, 2x surgery). Median time of treatment beyond PD was 10.7 months in patients with oligo-PD (IQR: 5.7-NR). Analyses of pretreatment and PD tumour tissue from a subset of patients will be presented.

Conclusions: In patients with acquired resistance to Osir, we observed a high rate of extracranial oligo-PD. Outcomes of patients with oligo-PD were favorable with the majority continuing Osir in addition to local therapy, supporting the concept of Osir treatment beyond progression in combination with local therapy of progressing lesions.

Legal entity responsible for the study: St. Georg Krankenhaus.

Funding: None.

Disclosure: None.

1450P Osimertinib treatment for patients with EGFR exon 20 insertion positive non-small cell lung cancer

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Background: Epidermal growth factor receptor (EGFR) exon 20 insertions are identified in 4-10% of EGFR mutations in non-small cell lung cancer (NSCLC) and are generally associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). In vitro and preclinical animal studies have shown that osimertinib exerts antitumor activity in EGFR exon 20 insertion positive NSCLC cell lines. We report on a cohort of advanced stage NSCLC patients, harboring an EGFR exon 20 insertion, that was treated with osimertinib.

Methods: 17 patients with advanced NSCLC harboring an EGFR exon 20 insertion were treated with osimertinib 80 mg once daily, in four institutions in the Netherlands. Data were obtained retrospectively. EGFR mutation status was assessed by next-generation sequencing. Progression free survival (PFS), disease control rate (DCR) and objective response rate (ORR) were assessed using RECIST v1.1.

Results: Median age was 63 years (range 55 – 81), 71% was female and median number of prior systemic treatments was 1 (range 0 – 3). Ten patients (59%) received prior platinum-based chemotherapy, and 2 patients afatinib, one patient experienced stable disease for 11 months, the other patient showed progression. Among all patients treated with osimertinib, we observed 1 partial response, 13 patients with stable diseases and 3 with progressive disease as best response (ORR 6%). Two patients were still on osimertinib treatment at the cut-off date. Median PFS was 3.7 months (95% CI: 2.3 – 5.4 months). Six of seventeen patients (35%) achieved DCR at five months.

Table: 1450P

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EGFR, epidermal growth factor receptor; RECIST: Response Evaluation Criteria in Solid Tumors; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression free survival
Conclusions: Osimertinib has limited antitumor activity in patients with EGFR exon 20 mutated NSCLC, with an ORR of 6%. A subset of patients (35%) seems to derive benefit from osimertinib treatment with durable disease control for more than five months.

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1451F The characteristics and clinical outcome of metastatic NSCLC harboring uncommon EGFR mutation at Thailand’s tertiary referral center

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Background: An uncommon EGFR-mutant NSCLC is a rare subset of NSCLC. Prevalence and clinical outcome of this entity remain unclear. Several studies have reported the benefit of EGFR-tyrosine kinase inhibitor in patients harboring complex or uncommon EGFR mutations but there are insufficient data to determine the advantage of EGFR-TKI over chemotherapy. This study aimed to review the prevalence and clinical outcome of treatment of uncommon EGFR-mutant patients in real-world practice.

Methods: We retrospectively reviewed medical records of 681 patients tested for EGFR mutation NSCLC during 2014-2018 to collect the mutational status and to compare the survival outcomes between the patients treated with EGFR-TKI and chemotherapy.

Results: At a median follow-up of 19.1 months, 317 (47%) patients were identified with EGFR-mutant NSCLC. Twenty-eight patients (8.8%) harbored uncommon EGFR mutations. Of those 28 patients, the most frequent single mutation was exon20 insertion (21%, n = 6); 5 were L861Q and 4 were G719X. 13 (46%) patients had compound mutations: 4 were G719X plus S768I; 4 were de novo T790M plus either L858R or deletion (del)19; 2 were L858R plus del19; 1 was L858R plus Ex20Ins; 1 was del19 plus KRAS mutation. 57% of the 28 patients were treated with EGFR-TKI, mostly 1st generation, and 29% were treated with chemotherapy alone. The objective response rate was 56% in the TKI group. Median progression-free survival (PFS) in the TKI group was 10.2 months. 5-year overall survival (OS) rate was 34%. Patients treated with TKI had significantly better 5-year OS rate than those who had never received TKI (54% vs. 17%, 95%CI 1.23-14.66, p log-rank= 0.02). The longest OS was 73.6 months in a patient with del19 plus de novo T790M.

Conclusions: This study demonstrated the benefit of 1st generation EGFR-TKI was greater than with chemotherapy alone in the patients with uncommon or compound EGFR mutation NSCLC. Rare EGFR mutations can be detected in squamous cell carcinoma. There was a high prevalence of smoking among the male patients with G719X-mutant NSCLC.

Legal entity responsible for the study: Jomjit Chantharasamee.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1452P Combination of the S49076 with gefitinib in NSCLC patients progressing on EGFR-TKI and harboring MET/AXL dysregulation

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Background: EGFR T790M mutation is the most common acquired mechanism of resistance in NSCLC patients treated with EGFR-TKI. Alternative mechanisms include activation of the receptor tyrosine kinases MET or AXL. S49076 is a multi-target inhibitor and a potent ATP-competitive TKI that targets MET, AXL and EGFR/2/3. Here we report phase 1 molecular and safety data of resistant patients without the EGFR T790M mutation that were treated with S49076 combined with gefitinib.

Methods: A dose-escalation of S49076 in combination with gefitinib 250 mg once daily was conducted using a modified Bayesian Continual Reassessment Method. Toxicity was evaluated according to Common Terminology Criteria for Adverse Events (v4.0). Resistant patients were selected according to a tumor molecular profile including presence of the activating EGFR mutation, absence of T790M and at least one of the following: MET amplification, or MET or AXL overexpression.

Results: The molecular profile screening has been performed in 46 EGFR/T790M-negative tumour samples. In total, 23/46 met the molecular eligibility criteria: 21 with MET dysregulation (11 MET amplification, 20 MET overexpression and 4 both MET / AXL dysregulations), and 2 with AXL overexpression only. Fourteen patients were treated: 4 received the 500 mg dose and 10 received the 600 mg dose, which was considered an DLT at 600 mg (grade 3 stomatitis); 2 patients experienced 3 serious related AEs (asthenia, atrial fibrillation and diarrhoea). No grade 4-5 AEs were reported. Concomitant intake of gefitinib did not appear to modify the S49076 PK profile as compared to previous data. Limited anti-tumour activity was observed in the 12 evaluable patients: 1 partial response and 9 stable diseases.

Conclusions: S49076 combined with gefitinib is well tolerated and data are consistent with the overall safety profile of each drug. The observed frequency of MET dysregulation was comparable to those reported in the literature whereas AXL overexpression was lower than expected.

Clinical trial identification: EudraCT: 2015-00264631.

Legal entity responsible for the study: Servier group.

Funding: Servier group.

Background: The second-generation afatinib has shown longer Progression-Free Survival (PFS) than gefitinib in the first line treatment of advanced EGFR mutation-positive NSCLC. As for other targeted agents, it is questionable if dose selection should be based on biological active dose instead of maximum tolerable dose. Here we aimed to quantify the starting dose of 40mg/day, but in real-life practice dose reductions due to toxicity are common. As for other targeted agents, it is questionable if dose selection should be based on biological active dose instead of maximum tolerable dose. Here we aimed to quantify the starting dose of 40mg/day, but in real-life practice dose reductions due to toxicity are common.

Methods: Initiation of TKI treatment declined from 23% to 9% in 2010 and 2015, respectively. Switching and re-challenge patterns were more common at the end of observation, and the median treatment length was prolonged at the end of observation, and the median treatment length was prolonged. Of 9,992 stage IIIB/IV NSCLC patients (mean age 70 years, female 49%), 1419 (14.2%) received a TKI at least once, of whom 573 (40.3%) had similar clinical outcomes regardless of DI, and patients that required a reduction to the lowest dose of 20mg/day (n=28) achieved similar PFS (HR 0.65 (0.37-1.14); p=0.143) and OS (HR 0.41 (0.16-1.08); p=0.062) as the rest (n=70).

Results: Our results suggest equal clinical efficacy in patients treated with a lower DI of afatinib, and a reduced need for dose reductions in patients at 30mg/day. Prospective tolerability and efficacy of afatinib starting at 30mg/day will be quantified in a phase II UK study.

Legal entity responsible for the study: The Clatterbridge Cancer Centre NHS Trust.

Funding: Has not received any funding.


**Conclusion:**

Clinical stage, ECOG PS, line of treatment, brain metastasis, and minor or compound mutation in 112 pts. 95.1% were histologically diagnosed with adenocarcinoma, and 81.1% were with 0 to 1 of ECOG PS. Median OS (months [95%CI]) were 30.9 [27.7-33.9] in 1G (gefitinib, 32.2 [28.4-36.4]; erlotinib, 28.1 [24.9-33.3]), and 38.6 [32.2-38.8] in 2G (afatinib), respectively. The trend of longer OS for afatinib against first-generation EGFR-TKIs remained even after adjusted by propensity score. (unadjusted, HR 0.89, p = 0.002; adjusted by IPTW, HR 0.783 < 0.0001; adjusted by matching [1:2]; HR 0.747, p = 0.062). Subgroup analysis showed that the patients with exon 19 deletion had significantly longer overall survival benefit from afatinib than 1G EGFR-TKI. (vs. gefitinib, p = 0.014; vs. erlotinib, p = 0.1238).

Disclosures: From this analysis of 1354 data records, using propensity scoring, afatinib therapy than 1G EGFR-TKI. (vs. gefitinib, p = 0.014; vs. erlotinib, p = 0.1335).

Conclusions: From this analysis of 1354 data records, using propensity scoring, afatinib therapy than 1G EGFR-TKI. (vs. gefitinib, p = 0.014; vs. erlotinib, p = 0.1335). Against first-generation EGFR-TKIs.

Clinical trial identification: UMIN000030121.

Legal entity responsible for the study: Aichi Cancer Center Hospital.

Funding: Boehringer Ingelheim.

**Background:** The irreversible f Erl family blocker, afatinib, is approved for first-line treatment of metastatic NSCLC harbouring non-resistant EGFR mutations. While afatinib has demonstrated a predictable and manageable safety profile in pts with EGFR mutation-positive (EGFRm+) NSCLC, elderly pts are often under-represented in clinical trials. Here, we summarise the current status of, and preliminary data from, an ongoing Phase IV trial of afatinib in elderly pts with Del19/L858R EGFRm+ NSCLC (NCT02514174).

**Methods:** Pts aged ≥70 yrs with Stage IV recurrent Del19/L858R EGFRm+ NSCLC naïve to prior systemic therapy have been enrolled to sites in the USA. Pts receive afatinib QD (starting dose 30 mg/day) until disease progression/intolerable AEs. Dose reduction to 20 mg/day is permitted in the case of select Grade ≥2 AEs. The primary endpoint is the occurrence of AEs leading to dose reduction. Secondary endpoints include occurrence of Grade ≥3 diarrhoea and Grade ≥3 rash/ acne, stomatitis and paronychia (grouped terms). Other endpoints are AEs by NCI CTCAE grade, objective response (OR), PFS and overall survival. Preliminary safety data are reported here.

**Results:** As of Feb 2018, 26 pts have been enrolled across 9 sites, and 24 pts have entered into the trial. Twenty-three pts have been treated: 57% female; 50% Asian; 26%/74% ECOG PS 0/1; median age (range) 79 (71–93) yrs. Thirteen (57%) pts remain on treatment. Reasons for treatment discontinuation were progressive disease (28%), AEs (9%), refusal to continue study medication (4%), and other (4%). All pts have had at least one AE of any cause (Grade 3/4: 32%/30%; most commonly (preferred term [PT]) diarrhoea (87%), rash (61%) and fatigue (48%). The most common treatment-related AEs (PTs) reported are diarrhoea (48%), rash (53%) and dry skin (39%), and the most common serious AEs (PTs) reported are vomiting and dehydration (both 9%). Ten (43%) pts has achieved confirmed OR (complete/partial response: 1/4% [9/39%]) and 13 (50%) pts have had stable disease.

**Conclusions:** In this preliminary analysis, afatinib (30 mg/day) demonstrated a predictable safety profile in pts aged ≥70 yrs with Del19/L858R EGFRm+ NSCLC. Updated data will be presented.

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**Legal entity responsible for the study:** Boehringer Ingelheim.

**Funding:** Boehringer Ingelheim.

Biopsy on progression in EGFR mutation positive (EGFMrn) advanced non-small cell lung cancer (aNSCLC) patients (pts): A Canadian experience

Q.S-C. Chu1, A. Agha2, N.C. Devost3, R. Walton4, S. Ghosh5, C. Ho6

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Background: EGFR tyrosine kinase inhibitors (EGFMrns) are standard therapy for EGFMrn aNSCLC. Upon progression, 50-60% will develop the secondary T790M mutation. Recent trials demonstrated improvement in outcomes with osimertinib over standard platinum-based chemotherapy as second-line therapy for T790M-positive EGFMrn aNSCLC. To identify T790M, tumour biopsy or plasma testing is necessary. This study aimed to evaluate biopsy procedures and mutational analysis at two Canadian cancer centres.

Methods: BC Cancer-Vancouver and Cross Cancer Institute performed a retrospective review of pts who signed consent to enroll to the AURA2, AURA3 or ASTRIS studies. Pt characteristics, biopsy method, rebiopsy methods/complications, number of rebiopsies performed, and incidence of the T790M mutation were collected.

Results: 84 pts were considered for trial enrolment. 80 signed consent with M:F 32:68%; ECOG 0/1/2: 11/66/23%; smoker/ex-smoker/never smoker: 6/21/73%; exon mutations: 29/49/8%; prior curative intent treatment in 18%. 78 pts underwent biopsy, and incidence of the T790M mutation were collected. The median age was 69 (range: 30-90) yrs, 24% females. Median number of biopsies performed was 1 (range: 1-3). Tumour biopsy was used in 73 pts, plasma ctDNA in 45 pts (58.1%) and from other sources in 53 pts (67.5%). Estimated median progression-free survival (PFS) was 10.1 months (95% CI 8.5, 21.2), median overall survival (OS) was 23.7 months (95% CI 18.9, 31.6), and objective response rate was 55.3% (95% CI 39.8, 68.1).

Conclusions: In this Canadian dataset from ASTRIS, clinical activity (response and PFS) with osimertinib in patients with T790M-positive NSCLC is similar to that observed in the global ASTRIS population and the wider osimertinib clinical trial program with no new safety signals.

Clinical trial identification: NCT02474335.
Results: 58 pts were analysed; median age: 67, males 66%, non-squamous 64%, 53% had PD-L1 TP 1/4.9%. After median follow up of 5.2 months, 36/58 (66%) pts pro-
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Conclusions: Our cohort demonstrated similar survival outcomes to KEYNOTE-010. Baseline LIPI, LDH, D1, PD-L1 TP and LIPI score were not significantly predic-
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Disclosure: R. Califaño: Honoraria for consultancy and advisory boards: MSD. All other authors have declared no conflicts of interest.

Table 1463P: Lung immunologic prognostic index (LIPI)

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Phase I dose escalation of pembrolizumab given concurrently with palliative thoracic radiotherapy (RT) for NSCLC

Kumar, D.P. Walder1, A. Pejanaute1, S. Gunapala1, J. Bhosle1, N. Yousef3, S. Popat3, F. McDonald1, I. Locke2, K. Harrington4, A. Tree1, S. Lalondrelle, R. Gunapala3, M.E.R. O’Brien1, M. Ahmed3


Background: Pembrolizumab is used routinely in advanced NSCLC. Combination strategies, such as with RT are of great interest. We report on safety and tolerability of an open-label phase 1 trial for cohort 1 of pembrolizumab with 2 schedules of palliative RT.

Methods: All cohort 1 patients started with a pembrolizumab dose of 100mg given 2 weeks prior to RT, and then received pembrolizumab 100mg 2-weekly concurrently with RT, followed by maintenance dose 200mg pembrolizumab 3-weekly. The RT was either 20Gy/5f (low dose RT - LD) or 36Gy/12f (high dose RT - HD). Cohort 2 pembrolizumab dose will be 200mg, for all doses, with the same RT schedules. Dose limiting toxicity (DLT) period, 2 months from completing RT, is defined as grade (G) 2 pneumonia, G4 oesophagitis or G2 myelitis.

Results: 3/6 pts in the LD and 6/8 pts in the HD were evaluable for DLTs. Mean age was 61 years, 64% were female, 71% were smokers, ECOG performance status was 1 in 100%. 39% were of non-squamous histology with no driver mutations, and 64% were PD-L1 positive (TPS ≥ 1%). All pts had adverse events (AEs): G3–4 AEs were seen in 66.7% in the LD and 37.5% in the HD. There were no DLTs. In the LD, G3 AEs included: anemia (n=1), back pain (n=1), bronchitis (n=1), dyspnoea (n=1), fatigue (n=1), hypokalaemia (n=1), hypophosphataemia (n=1), and syncope (n=2). In the HD, 1 pt had drug induced liver injury (G1 ALT, G2 AST, G1 bilirubin, G3 GGT), and so the cohort was expanded by a further 3 pts. No DLTs were seen. G3 AEs included: pneumonia (n=1), dehydration (n=1), radiation dermatitis (n=1), diarrhoea (n=1), hyperglycaemia (n=1), and hypokalaemia (n=2). 1 pt had G4 urosepsis. In the LD and HD, pts also had RT dermatitis (G1 n=12, G2 n=2), RT esophagitis (G1 n=10, G2 n=4), and RT pneumonitis (G1 n=6). With a median follow-up of 7.9 months, median PFS was 1.3 months in the LD and 3.7 months in the HD (HR 0.28, P = 0.006). Median OS was 5.2 months in the LD and 8.3 months in the HD (HR 0.59, P = 0.441). Disease control rate (DCR) was 37.5% in the LD (3 SD) and 62.5% in the HD (3 PR, 2 SD, P = 0.392). DCR did not correlate with PD-L1 status (P = 1.00).

Conclusions: Combining pembrolizumab and palliative thoracic RT appears to be safe and tolerable with both RT doses. This trial continues to recruit to cohort 2.

Clinical trial identification: NCT02587640, originally posted October 19, 2015.

Legal entity responsible for the study: Royal Marsden Clinical Trials Unit, Royal Marsden NHS Foundation Trust, Downs Road, Sutton, United Kingdom.

Funding: Merck Sharp Dohme.


75 mg/m² followed by maintenance pembrolizumab + placebo + pem. Randomization was stratified by TPS (<1% vs ≥ 1%), platinum (carbo vs cis), and smoking status (current/ former vs never). Primary end points were OS and PFS; ORR and safety were secondary.

Results: Carbo was chosen for 72% of pts in both arms. OS, PFS, and ORR were improved in the pembrolizumab plus platinum arm in both carbo and cis recipients (Table). In the pembrolizumab vs placebo arm, 83% vs 72% received 4 carbo doses and 81% vs 79% received 4 cis doses. 76% vs 65% and 78% vs 72%, respectively, received ≥5 pem doses. Grade 3–5 AE rates for pembro vs placebo were 70% vs 66% with carbo and 59% vs 65% with cis. Rates of the most common any-grade AEs were generally similar for carbo and cis: nausea 54% with pembro vs 48% with placebo for carbo and 60% vs 63% for cis, anemia 45% vs 48% and 50% vs 44%, and fatigue 44% vs 43% and 33% vs 26%. Rates of acute kidney injury in the pembro arm were 5.1% with carbo and 5.4% with cis.

Conclusions: Pembrolizum plus platinum and pem improved efficacy and was generally tolerable compared with placebo plus pem and platinum regardless of the chosen platini. These data support the use of both carbo and cis in combination with pembro and pem as first-line therapy for metastatic non-squamous NSCLC.

Clinical trial identification: NCT02587640, originally posted October 19, 2015.

Editorial acknowledgement: Melanie Leiby, Merck & Co., Inc., Kenilworth, NJ, USA.

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

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

Disclosure: D. Rodriguez Abreu: Honorarium, travel expenses, and Advisory board: MSD, Bristol-Myers Squibb, Roche-Genentech, and Boehringer Ingelheim. M.C. Garassino: Consultancy and lecture fees: AstraZeneca, Roche, Boehringer Ingelheim. F. Felip: Consulting fees: Boehringer Ingelheim, Eli Lilly, Pfizer, Roche, MSD, and Abbvie; Lecture fees: AstraZeneca, Bristol-Myers Squibb, and Novartis. S.F. Powell: Research support to institution: MSD, Bristol-Myers Squibb, Incyte, Pfizer, Vyriad, Genentech. N. Peled: Advisory board member: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, Guardant360, MSD, Novartis, NovoFluxRx, Pfizer, Roche, Takeda; Grant to institution: AstraZeneca, Bristol-Myers Squibb, MSD, Roche. R. Hui: Advisory board member: MSD, AstraZeneca, Novartis, Roche and Speaker Honorarium: AstraZeneca, Novartis, Bristol-Myers Squibb, Roche Ingelheim. M. Reck: Advisory board member and Speaker: Hoffmann-La Roche, Lilly, AstraZeneca, Bristol-Myers Squibb, MSD, Boehringer Ingelheim, Pfizer, Novartis, Merck, Novartis. E.B. Garon: Clinical trial fellowship: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Foundation Medicine, Radiant1360, MSD, Novartis, NoveFluxRx, Pfizer, Roche, Takeda; Grant to institution: AstraZeneca, Bristol-Myers Squibb, MSD, Roche. R. Hui: Advisory board member: MSD, AstraZeneca, Novartis, Roche and Speaker Honorarium: AstraZeneca, Novartis, Bristol-Myers Squibb, Roche Ingelheim. M. Reck: Advisory board member and Speaker: Hoffmann-La Roche, Lilly, AstraZeneca, Bristol-Myers Squibb, MSD, Boehringer Ingelheim, Pfizer, Novartis, Mirati, Dynavax, Merck & Co., Inc. M. Boyer: Grant support: MSD, AstraZeneca, Genentech/Roche, Amgen, Bristol-Myers Squibb, Pfizer, Novartis, Peregine Pharmaceuticals. F. Grossi: Advisory board: MSD, Bristol-Myers Squibb, Pierre Fabre, Pfizer, Novartis, Boehringer Ingelheim; Lectures: MSD, Bristol-Myers Squibb, AstraZeneca, Pierre Fabre, Pfizer, Novartis, Boehringer Ingelheim, Amgen, Roche; Research funding: Bristol-Myers Squibb. J. Yang: Employee: Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA; Stock options in the Company. S.M. Gedgale: Advisor: Abbvie, AstraZeneca, Genentech/Roche, Ariad/Takeda. All other authors have declared no conflicts of interest.

Table: 1464P

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abstracts

viii530 | NSCLC, metastatic

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Annals of Oncology
Efficacy and safety of nivolumab for cytotoxic chemotherapy unfit patients with advanced non-small cell lung cancer: A phase II study

Y. Okumura1, S. Kitano2, K. Watanabe1, M. Yamota3, Y. Hosomi3, Y. Zenke1, N. Yamamoto3

Background: This single-center phase II study aimed to examine the efficacy and feasibility of nivolumab for patients with advanced non-small cell lung cancer (NSCLC) who were unsuitable for single-agent chemotherapy or targeted agents because of their poor performance status (PS).

Methods: In this study, we enrolled previously treated patients with advanced NSCLC with poor PS of 2−4 without any indication of cytotoxic chemotherapy or targeted therapies. All enrolled patients received nivolumab (3 mg/kg, every 2 weeks) until progression or unacceptable toxicities. In addition, we prospectively obtained peripheral blood mononuclear cells (PBMC) and plasma from patients after obtaining their informed consent before treatment.

Results: Between April 2016 and December 2017, we enrolled 33 patients with NSCLC and poor PS, including 23 patients with PS 3−4. In this study, the response rate was 29.0% (90% confidence interval (CI), 17.7%−43.7%), and the disease control rate was 41.5% in 31 evaluable patients. PFS improvement was 29.0%. In addition, the median progression-free survival (mPFS), median overall survival (mOS), and 1-year survival rates were 1.5 (95% CI, 1.0−2.7) months, 3.8 (95% CI, 2.4−6.3) months, and 36.6%, respectively. Among patients harboring EGFR-mutations (mut), the mPFS was 3.1−6.1 months in EGFR-wild type (wt) and EGFR-mut (p < 0.01), respectively, and the mOS was 3.9 and 1.9 months in EGFR-wt and EGFR-mut (p = 0.029), respectively. During the study period, treatment-related deaths were observed in 2 patients (6.1%). We obtained blood samples from 75% of the enrolled patients (data will be updated in the meeting).

Conclusions: To the best of our knowledge, this is the first trial to investigate the efficacy of immune checkpoint inhibitors in patients with advanced NSCLC with poor PS. Although the response rate was similar to those with good PS, shorter survival was observed. Excluding patients harboring driver mutations may enhance treatment efficacy to show a survival benefit even for poor PS patients. Nevertheless, the biomarker investigation warrants focus on the PBMC analysis.

Clinical trial identification: Clinical trial registration: UMIN000020855/ UMIN00001734.

Legal entity responsible for the study: Tokyo Metropolitan Komagome Hospital.

Funding: Has not received any funding.

Disclosure: Y. Okumura: Research Funding: Chugai Pharma (Inst). Y. Hosomi: Honoraria: AstraZeneca; Boehringer Ingelheim Japan; Bristol-Myers Squibb Japan; Chugai Pharma; Eli Lilly Japan; Ono Pharmaceutical; Taiho Pharmaceutical; Research Funding: Chugai Pharma (Inst); Eli Lilly Japan (Inst); Ono Pharmaceutical. N. Yamamoto: Honoraria: AstraZeneca; Bristol-Myers Squibb Japan, Chugai Pharma, Eli Lilly Japan, Ono Pharmaceutical, Pfizer; Research Funding: Astellas Pharma (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Chugai Pharma (Inst), Daiichi Sankyo (Inst), Eisai (Inst), Kyowa Hakko Kirin (Inst), Eli Lilly Japan (Inst), Novartis (Inst), Pfizer (Inst), Quintiles (Inst), Taisho Pharmaceutical (Inst), Takeda (Inst). All other authors have declared no conflicts of interest.

1467P Efficacy and safety of nivolumab for cytotoxic chemotherapy unfit patients with advanced non-small cell lung cancer: A phase II study

Y. Okumura, S. Kitano, K. Watanabe, M. Yamota, Y. Hosomi, Y. Zenke, N. Yamamoto

Background: Immunotherapy (IO) has improved the outcome of metastatic non-small cell lung cancer (mNSCLC), but only a minority of patients (pts) derives a benefit from treatment (tx). Recent evidences supported a role of gut flora in influencing systemic response against tumors. The use of antibiotics (Abs) may impair the balance of microbiota and negatively affect the efficacy of IO. We aimed at analyzing this topic in a cohort of mNSCLC pts.

Methods: Data about all consecutive mNSCLC pts treated with IO at Istituto Nazionale dei Tumori, Milan, Italy, from 2013 to 2018 were retrospectively collected. We considered relevant for the analysis the use of Abs between 1 month (mo) before and 3 mo after the beginning of IO. We also evaluated the variable “Abs exposure” (AE), defined as the % “days of ab by days of IO”. Survival was estimated with Kaplan-Meier method; curves were compared with log-rank test. Cox proportional model was used for multivariate analyses.

Results: We identified 157 cases. Most pts had a performance status (PS) ECOG ≥2 (52.2%) and ≥2 sites of metastatic disease (86.0%). IO was either an anti-PD1 (62.4%), an anti-PD1/CTLA4 (32.5%), or a combination anti-PD1/CTLA4 (5.1%); it was prescribed in first line in 25 pts, in second line in 66 pts, in a more advanced lines in 66 pts. Abs were administered to 27 pts, mostly for pneumonia. The most common were levofloxacin (55.6%), amoxicillin-clavulante (25.9%) and ceftazidim (14.8%). Progression free survival (PFS) and overall survival (OS) did not differ between Abs-treated and Abs-unintreated pts (p = 0.18−24, respectively). Median AE of the Ab-treated pts was 4.3% (range 0.6%−42.9%). Both PFS and OS were significantly lower in pts with a higher AE (p < 0.015), respectively.

Conclusions: These results suggest that the length of Abs, rather than their simple use in a defined time frame, may impair the efficacy of IO. Further research is needed to support this evidence. However, it may be advisable to carefully evaluate the prescription of long Ab cycles to mNSCLC pts receiving IO.

Legal entity responsible for the study: Istituto Nazionale dei Tumori.

Funding: Has not received any funding.


1468P GECF 1605/NIVEX TRIAL nivolumab in the real world: The SPANISH expanded access program experience in pretreated advanced NSCLC


Background: Nivolumab is a standard treatment for second line in patients (pts) with advanced NSCLC. Real world data about toxicity and efficacy of nivolumab is lacking.

Methods: We have analyzed 665 pts from the Expanded Access Program, which included pts with pretreated NSCLC who received >1 dose of nivolumab 3mg/kg qw from 01/2015 for squamous (Sq) and 06/2015 for non-Sq NSCLC, to 11/2017.

Results: Median age was 61 (32−85) years, 73% were men, 85% had ECOG 0−1, 388 were current/former smokers and 15% had brain M1. 128 (19.2%) pts presented Sq and 537 (80.8%) Non-Sq NSCLC. 7% of pts presented EGFR mutation. PD-L1 was ≥1% in 33% of analyzed pts. Nivolumab was administered as 2nd/3rd line in 53% and 67% of pts. Post-nivolumab treatment was administered to 25% pts that received nivolumab in 2nd line and to 23% that received nivolumab in 3rd line. After a median follow-up of 8.2 months, the median OS of 24.3 months, and the median PFS was 3.23 (95% CI 2.77−3.70) months. Estimated 1-year OS was 42.4% (95%CI 38.5−42.8%) and estimated 1-year PFS was 22.2% (95% CI 19.1−25.3%). No differences in OS or PFS were observed according to histologies. Among pts that received nivolumab in 2nd line, the median OS was 9.8 (95% CI 7.3−12.0) months and the median PFS was 3.3 (95%CI 2.4−4.2) months. Among pts that received nivolumab in ≥3rd line the median OS was 8.6 (95% CI 7.2−10.0) months and the median PFS was 3.1 (95%CI 2.6−3.7) months. Median OS for pts that received post-nivolumab treatment in 3rd line was 9.3 (95 CI 7.0−11.6) months. 296 (44.5%) pts presented toxicity to nivolumab, which was grade ≥3 in 69 (10.4%) pts. According to the presence of grade ≥3 toxicity, the median OS was 14.57 (95% CI 8.45−20.68) months for pts with and 8.73 (95% CI 7.50−9.96) months for pts without grade ≥3 toxicity (p = 0.074). Additional efficacy and safety data, including PS2, brain M1, response to first line, or post-nivolumab treatment will be presented.

Conclusions: Efficacy and safety of nivolumab was in line with previously shown data. There was a trend to a better OS for those pts experiencing grade ≥3 toxicity.

Clinical trial identification: NCT03132493.

Legal entity responsible for the study: Spanish Lung Cancer Group.

Funding: BMS.

Disclosure: All authors have declared no conflicts of interest.
EVIDENS: An observational study of nivolumab-treated patients in advanced non-small cell lung cancer (NSCLC) in a real-world setting: Initial results on 1394 patients

Background: Nivolumab demonstrated efficacy and safety in patients previously treated for advanced NSCLC in two phase 3 trials: CheckMate 017 and 057. Real-world data in a large unselected population are needed to support these results. EVIDENS aims to describe clinical characteristics of NSCLC patients treated with nivolumab in real-life in France and to assess its efficacy and safety.

Methods: EVIDENS is an observational, multicenter, longitudinal cohort study of adult NSCLC patients treated with nivolumab in a representative sample of general hospitals, university hospitals and private clinics in France. From Dec 2016 to Nov 2017, 186 sites participated in the study. We report here a pre-planned analysis including patients with confirmed NSCLC treated with at least one dose of nivolumab with a minimum of 6 months of follow-up. Kaplan-Meier estimates were derived for PFS and medians with their 95% confidence intervals.

Results: At data cut off Apr 20, 2018, 1394 NSCLC patients received nivolumab, including 434 (31.1%) with Squamous (Sq)-NSCLC and 960 (68.9%) with non-Sq-NSCLC. Baseline patient characteristics were representative of a standard advanced NSCLC. Real-world in France and to assess its efficacy and safety.

Conclusions: These preliminary results of EVIDENS confirm both the activity and safety profile of nivolumab in the ≥2L line setting in usual clinical practice, including patient populations under-represented in pivotal clinical trials. Outcomes over a longer follow-up period (minimum potential 12 months) and OS data will be presented during the congress.

Clinical trial identification: NCT03382496.

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


Other authors have declared no conflicts of interest.

Table: 1470P Ranking outcomes of expected 5-year overall survival (intention-to-treat primary population of 850 pts from the OAK study; extended network including pembrolizumab)

<table>
<thead>
<tr>
<th>Unadjusted Analysis</th>
<th>Switching-Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Rank (95% CrI)</strong></td>
<td><strong>SUCRA</strong></td>
</tr>
<tr>
<td>Nivolumab 3 mg/kg</td>
<td>2 (1, 9)</td>
</tr>
<tr>
<td>Atezolizumab 1200 mg</td>
<td>3 (1, 10)</td>
</tr>
<tr>
<td>Pembrolizumab 2 mg/kg</td>
<td>3 (1, 13)</td>
</tr>
<tr>
<td>Docetaxel 40 mg/m² qw</td>
<td>7 (1, 18)</td>
</tr>
<tr>
<td>Ramucirumab + docetaxel 60 mg/m²</td>
<td>7 (1, 18)</td>
</tr>
<tr>
<td>Erlotinib 150 mg</td>
<td>8 (3, 14)</td>
</tr>
<tr>
<td>Ramucirumab + docetaxel 75 mg/m²</td>
<td>8 (2, 17)</td>
</tr>
<tr>
<td>Erlotinib 300 mg</td>
<td>8 (1, 18)</td>
</tr>
<tr>
<td>Pemetrexed or docetaxel</td>
<td>9 (2, 17)</td>
</tr>
<tr>
<td>Docetaxel q3w pooled</td>
<td>9 (4, 15)</td>
</tr>
<tr>
<td>Nintedanib + docetaxel 75 mg/m²</td>
<td>9 (2, 17)</td>
</tr>
<tr>
<td>Paclitaxel polyglumex</td>
<td>9 (2, 18)</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m²</td>
<td>11 (7, 15)</td>
</tr>
<tr>
<td>Docetaxel qw pooled</td>
<td>12 (5, 17)</td>
</tr>
<tr>
<td>Pemetrexed 900 mg/m²</td>
<td>15 (4, 18)</td>
</tr>
<tr>
<td>Pemetrexed 500 mg/m²</td>
<td>15 (8, 17)</td>
</tr>
<tr>
<td>Placebo</td>
<td>16 (7, 18)</td>
</tr>
<tr>
<td>Pemetrexed 1000 mg/m²</td>
<td>18 (9, 18)</td>
</tr>
</tbody>
</table>

CRI, Credible interval; SUCRA, surface under the cumulative ranking curve; q3w, every 3 weeks; qw, once a week.

Fractional polynomial network meta-analysis: A different approach to indirectly assess the comparative efficacy of 2L+ cancer immunotherapy (CIT) treatments for metastatic NSCLC

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Background: CIT is associated with delayed onset of clinical effect and long-term (LT) survival, making traditional proportional hazards models less applicable. This study used a novel method, Bayesian fractional polynomial (FP) network meta-analysis.
Conclusions: low in both groups (RT 4.6% vs no RT 5%). Associated with an increase in toxicity and Grade 2 or greater pneumonitis rates were associated with superior PFS over nivolumab alone with no evidence of increase in survival and toxicity data were collected prospectively. Patients were categorized into RT versus no RT (p = 0.20). RT was not associated with improved disease control in patients with metastatic non-small cell lung cancer (NSCLC) treated with nivolumab.

Methods: We conducted a retrospective study of patients receiving nivolumab as second- or subsequent line therapy for metastatic NSCLC across four tertiary oncology centers. All patients received nivolumab at a dose of 3mg/kg every 2 weeks intravenously. Median PFS was 4.4 months (0.5-25 SD 5.53). In the Cox regression analysis, PFS was not associated with an increase in toxicity and Grade 2 or greater pneumonitis rates were low in both groups (RT 4.6% vs no RT 5%).

Results: Of 255,156 screened publications, 35 studies of chemotherapy (chemo), PD-(L)1 inhibitors, targeted and other non-chemo agents, and placebo were included in the FP-NMA. In this model, all CPT-SD(R)-1 inhibitors (nivolumab, atezolizumab, pembrolizumab [pembro] in rank order) had similar estimated 5-year OS and ranked above all other treatments (Table). When adjusted for switching, all CPT-SD(R)-1 inhibitors maintained the highest expected ranks (put in 2L treatments) and that factors such as switching affected OS benefit. These results, which vary from prior models, suggest that FP-NMA may be a more relevant and viable method for assessing LT clinical benefit in pts treated with CPT-SD(R).

Editorial acknowledgement: Jeff Frimpter, Health Interactions.

Legal entity responsible for the study: M. Hofmann-La Roche AG.

Funding: M. Hofmann-La Roche AG.


Background: Preclinical and retrospective clinical studies suggest that combining radiotherapy (RT) with programmed cell death protein 1 (PD-1) blockade may elicit a synergistic anti-tumour response. We aimed to assess whether prior or current RT was associated with improved disease control in patients with metastatic non-small cell lung cancer (NSCLC) treated with nivolumab.

Methods: We conducted a retrospective study of patients receiving nivolumab as second- or subsequent line therapy for metastatic NSCLC across four tertiary oncology centers. All patients received nivolumab at a dose of 3mg/kg every 2 weeks intravenously. Survival and toxicity data were collected prospectively. Patients were categorized into those who received any RT for NSCLC (with curative or palliative intent, thoracic or otherwise) prior to or during nivolumab therapy, and those with no history of RT for NSCLC. Kaplan-Meier survival analysis was performed for progression-free survival (PFS) and overall survival (OS) following commencement of nivolumab.

Results: 85 patients (32 female, 53 male) received nivolumab between July 2015 and December 2016. Patients had a median age of 67 years (range 42-84) at commencement of nivolumab and were followed up for a median of 15 months. 65 patients (76.4%) received RT prior to or during nivolumab and 20 patients (23.6%) received nivolumab alone. Baseline characteristics of age, performance status, histology, smoking status, sites of metastatic disease and previous therapy were similar between the two groups. Prior or concurrent RT was not associated with improved disease control in patients with metastatic non-small cell lung cancer (NSCLC) treated with nivolumab.

Conclusions: RT prior to or concurrent with nivolumab for metastatic NSCLC was associated with superior PFS over nivolumab alone with no evidence of increase in adverse effects. RT may potentiate the effect of anti-PD-1 immunotherapy in NSCLC.

Legal entity responsible for the study: Royal Brisbane and Women's Hospital, Herston, Queensland.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: In 2016, nivolumab could be prescribed according to French registration in stage IIIIB/IV NSCLC after disease progression with prior platinum-based chemotherapy and TKI therapy for patients with EGR mutation. The Observatory of Drugs, Medical Devices and Therapeutic Innovations (OMEDIT), a network from the Health Ministry has evaluated the use, current practices and medico-economic approach in the Bretagne and Pays de la Loire areas.

Methods: All consenting adult patients with stage IIIB/IV NSCLC who initiated nivolumab (3 mg/kg every 2 weeks) in 2016 were included. Minimum follow-up for survival was 12 months. Sex, age, mutation profile, toxicities, Clinic Benefit (CB: pts with complete/partial response/stable disease as the best response), progression-free survival (PFS) and overall survival (OS) have been studied for ECOG PS 0-1 pts (according to registration).

Results: 377 pts with squamous (113 pts), non-squamous (197) and undifferentiated (67) NSCLC have been included. The median number of courses was 8 (1-144). 140 pts (37%) had to 4 courses, 67 pts (18%) 5 to 10 courses and 170 pts (45%) more than 8. 247 pts were treated in 2nd line, 98 in 3rd line. All lines combined, CB was experienced by 92% of pts with squamous, 88% with non-squamous and 82% with undifferentiated disease. The ORR was 20.0% (95% CI: 15.5–24.7) vs 4.2% in the post-nivolumab period.

Conclusion: Hyperprogression is now observed more frequently in the clinical setting. One of the major concerns for clinicians is hyperprogression, perceived as a reality by many but for which there is still discussion and has no standard definition. The aim of our work is to analyse the patterns of response to nivolumab in a homogeneously treated population of patients with NSCLC and identify cases with hyperprogression.
with Docetaxel (D). The preliminary results were detailed in the table (Legend: CI95%: 95% Confidence Interval; *: Pooled Analysis; **: Network Meta-Analysis).

### Table: 1476P

<table>
<thead>
<tr>
<th>Group</th>
<th>OS Hazard Ratio CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs D (PD-L1 1%-49%)</td>
<td>0.571 [0.423-0.771] 0.001</td>
</tr>
<tr>
<td>N vs D (PD-L1 1%-49%)</td>
<td>0.62 [0.467-0.882] 0.001</td>
</tr>
<tr>
<td>P vs D (PD-L1 1%-49%)</td>
<td>0.76 [0.604-0.956] 0.019</td>
</tr>
<tr>
<td>A vs N (PD-L1 1%-49%)</td>
<td>0.66 [0.555-0.786] 0.001</td>
</tr>
<tr>
<td>N vs P (PD-L1 1%-49%)</td>
<td>0.921 [0.609-1.392] 0.696</td>
</tr>
<tr>
<td>A vs P (PD-L1 1%-49%)</td>
<td>0.751 [0.541-1.043] 0.087</td>
</tr>
<tr>
<td>N vs P (PD-L1 1%-49%)</td>
<td>0.816 [0.597-1.116] 0.491</td>
</tr>
<tr>
<td>A vs D (PD-L1 &lt;1%)</td>
<td>0.9 [0.66-1.214] 0.491</td>
</tr>
<tr>
<td>I vs D (PD-L1 &lt;1%)</td>
<td>1.04 [0.619-1.747] 0.882</td>
</tr>
<tr>
<td>I vs C/D (PD-L1 &lt;1%)</td>
<td>0.933 [0.72-1.21] 0.001</td>
</tr>
<tr>
<td>P vs D (EGFR+)</td>
<td>0.88 [0.453-1.71] 0.706</td>
</tr>
<tr>
<td>N vs D (EGFR+)</td>
<td>1.18 [0.687-2.004] 0.542</td>
</tr>
<tr>
<td>I vs S (EGFR+)*</td>
<td>1.052 [0.695-1.594] 0.81</td>
</tr>
</tbody>
</table>

**Conclusions**: Our data seem to confirm the role of adAPNS in NSCLC with PD-L1 1%-49%. On the contrary, not-significant benefits in terms of OS seem to emerge for patients with PD-L1 <1% or EGFR+ expression. Likewise, no significant differences seem to emerge from the indirect comparisons between A, N, and P for patients with a PD-L1 1%-49% expression. Although all these data need to be analyzed with caution, as expression of indirect comparisons, waiting further confirmations from clinical trials they can support clinicians for daily clinical practice.

**Legal entity responsible for the study**: The Authors.

**Funding**: Has not received any funding.

**Disclosure**: All authors have declared no conflict of interest.

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### 1477P

**Evaluation of progression-free survival (PFS) and one-year (1y) survival as surrogate endpoints (SE) in previously treated advanced non-small cell lung cancer (adNSCLC) in the era of immuno-oncology (IO)**

S. Zhao, Z. Zhang, T. Zhou, Y. Zhang, L. Zhang

**Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China**

**Background**: The advent of IO has led to greater availability of effective subsequent treatments and extended survival of patients, increasingly complicating the evaluation of overall survival (OS) in adNSCLC trials. To expedite drug developments and allow timely approvals of potentially effective agents for previously treated adNSCLC, we assessed the validity of PFS and 1y survival as SE in 2nd-line adNSCLC trials, especially in those containing immunotherapies.

**Methods**: We conducted a systematic literature search of 2nd-line adNSCLC trials. A weighted linear regression analysis between post 2nd-line treatments and OS was performed to establish the necessity of SE in 2nd-line trials. Adopting Buxey’s criteria for surrogacy, a two-stage meta-analytic validation model was used to assess associations between SE and OS at patient-level and trial-level. The strength of association was quantified by the coefficient of determination ($R^2$). $R^2 \geq 0.6$ was defined a priori as clinically relevant. Results were validated with leave-one-out cross validation methods.

**Results**: Of 1680 studies identified, 85 trials with 166 arms and 25,698 patients were included. Data of 22,804 patients from 30 trials (103 arms) were used for surrogacy assessment. A significant correlation between percentages of post 2nd-line treatments and OS improvements was identified ($R^2$ [95% confidence interval] = 0.347 [0.385-0.551], $P_{\text{univariate}} < 0.0001$, $P_{\text{multivariate}} < 0.0001$). PFS showed weak patient-level (0.100 [0.098-0.102]) and trial-level (0.094 [0.098-0.099]) associations with OS, while 1y survival strongly correlated with OS at both levels ($R^2_{\text{univariate}}$ = 0.707 [0.704-0.710], $R^2_{\text{multivariate}}$ = 0.829 [0.828-0.831]). Subgroup analysis of IO trials yielded similar results (PFS: $R^2_{\text{univariate}}$ = 0.177 [0.128-0.200], $R^2_{\text{multivariate}}$ = 0.83 [0.791-0.918]; 1y survival: $R^2_{\text{univariate}}$ = 0.965 [0.960-0.969], $R^2_{\text{multivariate}}$ = 0.778 [0.734-0.851]).

**Conclusions**: A valid SE is needed in 2nd-line adNSCLC trials in the era of IO. PFS poorly correlated with OS at both patient-level and trial-level, while 1y survival showed the potential of being a valid SE in future 2nd-line adNSCLC trials.

**Legal entity responsible for the study**: The Authors.

**Funding**: Has not received any funding.

**Disclosure**: All authors have declared no conflicts of interest.

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### 1477P

**First analysis of patients (p) with stage IV non-small cell lung cancer (NSCLC) of the thoracic tumor registry (RTT) of the Spanish Lung Cancer Group (SLCG)**

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**Background**: In September 2016, the SLCG began a RTT in 53 Spanish hospitals. In this study, we present data on patients with NSCLC with advanced disease.

**Methods**: The study comprises all the patients included in the RTT since September 2016 with stage IV disease. Progression-free survival (PFS) and overall survival (OS) were evaluated with the Kaplan-Meier curves and the groups were compared using the Log-rank test. The variables related with the patients that were analyzed included: age, gender, smoking habit, comorbidities, performance status (PS) by ECOG and histology of the tumor. The molecular tests performed in the group of patients with advanced disease were also analyzed. We also analyzed the treatment received in this patient cohort. Results: Out of the total of 2361 patients included, diagnosed between July 1991 and April 2018, 1194 had stage IV NSCLC. Mean age was 65.2 years, 824 (69%) were males, 473 (39.6%) active smokers and 475 (39.8%) ex-smokers. The most frequent histology...
was adenocarcinoma, in 894 patients (74.9%), and squamous cell, in 220 patients (18.4%). A total of 78.6% (938) of the patients had some type of comorbidity: HBP (38.9%), dyslipidaemia (28.1%), diabetes mellitus (16.3%) and COPD (14.7%). A total of 978 patients (81.9%) underwent some type of molecular test. The EGRF analysis was performed in 890 patients (75.4%), and was positive in 25.6%. ALP was analyzed in 763 patients (63.9%), mostly by HLC (44.7%), 5.2% being positive by this method. Of the total, 158 patients (13.2%) did not receive any treatment, 538 patients (44.4%) received 1 treatment line, 295 patients (24.7%) two lines, 128 patients (10.7%) three lines, and 50 patients (2.5%) 4 or more lines. A total of 60.9% of the patients received a platinum doublet in first line, the most commonly used being the combination of platinum with pertrimeth (34%). 171 patients are evaluable for overall survival, with a median survival of 17.4 m (95% CI 14.6-20.2 m).

**Conclusions:** In this cohort of patients, the clinical characteristics are those expected for this group of patients with advanced disease. However, a greater percentage than that expected of the EGRF mutations appears, perhaps due to a population supraselection.

**Legal entity responsible for the study:** Spanish Lung Cancer Group / Grupo Espanol de Càncer de Pulmón (SLCG/GECIP).

**Funding:** Lilly, MSD, Novartis.

**Disclosure:** All authors have declared no conflicts of interest.

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### 1483P

**Table: 1483P**

<table>
<thead>
<tr>
<th>Stage I (N = 4138)</th>
<th>Stage II (N = 2322)</th>
<th>Stage IIA (N = 3594)</th>
<th>Stage III B (N = 3735)</th>
<th>Stage IV (N = 16486)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment, %</td>
<td>Initial treatment, %</td>
<td>Initial treatment, %</td>
<td>Initial treatment, %</td>
<td>Initial treatment, %</td>
</tr>
<tr>
<td>Surgery</td>
<td>49.9</td>
<td>62.4</td>
<td>59.0</td>
<td>59.0</td>
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<tr>
<td>Surgery with neoadjuvant or adjuvant SACT</td>
<td>7.8</td>
<td>29.4</td>
<td>18.0</td>
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<tr>
<td>Radiotherapy only</td>
<td>20.2</td>
<td>14.2</td>
<td>16.7</td>
<td>12.3</td>
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<td>SACT and radiotherapy</td>
<td>1.8</td>
<td>7.1</td>
<td>24.4</td>
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<tr>
<td>SACT only</td>
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<td>5.9</td>
<td>18.6</td>
<td>35.7</td>
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<td>Unintreated (ie, none of the above)</td>
<td>6.9</td>
<td>8.0</td>
<td>9.5</td>
<td>14.5</td>
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<td>SACT regimen in initial treatment, %</td>
<td>12.1</td>
<td>42.4</td>
<td>61.0</td>
<td>64.3</td>
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<tr>
<td>No SACT in initial treatment, %</td>
<td>87.9</td>
<td>57.6</td>
<td>39.0</td>
<td>35.7</td>
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</tbody>
</table>

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**Background:** Describing initial treatment (tx) post-NSCLC diagnosis is important in order to understand clinicians’ intent in routine care, based on pt/disease characteristics and disease stage at diagnosis. The SCAN-LEAF project aims to describe the epidemiology, clinical care and outcomes of NSCLC pts in Scandinavia. Here, we report initial tx and outcomes among pts with incident NSCLC in Denmark from 2005-2015.

**Methods:** Descriptive statistics are used for the study population. Cox regression is used to estimate the hazard ratio (HR) and 95% confidence interval (95% CI) of predictor variables for progression-free survival (PFS) and overall survival (OS) in different subgroups. A propensity score matched pairs analysis was performed on a set of patient and disease variables in 1818 patients, treated for synchronous NSCLC (including non-small cell and neuroendocrine lung cancer) with ≥3 metastatic lesions between 2000 and 2016 in 3 specified lung cancer centers in Berlin, Germany. Patients that had either received LAT for all sites of disease (intervention group) by surgery or stereotactic ablative body radiation, or standard chemotherapy, if necessary combined with a palliative-intended local treatment (control group).

**Results:** Median follow-up time was 32.2 and 18.8 months for the intervention and control group, respectively. Substantial benefits in median progression free survival (PFS: 25.3 vs. 8.2 months; HR: 0.30; 95% CI: 0.21–0.43; p < 0.001) and overall survival (OS: 60.4 vs. 22.5 months; HR: 0.42; 95% CI: 0.28–0.62; p < 0.001) were associated to LAT. Histology of adenocarcinoma (PFS: HR: 0.58, 95% CI 0.37–0.91; p = 0.02; OS: HR: 0.53, 95% CI 0.30–0.86; p = 0.01) and small primaries (PFS: HR: 0.55, 95% CI, 0.36–0.95, p = 0.02; OS: HR: 0.39, 95% CI 0.18–0.84; p = 0.02) also predicted a favorable prognosis concerning PFS and OS. Nodal stage (N0— vs. 3, HR: 0.49, 95% CI, 0.25–0.97; p = 0.04) and number of metastases (1 vs. 2,4; HR: 0.61, 95% CI, 0.41– 0.96; p = 0.03) was associated with an extended PFS, whereas initial ECOG-PS (0–1 vs. 2, HR: 0.42, 95% CI, 0.20–0.91; p = 0.03) predicted OS.

**Conclusions:** LAT was the strongest predictor for PFS and OS in patients with OMD and ≤4 metastases. Survival observed in the control group identifies OMD as a subset of lung cancer with a generally more favorable prognosis.

**Legal entity responsible for the study:** The authors.

**Funding:** Has no receiving any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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### 1484P

**Local ablative treatment for synchronous oligometastatic lung cancer: A propensity score analysis of 180 patients**

**Background:** Local ablative treatment (LAT) improves outcome in lung cancer with oligometastatic disease (OMD) and potentially leads to long term survival. The aim of this retrospective study was to evaluate and quantify the additional benefit of LAT in synchronous OMD and to further identify prognostic factors for outcome and survival.

**Methods:** A propensity score matched pairs analysis was performed on a set of patient and disease variables in 1818 patients, treated for synchronous OMD (including non-small cell and neuroendocrine lung cancer) with ≥3 metastatic lesions between 2000 and 2016 in 3 specified lung cancer centers in Berlin, Germany. Patients that had either received LAT for all sites of disease (intervention group) by surgery or stereotactic ablative body radiation, or standard chemotherapy, if necessary combined with a palliative-intended local treatment (control group).

**Results:** Median follow-up time was 32.2 and 18.8 months for the intervention and control group, respectively. Substantial benefits in median progression free survival (PFS: 25.3 vs. 8.2 months; HR: 0.30; 95% CI: 0.21–0.43; p < 0.001) and overall survival (OS: 60.4 vs. 22.5 months; HR: 0.42; 95% CI: 0.28–0.62; p < 0.001) were associated to LAT. Histology of adenocarcinoma (PFS: HR: 0.58, 95% CI 0.37–0.91; p = 0.02; OS: HR: 0.53, 95% CI 0.30–0.86; p = 0.01) and small primaries (PFS: HR: 0.55, 95% CI, 0.36–0.95, p = 0.02; OS: HR: 0.39, 95% CI 0.18–0.84; p = 0.02) also predicted a favorable prognosis concerning PFS and OS. Nodal stage (N0— vs. 3, HR: 0.49, 95% CI, 0.25–0.97; p = 0.04) and number of metastases (1 vs. 2,4; HR: 0.61, 95% CI, 0.41– 0.96; p = 0.03) was associated with an extended PFS, whereas initial ECOG-PS (0–1 vs. 2, HR: 0.42, 95% CI, 0.20–0.91; p = 0.03) predicted OS.

**Conclusions:** LAT was the strongest predictor for PFS and OS in patients with OMD and ≤4 metastases. Survival observed in the control group identifies OMD as a subset of lung cancer with a generally more favorable prognosis.

**Legal entity responsible for the study:** The authors.

**Funding:** Has no receiving any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Methods: The Danish cohort, established by linkage of Danish national registries, includes all adult patients with incident NSCLC from 2005-2015 (follow-up until Dec 2016). Initial tx includes lung surgery, radiotherapy (RT) and systemic anticancer therapy (SACT) captured through procedure codes (no drug names); it is defined as the first tx received at any time after diagnosis associated with any other tx received within 12 wks of its first tx start. Further analyses will assess the changes in initial tx patterns and overall survival over time, using the Kaplan–Meier method.

Results: Of the 31,939 pts with incident NSCLC, mean age was 68.4 yrs (13.3% >80 yrs) and 48.0% were women. TNM stage distribution (stage I, II, IIIA, IIIB, IV, missing) was 12.9%, 7.3%, 11.2%, 11.7%, 31.6% and 5.2%, respectively. 34.4% had non-squamous cell carcinoma and 26.5% squamous cell carcinoma. Initial tx is shown in the table. The proportion of pts receiving SACT (alone or with surgery/RT) was 12.3%, 42.4%, 61.0%, 64.3% and 55.4% in stages I–IV, respectively. The proportion of untreated pts increased from 6.9% in stage I to 24.1% in stage IV.

Conclusions: From 2005-2015, half of NSCLC pts were diagnosed at stage IV. Most pts at stage I and II were treated with surgery, adjuvant/neoadjuvant SACT being relatively uncommon. At stage III, most pts received SACT either as adjuvant/neoadjuvant tx (1/3 of stage IIIA), associated with RT (1/4 of stage IIIA/B) or alone (1/3 of stage IIIA, 1/3 of stage IIIB). Only half of metastatic pts received SACT, highlighting a significant unmet treatment need in NSCLC.

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

Funding: Bristol-Myers Squibb.

Disclosure: S. Ekman: Grants: Bristol-Myers Squibb, during the conduct of the study. P. Horvat, D. Layton, J. Kim, M. Rosenlund: Employee: IQVIA. A. Juarez-Garcia: Employee: Bristol-Myers Squibb. H.C. Jacobs: Personal fees: Bristol-Myers Squibb, during the conduct of the study. L. Lacoin: Consultant epidemiologist contracted: Bristol-Myers Squibb for the SCAN-LEAF project. All other authors have declared no conflicts of interest.

1484P Treatment patterns in patients (pts) with stage IIIb-IV non-small cell lung cancer (NSCLC) in Sweden: The SCAN-LEAF study

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Background: A better understanding of real-world treatment (tx) patterns and associated clinical outcomes in the rapidly changing landscape of NSCLC is critical for informing clinical decision-making and maximising pt benefits. The SCAN-LEAF project aims to describe epidemiology, clinical care and outcomes of NSCLC pts in Scandinavia. Here, we report tx patterns and outcomes in pts with incident stage IIIB-IV NSCLC in 2 university hospitals in Sweden.

Methods: This retrospective cohort study includes all adult pts diagnosed with stage IIIb-IV NSCLC from 2012-2015, and followed in Uppsala and Stockholm University hospitals (follow-up until end of 2016). Electronic medical records were extracted and linked with national registries. Lines of therapy (LoTs) were defined using an algorithm based on systemic anticancer therapy (SACT). Descriptive results are shown by histology. Ongoing analyses will assess LoTs by mutation status, to inform next LoT and overall survival using the Kaplan–Meier method.

Results: 1625 pts diagnosed at stage IIIb-IV were identified (58.5% of all incident NSCLC). Mean age was 69.1 yrs (15.6% >80 yrs) and 49.3% were women. Histology dist ribution was: 70.9% non-squamous cell carcinoma (NSQ), 17.7% squamous-cell carcinoma (SQ), 10.3% not otherwise specified (NOS) and 3.4% other NSCLC. Of 831 EGFR-tested pts (51.3%), 21.2% had mutant EGFR, of 612 ALK-tested pts (37.7%), 10.0% had ALK translocations, of 33 PD-L1-tested pts (2.0%), 45.3% had PD-L1 expression ≥1%. Overall, 888 pts (54.7%) received a 1st LoT, of whom, 276 received a 2nd LoT (31.1%). SACT regimens are shown in the table.

Table: 1484P

<table>
<thead>
<tr>
<th>SACT regimens in stage IIIb-IV NSCLC (used in ≥5 patients)</th>
<th>All NSCLC</th>
<th>NSQ</th>
<th>SQ</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line of therapy, % (N = 888)</td>
<td>(N = 618)</td>
<td>(N = 119)</td>
<td>(N = 99)</td>
<td></td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>80.3</td>
<td>77.4</td>
<td>88.2</td>
<td>87.9</td>
</tr>
<tr>
<td>Non-platinum single agent</td>
<td>5.2</td>
<td>4.4</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor (mainly erlotinib)</td>
<td>14.4</td>
<td>18.0</td>
<td>5.0</td>
<td>6.1</td>
</tr>
<tr>
<td>2nd line of therapy, % (N = 276)</td>
<td>(N = 201)</td>
<td>(N = 40)</td>
<td>(N = 24)</td>
<td></td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>23.6</td>
<td>19.9</td>
<td>30.0</td>
<td>25.0</td>
</tr>
<tr>
<td>Non-platinum single agent</td>
<td>56.5</td>
<td>55.7</td>
<td>62.5</td>
<td>66.7</td>
</tr>
<tr>
<td>&gt;Doxorubicin</td>
<td>39.5</td>
<td>37.3</td>
<td>47.5</td>
<td>54.2</td>
</tr>
<tr>
<td>&gt;Pemetrexed</td>
<td>8.7</td>
<td>10.9</td>
<td>2.5</td>
<td>4.2</td>
</tr>
<tr>
<td>&gt;Vinorelbine</td>
<td>8.0</td>
<td>7.5</td>
<td>12.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor</td>
<td>19.6</td>
<td>24.4</td>
<td>5.0</td>
<td>8.3</td>
</tr>
<tr>
<td>&gt;Erlotinib</td>
<td>8.4</td>
<td>10.0</td>
<td>5.0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;Crizotinib</td>
<td>6.9</td>
<td>9.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt;Afatinib</td>
<td>2.9</td>
<td>3.5</td>
<td>0.0</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Conclusions: During the 2012-2016 period (mainly prior to immunotherapy reimbursement), approximately half of incident stage IIIb-IV pts received a 1st LoT and only one-third of those received a 2nd LoT, mostly with non-platinum chemotherapy or tyrosine kinase inhibitors. Almost half of stage IIIb-IV NSCLC pts remained untreated after diagnosis (no SACT regimen).

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

Funding: Bristol-Myers Squibb.

Disclosure: S. Ekman: Grants: Bristol-Myers Squibb, during the conduct of the study. P. Horvat, D. Layton, J. Kim, M. Rosenlund: Employee: IQVIA. A. Juarez-Garcia: Employee: Bristol-Myers Squibb. H.C. Jacobs: Personal fees: Bristol-Myers Squibb, during the conduct of the study. L. Lacoin: Consultant epidemiologist contracted: Bristol-Myers Squibb for the SCAN-LEAF project. All other authors have declared no conflicts of interest.

1485P NSCLC with well controlled extra-cranial disease but uncontrolled brain metastases

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Background: Brain metastases are currently both common in clinical oncology and a critical problem, since they negatively affect patients’ quality of life as well as survival. In the era of targeted therapy, survival for metastatic, recurrent lung cancer has improved. However, improved systemic treatment modalities have led to prolonged disease courses and subsequently to an increased incidence of brain metastases.

Methods: We recruited patients who were diagnosed with non-small cell lung cancer at a Samsung Medical Center from 2008 to 2017. We collected clinical characteristics and treatment pattern by medical chart review and analyzed their mutation status by NGS (ampliseq and cancer scan).

Results: Among 12918 patients who were diagnosed with non-small cell lung cancer and received chemotherapy, 1366 patients received gamma knife surgery and 1209 patients received whole brain radiotherapy. 3922 were EGFR mutant non-small cell lung cancers and received EGFR tyrosine kinase inhibitors (erlotinib: 1424; gefitinib: 2215; afatinib: 606; dacomitinib: 24). Among EGFR-mutant patients, 663 (16.9%) patients received whole brain radiation therapy (WBRT) and 765 (19.5%) received gamma-knife surgery. 320 patients who were diagnosed with ALK-positive non-small cell lung cancer received ALK inhibitors (crizotinib: 508; alectinib: 54). Among them 51 (15.9%) received WBRT and 81 (25.3%) patients received gamma-knife surgery. 268 patients received gamma-knife surgery three times or more. 51 patients received gamma-knife surgery five times or more (maximum 14 of gamma-knife surgery). Among them, 27 (52.9%) patients were EGFR mutant and 11 (21.6%) patients were ALK-rearrangement non-small cell lung cancer.
**Abstracts**

**Table: 1486P UV and MV Cox-Regression survival analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>UNIVARIABLE</th>
<th>MULTIVARIABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>RPA Group</td>
<td>5.7 (3.10-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-Stage</td>
<td>2.8 (1.4-5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N-Stage</td>
<td>2.2 (1.1-4.4)</td>
<td>0.031</td>
</tr>
<tr>
<td>Histology</td>
<td>1.2 (1.1-1.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusions:** RPA group classification may adequately stratify BOO-NSCLC pts into favorable, intermediate and adverse prognostic groups. The addition of histology, T-stage and N-stage of the primary tumor may improve the prognostic accuracy of the model. These findings require prospective validation.

**Legal entity responsible for the study:** University Hospital La Fe.

**Disclosure:** All authors have declared no conflicts of interest.

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**Background:** Brain metastases (BM) have traditionally been associated with adverse outcome. BOO-NSCLC, however, may represent a distinct population subtype in whom a radical therapeutic approach may be feasible. We aimed to assess the impact of the RPA group classification in this population subtype.

**Methods:** Retrospective analysis of pts with BOO-NSCLC (1-5 BMs as only metastatic site) treated between 2010-2018 at a single institution. RPA classification and other clinical variables was derived from electronic patient records. Survival analyses were performed with Kaplan-Meier and uni- (UV) and multivariable (MV) Cox-regression models. Performance of the survival models was assessed by ROC AUCs and weighted c-indices.

**Results:** 67 pts were identified. Median age: 59 years. The majority were men (71.6%) with adenocarcinoma histology (73.1%). Median overall survival (mOS) was 20.2 months (95%CI:11.5-28.9). RPA group score was significantly associated with OS: not reached (NR) vs 16.2m vs 4.5m for RPA group I, II and III pts respectively (HR: 5.7; 95%CI: 3.10-8; p < 0.001). The model based on RPA only had a ROC AUC of 79.6% and a c-index of 0.743. T-stage (T1-2 vs T3-4), N-stage (N0-N1 vs N2-N3) and histology were associated with OS in UV Cox-regression models, and were included in the MV model (Table). The addition of these variables to the RPA model increased the ROC AUC to 92.3% (p = 0.008) and c-index to 0.854.

**Conclusions:** RPA group classification may adequately stratify BOO-NSCLC pts into favorable, intermediate and adverse prognostic groups. The addition of histology, T-stage and N-stage of the primary tumor may improve the prognostic accuracy of the model. These findings require prospective validation.

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**Background:** LURET phase II trial evaluated the efficacy and safety of vandetanib in patients with advanced RET-rearranged non-small cell lung cancer (NSCLC).

**Methods:** In all, 19 patients with advanced RET-rearranged NSCLC continuously received 300 mg of oral vandetanib daily. The variant types of RET fusion included 10 KIF5B-RET, 6 CCDC6-RET, and 3 unknown. The data cutoff date was Aug 31, 2017, for a final analysis. In this final analysis, the data on progression-free survival (PFS), overall survival (OS) and safety were updated.

**Results:** At the final data cutoff, 1 patient was still receiving vandetanib without disease progression. Among all 19 patients in the intention-to-treat population, median PFS was 6.5 months (95% CI, 2.8-8.3) as determined by the independent radiology review committee. Median OS was 13.5 months (95% CI, 9.8-28.1) and the overall survival rate at 12 months was 52.6% (95% CI 28.7-71.9). In the subgroup analysis according to the type of RET fusion, median PFS and OS were 29 months (95% CI 1.1-15.7) and 10.5 months (95% CI 1.1-18.1) in patients with KIF5B-RET whereas 8.4 (95% CI 4.7- not reached [NR]) and NR (95% CI 9.9-NR) in those with CCDC6-RET. No adverse drug events were observed compared with previous studies in unsellected NSCLC.

**Conclusions:** Our results found that vandetanib to be effective in patients with advanced RET-rearranged NSCLC, and that RET rearrangement may be a favorable molecular subgroup of NSCLC suitable for targeted therapy.

**Clinical trial identification:** This study is registered with UMIN-CTR, number UMIN000010095.
Treatment patterns and overall survival in patients with BRAF-mutated metastatic non-small cell lung cancer

R.K. Goyal 1, A. Kron 1, J. Mazieres 1, C. Chouaid 4, K.L. Davis 5, M. Perrinjaquet 6, S. Knoll 1

Background: BRAF mutations are observed in 2%–4% of all non-small cell lung cancer (NSCLC) patients, but few targeted therapies are available, with limited practice level data on utilization and outcomes. This study therefore aimed to document, from a “real-world” perspective, treatment patterns, testing characteristics, and overall survival (OS) in patients with BRAF-positive (BRAFi-) metastatic NSCLC (mNSCLC).

Methods: This was a multinational, retrospective medical record review of patients with BRAFi- mNSCLC (diagnosed 2005-2016) in EU, Canada and S Korea. Patients were ≥18 years of age at mNSCLC diagnosis (“index”) and had ≥12 months of post-index follow-up time, except for patients who died sooner. Study measures included baseline patient characteristics, timing of mutational testing, systemic therapies for mNSCLC, and OS. Kaplan-Meier analyses were conducted to descriptively analyze OS dependent on treatment with a BRAF inhibitor (BRAFi).

Results: Of all patients (n = 76, median age = 64 years), 24% had been tested for BRAF mutation at index; 61% had been tested before initiating the first line of therapy (LOT-1), 79% before LOT-2 and 85% before LOT-3. Chemotherapy was the most common first (76%), second (46%), and third (38%) LOT. BRAFi (+/- a MEK inhibitor) was received by 33% of all patients initiating a systemic therapy (n = 66) in any LOT. Median OS from index was 19.4 months (95% CI = 13.3-22.8) in all patients, 23.4 months (95% CI = 18.5-98.4) in patients treated with BRAFi, and 11.8 months (95% CI = 4.5-20.0) in patients not treated with BRAFi, in any LOT. Three-year OS rates from LOT initiation are summarized in the table.

Conclusions: The majority of confirmed BRAFi+ mNSCLC patients were tested for BRAFi mutation before initiation of LOT-1. Chemotherapy was the predominant front-line therapy and BRAFi was utilized mainly in second and later LOTs. Median OS was numerically higher in patients treated with BRAFi versus patients not treated with BRAFi in any LOT.

Legal entity responsible for the study: Novartis Pharmaceuticals Corporation.

Funding: Novartis Pharmaceuticals Corporation.

Disclosure: R.K. Goyal: Employee: RTI Health Solutions, which has received contract research funding in the past 2 years from the following companies for which he has or currently has conducting health outcomes research projects: Novartis, Pfizer, AstraZeneca, Eli Lilly and Company, and Amgen. J. Mazieres: Consulting or advisory role to: Abbvie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Ignyta, Lilly, MSD, Novartis, Pfizer, Roche: Research funding: BMS, MSD, Novartis, Pfizer: Travel, accommodations, or expenses: Abbvie, AstraZeneca, BMS, Boehringer-Ingelheim, Chugai, Ignyta, Lilly, MSD, Novartis, Pfizer, Roche. J. Chouaid: Honoraria: AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, GSK, MSD, Lilly, Novartis and Amgen; Consulting or advisory role: AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis; Travel, accommodations, or expenses: AstraZeneca, Boehringer Ingelheim, Roche, BMS, MSD, Lilly, K.L. Davis: Employee: RTI Health Solutions, which has received contract research funding in the past 2 years from the following companies for which I have (or currently are) conducting health outcomes research projects: Novartis, Pfizer, AstraZeneca, Shire, Eli Lilly and Company, Takeda, Celgene. S. Knoll: Stock or other ownership: Novartis, GSK, Roche, Merck KGA, Gilead, Incyte. All other authors have declared no conflicts of interest.

Table: 1489P OS rates from start of LOTs

<table>
<thead>
<tr>
<th></th>
<th>LOT-1</th>
<th>LOT-2</th>
<th>LOT-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAFi (n = 34)</td>
<td>No BRAFi (n = 28)</td>
<td>BRAFi (n = 28)</td>
<td>No BRAFi (n = 16)</td>
</tr>
<tr>
<td>3-year OS rate (standard error)</td>
<td>33.9% (0.09)</td>
<td>17.1% (0.09)</td>
<td>37.5% (0.10)</td>
</tr>
</tbody>
</table>
Results: Until completion of enrollment of HOT1303-B, 129 eligible pts with advanced NSCLCs including 108 adenocarcinoma pts were enrolled to this study. IHC3+ was observed in 6 pts (4.6%), all of whom showed DISH- +. IHC2+/DISH- were also observed in 6 pts (4.6%). Hotspot mutations (5 vs 20 YVMA insertions and 2 S310F mutations) were detected in 7 pts (5.4%) and non-hotspot mutations including a previously unknown L755_N758delinsPST mutation were detected in 12 pts (9.9%). Amplifications and hotspot mutations were mutually exclusive except a case with IHC2+/DISH+ and S310F. When we defined amplifications and hotspot mutations narrowly as HER2 alterations (18 pts, 14%), they correlated with smoking inversely (p = 0.03), but not with age, sex, chemotherapy response or overall survival from 1st line therapy. The 48 gene NGS analysis was conducted in 91 pts. Number of mutations per pt (median, 2; range, 0-25) did not correlate with HER2 alterations. The most frequently mutated gene was TP53, mutations of which tended to correlate with HER2 alterations (11/14, 79% vs. 4/17, 35%; p = 0.08). Although there were no gene mutations of which were significantly associated with HER2 alterations, HER2 altered tumors had no oncogenic driver mutations including K-RAS and B-RAF.

Conclusions: HER2 alterations were relatively frequently observed. Hotspot mutations and amplifications were almost mutually exclusive and tended to be associated with TP53 mutations. Precise roles of distinct HER2 alterations should be determined in larger cohorts.

Clinical trial identification: UMIN000012552

Legal entity responsible for the study: Hirofumi Hattori-Matsushita, Akita University School of Medicine, Akita, Japan

Background: MET exon 14 splice sites mutations define a unique subset of NSCLC patients who may benefit from MET inhibitors. Patterns of disease spread and response to chemotherapy in these patients are still poorly known.

Methods: Clinicopathologic characteristics and outcome of patients harboring MET exon 14 splice sites mutations identified in a single molecular center were retrospectively collected.

Results: We identified 39 patients from 12 french institutions between July 2009 and February 2018. Median age was 75 (range 55-91), sex ratio was 1.16 (M/W), 15 patients (38%) were never smokers. Histologic type was adenocarcinoma in 31 patients (79%) pulmonary sarcomatoid carcinoma in 3 tumors (8%) and NOS NSCLC in 5 tumors (13%). MET exon 14 alterations were deletions in 21 patients (54%), point mutations in 14 patients (36%) and delsins in 4 patients (10%). Ten patients had a concurrent TP53 mutation, 3 patients had a RAS mutation, and 1 patient had a PIK3CA mutation. Among the 14 patients tested for PDL1 expression, 9 (64%) were PDL1 high (>90%). The disease was diagnosed at stage IIIIB/IV in 24 patients (62%). Among those, the most frequent metastatic sites at diagnosis were bones (61%), lung (43%), pleura (39%) and brain (13%). 17 patients received at least one line of chemotherapy. Objective response and for first line chemotherapy was 44%. Anti-PD1 agent was initiated in 6 patients, 1 patient (16%) achieved an objective response. MET TKI was initiated in 7 patients. Median overall survival for stage IIIIB/IV patients was 8.5 months. Conclusions: MET exon 14 splice sites patients harboring a MET exon 14 splice sites mutation are characterized by older age, never smoking status in half of the cases, and metastatic spread to bones. Future efforts should focus on identifying predictive markers of response to MET TKIs.

Legal entity responsible for the study: Alexis Cortot.

Disclosure: Has not received any funding.

Funding: 

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Risk of lung cancer following pulmonary tuberculosis: A nationwide population-based cohort study, South Korea

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Background: Some epidemiologic studies on lung cancer have reported findings that suggest the possibility of association between lung disease and lung cancer. The association of pulmonary tuberculosis (TB) and lung cancer has attracted attention for several years and has remained controversial. Therefore, we investigated that the relationship between pulmonary TB and lung cancer by considering the time of TB diagnosis in this study.

Methods: This study was used the National Health Insurance Service – National Sample Cohort in South Korea. Patients with pulmonary TB diagnostic codes and treated with anti-tuberculosis in adults over 20 years of age were defined as pulmonary TB patients. It was monitored the incidence of lung cancer after diagnosis of active pulmonary TB. We compared 3,776 patients with pulmonary TB and 18,880 controls matched for sex and age from 2003 to 2013. Multivariate Cox proportional model was used to calculate the adjusted hazard ratio of lung cancer after adjusting for sex, age, house income, smoking status. The incidences of lung cancer were compared according to duration time after TB infection by calculating the incidence rates ratio (IRR).

Results: During the study period, 194 patients were diagnosed with lung cancer. A total of 86 lung cancer patients were diagnosed in 3,776 pulmonary TB patients and 108 patients were diagnosed in 18,880 control group. The IRR in TB group was higher than the control group. The IRR in the first line or successive, between November 2015 and December 2017. Data were collected from the clinical history, with attention to baseline neutrophil and lymphocyte counts, number of response by criteria RECIST 1.1 and overall survival (OS) defined from the beginning of treatment until death.

Results: Sixty-six patients (22 women and 44 men) with a mean age of 64 years (44-78) were analyzed. 9.3% (9 patients) received immunotherapy as first line treatment, 69.7% (46p) received as 2nd line and 21.2% (14p) as 3rd line treatment. Regarding the type of IT, 49p (74.2%) received treatment with Nivolumab and 17p (25.8%) were treated with Pembrolizumab. Two brackets of baseline N/L ratios (< 5 (low) and > 5 (high)) were defined. Low ratio N/L (L < (≤5%) was identified in 47p (71.2%) of the patients treated with IT and high ratio N/L (N > (>) 5) in 19p (28.8%). The IRR in the patients with a low ratio: 2.2p (46.8%) had some type of response or stabilization of their disease, 15p (31.9%) had progression and 10p (21.3%) received less than months of treatment, 3p for P5rE5 retention and the other 3p continue with the treatment and are pending revaluation. Among the 19p patients with high N/L quotient: 4p (21.1%) presented response or stabilization of the disease, 1p (78.9%) presented progression or treatment was interrupted due to deterioration of the ECOG. The average survival in the group with a low N/L ratio (< (≤5) was 87.85 weeks compared to the group with a high N/L ratio (> (>) 5) 25.74 weeks (p < 0.05).

Conclusions: The N/L ratio has been identified in some studies as an adverse prognostic factor in patients treated with IT. Our data from the usual clinical practice support this theory. If these findings are confirmed in future studies, it could be used as a response biomarker for better patient selection.

Legal entity responsible for the study: Fundación Biomédica Galicia Sur.

Disclosure: Has not received any funding.

Funding: 

Disclosure: All authors have declared no conflicts of interest.

Intracranial activity of esansitibir in patients with anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC)


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Background: Esansitibir is a potent ALK small molecule tyrosine kinase inhibitor (TKI). It has shown efficacy in intracranial tumor models. The activity of esansitibir is being evaluated in an ongoing phase 2 study of ALK positive NSCLC patients (pts). As progression due to growth of pre-existing brain metastases (BrM) or development of new BrM is a common mechanism of treatment resistance, we examined the clinical intracranial activity of esansitibir in pts with known BrM (target or non-target) at baseline or subsequent central nervous system (CNS) progression.

Methods: Pts who were either ALK TKI naïve (1st line), had received prior crizotinib and no other ALK TKI (2nd line), or had received prior crizotinib and a 2nd generation ALK TKI (3rd line) received esansitibir 225mg QD until disease progression (PD), 

Conclusions: Pulmonary tuberculosis is a risk factor for lung cancer. In patients with metastatic disease, it may be considered the co-existence of lung cancer and be necessary to carefully observe the occurrence of lung cancer for a certain period of time after diagnosis of pulmonary TB, especially in younger patients. Legal entity responsible for the study: Seon-Sook Han.

Disclosure: Has not received any funding.
Unacceptable toxicity or investigator discretion. Tumor assessments were performed locally every 8 weeks. Pts with asymptomatic BrM at baseline were allowed to enroll. To be considered a CNS target lesion, it had to be >3 mm in diameter and, if previously treated, must have been at least 4 weeks post whole brain radiation therapy with documented tumor growth and may not have been treated by stereotactic radiosurgery. Results: As of the data cut-off (May 1, 2018), 77 ALK evaluable pts (ALK+ NSCLC pts at >20mg QD with a post baseline response assessment) were assessed. Overall, 23 pts (30%) had BrM progression (new or existing lesions). For 41 pts who had no BrM at baseline and received ensartinib as 1st line (10 pts), 2nd line (18 pts) or 3rd line (13 pts), only 2 pts (5%) progressed due to the development of BrM. For 36 pts who had BrM at baseline (5 as 1st line, 19 as 2nd line, 12 as 3rd line), 21 pts (58%) had BrM progression, some at the time of systemic progression. For patients with baseline CNS target lesions, the CNS objective response rate was 100% (n = 3) for 1st line pts, 54% (n = 13) for 2nd line pts, and 33% (n = 3) for 3rd line pts, with a CNS disease control rate of 100% for all pts. Complete CNS responses were observed in 3 pts with target CNS lesions and in 3 pts with only non-target lesions. Conclusions: The data indicate that ensartinib has promising CNS activity.

Clinical trial identification: NCT016625234.

Legal entity responsible for the study: Xcovery Holdings, Inc.

Funding: Has not received any funding.


**Table: 1498P PFS of ICIs according to interval from preceding TRT or other RT in comparison with patients without RT**

<table>
<thead>
<tr>
<th>Time Interval from RT</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6 months</td>
<td>1.22 (0.67-2.27)</td>
<td>0.09 (0.53-1.48)</td>
</tr>
<tr>
<td>&gt;6 to 12 months</td>
<td>0.35 (0.17-0.71)</td>
<td>0.92 (0.59-1.43)</td>
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<tr>
<td>&gt;12 months and &gt;24 months</td>
<td>0.29 (0.17-0.48)</td>
<td>0.001 (0.001-0.005)</td>
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**Results:** A total of 294 patients with NSCLC received ICIs. Patients’ characteristics, driver oncogene alteration (EGFR, ALK and ROS1), RT before ICIs (no RT, definitive or palliative thoracic radiotherapy [TRT] and palliative RT for other sites [other RT]) and PFS were investigated. The interval between the initial day of ICIs and the start date of RT (in patients with RT) or first line chemotherapy (in patients without RT) was classified as follows, within 6 months [<6], 6 to 12 months [6-12] and 12 months or longer [>12].

**Results:** A total of 294 patients with NSCLC received ICIs; male / female: 186 / 108, median age: 66 range (32-85), squamous (8%) non-squamous (85%) 234, driver oncogene alteration (positive / negative or unknown): 67 / 247, regimen (nivolumab / pembrolizumab): 235 / 59, RT (no RT / TRT / other RT): 131 / 83 / 80 and interval time categories (<6 / 6-12 / >12) 91 / 74 / 129. Significantly better PFS of ICIs was demonstrated in patients after TRT (HR 0.71, 95% CI 0.52-0.97) According to the interval time to preceding RT, efficacy of ICIs was especially enhanced with 6-12 month interval from RT, even after adjusting by PS, sex, age, histology, tobacco history, IC regimen and driver oncogene status (adjusted HR 0.37, 95% CI 0.18-0.76).

**Background:** Based on the preclinical findings, preceding RT enhances efficacy of ICIs. Phase III trial (PACIFIC) evaluating efficacy of durvalumab as consolidation after chemotherapymRT showed significant improvement in progression-free survival (PFS) in patients with stage III NSCLC (Antonia et al., NEJM 2017). Retrospective analysis showed previous RT resulted longer PFS by ICIs (Shavridian et al., Lancet Oncol 2017). However, the optimal interval between preceding RT and ICIs has not been clarified.

**Methods:** Between Dec 2015 and Apr 2018, we analyzed consecutive NSCLC patients received ICIs. Patients’ characteristics, driver oncogene alteration (EGFR, ALK and ROS1), RT before ICIs (no RT, definitive or palliative thoracic radiotherapy [TRT] and palliative RT for other sites [other RT]) and PFS were investigated. The interval between the initial day of ICIs and the start date of RT (in patients with RT) or first line chemotherapy (in patients without RT) was classified as follows, within 6 months [<6], 6 to 12 months [6-12] and 12 months or longer [>12].

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**Results:** A total of 294 patients with NSCLC received ICIs; male / female: 186 / 108, median age: 66 range (32-85), squamous (8%) non-squamous (85%) 234, driver oncogene alteration (positive / negative or unknown): 67 / 247, regimen (nivolumab / pembrolizumab): 235 / 59, RT (no RT / TRT / other RT): 131 / 83 / 80 and interval time categories (<6 / 6-12 / >12) 91 / 74 / 129. Significantly better PFS of ICIs was demonstrated in patients after TRT (HR 0.71, 95% CI 0.52-0.97) According to the interval time to preceding RT, efficacy of ICIs was especially enhanced with 6-12 month interval from RT, even after adjusting by PS, sex, age, histology, tobacco history, IC regimen and driver oncogene status (adjusted HR 0.37, 95% CI 0.18-0.76).
Tumor treating fields concurrent with standard of care for stage 4 non-small cell lung cancer (NSCLC) following platinum failure: Phase III LUNAR study

U. Weinberg1, 2, O. Farber1, M. Giladi1, Z. Bomzon1, E. Kirson1

Background: Tumor Treating Fields (TTFields) is a non-invasive, anti-mitotic treatment approved for glioblastoma based on significantly improved survival outcomes in a Phase 3 trial. Efficacy of TTFields in NSCLC has been shown preclinically and the safety confirmed in a phase I/II pilot study combined with pemetrexed. We hypothesize that adding TTFields to immune checkpoint inhibitors or docetaxel following platinum doublet failure will increase overall survival (OS) in stage 4 NSCLC.

Trial design: The LUNAR trial [NCT02973789] is enrolling patients (N = 334), with squamous or nonsquamous NSCLC who are stratified per selected standard therapy (immune checkpoint inhibitors or docetaxel), histology (squamous vs. nonsquamous) and geographical region. Key inclusion criteria include disease progression while on/after platinum-based therapy, ECOG 0-2, no electronic medical devices in the upper torso, and absence of brain metastasis. Docetaxel or immune checkpoint inhibitors are granted at standard doses. TTFields are applied to the upper torso for 18 hours/day, allowing patients to maintain daily activities. TTFields are continued until progression in the thorax and/or liver. Follow-up is performed every 4 weeks using CT scans of the chest and abdomen. On progression in the thorax and/or liver, patients have 3 post-progression follow-up visits and are then followed monthly for survival. The primary endpoint is superiority in OS with TTFields in combination with the standard of care treatments versus (vs) standard of care treatments alone. Key secondary endpoints compare the OS in patients treated with TTFields and docetaxel vs docetaxel alone, and patients treated with TTFields and immune checkpoint inhibitors vs those treated with immune checkpoint inhibitors alone. An exploratory analysis will test non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Secondary endpoints include progression-free survival, radiological response rate, quality of life based on the EORTC QLQ C30 questionnaire and severity and frequency of adverse events. The sample size is powered to detect a HR of 0.75 in TTFields-treated patients versus control group.

Clinical trial identification: NCT02973789.

Legal entity responsible for the study: Novocure.

Funding: Novocure.

Fostering efficacy of anti-PD-1 treatment: Nivolumab plus radiotherapy in advanced non-small cell lung cancer: The FORCE trial


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Background: Hypofractionated palliative radiotherapy for metastatic lung cancer patients is frequently used in order to ease pain, to increase bone stability, to treat local mass effect or to prolong progression-free survival at critical sites. Recently introduced, immunotherapy for patients with non-squamous non-small cell lung carcinoma (NSCLC) has significantly improved outcome in this cohort. Preclinical and early clinical data suggest that the combination of photon radiation with PD-1-targeting immunotherapies may promote a strong and durable immune response against tumor manifestations both within and beyond radiation targets.

Trial design: In this prospective, two-armed, non-randomized, open-label phase II trial, 150 patients with stage IV non-squamous non-small cell lung cancer in 2nd-line or 3rd-line treatment will be included. 65 patients with a clinical indication for palliative radiotherapy to non-cerebral non-pulmonary metastatic sites will receive nivolumab 240 mg followed by palliative radiotherapy with 5 Gy–2 Gy photon radiation, which will be administered within 72 hours after first nivolumab administration (Group A). 65 patients without an indication for radiotherapy will receive nivolumab (Group B).

Nivolumab will be administered every two weeks in both groups and will be continued until progression or until limiting toxicities. The primary endpoint will be the objective response rate according to RECIST criteria 1.1. Secondary endpoints will be progression-free survival until RECIST 1.1, overall survival, descriptive subgroup analyses according to PD-L1 expression, toxicity and quality of life. An extensive exploratory translational research program attached to this trial will focus on mechanisms of the immune-stimulating effect of radiotherapy and the identification of potential biomarkers predicting benefit from nivolumab. The FORCE trial will provide prospective data to the observation that the combination of hypofractionated photon radiotherapy and medical immunotherapy is not only safe but will also promote antitumour immune responses.

Clinical trial identification: NCTN: N3044626, Eudra-CT NC: 2015-005741-31
Legal entity responsible for the study: The authors.

Funding: Boehringer Ingelheim.

enteric biomarkers with efficacy. Primary endpoints in part 2 are the association of ORR with baseline tissue and blood TMB; secondary endpoints are ORR, PFS, OS, safety, and the association of enteric biomarkers with efficacy. The start date was March 2017. The estimated primary completion date is March 2019.

Clinical trial identification: NCT03001882

Editorial acknowledgement: Proven medical writing and editorial assistance were provided by StemScientific, funded by Bristol-Myers Squibb.

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

Funding: Bristol-Myers Squibb.


1504TP Nintedanib plus docetaxel in routine clinical practice: VARGADO, a German prospective non-interventional study (NIS) reflecting routine treatment conditions in an evolving NSCLC treatment landscape

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Background: Nintedanib is an oral, triple angiogenesis inhibitor approved by the EMA and other countries in combination with docetaxel for the treatment of adenocarcinoma NSCLC patients after first-line chemotherapy. Nintedanib plus docetaxel demonstrated significant and clinically meaningful OS benefits in adenocarcinoma patients, which were more pronounced in patients with aggressive or refractory tumors. During the past years, the treatment landscape for advanced NSCLC has changed tremendously impacting individual treatment decisions and choice of adequate treatment sequences. Here we present the ongoing NIS VARGADO study design and set up to assess the efficacy and tolerability of nintedanib and docetaxel in daily clinical routine in Germany.

Trial design: The NIS VARGADO (NCT02392455) is currently recruiting patients. Four hundred patients are planned to be enrolled at one hundred German centers. Adult NSCLC patients with advanced adenocarcinoma who are initiating treatment with nintedanib according to its label as part of routine clinical practice are eligible. The primary endpoint of the study is the one-year overall survival rate after start of therapy with nintedanib and docetaxel. Progression-free survival is one of the key secondary endpoints. Patients with aggressive or refractory tumors will be analyzed in detail with respect to efficacy in this real world setting. Documentation of patients treated with nintedanib plus docetaxel in combination following first-line chemotherapy and/or immunotherapy will allow for analyses on treatment sequence. Analysis of tolerability will comprise the assessment of frequency and severity of adverse events. Furthermore, therapy management under routine conditions will be recorded and assessed.

Clinical trial identification: NCT02392455.

Legal entity responsible for the study: Boehringer Ingelheim Pharma GmbH & Co KG.

Funding: Boehringer Ingelheim Pharma GmbH & Co KG.

Disclosure: I. Zander: Consultancy: Boehringer Ingelheim, S. Kriger: Honoraria, Advisory boards and lectures: Boehringer Ingelheim. W.M. Bruck: Payments for membership on advisory boards: Boehringer Ingelheim. I. Atz, R. Kaiser: Employee: Boehringer Ingelheim Pharma GmbH & Co KG. All other authors have declared no conflicts of interest.

1505TP Phase I study of the AXL inhibitor DS-1205c in combination with osimertinib in subjects with metastatic or unresectable EGFR-mutant NSCLC


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Background: In patients with metastatic EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC), resistance to EGFR tyrosine kinase inhibitors (TKIs) arises from the T790M EGFR mutation in over half of cases; up-regulation of “bypass track” activity in non-EGFR signaling pathways is observed in other cases. Up-regulation of expression of the AXL tyrosine kinase has been observed in EGFRm NSCLC patients experiencing disease progression on osimertinib, and xenograft studies have suggested a role of AXL inhibition in combination with EGFR TKI treatment in overcoming such resistance. DS-1205c is a novel, orally administered, specific small molecule inhibitor of AXL.

Trial design: This is a multicenter, open-label, Phase 1, dose escalation and dose expansion study of DS-1205c in combination with osimertinib in metastatic or unresectable EGFR-mutant NSCLC subjects experiencing disease progression during treatment with osimertinib, gefitinib, or afatinib, and without T790M resistance mutation; or during treatment with osimertinib. Eligible subjects are at least 18 years of age, have ECOG PS 0 or 1, have radiological documentation of disease progression on osimertinib, gefitinib, afatinib, or osimertinib, and have at least one measurable lesion. This study includes two parts: Dose Escalation and Dose Expansion. In Dose Escalation, subjects receive DS-1205c during a run-in period, followed by combination treatment with DS-1205c and 80 mg daily of osimertinib. Escalation of DS-1205c dosing is guided by the modified Continuous Reassessment Method using a Bayesian logistic regression model following the escalation with overdose control principle. In Dose Expansion, subjects receive DS-1205c at the recommended dose for expansion (RDE) determined in Dose Escalation, in combination with 80 mg daily of osimertinib. Primary objectives are to determine safety, tolerability, and RDE of DS-1205c in combination with osimertinib. Secondary objectives are to assess pharmacokinetic parameters of DS-1205c free form (DS-1205c), osimertinib, and osimertinib active metabolites, and to assess antitumor activity (RCEST v1.1). Retrospective analysis of AXL expression will be conducted using tumor tissue collected prior to study treatment. Enrollment opened in December 2017.

Clinical trial identification: NCT03255083.
**Legal entity responsible for the study:** Daiichi Sankyo, Inc.

**Funding:** Daiichi Sankyo, Inc.


**1507TIP**


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**Background:** Currently, there is no possibility to detect early tumor response in lung cancer patients within the first days after chemotherapy (CTX) or tyrosine kinase inhibitor (TKI) therapy induction. Using the current gold standard for therapy monitoring, i.e. the measurement of morphologic differences according to RECIST 1.1 by CT and MRI, changes are detected only after weeks or months. Thus, patients may undergo eventually ineffective treatment and suffer from unnecessary toxicity, with both causing relevant costs. This highlights the importance of early response detection to guide and optimize therapy. Monitoring treatment response with diffusion-weighted and dynamic contrast perfusion MR imaging has been proposed for some time as a new powerful tool that will allow determining tumor response much earlier than RECIST.

**Trial design:** This is an observational, prospective, multicenter, non-randomized, open clinical study. Eligible patients with non-squamous NSCLC undergoing systemic treatment receive MRI before and after 1st-line therapy. The first follow-up (FU) MRI for patients undergoing chemotherapy is performed 24 hours post treatment. Patients treated with TKIs undergo MRI at days 7 and 14 after therapy induction. A thoracic MRI protocol is performed, including navigator diffusion-weighted imaging with the acquisition of 6 b-values, while the evaluation will focus on the non-perfusion sensitive b-values 400 and 800 (and the apparent diffusion coefficient (ADC)). Software-based analysis of user-defined ROIs is used to assess the ADC value inside the tumorous lesion. ROIs are put in the solid part of the tumorous lesion. So far, 54 patients (28 TKI, 26 CTX) have been included. Findings will be correlated with routinely performed FU CT-imaging and the clinical outcome during FU visits. Further, an accompanying biomarker program aims to elucidate ultra-early blood-bound signs of apoptosis in correlation with MRI signals. This multicenter study will address the unmet clinical need of ultra-early detection of therapy response in NSCLC in order to translate this promising approach into broad clinical practice.

**Legal entity responsible for the study:** Claus Peter Heussel.

**Funding:** German Center for Lung Research (DZL).

**Disclosure:** H.-U. Kauczor: Grant: Siemens; Speakers bureau: Boehringer Ingelheim, Philips; Grant: speakers’ bureau: Brocos, Bayer, M. Thomas: Speaker: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca; Advisory board: Lilly, BMS, MSD, Roche, Pfizer, AstraZeneca, Cellgene, Mediolanum. H. Golpon: Advisory boards: Roche, AstraZeneca, Boehringer Ingelheim, BMW. A. Tufman: Advisory boards: Roche, AstraZeneca, Boehringer Ingelheim. C.P. Heussel: Consultation or other fees: Schering-Plough, Pfizer, Basela, Boehringer Ingelheim, Novartis, Roche, Astellas, Gilead, MSD, Lilly, Intermune, Presenilis; Research funding: Siemens, Pfizer, MeVla, Boehringer Ingelheim; Lecture fees: Gilead, Essex, Schering-Plough, AstraZeneca, Lilly, Roche, MSD, Pfizer, Broca, Meda Pharma, Intermune, Chiesi, Siemens, Covidien, Pierre Fabre, Boehringer Ingelheim, Grifols, Novartis, Basalca, Bayer. F. Bozorgmehr: Research funding: BMS; Honoraria: MSD, Novartis. All other authors have declared no conflicts of interest.

**1508TIP**

**Durvalumab in frail and elderly patients with stage four NSCLC: The DURATION trial**

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**Background:** Elderly patients represent a major population of non-small cell lung cancer (NSCLC) patients in routine clinical practice, yet are underrepresented in clinical trials. In particular, data regarding efficacy and safety in frail or elderly patients with respect to immunotherapy is lacking. Importantly, immunosenescence in elderly patients can result in altered activities of immune-modulating drugs such as PD-1/PD-L1 inhibitors. Thus, there is an urgent need to assess safety and efficiency of such inhibitors in this group.

**Trial design:** In this prospective, open label, treatment stratified, and randomized phase 1B study, 200 patients with stage IV NSCLC, >70 years old and/or frail (Charlson Comorbidity Index >1) or restricted performance score (ECOG >1), who are amenable for at least chemotherapy with gemcitabine or vinorelbine, will be included. Patients are stratified after a modified CARG Score (a predicting chemotheraphy toxicity score) into: “Fit” patients are treated with doublet chemotherapy (carboplatin/nab-paclitaxel), while “unfit” patients receive mono chemotherapy (gemcitabine or vinorelbine). Patients are then 1:1 randomized and receive either 4 cycles of chemotherapy + follow-up every 8 weeks (Arm A) or 2 cycles of chemotherapy followed by 2 cycles of durvalumab and subsequent maintenance durvalumab every 4 weeks (Arm B/C). The primary endpoint is the rate of treatment related grade III/IV adverse events (CTCAE V4.03). As secondary endpoints progression-free survival according to RECIST 1.1, overall survival, descriptive subgroup analyses according to PD-L1 expression, and quality of life will be addressed. Geriatric screening assessments and functional tests will be performed to complete the description of a potential “frail” and “elderly” patient cohort (G8-questionaire, Timed up & go test, 6MWT). Further, a biomarker profiling program will analyse immune-related effects and potentially identify novel response predictors. The DURATION trial will prospectively investigate the safety and tolerability of PD-L1 treatment with durvalumab after chemotherapy in elderly and frail patients and thereby provide new insights into the effect of PD-L1 blockade and the impact of immunosenescence on the treatment cohort.

**Clinical trial identification:** EudraCT: 2016-003963-20.

**Legal entity responsible for the study:** AIO-Studien-gGmbH.

Clinical trial identification: NCT03360734.

Legal entity responsible for the study: Glycotope GmbH.

Funding: Glycotope GmbH.


Background: TO (CetuxGEX) is a second-generation anti-EGFR antibody that specifically binds to EGFR and acts as a competitive antagonist at the ligand binding site. Gemtuzumab ozogamicin (GO) is a novel humanized monoclonal antibody, which recognizes the tumor-specific epitope of mucin-1 (TA-MUC1) expressed on tumor cells. Both antibodies are glyco-engineered to potentiate antibody-dependent cellular cytotoxicity (ADCC). Compelling preclinical evidence suggests a complex interaction between EGFR and cell surface expressed TA-MUC1 in driving neoplastic processes and shows a synergistic antibody dependent cell cytotoxicity activity with the dual targeting of these molecules. Based on this evidence, this study aims to assess the tolerability, safety and preliminary activity of a combination with anti-EGFR and anti-TA-MUC1 glyco-engineered antibodies.

Trial design: The GATTO is an open label phase Ib dose evaluation study in patients with EGFR positive metastatic solid tumors, for whom no standard treatment is available. The proposed doses and schedule are 1200 mg Q2W for TO and 1400 mg Q2W for GAT. A staggered approach will be utilized in order to minimize the number of patients exposed and to evaluate the safety of the combination treatment. The first 6 patients will be enrolled into a safety run-in phase where the number of dose-limiting toxicities (DLT) will be evaluated. Assuming that the safety criteria are met (ie. observation of 0 or 1 DLT), the dose will remain unchanged and further patients will be recruited at the highest dose level. If this is not the case, a step-wise dose reduction approach will be applied. The antitumor activity of the combined treatment will be evaluated as secondary endpoints including best overall response rate (ORR), duration of objective response (DOR), progression-free (PFS) and overall (OS) survival. Extensive pharmacokinetics (PK) and pharmacodynamics (PD) (cellular immune status, serum and tissue biomarkers) will be also analyzed. As of the beginning of May 2018 the study is ongoing and 6 patients are being treated.

Clinical trial identification: NCT03360734.

Legal entity responsible for the study: Glycotope GmbH.

Funding: Glycotope GmbH.

PALLIATIVE CARE

1511O Training oncologists and preparing patients for shared decision making about palliative systemic treatment: Results from the randomized controlled CHOICE study


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1512O Automated survival prediction in metastatic cancer patients using high-dimensional electronic medical record data


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1513PD A prospective study examining cachexia predictors in patients with incurable cancer


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Randomized clinical trial of an individualized intervention promotes cancer patients' prognostic awareness and reduces CPR received in the last month

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Timing of palliative care referral before and after a cluster randomized controlled trial (RCT) of early palliative care

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Effectiveness of a randomized control trial of an individualized, interactive advance care planning intervention in improving terminally ill cancer patients' psychological symptoms, quality of life and concordance between preferred and received life-sustaining treatments

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Background: To examine the effectiveness of an advance care planning (ACP) intervention in facilitating concordance between cancer patients' preferred and life-sustaining treatments (LSTs) received in the last month and in improving quality of life (QOL), anxiety symptoms, and depressive symptoms over the dying process.

Methods: Terminally ill cancer patients (N = 460) were randomly assigned 1:1 to the experimental and control arms. Data were obtained from 430 participants who died through December 2017. The experimental arm received an individualized, interactive ACP intervention tailored to participants' readiness to engage in ACP. The control arm received a sham intervention of education on symptom management. Group allocation was concealed, data collectors were blinded, and treatment fidelity was ensured. Outcome measures included concordance of preferences for and receipt of six LSTs, QOL (McGill Quality of Life Questionnaire scores), as well as anxiety and depressive symptoms (Hospital Anxiety and Depression Scale scores). Intervention effectiveness was evaluated by intention-to-treat analysis.

Results: Concordance between LST preferences and LSTs received were 58.2-77.5% and 59.0-75.7% for the experimental and control arms, respectively. Between-arm differences in concordance between the six preferred and received LSTs were not significantly (odds ratios [95% CI]: 0.966 [0.653, 1.428]-1.107 [0.690, 1.775]). Participants in the experimental arm had significantly lower anxiety (β [95% CI] = -0.977, -0.189, p = 0.004) and depressive (β [95% CI] = -0.333, -0.030, p = 0.038) symptoms than those in the control arm, but QOL did not differ.

Conclusions: Our individualized, and interactive ACP intervention facilitated participants' psychological adjustment to the end-of-life (EOL)-care decision-making process, but did not improve their QOL nor facilitate EOL care that honored their wishes before death. Our findings can ensure clinicians that ACP intervention is not detrimental to patients' psychological well-being, but improves it at EOL.


Effectiveness of a randomized control trial of an individualized, interactive advance care planning intervention in improving terminally ill cancer patients' psychological symptoms, quality of life and concordance between preferred and received life-sustaining treatments

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Legal entity responsible for the study: Chang Gung University, School of Nursing.
Funding: National Health Research Institutes in Taiwan.

Disclosure: All authors have declared no conflicts of interest.

Background: Based on recommendations from several agencies, including the European Society for Medical Oncology, palliative care (PC) services are increasingly recognized as an essential part of oncology care. However, the implementation of integration of oncology and palliative care (IOP) seems to be evolving slowly and detailed progress of IOP remain unclear. This was a cross-sectional nationwide survey to clarify the current status of IOP in Japan.

Methods: We performed comparison between designated cancer hospitals (DCHs) and non-designated cancer hospitals (non-DCHs), since considerable number of patients in Japan are receiving cancer treatment at non-DCHs. We distributed the questionnaire to executives or directors of oncology departments at cancer hospitals in November 2017 and sent a reminder email later. Our questionnaire was developed based on indicators of IOP with international consensus. We conducted descriptive statistics, t-tests and Cochran-Armitage trend tests where appropriate. To adjust the difference of inpatient beds scale, estimates at non-DCHs were weighted by the distribution of inpatient beds at DCHs.

Results: Among the 399 DCHs and 478 non-DCHs that were surveyed, 269 (67%) and 53% (p < 0.001); the availability of outpatients service q 3 days per week, 48% vs. 21% (p < 0.001). Clinical tools for PC services were well equipped (e.g. symptom management guidelines, 89% vs. 79% (p = 0.238), PC referral criteria, 72% vs. 59% (p = 0.077)). However, strategies to identify suitable patients for PC referral seemed to be undeveloped (e.g. clinical care pathways, 17% vs. 5% (p < 0.001); referral using time trigger, 9% vs. 8% (p = 0.358); referral using needs trigger, 31% vs. 20% (p = 0.820)). Mutual rotation training for both oncology and PC fellows and research opportunities on IOP were limited.

Conclusions: Non-DCHs face a severe lack of PC resources, whereas DCHs might have relatively more resources to enhance IOP. Both education and research opportunities for IOP were limited. Further research is warranted to identify specific barriers to and facilitators for implementation of IOP.

Legal entity responsible for the study: Graduate School of Medicine, Kyoto University.
Funding: Ministry of Health Labor and Welfare in Japan (Health Labor Science Research Grant).

Disclosure: All authors have declared no conflicts of interest.

Access to palliative care before death in French cancer patients during the first two years after diagnosis: The national cancer cohort

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Background: Palliative care (PC) is a part of a multidisciplinary approach that improves the quality of life of patients with potentially terminal illnesses including cancer. However, referrals to PC occur relatively late for the management of physical and psychological distress. In France, the proportion of patients who actually receive PC is not clear. This study aims to provide the prevalence and characteristics of dead cancer patients who have been referred at least one time to PC, and to identify the delay between PC access and death.

Methods: All people living in France (67 million population) with universal insurance coverage and diagnosed, treated or followed up for a cancer, such as survivors, are included and followed for 25 years. Extracted from SNSD, the cancer cohort contains all healthcare consumption refunded data (i.e hospitalization, outpatient care, medication etc.) for subjects who have undergone cancer-related treatment since 2010. Every year, new cases are included in the cancer cohort. Data were extracted from the French “cancer cohort” databases for all people with cancer-related care between 2013 and 2015. Demographic characteristics, type of cancer, health care consumption, and delay between PC and death were determined.

Results: Of the 310 901 cancer patients included in the Cancer Cohort in 2013, 70 858 (22.8%) died between 2013 and 2015. Of these, the proportion of PC access was 52%. Access to PC of dead cancer patients was different according to age, gender, type of cancer and comorbidities. The median time between diagnosis and death, diagnosis and PC access, and PC access and death, were 225.0 days (Q1-Q3: 84.0 - 418.0), 158.0 days (Q1-Q3: 38.0 - 354.0) and 26.0 days (Q1-Q3: 11.0 - 56.0), respectively.

Conclusions: If more than half of cancer patients in our study had access to PC before death, differences in age and gender were observed confirming the results of previous studies. We also noted that the delay between PC access and death indicates a late referral to PC in the disease trajectory. General practitioners, PC specialists and the community at large need education so that cancer patients have access to quality PC as soon as possible and without necessarily being in near end-of-life situations.

Legal entity responsible for the study: French National Cancer Institute (INCa) - Cohort Cancer Group.
Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Anticancer therapy at the end of life of breast, prostate, and colorectal cancer patients

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Background: The study addresses growing concerns regarding aggressive cancer treatment at the end of life. The extent of anticancer treatment at the end of life of breast, prostate, and colorectal cancer patients aged 60 and older as well as its development in recent years is investigated.

Methods: Routine data of the statutory health insurance company AOK Hessens in Germany (approx. 1.4 million assured persons in 2014) for 2008-2013 are analyzed. Cancer patients are identified using ICD-10 codes: breast (C50), prostate (C61), and colorectal cancer (C18-21), and validated using inpatient and outpatient diagnoses. The last year before death is examined in 90-days periods and, in addition, the last 90 days in 30-days periods.

Results: Key results are that cancer patients aged 80 years and older less often receive anticancer therapy at the end of life (e.g. women with breast cancer in 2013: 20% in the last 90 days, 6% in the last 30 days before death) than patients aged 60-69 (56% and 29%) or 70-79 (46% and 18%). There is no clear development toward a reduction in anticancer treatment in women with breast cancer at the end of life between 2008 and 2013. The number of anticancer therapies at the end of life in men with prostate cancer aged 60-69 years reduced between 2008 and 2013, especially in the second (2008: 56%, 2013: 49%) and third 90-days period from last (2008: 57%, 2013: 45%) and reached the same level as patients aged 70-79. There are differences in the number of anticancer therapies between men and women with colorectal cancer at the end of life. Especially, women aged 80 and older with colorectal cancer rarely receive anticancer therapy in the year before death (in 2013: 5% in the last 90 days, 1% in the last 30 days before death) compared to men (12% and 5%).

Conclusions: These results support increased sensitivity regarding anticancer treatment at the end of life. To further investigate these results, studies should include cancer staging, general health status, and patient reported outcomes such as quality of life.

Legal entity responsible for the study: WINHO GmbH & Universitatsklinik Köln / PVF Forschungsgruppe.
Funding: Zentralinstitut für die kassenärztliche Versorgung.

Disclosure: All authors have declared no conflicts of interest.

Perspectives and attitudes towards the integration of oncology and palliative care in Japan: A nationwide survey

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Background: Integration of oncology and palliative care (IOP) is recommended by several agencies, including the European Society for Medical Oncology. Given the slow evolution of IOP in practice, several barriers to its implementation may exist. Lack of institutional support is known to be one of the key barriers to IOP. However, institutional recognition towards IOP is less investigated. This was a cross-sectional nationwide survey to clarify the institutional perspectives and attitudes towards IOP in Japan.
1521P Evolving concurrent integration of oncology and palliative care at an ESMO designated center over a decade

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Background: Streamlining oncology (Onc) and specialist palliative care (SPC) into integrated patient (pt) care is increasingly a gold standard of optimized cancer care. The ways that integrated Onc/SPC manifests in clinical practice may change over time. Little is known about factors that drive evolution in integrated care practices.

Methods: From a pt’s first appointment with outpatient SPC, all visits were chronologically color coded for Onc, SPC, and Neutral (e.g. emergency) or joint visits (Onc/SPC same day). Visual Graphic Analysis revealed 4 patterns of integration (Onc only; SPC only; CONC: current: permanent exchange of Onc and SPC, >5 switches, joint visits; SEGmented: alternating periods of Onc or SPC, <4 switches), independent researchers approved reliability of patterns definitions. Data from 2006-2009 (presented 34-ESMO 2009) were compared with 2016-2017. Exploratory factors for patterns evolution were derived from multi-professional, consensus review discussing descriptive statistics (e.g. impact of inpt admission on patterns, pattern stability over 3 months intervals, anticancer treatment administered by SPC, pt characteristics) and further explored in the data.

Results: 345 pts from 2006-09 and 64 from 2016 met eligibility criteria and were included. CONC occurred in 18% in 2006-09 and 45% in 2016 (X² (1, N = 409) = 22.66, p < 0.001), and 14% vs 50% remained in the CONC pattern comparing 3 months intervals. Elimination of inpt visits left 3/4 of patterns unchanged. A double-boarded Onc/SPC physician saw 94% of pts in the 2016 sample and prescribed systemic anti-cancer treatment in > 1/3 of these visits, 77% of these pts were in the CONC Pattern. Joint Onc/SPC visits were increasing over time, also (bi-)weekly alternating visits by Onc and SPC (double-boarded). Pts of CONC had complex and high needs for palliative interventions, were in phase I studies, or refused standard anticancer treatment, but accepted later.

Conclusions: Concurrent Onc/SPC is an increasing and consistent pattern, not explained by mere bed availability. Prescribing anticancer therapy by a double-boarded physician may foster integration. Further research may determine how CONC affects pt outcomes and the influence of pt and physicians’ characteristics.

Legal entity responsible for the study: Cantonal Hospital St. Gallen. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

1522P The impact of inclusion in home palliative program and distance to hospital on chemotherapy near end of life

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Background: Chemotherapy (CT) near end of life is considered a marker of inadequate palliative care for cancer patients. The objectives of our work were to determine the influence of palliative care at home and the distance between the residence area and the cancer referral center on the interval between last chemotherapy cycle and death.

Methods: A retrospective observational study was conducted in a tertiary care hospital. All cancer patients deceased between January 2013 and June 2014 were included. Clinical, demographical and treatment variables were obtained from medical records.

Results: Our population of 951 patients had a mean age of 63 years; male: 601 (63%), females: 350 (37%). Tumor locations: lung, 261 (28%); colorectal, 125 (13%); breast, 99 (10.8%); pancreas, 79 (8.8%). The table shows an analysis of the CT used in all patients, indicating a high proportion of CT use near the end of life (68% in the last 3 months). Average time elapsed between the end of treatment and death was significantly longer in the group of patients included in home palliative care programs (n = 111; 24.5%) vs. those not included (n = 367; 25.9%). 43.2 vs. 24.7 days (p < 0.05). CT was stopped earlier in patients belonging to geographical areas farther from the referral center, with median times between last cycle of CT and death of 14.9 days for patients living near the referral hospital versus 51.9 days for > 70 km (p = 0.041) and 58 days for > 100 km (p = 0.013).

Table: 1522P Analysis of CT use in all patients

<table>
<thead>
<tr>
<th>N = 901</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment No CT CT</td>
<td>198 (22) 703 (78)</td>
</tr>
<tr>
<td>Nr of lines of CT 1 2 3 4 or more</td>
<td>441 (49) 192 (22) 135 (15) 127 (14)</td>
</tr>
<tr>
<td>Nr of drugs in last line of CT 1 2 3</td>
<td>378 (42) 414 (46) 109 (12)</td>
</tr>
<tr>
<td>CT in the last 3 months</td>
<td>604 (67)</td>
</tr>
<tr>
<td>CT in the last 4 weeks</td>
<td>405 (45)</td>
</tr>
<tr>
<td>CT in the last week</td>
<td>63 (7)</td>
</tr>
</tbody>
</table>

Conclusions: In our population, a high percentage of CT was observed in the final stage of life of a high use of third and successive lines of treatment. Patients included in home palliative care programs and/or belonging to more distant geographical areas finished active treatment before, thereby suggesting that both factors impact on decision making for patients with advanced cancer. Understanding the factors that determine the use of CT near the end of life may contribute to limit its inadequate indication.

Legal entity responsible for the study: Hospital Universitario Santa Lucia, Cartagena. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

1523P Cancer patients’ perceptions of palliative care

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Background: Despite clear benefits and increased efforts towards earlier integration of palliative care (PC) with oncology, there are concerns that PC remains stigmatized and predominantly associated with end-of-life care (EOLC). This project aims to explore current perceptions and understanding of PC in cancer patients.

Methods: Prospective survey conducted in the oncology ward of a tertiary academic hospital in Melbourne, Australia. Over a 4-month period a 16-item questionnaire was distributed to all cancer patients upon admission to the ward (N = 103). Chi-Squared test was used to examine for significant factors related to patients’ perceptions of PC. Results: Ninety-six patients (93%) completed the questionnaire; of which 79% had metastatic cancer. Of the domains explored, salient findings were: 1) Familiarity and experience: 76% had heard of PC, while only 21% had received PC. Self-rating of PC knowledge was varied, and evenly distributed: 31% good/excellent, 36% average and 33% below average/poor. 2) Roles of PC and oncology: 86% believed they could receive concurrent oncology and palliative care and 81% believed they could receive anti-cancer treatment whilst receiving PC. Those who had heard of PC were significantly more likely to respond that they could receive concurrent anti-cancer treatment (p = 0.003), as well as those who had better self-rated PC knowledge (p = 0.045). 3) Perceptions: 45% believed PC was only associated with EOLC. Those more likely to disagree with this statement had received PC services (p = 0.039). The majority (77%) felt comfortable with PC involvement; this was significantly associated with older age (p = 0.047) and
an understanding that oncology (p < 0.005) and anti-cancer treatment (p = 0.013) could continue. However, 40% felt frightened and 29% felt hopeless about a referral to PC. Notably, 50% felt more comfortable with “supportive care” services (versus PC), 25% were neutral and 25% were not.

Conclusions: This survey had an excellent response rate and results were reassuring that, in general, respondents had an accurate understanding of and positive perceptions of PC. Familiarity and comfort with PC were associated with significantly better understanding of PC. This may reflect overall progress in integration of PC and oncology care.

Legal entity responsible for the study: Research Support Services, Monash Health.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Terminally ill patients can draw up Physician Orders for Life-Sustaining Treatment (POLST) with physicians to decide whether they want to suspend life-prolonging treatment near death. We conducted a multicenter, prospective study to assess the feasibility of completing the POLST in real practice for cancer patients.

Methods: The inclusion criteria were patients with terminal cancer, age ≥19, and able to communicate. The purpose and concept of POLST was introduced first, and POLST was discussed with those whom wanted. Primary endpoint of this study was the completion rate of the POLST form in Korea.

Results: From June to December 2017, 336 patients were enrolled from seven hospitals. The median age was 66 (20-97) years, 177 (52.7%) were male, and 203 (60.4%) showed the feasibility of completing the POLST in real practice for cancer patients.

Conclusions: Only one-third of patients completed the POLST, and various barriers were found among physicians, patients, and families.

Legal entity responsible for the study: The authors.

Funding: This study was supported by grants from the Korean Cancer Study Group.

Disclosure: All authors have declared no conflicts of interest.

Methods: We conducted a retrospective observational study selecting all patients with a first consultation in the Medical Oncology Unit of the Puerta de Hierro University Hospital during 2014 and 2015, who died before December 31st, 2017. Treatments carried out, assessment by a PCU and home palliative care services (HPCS), during the last 6 months of life and place of death (hospital, home or PCU) were reviewed. We aimed to assess quality of care evaluating the use of active therapies and PCU using a novel approach considering what was done during the last six months of life.

Results: 622 patients were selected (36% female/64% male), median age of 69 years (IQR 61-76), 89% were stage IV. Lung (32%) and gastrointestinal (31%) cancer were the most frequent. In the last 6 months of life, 59% of patients received chemotherapy (CT), 26% radiotherapy (RT) and 8% undergone surgery. Median time from the last CT and RT to death was 39 days (IQR 23-75) and 57 days (IQR 21-100) respectively. 28% of patients were not assessed by a PCU from whom 52% were first evaluated in the last 30 days before death and 28% had been followed for more than 60 days. Only 44% were followed by HPCS. In patients with HPCS, the number of deaths at home (41%) and at PCU (29%) was significantly higher, with only 30% dying at hospital. By contrast, among those never assessed by HPCS: these figures were 12%, 24% and 64% respectively (p < 0.001).

Conclusions: 1/3 of patients had never been assessed by a PCU and the selection of patients who benefit from active therapies in the last months of life must be clearly improved. The association between place of death and assessment by a HPCS suggests the efficiency of these units and the benefit of increasing their resources. The objective of a global approach for palliative care to all patients with advanced cancer is close but not achieved yet.

Legal entity responsible for the study: Medical Oncology Department, Puerta de Hierro University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Current management strategies of cancer patients are adopting multidisciplinary meetings (MDM) and including the earliest palliative care intervention to improve the quality of life and survival. We have established, since 2015, a monthly onco-palliative care MDM for the management of our cancer patients. This study reports on the role of onco-palliative MDM in Hotel Dieu de France University Hospital, an ESMO Designated Center of Integrated Oncology and Palliative Care.

Methods: All cancer patients referred to the mobile palliative care unit and/or transferred to the palliative care unit, are presented and discussed during the onco-palliative care MDMs held between May 2015 and November 2017. Demographic, clinical and long-term characteristics were obtained from the electronic medical records and retrospectively nalysed. Demographic and survival data were compared between 2015 and 2017.

Results: 245 patients were presented during 20 MDMs. Median age was 68 years (range 59-77) and 58% of patients were male. The most common motive for palliative care consultation was social support (40%). Over the study period, no significant effect on the place of death was retained. However, patients had significant improvement in the symptomatic management of their disease between 2015 and 2017 (41.6% vs 7% in 2015) and better social support (60.7% vs 32.4% in 2015) (p < 0.001). The median survival of patients after the onco-palliative care MDMs was 23 days (9.3- 26.7). No significant difference in survival was noted over the 3 year course (p = 0.315). Using the univariate cox regression model, in comparison to 2015, the hazard ratio is 0.780 (0.556 – 1.094, p = 0.149) for 2016, and 0.924 (0.635 – 1.309, p = 0.656) for 2017.

Conclusions: The onco-palliative care MDMs is an innovative approach in Lebanon, a small conservative Middle Eastern society. These MDMs were shown to improve the quality of life of cancer patients with better symptomatic and social support. However, no significant impact on survival was demonstrated so far.

Legal entity responsible for the study: Saint Joseph University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
End of life resource utilization among patients receiving immunotherapy for advanced cancer

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Background: Patients (pts) with advanced cancer have high rates of healthcare resource utilization at the end of life (EOL). Immunotherapy (IO) has changed the landscape for many patients with cancer. The impact of IO on resource utilization at the EOL for pts with metastatic disease, including emergency department (ED) visits, hospitalizations, and referrals to hospice is unknown.

Methods: We conducted a single center, retrospective analysis of pts treated with PD-1/1-L or CTLA-4 antibodies alone or in combination from 2011 – 2017. We identified 1,115 pts from electronic health records and present here clinical information for 506 pts with metastatic disease and end of life outcome data for 188 decedents. Survival curves were compared using log rank test for pts by disease, treatment type, ECOG performance status (PS) at treatment start, and age. Hospice referral rate was compared using Fisher’s exact test.

Results: Of the 506 pts, 131 (43%) had melanoma, 42 (14%) had renal cell carcinoma, 33 (11%) had non-small cell lung cancer, 22 (7%) had head and neck cancer, and 78 (25%) had another advanced malignancy. Treatment consisted of nivolumab in 130 (42%) pts, ipilimumab in 73 (24%), pembrolizumab in 59 (19%), nivolumab/ipilimumab in 23 (6.3%), atezolizumab in 9 (3%), and other IO combinations in 12 (4%). Of the 188 (61%) pts who died, 93 (49%) had at least one ED visit in the last month of life, 50 (59%) had at least one hospitalization, and 21 (11%) died in the hospital. Of all pts who died, 156 (83%) had hospice referral with a median of 11 days (range 1-420) between hospice referral and death. Overall survival (OS) was not associated with disease type (p = 0.11) or treatment (p = 0.832), but was associated with ECOG PS (p = 0.015). Referral to hospice did not vary by disease type (p = 0.945), treatment type, (p = 0.809) or age (p = 0.432), but did vary by ECOG PS (p = 0.006). Death within 72 hours of hospice referral rate varied significantly by inpatient or outpatient referral (p = 0.002).

Conclusions: Hospitalizations and ED visits are frequent at the EOL among pts who received IO for advanced malignancies. There was a high referral rate to hospice, but the median time between hospice referral and death was short. Interventions to decrease aggressive EOL care are needed.

Legal entity responsible for the study: Jarrett Burkart.

Disclosure: A.M. Noonan: Paid member of data safety monitoring board from 2016-2017. Helsinn. All other authors have declared no conflicts of interest.

Palliative chemotherapy for patient with advanced tumor and poor performance status: Are oncologists’ hopes of benefit justified?

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Background: The recommendation to use palliative chemotherapy (PC) in patients (pts) with advanced cancer and poor performance status (ECOG-PS) is controversial and could be harmful. However, in routine practice some oncologists still recommend it. We sought to identify the outcomes and related prognostic factors of PC in these pts treated in a large academic cancer center.

Methods: We retrospectively reviewed all consecutive pts with poor ECOG-PS meta-static solid tumors who received PC during hospitalization for symptom control from January 2015 to September 2017. Eligible pts had ECOG-PS 3/4 and started first line PC or had ECOG-PS ≥ 2 and started second or further lines. Pts with known chemo-sensible tumors (gastrointestinal, small cell lung cancer) and primary central nervous system were excluded. The primary end point was survival rate within 30 days from the date of first cycle. Logistic regression was used to identify prognostic factors associated with this mortality rate.

Results: We identified 228 consecutive pts. The median age was 56 years old, 133 pts (58%) were female, 150 pts (66%) were chemotherapy-naïve and almost half of pts had primary gastrointestinal tumors. 21.9%, 66.7% and 11.4% pts had ECOG-PS 3, 2 and 1, respectively. With a median follow-up of 49 days, 224 pts (98.2%) died. Nearly two thirds (N = 142) of pts died while hospitalized, with 31 (13.8%) dying while in ICU. 27 pts (12%) died in a hospice and 2 pts passed away at home. The median overall survival was 38.5 days and the survival rates within 30 and 60 days of chemotherapy were 35.7% and 38.5%, respectively. In the multivariate analysis, ECOG-PS 3/4 (OR 2.45; p = 0.015) and baseline values of anemia (OR 0.41; p = 0.034), hypercalcemia (OR 2.71; p = 0.410) and elevated total bilirubin level (5.14; p = 0.011) were significantly associated with 30-day mortality.

Conclusions: Most pts with advanced cancer and poor performance status clearly do not benefit from PC, especially those with ECOG-PS 3/4, hypercalcemia and elevated bilirubin. Transparent conversation with pts and their families about prognosis and the inefficiency of PC in this setting is crucial to avoid futile interventions.

Integration of oncology and palliative care

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Background: Integration of oncology and palliative care (PC) combines two paradigms: the tumour-directed approach, which is the main focus of oncology, and the host-directed approach, which is the focus of PC. Contemporary PC aims to prevent, treat and reduce symptoms and suffering and to preserve and improve quality of life. A Lancet Oncology Commission was written on how PC and oncology can be integrated by combining these two approaches focusing content, models, organization of cancer care, public health, politics, education and research.

Methods: An international panel was established, consisting of experts in oncology, PC, public health and psycho-oncology. Literature searches were conducted, author meetings were held, and an interactive writing process was conducted.

Results: Integration is a complex process that involves various components of the health care system. The published RCTs on integration demonstrate health gains, but how and when to integrate is uncertain. Still, early delivery of specialist palliative care promotes patient-centeredness including shared-decision making, family involvement and similar use of patient-reported outcome measures. Barriers to integration include the perception of PC as end-of-life care, deficient planning at local, national and international levels, and insufficient infrastructure and funding. Furthermore, death and dying are stigmatized. The present competence in combined oncology and PC varies substantially and must be defined at all levels. The commission proposes to use standardized care pathways (SCPs) and multidisciplinary teams (MDTs) to promote integration. Integration raises new research questions: how much, when and how should PC be delivered and what is the minimum model for good care.

Conclusions: Integration involves the transition from a dualistic perspective - the tumor and the host- to a combined perspective. Integration must be recommended by health care authorities and decision-takers, followed by resource allocation and priority-setting. In all areas, the present volume of PC is too small to support integration on a broad scale. Implementation of integrated models is best secured by MDTs and SCPs. The combined perspective must be reflected in care models, education and research funding.

Legal entity responsible for the study: Oslo University Hospital.

Disclosure: Has not received any funding.

Understandability of the standard arabic translation of the EORTC QLQ-C15-PAL questionnaire by Egyptian patients with incurable cancer

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Background: Many of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires is translated into standard Arabic. However, standard Arabic is not the language used for daily life communication in Arab countries where each country has its own local dialect. The aim of this study was to explore the understandability of the current standard Arabic version of the EORTC QLQ-C15-PAL by Egyptian advanced cancer patients with different educational levels.

Methods: The study included 100 adult patients with incurable cancer and different educational levels. Literate patients were asked to read the standard Arabic QLQ-C15-PAL...
Early outpatients palliative care (EPC) in patients with metastatic cancer has been shown to impact quality of life and decrease healthcare utilization, but data concerning PS, including relatives’ perception, in order to inform current practice patterns.

**Results:** Professionals should integrate EPC for patients with advanced cancer. Advantages to EPC include improvement in patient’s quality of life, reduced aggressive care at the end of life, increased advanced directives. A web-based application for monitoring comfort in patients receiving EPC is currently being evaluated.

**Legal entity responsible for the study:** Hugues Bourgeois.

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**How to practice oncology with a supportive and palliative care ambulatory unit: A French experience (HOASIS)**

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**Background:** Early outpatients palliative care (EPC) in patients with metastatic cancer has been shown to impact quality of life and decrease healthcare utilization, but data describing these benefits are limited and referrals to palliative care services are often late. Our Ambulatory Unit named HOASIS offers an interdisciplinary approach to cancer management for patients.

**Methods:** HOASIS was created in March 2017 to receive EPC patients in order to foster autonomy and quality of life, both for patients and families. Multi-professional teams provide care in cooperation with physician. This retrospective study analyzed 152 EPC patients from March to December 2017.

**Results:** In total, 152 patients were evaluable. 97% had solid tumor (mainly breast and digestive cancer, respectively 24% and 37%) and 3% had hematologic malignancies. Median age was 66 years, ECOG PS 0-1 (118%), PS 2 (52%) and PS 3-4 (28%). Most common services used were nutrition (67%), psychological counseling (39%), physical therapy (33%) and social work intervention (30%). Patients were supported to understand their prognosis with clear information about their disease and treatment (45%) and make care decisions (11%). Medical prescriptions included pain control (46%), symptomatic treatment (38%), physiotherapy (27%), psychotropics (6%) and nutritional supplements (12%). Nurses delivered the information allowing 49% to chose their trusted person and 13% both completed advance directives and trusted person. After evaluation, 29% needed oxygen supplementation, 66% had oncology consultation, 26% had phone consultation and 26% were hospitalised. Home service was supplied to 63% of them. Out of the 152 patients, 13 (9%) were left in our unit, less than 1 month before death, and 83 (55%) were seen more than 1 month before death. Full data about chemotherapy around end of life will be delivered during the meeting.

**Conclusions:** Professionals should integrate EPC for patients with advanced cancer. Advantages to EPC include improvement in patient’s quality of life, reduced aggressive care at the end of life, increased advanced directives. A web-based application for monitoring comfort in patients receiving EPC is currently being evaluated.

**Legal entity responsible for the study:** Hugues Bourgeois.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**abstracts**

**Prognostic impact of end-of-life chemotherapy in the last weeks for patients with advanced cancer**

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**Background:** Appropriately timed cessation of chemotherapy is important for patients with advanced cancer at the end of life stage. There are frequent discussions on how to optimize the over-treatment of end-of-life chemotherapy currently, but the definition of end-of-life chemotherapy remains unknown.

**Methods:** We analyzed patients’ data between August 2011 and August 2016. The primary endpoints were prognostic factors (age, sex, primary site, clinical stage, comorbidity, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and Glasgow Prognostic Score (GPS)) following the last administration of chemotherapy within 14 days of death. Patients with either C-reactive protein levels >1.0 mg/dl or albumin levels <3.5 g/dl were classified as GPS1; patients with both were classified as GPS2, and those with neither of the two were classified as GPS0. The secondary endpoints were prognostic factors following the last administration of chemotherapy within 30 days of death. The associations between end-of-life chemotherapy and the frequency of end-of-life symptoms (delirium, cancer pain, dyspnea, nausea and vomiting, and fatigue) and treatment (hydration, continuous sedation, and epoides) were evaluated.

**Results:** We obtained 300 patients’ data including complete information about the last administration of chemotherapy. The number of patients within 14 and 30 days of death from the last administration of chemotherapy were 16 (5.3%) and 50 (16.7%), respectively. In multivariate analysis for end-of-life chemotherapy, ECOG-PS (odds ratio 0.26, p = 0.046) and GPS2 (odds ratio 0.19, p = 0.043) were significant prognostic factors within 14 days of death, while ECOG-PS (odds ratio 0.34, p = 0.046), GPS1 (odds ratio 0.28, p = 0.001), and GPS2 (odds ratio 0.32, p < 0.001) were significant prognostic factors within 30 days of death. The median survival time from the last administration of chemotherapy of patients with both GPS2 and ECOG-PS (≥2) was 41 days, and that of patients with both GPS0 and ECOG-PS (0-1) was 162.5 days. Prevalence rates at the end-of-life stage for nausea and vomiting (25.0%) within 14 days of death were significantly higher than those (7.4%) over 14 days of death. The mean amounts of hydration (0.50 L/day) at the end-of-life stage with 14 days of death were significantly higher than those (0.20 L/day) over 14 days of death.

**Conclusions:** GPSs and ECOG-PS were significant prognostic factors for over-treatment of end-of-life chemotherapy. Information about these factors can aid clinical decision-making in individual patient risk stratification, especially in palliative care settings, and in the further development of prospective cohort studies about end-of-life chemotherapy.

**Legal entity responsible for the study:** Mitsubishi Kyoto Hospital.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
1534P Congruence between actual place of death and preferences of Egyptian patients with advanced cancer and their family caregivers

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Background: Identifying the preferred place of death (PPoD) of incurable cancer patients and their family caregivers is important for the delivery of end-of-life care that meets their needs. The PPoD was not studied before in our region where talking with patients about death is largely perceived as unacceptable. Our aim was to study the PPoD of Egyptian patients with incurable cancer and their family caregivers and the actual place of death (APoD) of these patients.

Methods: A prospective observational cohort study that included 92 patient/family caregiver dyads. Patients and family caregivers were asked about their PPoD (home, hospital or other) in the event of patient’s death. Patients were followed up until death to know the APoD.

Results: Of the 92 PPoD, 86% (79/92) indicated home as the PPoD for the vast majority of Egyptian patients with incurable cancer and their caregivers. Although the majority of patients died at home, other patients died in hospital contrary to their home-death preference.

Legal entity responsible for the study: Kasr Al-Ainy School of Medicine, Cairo University.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1535P Sarawak: Healthcare professionals’ perception of palliative care at end of life

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Background: Palliative care is fundamental to health and a basic human right. Healthcare professional are often the gatekeeper to palliative care for their patients, but there is great disparity in access to palliative care across Malaysia, and little knowledge about healthcare professionals’ perception towards palliative care at the end of life in Sarawak.

Methods: We surveyed all healthcare professionals who attended a palliative care seminar and talk by Prof Dr Anne Merriman, founder and director of policy and International program, Hospice Africa when she visited Kuching, Sarawak on 5th and 6th April 2018. Participants were asked to answer a questionnaire designed by Prof Merriman which comprises of 25 questions in trochotomous scale.

Results: A total of 186 responses were obtained, of which 66% (127) were doctors and 25% (46) were nurses. 80% (149) responded that they would like to die at home, while only 5% (9) preferred to pass away in hospital. 96% (179) wished to have family with them and 84% (157) wanted spiritual guidance at the end of life. Only 41% (76) reported that they were afraid to die, yet majority responded that they were afraid of a painful death (86%;160), a prolonged dying process (89%; 164) and troubling others (96%; 167). Less than 50% of healthcare professional surveyed felt that they were able to help patients achieved adequate pain control (43%;90) or support patients emotionally (42%;78). and majority (58%) reported lack of knowledge being the barrier. 95% (176) reported that they would like to attend more palliative care seminars and 92% (171) would like to have palliative care in their unit. 26% (48) responded that they would like it to be lawful to practice euthanasia, but only 15% (28) were prepared to actively practice euthanasia if it is legal.

Conclusions: Home is the preferred place of death even amongst healthcare professionals in Sarawak. Lack of knowledge and professional training remains a major barrier to access of palliative care. The survey highlighted the need for palliative care training for local healthcare professional as well the need to develop hospice home care services in our State to provide better end-of-life care for patients and families. Advocacy for advanced directives should be initiated.

Legal entity responsible for the study: Winnie Hui Yee Ling.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1536P Factors associated with length of stay in an acute palliative care unit: A retrospective analysis

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Background: Acute palliative care units (APCUs) admit patients with cancer for symptom control, transition to community palliative care unit/hospice or end-of-life care. Prognostication is crucial for decision-making. We evaluated factors associated with patients’ length of stay (LOS) on an APCU in a cancer centre.

Methods: We analyzed demographic, administrative and clinical data for patients admitted to the APCU in 2015. Clinical data included cancer diagnosis, palliative performance scale (PPS) on admission, delirium screening using the short Confusion Assessment Method (CAM), and Edmonton Symptom Assessment System (ESAS) symptoms. ESAS distress score (EDS; sum of all 9 symptoms) and FDSA sub-score (fatigue, drowssness, shortness of breath, appetite) were calculated. We conducted unvariable (UVA) and multivariable (MVA) regression analyses of factors associated with LOS of patients who died on the APCU and of those who were discharged.

Results: Among 280 patients, 156 (56%) died on the unit and 124 (44%) were discharged. Median LOS was 14 days for discharged patients and 8 days for those who died (p = 0.001). Discharged patients were older (median age 68 vs 64, p = 0.003) and had higher functional status (median EDS 44 vs 38, p < 0.009), were more likely to be admitted from an inpatient unit (p < 0.001) and for terminal care (p = 0.001), and were more likely to develop delirium (p = 0.04). On MVA of patients who died on the APCU, for reason (p = 0.007), delirium (p = 0.02) and FDSA score (p = 0.002) were associated with LOS. Shorter LOS was associated with admission for terminal care (p = 0.05) and missing FDSA (patients were too ill to complete) (p = 0.001). Longer LOS was associated with delirium (p = 0.02). For patients who were discharged from the APCU, delirium was associated with longer LOS (p = 0.02).

Conclusions: In cancer patients admitted to an APCU, development of delirium was associated with longer LOS in patients who died on the unit as well as in patients who were discharged home or to PCU/hospice.

Legal entity responsible for the study: Camilla Zimmermann.

Funding: Canadian Institutes of Health Research.

Disclosure: All authors have declared no conflicts of interest.

1537P Medical-aid-in-dying use in the US Pacific Northwest

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Background: Eight venues in the US allow terminalily ill residents to self administer prescribed oral drugs to end life. The Pacific Northwest states Oregon (OR) and Washington (WA) report number of prescriptions written, pt demographics, and motives underlying the requests. To study reasons for medical-aid-in-dying (MAID) requests and to assess patterns of use, we evaluated a combined 28 years of information from the most extensive database in North America.

Methods: OR and WA Health Authorities monitor MAID compliance. Website data from 1998 –2017 (OR) and 2009-2016 (WA) were collated. Characteristics of those dying from ingested drugs were calculated independently by state and then combined. Time trends for deaths vs. prescriptions written were analyzed using logistic regression.

Results: 3368 prescriptions were written; 2282 pts took drug and died. The percent ingesting medication per yr ranged from 48-87, with no significant time trend in OR but with an increase over time in WA (2-sided p = 0.59 and <0.01, respectively). 77% of pts had cancer; 10% neurologic illness; 5% lung disease (dz); 5% heart dz; 3% other. 4% were sent for psychiatric evaluation. MUF (%): 31/49. 31% were in the largest pt age group represented: 65-74 yrs (overall range 20-102). Race white/other/unknown (%): 95/4/0.8. Eighty-three percent died at home (93 OR, 71 WA); a prescriber was present in 10% of cases (16 OR: 5 WA). Time between drug intake and coma ranged from 1 to 6240 min. Fewer than 0.5% awoke in OR. Reasons for MAID (%): Poor QOL 87; loss of autonomy 68; inadequate pain control 30 (OR 26; WA 56); financial concerns 6.

Conclusions: Unlike European countries allowing euthanasia, US MAID consists only of terminally ill pts self-administering lethal medication. Up to half the pts requesting prescriptions do not take the drugs. Pts must be legally competent but rarely are referred to psychiatrists for that assessment. Most MAID pts have cancer and most use MAID for conditions that are difficult to palliate (loss of autonomy/dignity/QOL). Of concern, some use it because of inadequate pain control or finances. MAID merits formal study, such as how to develop faster-acting medications, as well as comparing effectiveness and demographics (especially age) with assisted dying data from Canada and Europe.
Brain metastases in Norway: A prospective cohort study

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Background: Brain metastases (BM) cause significant morbidity and mortality, and the incidence is increasing. With continuous developments in neurosurgery, radiation techniques such as stereotactic radiotherapy, and novel systemic therapies, treatment decisions have become more challenging. Also, the role of whole brain radiotherapy is being debated due to its marginal survival benefits and potentially significant side-effects. International guidelines on treatment and follow-up exist, but the scientific evidence supporting these guidelines is limited. To improve patient-centered care and promote shared decision-making, systematic, population-based registrations of patient, disease, treatment, and outcome variables are necessary. We have launched a prospective cohort study in the South-East health-care region of Norway (appr. 3 million inhabitants). The study population will consist of consecutive patients newly diagnosed with BMs recruited over a two-year period. Follow-up will be for up to two years or until death. The primary aim is to establish a prospective, clinical registry with data on diagnostics, treatment, and follow-up, including Patient Reported Outcome Measures (PROMs). With this prospective information, evidence-based diagnostic and treatment algorithms and follow-up guidelines can be developed. Study outcomes include: • Detailed description of the study cohort (including patient-, disease-, and treatment characteristics) • Overall survival (from BM diagnosis) • Association between disease, treatment, and patient characteristics and survival • Patient reported symptoms and quality of life.

Trial design: This is a prospective cohort study conducted in the South-East health-care region of Norway. Inclusion criteria: •Radiologically confirmed BMs from solid cancers diagnosed during the study period, regardless of planned treatment for BM. •No previous treatment for BMs •Age > 18 years Timeframe: Two-year consecutive inclusion, started November 2017. Estimated target population: 1,000 cases Data collection: Clinical data are registered every 3 months for up to 24 months. Patient-reported symptoms and quality of life are assessed with standardized questionnaires (EORTC QLQ-C15-PAL, BN-20, and EQ-5D) monthly for up to 12 months.

Clinical trial identification: NCT03346655.

Legal entity responsible for the study: Oslo University Hospital.

Funding: Norwegian Cancer Society, South-East Health Region in Norway.

Disclosure: All authors have declared no conflicts of interest.
1539D Post-traumatic growth and death anxiety in caregivers of cancer patients: PHOENIX study

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1540PD Health-related quality of life in randomized controlled trials: A systematic review of prognostic significance

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1541P Partners’ perceptions of women’s body image problems and satisfaction of breast reconstruction long-term after risk-reducing mastectomy

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Background: Knowledge is lacking about partners’ perception of women’s body image problems and satisfaction of breast reconstruction long-term after risk-reducing mastectomy (RRM) with immediate breast reconstruction (IBR) due to increased risk of hereditary breast cancer.

Methods: Partners’ contact information was provided by women participating in a prospective long-term follow-up after going though RRM and IBR 6–18 years ago. They received an information letter about the study and questionnaires to be completed/returned in a prepaid return envelope. The Hospital Anxiety and Depression scale and the Swedish Short Term-36 Health Survey (SF-36) were answered from the partners’ perspective, and the Breast Reconstruction Questionnaire (EORTC QLQ-BRR26), the Body Image Scale, and the Sexuality Activity Questionnaire from partners’ perception of the women’s experience. Partners’ responses were compared to the women’s responses, and with the SF-36 in the normative Swedish population.

Results: Sixty partners’ names were provided by the 146 (73%) women participating in the long-term follow-up study. Thirty-six (69%) partners participated in total. The partners’ perception of the women’s satisfaction with the IBR was lower than the
Ostracism Experience Scale for Adolescents (OES-A) and Kutcher adolescent depression scale (KADS) were used.

Results: Between December 2017 and April 2018, 52 patients were evaluated in 4 different cancer centers. Median age was 21 (14-24), 40.4% of them were female and most of them were university student (25, 44.2%). Median OES-A score was 23.5 (11.0-41.0). While female sex (28.0 vs 19.0, p = 0.008) and low family income (28.0 vs 21.0, p = 0.02) were associated with more ostracization; patients working full/part time (19.0 vs 25.0, p = 0.01) and university students (19.0 vs 27.0, p = 0.01) were less ostracized. In multivariate analysis, being female was associated with high OES-A scores (OR: 7.8, CI(95%) 1.4-42.9, p = 0.018). Being university student (OR: 0.14, CI(95%) 0.02-0.71, p = 0.018) and working (OR: 0.07, CI(95%) 0.007-0.7, p = 0.02) were associated with low OES-A scores (Table). Higher OES-A scores were associated with high KADS scores (9.0 vs 7.5, p = 0.16).

Conclusions: It is the first data about ostracism in adolescent cancer patients. OES-A score was higher than the scores of adolescents without cancer. While female adolescent patients were found to be under risk of ostracism, working and being university student were protective against ostracism. Ostracism in adolescent cancer patients should be studied in larger series.

Legal entity responsible for the study: Ali Alkan.
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Disclosure: All authors have declared no conflicts of interest.

Abstracts

Table: 1543P

<table>
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<th>Characteristics</th>
<th>OR</th>
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<th>p</th>
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<tr>
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<td>7.8</td>
<td>1.4-42.9</td>
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<td>Low income</td>
<td>3.2</td>
<td>0.6-16.3</td>
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<td>University student</td>
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<td>0.018</td>
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<tr>
<td>Working</td>
<td>0.07</td>
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Cognitive functions, coping strategies and psychological distress in patients with resected non-advanced cancer receiving chemotherapy: NEOcoping study data

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Background: The loss of cognitive functions is a symptom that impairs the quality of life. The aim of this study is to analyze cognitive dysfunction in cancer patients who initiate chemotherapy and to study the relationship between coping strategies and psychological distress.

Methods: NEOcoping is a national, multicenter, cross-sectional, prospective study of the Continuous Care Group of the Spanish Society of Medical Oncology conducted between January 2016 and January 2018 in 14 Medical Oncology departments in Spain. The population consisted of patients with histologically confirmed, non-advanced cancer treated with surgery for which international clinical guidelines considered that adjuvant treatment could be an option. The information was collected and updated by medical oncologists through a web-based platform (www.neocoping.es).

Questionnaires for doctors and patients were filled out before starting adjuvant chemotherapy and at the end of the treatment. The applied tests were: Mini-Mental Adjustment to Cancer (Mini-MAC), EORTC core quality of life questionnaire (EORTC QLQ-C30, cognitive function scale), and Brief Symptom Inventory (BSI-18).

Results: Seven hundred and ninety-five patients were recruited. The median age was 58 years and 60% were women. Most were married or partnered (77%) and had a primary level of education (56%). The most common employment status was retired (59%). The primary tumour localization was mainly colorectal (41%) and breast (34%) and the stage was I-II (56%) or III (44%). The results indicate that patients who perceived their
Physical condition or chemotherapy interfered with their cognitive functions had more anxious coping strategies characterized by constant preoccupation with the type of health, fear of cancer recurrence and this led to a search for frequent reassessment (p < 0.008). The cognitive function problems were negatively related with somatization (p < 0.001), depression (p < 0.001) and anxiety (p < 0.001).

Conclusions: The perception of impaired cognitive abilities and uncertainty about the prognosis of cancer can make it difficult for patients to adapt to their situation, deteriorate quality of life and increase emotional distress.

Legal entity responsible for the study: Continuous Care Group of the Spanish Society of Medical Oncology (SEMOC). 

Funding: Sociedad Española de Oncología Médica (SEMOC).

Disclosure: All authors have declared no conflicts of interest.

**1546P** Cancer stigma related to beliefs of patients and care providers

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Background: Stigma refers to distinctive, discrediting characteristics, rendering its bearer tainted by others and recognises difference and devaluation. Evidence suggests that cancer is a stigmatized disease. Cancer-related stigma is not documented in India, little is known about how it impacts health-seeking behavior, treatment adherence, quality of life and psychosocial wellbeing in cancer patients. Limited study has explored perceptions and cultural representations of cancer. This context specific information is essential for relevant, effective intervention.

Methods: This qualitative study was conducted in two districts Kolkata and North 24 Parganas of West Bengal, India, and included participants from a range of cultural and racial groups. Cancer patients over 18 yrs (n = 300) were recruited through Salt Lake City Medical Centre to participate. Six focus groups and 40 in depth interviews were conducted with cancer patients. Data collection focused on understanding patient experiences of cancer stigma, cognitive, emotional and behavioural responses to this, and inputs on interventions to address this. Six focus groups were also conducted with friends and non-related service providers, (n = 240) in order to explore cultural perceptions of cancer and reasons for stigmatization. Data were recorded and were authentically translated and transcribed; and analysed by thematic analysis.

Results: Results indicated very poor knowledge of cancer in patients and care givers. Findings highlight the perception of cancer as a ‘death sentence’ and a punishment from providence, influencing patients’ interactions with others in numerous ways. The influence of cultural beliefs was relevant, exacerbating stigma in some cases. The location of the cancer also played a role in determining level of stigmatization. Certain body parts (associated with masculine and feminine roles) as well as more visible cancers/ parts (associated with masculine and feminine roles) as well as more visible cancers/ body parts (associated with masculine and feminine roles) as well as more visible cancers/ side effects were more stigmatised.

Conclusions: Stigmatization is a factor for cancer patients and is related to education and social background, increasing social isolation and negatively impacting quality of life. The implications of the findings for intervention development will be discussed. Education is needed but requires a different focus for different cultural groups.

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Disclosure: All authors have declared no conflicts of interest.

**1547P** Evaluation of the distinction and temporal relationship between prolonged grief disorder and depression in terminally ill cancer patients’ caregivers’ first two years of bereavement

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Background: Prolonged grief disorder (PGD) and depression are common emotional disorders influencing bereaved caregivers’ quality of life (QOL). However, the conceptual distinctiveness and temporal relationship of PGD and depression have been partially and not established, respectively. To fill these knowledge gaps, we conducted this longitudinal study.

Methods: Our convenience sample included 291 caregivers of terminally ill cancer patients. Caregivers’ PGD, depression, and psychological QOL were measured 6, 13, 18, and 24 months postloss using the Prolonged Grief-13 scale (PG-13), Center for Epidemiologic Studies-Depression (CESD) scale, and Short Form-36 Health Survey mental health summary, respectively. We examined the associations of PGD and depression with psychological QOL by an incremental validity test, thereby clarifying their conceptual distinctiveness. The temporal relationship between PGD and depression was examined by longitudinal, lower-level mediation analysis with a lagged approach.

Results: After the variance in psychological QOL was significantly explained by CESD scores (pseudo R² = 44.19%, p < 0.001), PGD significantly, incrementally increased the explained variance in psychological QOL (pseudo R² = 21.8%, p < 0.001), confirming the distinction between PGD and depression. Lower-level mediation analysis showed that CESD scores (depressive symptoms) mediated 90% of the relationship between time and PG-13 scores, whereas PG-13 scores only mediated 76% of the relationship between time and CESD scores. This result indicates that CESD scores assessed at a previous time mediated caregivers’ current PGD during bereavement rather than vice versa.

Conclusions: PGD and depression are conceptually distinct disorders, and depression precedes development of PGD. Clinicians must distinguish between the two disorders and appropriately manage bereaved caregivers’ depressive symptoms. Alleviating caregivers’ depressive symptoms will prevent development of PGD, thus improving QOL.

Clinical trial identification: (NHRI-EX107-10704P) and Ministry of Science and Technology (MOST 104-2314-B-182-027-MY3), National Science Council (NSC 96- 2314-B-182-029-MY2), and Chang Gung Memorial Hospital (BMRP888).

Legal entity responsible for the study: Chung Gung University.

Funding: Ministry of Science and Technology, National Science Council, and Chang Gung Memorial Hospital.

Disclosure: All authors have declared no conflicts of interest.
Patients’ and partners’ views of treatment and care provided for metastatic castrate resistant prostate cancer (mCRPC) in the UK

S.L. Catt, L. Matthews, H. Payne, M.D. Mason, V. Jenkins

Background: Appraisals of information needs, experiences and expectations of treatment in prostate cancer have highlighted the lack of relevant data in advanced disease. We report interview data from the Experiences of TRTreatment and Quality Of Life of men with mCRPC study (EXTRIQOL). It aimed to examine factors driving treatment decision-making from the perspectives of patients and healthcare professionals and gather data on the impact of treatments on quality of life (QOL).

Methods: A prospective longitudinal mixed-methods observational design was employed. This included semi-structured interviews conducted with patients and their partners, in-person or by phone, at baseline — within 14 days of starting a systemic treatment (any line) for mCRPC and after 3 months of treatment. Topics explored included experiences of treatment decisions, information provision, what assisted decision-making and how perceived benefits and harms of treatment affected patients’ and families’ lives.

Results: Thirty men (36-89ys) and their female partners (54-79ys) from 15 UK centres participated. They believed treatment aimed to delay progression (>75%), improve QOL (33%), alleviate pain (>12%) and extend life (15%-patients, 36%-partners). >50% made a joint treatment decision with the doctor and 39% had as long as they needed to decide. The worst symptom most frequently identified was pain (46%-patients, 33%-partners). At baseline and 3 months (50% and 67% respectively) did not need to discuss pain control, those that did received “very”/“fairly” useful information. At baseline fatigue, nausea/vomiting and diarrhoea were the worst anticipated or experienced side-effects (SEs). The worst SE at 3 months was fatigue. 33% experienced unexpected SEs and 52% sought help for SEs. 75% had helpful SE discussions, 85% received written information and internet searching about SEs was common (33%-patients, 55%-partners). Only 50% had opportunity to talk with a specialist nurse and 50% accessed other supportive services.

Conclusions: More help to manage pain and other symptoms is required. Dedicated clinics maybe warranted, better specialist nurse access and earlier palliative care links would help to optimise symptom control.

Legal entity responsible for the study: Brighton & Sussex Medical School, University of Sussex.

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Disclosure: H. Payne: Honoraria for advisory boards, travel expenses, consultant: Astrazeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Amgen, Ipsen, Ferling, Sandox, Novartis, Work support: UCLH/UCL Comprehensive Biomedical Research Centre. M. Mason: Scientific expert: Ellipsia Pharma. All other authors have declared no conflicts of interest.

Exploring the effectiveness of crisis counselling and psycho-education in relation to improving mental wellbeing, quality of life and treatment compliance of breast cancer patients in Qatar

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Background: Insufficient number of studies have been carried out in the Middle East to evaluate the role of structured psychotherapeutic interventions in breast cancer patients. This study has been designed to explore the benefit of two structured interventions ‘crisis counselling’ and ‘psycho-education’ in enhancing breast cancer patient’s psychological well-being, quality of life and treatment compliance in Qatar.

Methods: A total of 201 women with early stage breast cancer from Qatar were recruited and randomised into either the control group or one of the treatment groups (crisis counselling or psycho-education). Each of the two treatment interventions consisted of a total of six 60–90 minute sessions, which were provided over a period of 12 weeks. The short- and long-term benefits of the crisis counselling and psycho-education interventions were evaluated in terms of improving patients’ psychological well-being, quality of life and treatment compliance through DASS21 and QLQ-C30 instruments and by monitoring their compliance to chemotherapy and radiotherapy treatment.

Results: This study revealed that both of the study interventions ‘crisis counselling’ and ‘psycho-education’ were effective in improving women’s psychological well-being and quality of life over time in comparison to the control group but had no significant impact on patients’ compliance with treatment. In addition, the study showed that psycho-education conferred a greater advantage than did the crisis counselling model, especially on improving women’s psychological well-being over time.

Conclusions: This study is considered the first of its kind in Qatar to provide evidence on the benefit of crisis counseling and psycho-education interventions in improving the psychological wellbeing and quality of women with early-stage breast cancer. In addition, this study has provided an innovative research that can be used as evidence to propose changes to the psychotherapy services for breast cancer patients in Qatar and which will hopefully lead to a better healthcare system for other cancer patients in the country.

Legal entity responsible for the study: Hamd Medical Corporation.

Funding: Hamd Medical Corporation.

Disclosure: All authors have declared no conflicts of interest.

Pilot study of anxiety, depression, and quality of life in patients with the diagnosis of metastatic uveal melanoma


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Background: Awareness of a patient’s anxiety, depression, and quality of life (QOL) in those with metastatic uveal melanoma (MUM) can influence care that meets patients’ bio-psycho-social-spiritual needs. Objectives: To measure the level of anxiety, depression, and QOL in MUM patients and explore differences by gender, age range, time to metastatic disease, and duration of illness since metastasis.

Methods: We used a descriptive-comparative design. From 9/1/2017 - 12/1/2017, a convenience sample of 70 MUM patients aged ≥ 18 years, treated at a Mid-Atlantic hospital were invited to complete a combined survey of the Hospital Anxiety and Depression Scale and the World Health Organization Quality of Life-BREF.

Results: There were 65 respondents (93% response rate). 30.8% (n = 20) had at least borderline anxiety, 13.8% (n = 9) had at least borderline depression, and 32.3% (n = 21) had a decrease in global QOL. Patients aged 18 to 60 years had a significantly higher anxiety score (7.52 ± 3.65; p = 0.003) and lower QOL in environmental health (32.48 ± 5.23; p = 0.006). There was a significant difference in anxiety scores by the duration of illness since metastasis (< 1 year [7.79 ± 3.72], > 1 year to < 5 years [5.75 ± 3.45], > 5 years [3.70 ± 2.79]; p = 0.01). No differences were found by gender or time to metastatic disease.

Conclusions: Up to 30% of participants had at least borderline anxiety and a decreased QOL while up to 10% had at least borderline depression. These findings support the integration of bio-psycho-social-spiritual practices in the care of MUM patients.

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Legal entity responsible for the study: Regine Nshimiyimana.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Making sense of self-conscious and emotion: Linking theory of mind and emotion in women with breast cancer

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Background: During the period of breast cancer’s treatment, they had to face many physical and facial changes that make them self-conscious. Self-conscious emotions are just like embarrassment and shame that are correlated with 2 factors of the theory of mind (ToM): 1. the ability to understand that behavior has social consequences in the eyes of others and (b) an understanding of social norms system. The present study aimed to link ToM with the recognition of self-conscious emotion.

Methods: We compared the performance of patients with breast cancer (N = 61) those who were diagnosed and were willing to undergo the psychological assessment, with no history of past psychiatric illness and with age and sex match healthy controls (N = 19) who are psychologically and physically stable using the widely used ToM task, Reading the Mind in the Eyes test (RMT). Facial expression, supplemented by clinical examination by experienced researchers.

Results: ToM was assessed with the breast cancer group performed significantly worse than the control group (p < 0.05). The present study reports that breast cancer patients have greater impairment in identifying self-conscious emotions compared to healthy control. The degree of impairment is midway in self-conscious emotion between patients with breast cancer and that of normal controls after statistically controlled ToM.

Conclusions: Therefore it can be said that the breast cancer patients suffering from self-conscious emotion may have an additional burden of impaired social cognition, which needs to be addressed urgently for the better quality of life.
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Background: The important issue of psychophysiological adaptation to malignant process is poorly studied. The aim of the research was to elucidate characteristics of the psychic, adaptive and hormonal status of patients with lung cancer (LC).

Methods: Studies were performed in 28 LC patients with receiving surgery and chemoradiotherapy. The patients were divided into 3 groups: 1 - unresectable tumors, 2 - resectable tumors with metastases, 3 - resectable tumors without detected metastases.

Personal (PA) and situational anxiety (SA) (Spieberger-Khanin test), depression (Zung test), the types of the mental response to disease (LOBI, Rechterew Institute Personality Inventory) were evaluated. With the help of blood count and the original computer program "Antistress", we calculated the quantitative indicator (QI) of the general nonspecific adaptation reactions of the body (AR) (Garkavi L. H. et al., 1975).

Results: The studied groups did not differ in PA and SA. The signs of tension of the PAS, elevated thyroxine level and decline in the adaptive status were noted. At the same time, QI of AR in patients of the group 3 was 1.8-2.7 times higher than in patients of other groups (p < 0.05). Depression was observed in only one patient. The euphoric type of response to the disease dominated in the groups (39% of cases), the harmonic type was the second most frequent (18% of cases). The patients of group 3 with euphoric reaction (referred to non-rational types of response) were characterized by an uncomplicated postoperative period and the maximal QI of AR in the studied groups, which exceeded by 2 times the indices in the patients of group 3 with harmonic and other reactions (p < 0.01).

Conclusions: QI of AR of patients with LC reflected the prevalence of the malignant process. In these patients depression was not expressed, and the euphoric reaction dominated. That could be due to central effects of thyroxin. We assumed that the euphoric reaction in the patients with resectable LC without detected metastases was a favorable diagnostic characteristic. So the questions arise about the clarification of the concept of the euphoric reaction and the ways of its identification.

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1553P

Characteristics of the psychosomatic state of patients with lung cancer

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1554P

Impact of cancer on the quality of life of Tunisian pediatric patients

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Background: The PedsQL (Pediatric Quality of Life Inventory) is an instrument which measures health-related quality of life (HRQOL) in children and young adults. The PedsQL 4.0 Generic Core Scales (GCS) are child self-report and parent proxy-report scales developed to be integrated with the PedsQL disease specific modules. The PedsQL 3.0 Cancer Module (CM) was designed to measure pediatric cancer specific HRQOL. The aim of this study was to evaluate the impact of their disease and its treatments on their physical, mental and social health.

Methods: This prospective study included 26 patients newly diagnosed and relapsed, on treatment, from the pediatric ward of Salah Azaiez Institute. Their ages were 5 to 25 years-old. The 23-item PedsQL 4.0 GCS encompasses 4 scales: physical, emotional, social, and school functioning. The cancer module scales has 27 items which encompasses 8 scales: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance and communication. The format instructions, response scale and scoring method are identical for GCS and CM. The scores are between [0–100]. We translated the English version of the GCS and the CM into arabic.

Results: All the children completed their self-report. The mean age was 15.5 years-old. 53.8% were boys. 27.07% of patients had brain tumors, 19.2% osteosarcoma, 19.2% Ewing sarcoma and 11.5% Undifferentiated nasopharyngeal cancer (UCNT). Twenty patients were newly diagnosed. Eight cases had metastatic disease. The child total GCS mean was 60.86 physical score mean 64.06 and social score mean 67.5. For the child total CM score mean, it was 61.53 ; pain score mean 75, nausea score mean 50 which is the lowest and the worry score mean 62.49 . We found that the nausea score is higher for children with intensive chemotherapy (p value=0.026). The parent proxy total GCS mean was lower than the child score 58.69 as well as the total CM parent score mean which was 60.17. We didn’t find significant difference between the age of the patient, staging of his disease and the pedsQL scores.

Conclusions: The HRQOL of children is adversely affected as a result of the uncontrolled symptoms from cancer treatment. In Tunisia, we should work more to improve the pediatric HRQOL.

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Disclosure: All authors have declared no conflicts of interest.
PUBLIC HEALTH POLICY

15560 Potential for value-based prescribing of oral oncology drugs

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15570 Relation between center volumes for pancreatic and esophageal cancer surgeries and outcome in Belgium: A plea for centralization

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15580 Worldwide comparison of colorectal cancer survival by topography and stage at diagnosis (CONCORD-2)

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15590 Increasing colorectal cancer incidence among young adults in England diagnosed during 2001-2014

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Major determinants of delayed access to innovative medicines for metastatic melanoma: The results of Melanoma World Society and European Association of Dermato-Oncology survey


Variation in oncology drug approvals in Canada, the United States and Europe

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Magnitude of clinical benefit of cancer drugs approved based on single-arm trials (SAT) by the US Food and Drug Administration (FDA)

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Magnitude of clinical benefit in trials supporting US Food and Drug Administration (FDA) accelerated approval (AA) and European Medicines Agency (EMA) conditional marketing authorisation (CMA) and subsequent trials supporting conversion to full approval

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Magnitude of clinical benefit of trials supporting US Food and Drug Administration (FDA) approval of breakthrough and non-breakthrough drugs

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1565PD Time to access to novel anticancer therapies in Slovenia in view of the ESMO-MCBS scores

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1566PD Cascade BRCA germline mutation (BGM) testing of women with breast (BC) or epithelial ovarian cancer (EOC) and their families with subsequent risk reducing surgery (RRS): A Canadian economics model

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1567PD Genetic testing of BRCA mutations in breast cancer in six European countries: Barriers and opportunities

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1568PD Public awareness of cancer in the Gaza-Strip: A cross-sectional study

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The impact of primary care access on mortality in lung cancer patients from Bronx, New York

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**Background:** Racial and ethnic disparities in cancer care are well described. Lack of access to primary care physicians (PCPs) may be an important contributor to disparities attributed to race and ethnicity. This study examined the effects of primary care access on mortality in lung cancer (LC) patients (pts) in an underserved community.

**Methods:** Medical records of all pts newly-diagnosed with primary lung cancer between 2012-2016 at a NCI-designated cancer center in the Bronx were reviewed. Demographic data and PCP status were collected. Addresses were correlated with the Health Resources and Services Administration (HRSA) database to identify residences located in primary care shortage areas (PCSA). Survival data from time of first imaging to death or the end of follow-up on January 1, 2018 were recorded. Data analysis was performed via univariate methods. Survival analysis was performed using Kaplan-Meier and Cox hazards modeling.

**Results:** Among 1062 pts, 874 (82%) resided in a PCSA, 314 (30%) were Hispanic (H), and 445 (42%) were African-American (AA). Hs and AAs were more likely to reside in PCSAs (p = 0.0002 and p = 0.0008) and in ZIP codes with lower income (both p < 0.0001). Hs and AAs were more likely to depend on public insurance (p = 0.01 and p = 0.02). Pts who live in PCSAs presented at higher stages at the time of diagnosis (p = 0.03) and were diagnosed predominantly in inpatient settings with acute symptoms (p < 0.0001) rather than outpatient clinics (p = 0.0002). In the overall population, PCSA residence (mean: 24 vs. 30 months, p = 0.03, HR = 1.27) and no established PCP (mean: 22 vs. 28 months, p < 0.0001, HR = 1.50) were associated with increased all-cause mortality. In Cox modeling adjusting for stage at diagnosis and PCSA residence, lack of established PCP still predicts increased mortality (p = 0.03, HR = 1.20).

**Conclusions:** Among new pts with LC, lack of established PCP is associated with increased mortality. Hs and AAs are more likely to reside in PCSAs, suggesting the link between increased mortality and race/ethnicity may be mediated by lack of access to primary care. Our results demonstrate that effective health policy efforts to reduce lung cancer mortality must include approaches to improve access to primary care. Legal entity responsible for the study: Albert Einstein School of Medicine, Montefiore Medical Center.

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**Disclosure:** All authors have declared no conflicts of interest.

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Breast cancer treatment waiting time, patient and provider contributions: An Egyptian breast cancer centre experience

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**Background:** Breast cancer is the most common type of female cancer in Egypt and worldwide. Most of the cases present as locally advanced or metastatic rather than early stages in Egypt. There is no data to assess waiting times in the Egyptian breast cancer patient journey from developing first symptom until initiating treatment.

**Methods:** This is a descriptive study in which the electronic records and paper notes of 200 patients presenting from April until September 2016 to a public non governmental breast cancer centre in Cairo were reviewed for different waiting times. The wait time from developing the first symptom until commencing treatment was divided into stages; Symptom to call (booking an appointment), call to review, review to diagnosis, diagnosis to multidisciplinary team meeting (MDT) and MDT to first therapy.

**Results:** The average time from developing symptoms to booking an appointment (patient factor) was 131 days /4.4 months. The time lag from booking until medical review was 47 days /1.5 months. This is because of the booking system waiting list. The mean time taken from review until getting a final diagnosis was 11 days. All cases were discussed in the MDT and therapy ensued the MDT by 17 days on average. The mean in hospital waiting time (time from review until commencing treatment whether surgery, systemic therapy or radiotherapy) was 37 days while the mean time for the whole journey (symptom to treatment) was 214 days /7.1 months. Patients contributed to 61% of the wait time (131 days / 4.4 months) whereas the provider contributed by 39% with average of less than 3 months.

**Conclusions:** Patients contributed to the biggest part of the delay. The second factor was the booking system waiting list. Once reviewed by the medical team the process was accelerated. This indicates a need to improve public awareness of breast cancer symptoms and facilitate patient access to services.

Legal entity responsible for the study: Baheya Research Centre (BRC).

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### 1573P

**Awareness and attitude towards breast cancer among Egyptian nurses at university affiliated hospitals: Tanta University Hospitals experience**

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**Background:** Breast cancer (BC) is the most common cancer among women. In Egypt, BC accounts for 38% of all types of cancer in females with the majority often present at advanced stages. This might be attributed to deficient health education programs and poor awareness. The aim of this study is to evaluate the knowledge, attitude and practice of Egyptian nurses at Tanta university hospitals towards BC.

**Methods:** 421 female nurses from Tanta university hospitals completed a questionnaire that administered through face-to-face interviews by medical students and interns. The questionnaire included five sections: sociodemographic data, knowledge about BC symptoms, risk factors, screenings methods and treatment of BC.

**Results:** Mean knowledge score was 18.75 ± 5.76 with 32.7% of participants knew the right answers of more than 50% of the questions. The least level of knowledge was in questions related to BC symptoms and risk factors with 60.3% and 52.2%, respectively, of participants had scores of < 30% of the total score. The knowledge for nurses aged 30-59 years-old, those from urban areas and those who have years of work experience ranged between 16 and 25 years had statistically lower levels of knowledge compared to other groups (p value, 0.035, 0.048, 0.005, respectively).

**Conclusions:** The level of BC knowledge among Tanta university hospitals nursing staff is fair. The knowledge about BC symptoms and risk factors needs more attention from health care authorities to specifically design educational programs focusing on these areas.

**Legal entity responsible for the study:** Tanta Faculty of Medicine, Egypt.

**Disclosure:** All authors have declared no conflicts of interest.

### 1574P

**Women oncologists participation at the Spanish Society of Medical Oncology (SEOM) annual meetings from 2009 to 2017 and their position in Spanish scientific societies**

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**Background:** Medical Oncology is a feminized profession in Spain. According to SEOM, 57.6% of the medical oncologists in this country are women. This situation will remain unchanged because women occupied 67% of the medical oncology training positions since 2008. However, women are underrepresented in leadership positions, which may influence their career development.

**Methods:** We reviewed the participation, role and gender distribution of 2110 professionals at SEOM annual meetings between 2009-2017, the position of the 237 members of SEOM executive boards (1976-2017) and the 335 members of the current executive boards of 13 of the most important Spanish cooperative groups.

**Results:** From 2009 to 2017 the 38.4% of the 2110 speakers at SEOM meetings were women. There wasn’t a progressive increase over the years. The only year with > 40% of female participation was 2017 (42.4%). At educational and clinical sessions, 26% of chairs and 35% of speakers were women. At original presentations sessions, 57% of presenters, 42% of discussors and 50% of chairs were women. At the plenary sessions, 50% of presenters, 17% of discussors and 5% of chairs were women. 31% of members of scientific committees were women; they chaired these panels in 22% of cases. Over the last decade, SEOM awarded 122 research grants, 42% of them to women. The SEOM executive board has been chaired 18 times by a man and 2 by a woman. The first female president was elected in 2011. There were no women at executive boards until 1987. Women occupied 17.3% of the positions. Currently, 40% of the executive boards members and 2 of the 13 cooperative groups chairs are women.

**Conclusions:** Spanish women oncologists developed an active scientific activity in their everyday practice and communicated their research data at national meetings. However they were asked to chair or share their expertise in fewer occasions than men. In addition, women were underrepresented at executive boards of the main oncology scientific groups. According to our results, we consider further efforts are required to achieve gender equality. A good example are initiatives like the ESMO Women for Oncology (W4O) network, the Forum of Women in Oncology in Greece or W4O Italy.

**Legal entity responsible for the study:** Julia Hidalgo Colomera.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

### 1575P

**Working arrangements after cancer diagnosis: Who, what, when and how?**

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**Background:** Each year, 355,000 new individuals are diagnosed with cancer in France, nearly half of them being in working age and interrupting their professional occupation during treatments. As having working arrangements has been found to facilitate return to work after a long absence, it is provided by French law. This study aims to describe the use of working arrangements and to investigate how it is related to job retention.

**Methods:** This study combines analyses of quantitative and qualitative data: 1) VICAN, a national representative survey on living conditions 5 years after cancer diagnosis conducted in 2015-2016 (n = 4,174), and 2) CAREMAJOR, a qualitative longitudinal study carried out in 2017 among patients on sick leave after a cancer diagnosis and interviewed about the impact of the disease on their working lives (n = 21). VICAN survey presents an overview about the use of working arrangements in France and the CAREMAJOR survey completes these results by giving the patients’ point of view in a more comprehensive manner.

**Results:** Among the 1,854 cancer survivors aged between 23 and 59 at time of the VICAN survey, and who were employed at diagnosis, 62.7% used working arrangement(s) within the five years following diagnosis. Nearly half of them (45.5%) had a working time arrangement. The other kind of working changes were about working hours (38.8%), working conditions (35.8%), occupation (32.8%), workplace (20.4%), and security at work (19.2%). Moreover, working arrangements are associated with job retention (88.9% of workers with working arrangement were still employed five years after diagnosis versus 69.6% of others). Furthermore, in CAREMAJOR survey, when patient returned to work without any working arrangement, this led to bad experience because of workload. However, some of those who did have an arrangement reported a negative impact on their professional life: they felt discriminated or thought that it has affected their professional credibility.
Conclusion: The French context, the use of working arrangement seems to be a good factor to enhance job retention. National surveys should however better take into account the context of the implementation of working arrangement to get better understanding of the potential selection bias.

Legal entity responsible for the study: INSERM, UMR_S_1235, « Sciences Economiques & Sociales de la Sante et Traitement de l’Information Medecine » (SESSTM).

Funding: Cancercpole PACA Institut National du Cancer (INCA).

Disclosures: All authors have declared no conflicts of interest.

157PP
Financial burden and financial toxicity in patients with colorectal, gastro-oesophageal, and pancreatic cancers: A UK study

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Background: How cancer affects a patient (pt) in the UK financially and how this changes throughout treatment is unknown. We aimed to assess financial burden (FB) at baseline and financial toxicity (FT) throughout treatment of pts with upper GI (UGI), pancreaticoabdominal (PB) and colorectal (CR) cancers.

Methods: Pts with UGI, CR and PB cancer enrolled in 5 clinical trials (REAL-3, RAINFALL, ESPAC-4, QOL, BIL and CAPITOL) at the Christie, Manchester, were identified. FB at baseline and FT throughout treatment were defined according to answers to the EORTC QLQ-C30 questionnaire (EQ): Q28 to which pts score financial difficulty relating to disease or treatment from 1 (not at all) to 4 (very much). p ≤ 0.05 was considered significant.

Results: 145 pts were included, 56 (41.1%) pts had CR, 85 (60.3%) PB and 41 (29.1%) UGI cancer. 87 (61.7%) had no FB (scored 1 on EQ), 11 (8.5%) scored 2, 12 (8.5%) scored 3 and 7 (5%) scored 4. 97 (68.8%) had CR, 85 (60.3%) PB and 41 (29.1%) UGI cancer. 87 (61.7%) had no FB (scored 1 on EQ), 11 (8.5%) scored 2, 12 (8.5%) scored 3 and 7 (5%) scored 4. 97 (68.8%) answered ≥2 EQs. Median EQ follow up was 6 months (range 0.5-63.1). 63.5% experienced no FT, 19.8% worse FT and 16.7% improving FT. The median index of multiple deprivation (IMD) of the region was 16,083 (range 3-32,041). Multiple regression analysis showed that younger age, lower IMD and tumor type were independent predictors of FB. Significant covariates included IMD below vs. above median (OR 2.64, 95%CI 1.33-4.55, p = 0.024) and age below vs. above median (OR 7.83, 95%CI 3.23-18.94, P < 0.001). Of those, no factor predicted FT. Pts who experienced FT were significantly younger compared to those who did not (median age 55 vs. 69, p < 0.001) and had significantly lower IMD (median 9,483 vs. 19,277, p = 0.002). IMD in our series did not show significant interaction with age (ρ = 0.270). Palliative treatment and lower IMD were independent predictors of worse overall survival.

Conclusion: We report the first study of FB and FT in pts with UGI, PB and CR cancers living in UK, identifying independent baseline parameters predicting FB and the prognostic role of IMD. Younger pts and those of lower IMD are at significantly higher risk and should be offered additional support.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

157OP
How advanced lung cancer patients are really treated at the population level? The Ontario, Canada experience

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Background: Clinical trials define treatment recommendations but patients in the real world may be unable or unwilling to undergo treatments with demonstrated efficacy in fit patients. The Canadian Partnership Against Cancer has developed a model of lung cancer (LC) management (OncoSim-lung) in 2008 based on clinical trials and expert advice. To credibly project the future clinical and economic impacts of cancer control measures using OncoSim, the model has been refined using real-world data.

Methods: Treatment data by histology and stage were extracted from the Ontario Cancer Registry for LC cohorts diagnosed in 2010 and 2013. All incident cases that satisfied the IARC rule of a new primary were included. Missing or unknown stage cases were excluded. Clinical pathways were validated by oncologists from different disciplines across Canada.

Results: The 2013 cohort included 8,086 staged LC: NSCLC (n = 7,143) Stage I 18.7%, II 8%, IIIA 11.4%, IIIB 4.5% IV 56.8%; SCLC (n = 943) limited 67.7%, extensive 32.3%. Of 813 stage III/IIa patients, only 26% underwent surgery, 41% of whom received adjuvant chemotherapy or postoperative radical radiotherapy (16%); 13% received trimodality treatment. Of the 73% of Stage III not receiving surgery, 26% had NAT and 21% had palliative radiotherapy alone. Of those receiving active treatment, 20% received combined chemo + radiotherapy and 13% each had chemotherapy alone or radical radiotherapy alone. Of 356 stage IIIb patients, 17% had NAT, 28% received palliative radiotherapy and only 30% had chemo + radical radiotherapy. 18% had chemo alone. Of 4055 stage IV NSCLC, 47% had NAT, 24% received chemotherapy alone and 23% had palliative radiotherapy only. Of those who received first-line chemotherapy (n = 1059), 47% received second line chemotherapy and of those, 37% received third line therapy.

Conclusion: Compared to prior expert opinion, there was a much lower frequency of chemo-radiotherapy in Stage III disease and a higher frequency of NAT across all stages of disease. The updated OncoSim model now have a credible real-world base from which the impacts of new treatment interventions on survival and budget impact can be better estimated.

Legal entity responsible for the study: Canadian Partnership Against Cancer.

Funding: Canadian Partnership Against Cancer.

Disclosure: All authors have declared no conflicts of interest.
Anticoagulant treatment of patients (pts) with cancer associated thromboembolism (CAT) in Germany: Real world data from a 4 million people sample generated by insurance captured data

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Background: CAT is a common complication of cancer with impact on overall prognosis. After 2003 low molecular weight heparin (LMWH) instead of vitamin K antagonists (VKA) became guideline recommended treatment. Direct oral anticoagulant drugs (DOAC) were investigated in CAT only recently. Little data is available concerning incidence and current treatment situation in Germany.

Methods: Data on drugs and coding of diagnosis for all continuously insured members of SHI were available. An anonymized health claims database (2011-2016) of German SHI was used for a retrospective analysis. With a wash out period of one year patients with preexisting conditions were eliminated. According to our definition pts with CAT had a new cancer diagnosis and a new VTE diagnosis and a prescription of any type of anticoagulant. Anticoagulant drug type and duration in CAT pts during the next year was analyzed and then classified according to their dominant (≥ 51 % of time) anticoagulant drug. Any coded bleeding diagnosis was captured as well. The study has descriptive character.

Results: Out of a sample of > 4 million MSHI which is 5.5% of the German SHI population 322,600 tumor pts and 13,131 (4%) pts with initial VTE diagnosis were identified. According to our definition 7,313 were CAT. Dominant anticoagulant was LMWH in 58% VKA in 24%, and DOAC in 18%, respectively. During prescription of anticoagulation approx. 20% of all pts with CAT suffered from bleedings with no significant differences between agents (LMWH, DOAC, VKA). The individual LMWH type (approved for secondary prophylaxis or not) and switch of therapy were analyzed as well.

Conclusions: Out of 7,313 pts with CAT more than half received secondary prophylaxis of VTE with LMWH in accordance with the German guideline. VKA (probably suboptimal choice) as well as DOAC (no data published before 2017) were used in a clinically relevant subset. Bleeding was comparable in different agents of anticoagulation. As compared to available small market research studies our data set offers more reliable information due to its comprehensive character. This has impact on future guidelines and education.

Legal entity responsible for the study: HGC Healthcare Consultants GmbH.

Funding: Aspen Germany GmbH


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*Significantly higher median age.

Age distribution for different types of cancer in the United States (1969-2015)

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Background: There has been an increasing concern about the changing incidence pattern of some types of cancers including age at diagnosis. While there is at least some evidence that some cancers currently occur at age earlier than that expected based on historical data, we still lack evidence about age trends in most types of cancers. This study aims to explore current age distributions for different types of malignancies in the United States based on data from SEER.

Methods: Data were obtained using SEER®Stat version 8.3.5, where (SEER 18 Regs Nov 2017 Submission) database was used as the data source. Only cases diagnosed between 1996-2015 with malignant behavior, known age, and microscopic confirmation were included. Data were exported using the case listing session and were analyzed using SPSS version 21.

Results: Median age at diagnosis was significantly higher in the period between 2006-2015 than in the period 1996-2005 for most types of cancers. GIT malignancies and CML, however, showed an exception with a significantly younger median age of diagnosis. The table shows age distribution as well as median age for some common types of cancers including comparison between cases in the 1996-2005 and 2006-2015 time periods.

Conclusions: Except for GIT malignancies and CML, cancer is still being diagnosed at higher median age. With few exceptions, patients who are over 55 years old are still constituting the vast majority of cases.

Legal entity responsible for the study: Mohamed Ala Gouda.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.
registry. The Canadian Postal Code Conversion File Plus (PCCF+) was used to link the patients’ postal codes with standard 2011 census geographic areas and neighbourhood income quintiles. Chi squared test was used for comparisons.

Results: 48,954 patients completed the PSSCAN-R and 45 164 had PCCF+ data available. Baseline characteristics: median age 66, 55% female, 17% presented with metastatic disease. Tumor distribution: 22% breast, 19% GI, 13% GU, 13% lung and 33% other. Income quintiles were grouped into lowest/medium-low, middle, medium-high/ highest. Community size: > 1,5M 53%, 1,5M – 10K 17%, < 10K 30%. Patients in low/est/medium-low compared to medium-high/highest income groups reported more distress around finances (19% vs 14.1%), getting to appointments (15.3% vs 9.7%) and accommodations during treatment (5.6% vs 3.8%). Concerns regarding school/work were larger (10.5% vs 10.9%). Patients in rural versus large communities (1.5M+) reported more distress around finances (19% vs 15.1%), getting to appointments (15% vs 11.9%), accommodations during treatment (9.7% vs 2.7%) and less distress around school/work (9.7% vs 11.8%).

Conclusions: Lower SES and rural geographic location are associated with higher levels of cancer patient distress in the practical domain, despite a publically funded medical system. Local navigational support services for workplace and income assistance should be developed to alleviate distress for patients in rural areas or with low income.

Legal entity responsible for the study: BC Cancer Foundation.

Disclosure: All authors have declared no conflicts of interest.

Overview on the use of patient reported outcomes in colorectal cancer care

1586P

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Background: The burden of colorectal cancer is high in Europe and still increasing. The disease and treatment can have profound impacts on the patients’ quality of life (QoL), emphasizing the importance of measuring QoL. An important tool in this process is Patient Reported Outcome Measures (PROMs). The goal of this study is to give an overview on the use of PROMs throughout the colorectal cancer care pathway in Europe.

Methods: Studies were searched via PubMed until end of April 2018 regarding the development, validation and use of PROMs in colorectal cancer, focusing on the whole care pathway, i.e., screening, diagnosis, treatment, rehabilitation, follow-up, and palliative care. Only studies conducted in Europe, with at least an abstract in English were included.

Results: In total, 49 studies and 7 systematic reviews were analysed. Thirty-six studies evaluated PROMs in clinical trial settings, while 20 focused on screening and patient management. Most of the studies were conducted in the Netherlands (n = 13) and United Kingdom (n = 19). Concerning care processes, most studies focused on treatment – systemic therapy, surgery and radiotherapy - in both trials and patient management. There is a great variation in the PROMs instruments used, as well as in the domains included in them (physical function, symptoms, psychological distress, general QoL, financial aspects, patient satisfaction/experience and decision sharing). The most used standardised instrument was EORTC QLQ C30, sometimes in combination with other colorectal cancer specific questionnaires. In almost all studies included, PROMs were assessed at predefined key moments: at least before the treatment, during the intervention and at three time points after the intervention (up to 12 months).

Conclusions: In Europe, the use and content of PROMs in colorectal cancer varies, but is still limited. Implementation of a core standardised set of PROMs would allow comparability of patient-perceived quality of care across Europe. Despite some current initiatives (e.g. ICHOM) more work is still needed. Incorporation of a requirement for the use of PROMs in quality assurance measures (e.g. European Initiative on Colorectal Cancer) may increase patient centredness of the care standards and improve patient experience.

Legal entity responsible for the study: Luciana Neamtie.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Completeness of staging investigation for colorectal cancer: Exploring the role of increasing age and comorbidity using mediation analysis

1585P

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Background: Older cancer patients often have fewer staging interventions and inferior treatment than younger patients. Suboptimal cancer management in older patients is frequently attributed to comorbidity, which may contraindicate procedures. We aim to examine how much of the age disparities in completeness of staging investigations for colorectal cancer (CRC) are explained by patients’ health status and their diagnostic route.

Methods: Population-based cancer registries provided information on CRC patients diagnosed in England during 2010-2012. Staging investigations and comorbidities in the six years before the cancer diagnosis was derived from the National Bowel Cancer Audit and Hospital Episode Statistics datasets. A mediation analysis quantified the proportion of the age effect on staging investigations mediated by health status, and by the diagnosis route. Sensitivity analyses for unmeasured confounding tested the robustness of the findings.

Results: Around half of patients had complete staging investigations. There was a U-shape association with more complete investigations among younger patients and those with fewer comorbidities. In the six years before the cancer diagnosis was derived from the National Bowel Cancer Audit and Hospital Episodes Statistics datasets. A mediation analysis quantified the proportion of the age effect on staging investigations mediated by health status, and by the diagnosis route. Sensitivity analyses for unmeasured confounding tested the robustness of the findings.

Conclusions: CRC patients’ health status and diagnostic route did not fully explain the age differential in the quality of staging investigations. Further research is needed to identify other factors, particularly in older patients. These findings were robust to strong assumptions of unmeasured confounding of the relationship between the diagnosis route and having complete staging investigations.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Cancer Research UK.

Disclosure: All authors have declared no conflicts of interest.

The quality oncology practice initiative program: Experience in Spain

1586P

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Background: Patient care quality is a discipline that has acquired enormous relevance in today’s healthcare. Quality Oncology Practice Initiative (QOPI) is a referral worldwide in terms of quality for oncology practices. ECO Foundation is a platform of experts representing the major Spanish hospitals involved in the treatment of cancer patients. ECO reached an agreement with QOPI to involve Spanish hospitals in the QOPI program.

Methods: Five rounds of data collection have taken place (Fall 2015 to Fall 2017). Practices had to register online and submit data into the QOPI platform. ECO Foundation offers all centres the necessary support. 16 Spanish hospitals have participated in the five rounds. 7 of them have repeated participation. Core and Lung Cancer modules were completed.

Results: During the five rounds, 1745 charts were submitted by the Spanish practices. In the majority of the rounds, the highest scores were: Pathology report confirming malignancy, Number of chemotherapy cycles documented, Patient consent for chemotherapy and 5 measures of the Lung Cancer module. The lowest scores were: Chemotherapy treatment summary provided to patient within 3 months of chemotherapy end, Chemotherapy treatment summary provided or communicated to practitioner(s) within 3 months of chemotherapy end, Smoking/tobacco use cessation counselling recommended to smokers/tobacco users in past year and Tobacco cessation counselling administered or patient referred in past year. The percentage of participating practices that presented results higher than 70% was successively 64%, 50%, 73% and 100% in the last two rounds. For the 7 hospitals that repeated participation, 3 reported an improvement of their global scores. Regarding QOPI Certification, three Spanish hospitals received this accreditation in September 2017.

Conclusions: These preliminary results are a good starting point for the continued implementation of the QOPI program in Spain, thus providing a well-structured approach to analyse cancer care. ECO Foundation will continue pursuing excellence and quality with further activities like the QOPI Certification program and Quality Training Program, these being performed for the first time in Spain in 2017 and 2018 respectively.

Legal entity responsible for the study: Fundación ECO.

Disclosure: All authors have declared no conflicts of interest.
Background: Management thinker Peter Drucker had famously said “If you can’t measure it, you can’t improve it.” Similar sentiment among practicing oncologists led to the establishment of QOPI by ASCO in 2006. The availability of guidelines to confirm preconceived benchmarks, but lead to improvement. Measures that were deemed not applicable in the Fall (F) and Spring (S) rounds of the QOPI-Certified practices. For the current analysis, we initiated the proof of concept and hypothesized that measuring quality would not only confirm preconceived benchmarks, but lead to improvement. Methods: Data for analysis was selected from countries’ practices that repeat self-measures should result in measurable and sustained improvement in cancer care. Data for analysis was selected from countries’ practices that repeat self-measures should result in measurable and sustained improvement in cancer care. QOPI was launched internationally in 2015. Now several countries are participating and 3 (Brazil, Greece and Spain) have QOPI-Certified practices. For the current analysis, we initiated the proof of concept and hypothesized that measuring quality would not only confirm preconceived benchmarks, but lead to improvement. Measures that were deemed not applicable in the Fall (F) and Spring (S) rounds of the table 1587 P. The availability of guidelines to confirm preconceived benchmarks, but lead to improvement.

Table: 1587P

<table>
<thead>
<tr>
<th>Round</th>
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<th>Measure 24</th>
<th>Measure 33</th>
<th>Measure 81</th>
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<tr>
<td>F15</td>
<td>75.2</td>
<td>59.5</td>
<td>49.2</td>
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</tr>
<tr>
<td>S16</td>
<td>58.2</td>
<td>67.1</td>
<td>27.3</td>
<td>16.6</td>
</tr>
<tr>
<td>F16</td>
<td>70.3</td>
<td>69.4</td>
<td>40.4</td>
<td>44.1</td>
</tr>
<tr>
<td>S17</td>
<td>74.3</td>
<td>80.3</td>
<td>43.4</td>
<td>27.9</td>
</tr>
<tr>
<td>F17</td>
<td>83.0</td>
<td>82.8</td>
<td>53.8</td>
<td>38.7</td>
</tr>
</tbody>
</table>

This analysis includes 331 physicians and 22 practices from 5 countries (Brazil, Greece, Romania, Saudi Arabia, and Spain) who participated in QOPI rounds between 2015 and 2017. While the scores fluctuated between rounds, first to last observation irrevocably showed improvement in mean scores. Conclusions: Measuring quality led to improvement in the lowest performing quality measures in these participating practices. This bodes well for our patients.

Legal entity responsible for the study: American Society of Clinical Oncology. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

1588P Treatment algorithm for multiple myeloma: Real-world insights across five European countries

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Background: Therapy of multiple myeloma (MM) is based on proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) used alone or in combination. Bortezomib, Thalidomide and Lenalidomide are approved in Europe but national differences in terms of reimbursement policies may determine their diverse use in MM treatment algorithm.

Methods: Anonymized MM patient level data collected through a large cross-sectional survey between April to December 2017 in 15 EU (France, Germany, Italy, Spain & UK) was used.

Results: 2472 patients (pts) were included in this study. In pts <65 years of age, PIs were largely used in first line across all countries (94% pts) followed by IMiDs (77% pts) with the exclusion of Germany (15% pts) where IMiDs were largely replaced by alkylating agents (78%). In second line, IMiDs were generally the drug of choice across most countries (90% pts) with the exclusion of the UK (36% pts). Opposite picture was observed for PIs: 73% of UK pts received these, whilst only 24% pts in Spain. In pts >65 years in first line, PIs were mostly used (70% pts) whilst IMiDs were only used in 35% pts. The use of alkylating agents varied from 32% (Germany) to 63% pts (France). In second line PIs ranged from 12% in France to 64% in the UK where IMiDs were less used (45%) compared to other countries. Irrespective of age, third line treatment was largely based on IMiDs. In Spain and Germany 1/3 of pts had access to monoclonal antibodies. Interestingly, bone protection treatment (99% bisphosphonate) was administered to 66% of pts in the UK, 52% in Germany and 42% in Spain, but only 24% in Italy and 22% in France.

Conclusions: IMiDs are the most used class of drug to treat MM as single agent or in combination irrespective of line of treatment even if in Germany their use is less common as first line. PIs are used particularly in first line with the exception of the UK where they are common part of second line treatment. Further analyses to determine the impact on progression-free survival of the different treatment algorithms by country are needed.

Legal entity responsible for the study: IQVIA. Funding: Has not received any funding. Disclosure: A. Rocci: Honoraria: Takeda, Sanofi, Celgene, Novartis, Amgen, Janssen; Advisory boards: Novartis, Janssen, Amgen. All other authors have declared no conflicts of interest.

1589P Are treatment recommendations provided by cognitive computing supported by real-world data (Watson for Oncology with Cota RWE) concordant with expert opinions?

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Background: Treatment selection requires review of patient (pt) and clinical features, medical literature, national guidelines, physician experience, and cost–value issues. The IBM Watson for Oncology with Cota RWE (WfO/Cota) point-of-care decision support tool ingests pt attributes from electronic health records and displays treatment recommendations (TRx) based on Memorial Sloan Kettering Cancer Center training and medical literature. The system has been recently supplemented with real world data curated by Cota listing historical treatments and survival outcomes drawn from the treating physician’s institution and a national database. WfO/Cota is undergoing testing at the John Theurer Cancer Center (JTCC, Hackensack, NJ, USA). Concordance of WfO/Cota with expert opinions is required to confirm that cognitive computing TRx match best practices.

Methods: 88 early stage post-menopausal breast cancer (BC) cases from the JTCC BC clinic were presented to 3 JTCC BC experts (without using WfO/Cota). The cases were compared against pts with similar demographic and disease characteristics from the Cota database (matched using Cota Nodal Address (CNA) algorithms).

Results: BC experts reviewed 223 cases (not all cases scored by each). WfO/Cota “recommended” option was concordant with selection by BC experts in 175 (78.5%) and “for consideration” option was selected in 21 (9.4%); experts agreed with WfO/Cota in 87.9%. 7 of 88 cases (8%) generated 59% of non-concordant responses with >2 doctors disagreeing with WfO. The BC expert who worked at Mskcc, deviated the least from MSKCC trained WfO. In the Cota database 69.3% of matched historical controls were treated with “recommended”, 11.4% “for consideration”, 19.3% “not recommended.”

Conclusions: WfO/Cota recommendations are largely concordant with disease expert best oncology practices. The observation that nearly a fifth of pts with similar disease (CNA) characteristics received non-recommended options in a real world database highlights a need. WfO/Cota is an innovative decision support tool that derives new insights based on existing real world evidence to reduce variations in practice.

Background: Obesity is a well-known risk factor for some types of cancer including post-menopausal breast cancer. Nevertheless, the influence of adiposity over life course on cancer risk remains poorly understood. The objective of this study was to assess body shape trajectories in early and middle life in relation to subsequent risk of breast cancer in a Mediterranean cohort.

Methods: We used a group-based modelling approach to assess body shape trajectories from age 5 to 40 years, among 106,797 women from the SUN cohort study from 1999 to 2014. Four distinct body shape trajectories were identified (lean-heavy increase, medium-stable, medium-heavy increase and heavy-stable). Cox regression models were used to estimate the hazard ratio (HR) for breast cancer according to the assigned body shape trajectory.

Results: Among 106,537 women-years of follow-up a total of 133 probable incident cases of breast cancer were identified (70 of these cases were confirmed). When compared to those in the medium-stable category, women who were lean and had a marked increase (lean-heavy increase category) showed a subsequent higher risk of probable breast cancer (HR = 1.55, 95%CI 1.05-2.29). When stratifying according to menopause status, there was a higher risk of probable postmenopausal breast cancer for women in the lean-heavy increase category (HR = 2.0, 95%CI 1.06-3.80) compared to the medium-stable group. The statistical power was reduced and significance was lost when we considered only confirmed cases.

Conclusions: This is the first Mediterranean cohort to suggest that a marked increase in body shape from age 5 to 40 years is associated with a higher risk of breast cancer, especially for postmenopausal women, indicating a role for lifetime adiposity in breast carcinogenesis.

Legal entity responsible for the study: The Seguimiento Universidad de Navarra (SUN) Project.

Funding: Spanish Government-Instituto de Salud Carlos III, the European Regional Development Fund, the Navarra Regional Government and the University of Navarra.

Disclosure: All authors have declared no conflicts of interest.

| 1591P | Total polyphenol intake and breast cancer risk in the SUN project |

<table>
<thead>
<tr>
<th>Probable cases</th>
<th>Overall breast cancer</th>
<th>Premenopausal breast cancer</th>
<th>Postmenopausal breast cancer</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cases / woman-years</td>
<td>HR (95% CI)</td>
<td>Cases / woman-years</td>
</tr>
<tr>
<td>Lean-heavy increase</td>
<td>43 / 18360</td>
<td>1.55 (1.05-2.29)</td>
<td>13/12456</td>
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<tr>
<td>Medium-stable</td>
<td>65 / 57061</td>
<td>1 (ref)</td>
<td>28/46602</td>
</tr>
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<td>Medium-heavy increase</td>
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<tr>
<td>Heavy-stable</td>
<td>3 / 7378</td>
<td>0.55 (0.17-1.76)</td>
<td></td>
</tr>
<tr>
<td>Confirmed cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean-heavy increase</td>
<td>20 / 18453</td>
<td>1.22 (0.70-2.13)</td>
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<tr>
<td>Medium-stable</td>
<td>37 / 5720</td>
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<td>18/46602</td>
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<tr>
<td>Medium-heavy increase</td>
<td>13 / 23811</td>
<td>0.86 (0.45-1.62)</td>
<td>8/20048</td>
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</tbody>
</table>

Table: 1590P

Present in diverse foods. Their role in chronic disease prevention including cardiovascular diseases and cancer has been repeatedly suggested. For this reason, we evaluated total polyphenol intake in association with the risk of BC in the SUN Project - a prospective cohort study in a Mediterranean population.

Methods: We included 10,709 middle-aged, Spanish female university graduates. Polyphenol intake was assessed using a validated semi-quantitative 136-item food frequency questionnaire and matching food consumption data with the Phenol-Explorer database. Diagnosis of BC was self-reported or by the next of kin or identified from death certificates. Self-reports of a medically-diagnosed BC were confirmed using medical records. Cox regression models were fitted to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (95%CI) for the association between tertiles of adherence to the total polyphenol intake and BC risk.

Results: After 10.3 years of median follow-up, 83 confirmed and 165 probable incident BC cases were identified. We observed a statistically significant inverse association between total polyphenol intake and BC risk for postmenopausal women when probable BC cases were used as outcome: HR for highest vs lowest tertile of total polyphenol intake 0.47 (95% CI 0.22-0.97; P for trend=0.041). No further significant associations were observed between total polyphenol intake and incident BC when total BC incidence or risk of premenopausal BC were considered.

Conclusions: Despite the small number of incident BC cases observed in this Mediterranean cohort, we observed that the higher total polyphenol intake, the lower risk of BC among postmenopausal women.

Legal entity responsible for the study: Universidad de Navarra.

Funding: The SUN Project has received funding from the Spanish Government-Instituto de Salud Carlos III, and the European Regional Development Fund (FEDER) (RD/06/0045, CIBER-OBN, Grants PI10/02608, PI10/02293, PI11/018615, PI14/01668, PI14/01798, PI14/01764, and G03/140), the Navarra Regional Government (45/2011, 122/2014), and the University of Navarra.

Disclosure: All authors have declared no conflicts of interest.

Background: Length time bias is a form of selection bias that lead to the perception that screened patients have better outcome as more indolent tumors are diagnosed during screening. However, tumors diagnosed in the interval between mammographies or detected by symptom onset are likely more aggressive. The aim was to analyze using a genomic platform if unscreened tumors were more aggressive than screened ones in a homogeneous cohort not affected by stage or subtype.

Methods: Since 2014 BC pts with T1-T2 N0-1mic tumors and/or high ki67 are selected for genomic platform-based risk assessment in order to guide adjuvant treatment. We performed an exploratory retrospective cohort study in a single institution between 2014 and 2018 in operated stage I-IA BC pts with ER and/or PR + who...
underwent an Oncotype risk assessment before deciding adjuvant therapy. Results of the Recurrence score (RS) were compared according to the type of diagnosis of breast cancer as 1) Screened: Diagnosis during screening (when diagnosed during a forensic/mammography visit); and 2) Unscreened: Diagnosis occurred outside screening (in an introspective mammography or by symptom onset).

**Results:** 105 pts were included. Median age was 56.4 y (45.2-74.6 y). All patients were ER+ (range 50-100%), HER2- and grade was I (12.4%) II (82.9%) or III (4.8%). Median tumor size was 13.7 mm (4.45). 89.5% were N0 and 10.5% N1M0. 68 pts (64.8%) were in the screened and 37 (35.5%) in the unscreened group. Screened adjuvant treatment was changed according to Oncotype results in 24.8% patients. Median RS was 18.2 (range 3-46). According to RS, risk categories 81% were classified as low, 9.5% as intermediate and 9.5% as high risk. Median RS was 17.6 in the screened vs 19.2 in the unscreened group, these differences were not significant (p = 0.34). Differences by RS categories were also not significant (Chi square p = 0.67 for two categories low vs intermediate/high risk with a RR 0.89 [0.62-1.38] and p = 0.2 for three categories).

**Conclusions:** No risk differences according to RS was seen between screened vs unscreened patients. These suggest that length time bias in a cohort not affected by stage or subtype might have minimum impact on screening outcomes.

**Legal entity responsible for the study:** Hospital Clinico Universitario de Valencia. INCLIVA.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

### 1593P Breast cancer screening: Impact on care pathways

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**Background:** Breast cancer screening represents a major public health challenge. In France, no evidence has been furnished that women with breast cancer diagnosed following a mammogram carried out within the framework of the screening programme (SP) underwent less aggressive treatment than women diagnosed by other means. The aggressiveness of treatment represents a supplementary indicator for studying the impact of SP.

**Methods:** To study this indicator, data from the “Cancer Cohort” were used. This consists of a unique cohort including all subjects suffering from cancer since 2010 in France, resulting in care at a hospital or medical practice. All women aged from 50 to 74 years, having undergone a mammogram within the framework of the SP (SP group) were compared to women having undergone a bilateral mammogram outside the SP, because of an opportunistic screening or a clinical symptom (NSP group).

**Results:** In 2014, 23,788 women aged from 50 to 74 years at average risk treated for inci dent breast cancer were identified: 13,530 (57%) in the SP group, and 10,258 (43%) in the NSP group. Women in the SP group had a higher rate of in situ or localised breast cancer than in the NSP group. They had a higher rate of breast-conserving surgery (82% vs 70%) and a lower rate of chemotherapy (34% vs 53%). These findings suggest that length time bias in a cohort not affected by stage or subtype might have minimum impact on screening outcomes.

**Legal entity responsible for the study:** Hospital Clinico Universitario de Valencia. INCLIVA. ***Funding:** Has not received any funding. **Disclosure:** All authors have declared no conflicts of interest.

### 1593P 10-year results of the breast cancer screening program in Khanty- Mansiysk state region Ugra

**N.A. Zakharonov**, **A.R. Brennill**, **J. Belaya**, **E. Blin**

**Oncology, Radiology and Radiotherapy, Khanty-Mansiysk State Medical Academy, Khanty-Mansiysk, Russian Federation, 2Centre for Cancer Prevention, Wolfon Institute of Preventive Medicine, Queen Mary University of London, London, UK, 3Oncology Centre, Khanty-Mansiysk State Clinical Hospital, Khanty-Mansiysk, Russian Federation.

**Background:** Breast cancer is the leading cancer in the female population and one of the most common causes of cancer deaths in women. Improved treatment and the implementation of mammography screening have contributed to substantial reductions in breast cancer mortality over recent decades. The main goal of this study was to evaluate 10-year results of the Breast Cancer Screening Program in Ugra since 2007.

**Methods:** Biannual mammography screening covers women 40 years old using single reading of two-view mammography. Screening data were obtained from the reports for the State Healthcare Department. Data on female population, breast cancer cases (invasive and in situ) and deaths were provided by the State Cancer Registry and State Information Centre. We studied expected absolute incidence and mortality from breast cancer were calculated over the years 2002-16. Expected absolute number of tumours T1N0M0 and with size over 20 mm detected among women 40+ were calculated over the period in question. Expected number assumed constant rate in pre/post screening epochs and its changes were only due to population size. Rate estimated using pre-screening epoch and were age-adjusted.

**Results:** During 2007-16 within the Program, 45139 women were screened. The screening coverage rate in the 2015-16 round was 41% (144777 women). 13464 (9.3%) of those screened were referred for further assessment. The screen detection rate was 3.5 per 1000 screened (1562 breast cancer cases). The test sensitivity for the first round was estimated as 80%. The observed T1N0M0 in 2016 was 126 compared with 73 expected (42% increase). The observed number of breast cancers more than 2cm was 231 compared with 292 expected (26% reduction). Breast cancer mortality in 2016 was 119 compared with 187 expected (35.3% reduction) using absolute mortality results.

**Conclusions:** Trends suggest that mammographic screening in Ugra has contributed to a significant improvement in the early disease diagnosis, and breast cancer mortality has fallen. Improved screening coverage is needed.

**Legal entity responsible for the study:** Khanty-Mansiysk State Medical Academy.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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### 1596P Malignant lymphoma detected by screening program with esophagogastrduodenoscopy of one private screening center in Japan


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**Background:** Malignant lymphoma is rarely encountered in health screening program. It is often difficult to recognize it at early stage although the earlier detection would bring the better prognosis like other malignancies.

**Methods:** Data of screening program with esophagogastrduodenoscopy (EGD) at Ota Memorial Hospital (OMH) in Japan from June 2012 through December 2017 were reviewed and cases of malignant lymphoma detected were analyzed to reveal characteristics.

**Results:** 2686 individuals participated in EGD screening program of OMH in that term. 91 cases of malignant neoplasm were detected and 66 (6.6%) were diagnosed as malignant lymphoma (detection rate 0.2%). They consisted of three gastric and three duodenal lymphomas. None of them had B symptom. Histopathological exam diagnosed all gastric cases as MALT lymphoma locating at middle part of stomach.

**Conclusions:** The endoscopic findings were as follows; one was scar-like whitish mucosa without stricture, another was whitish mucosa mixed with erythema, and the other was scar-like lesion surrounded nodular and granular mucosa. Although all gastric lymphomas had no eradication history of Helicobacter pylori (Hp) and serum anti-Hp IgG antibody were less than 3 U/ml, one of them had advanced chronic atrophic gastritis. All gastric MALT lymphoma took irradiation therapy. All duodenal lymphomas were diagnosed as follicular lymphoma. One of them located around duodenal papilla was recurrent lesion that had originated in mesenteric lymph nodes and been treated with chemotherapy six years before. Its endoscopic findings were polyploid and granular lesions. Other two duodenal lymphomas were detected at inferior duodenal angle as nodular and granular appearance. The recurrent follicular lymphoma had the second line chemotherapy. Other two cases were treated by irradiation and molecular targeting therapy with rituximab respectively.

**Legal entity responsible for the study:** Ota Memorial Hospital.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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1597P

Worldwide trends in survival from childhood glioma 2000-2014 (CONCORD-3): Preliminary findings and plans for further research

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Background: The CONCORD programme was the first to establish global surveillance of cancer survival. The third cycle (CONCORD-3) collected data from 322 cancer registries in 71 countries. Survival from all brain tumours combined varied widely between countries, particularly in children. We propose to examine survival trends by relevant explanatory variables to help explain these disparities.

Methods: We present the numbers of children diagnosed with a glioma (ICD-O-3 morphologic codes 938-941) and by each of the main glioma subtypes. Five-year net survival will be estimated by morphology, WHO grade, topography, sex, country and calendar period of diagnosis. Net survival is the probability that patients survive their cancer until a given time since diagnosis (e.g. 5 years), after controlling for competing risks of death (background mortality).

Results: Data were obtained for 56,507 children (aged 0-14 years) diagnosed with a glioma: 19,080 in Europe, 26,751 in North America, 6,111 in Asia, 3,103 in Central and South America, 1,579 in Oceania and 83 in Africa. In Europe, 5% of gliomas were ependymomas, 26% pilocytic astrocytomas, 8% astrocytomas, not otherwise specified (NOS), 5% glioblastomas NOS and 15% medulloblastomas NOS. The distribution was similar in North America. In Africa, Asia, and Central and South America, and in Oceania, pilocytic astrocytoma was less frequent (10%-13%) than in Europe or North America. In Africa, Asia, and Central and South America, astrocytoma NOS was more common (11-32%). The frequency of medulloblastoma was higher in Central and South America (28%) and Asia (23%). The distribution of the morphologic subtypes of childhood glioma varies widely around the world. Survival differs between morphologic groups. We will assess the extent to which the distribution of morphologic subtypes contributes to international variation in childhood glioma survival worldwide.

Conclusions: When comprehensive survival analyses are available for each type of glioma, this project will become the benchmark for future international comparisons of brain tumour survival in children, to inform cancer control plans.

Legal entity responsible for the study: London School of Hygiene and Tropical Medicine.

Funding: Children With Cancer UK.

Disclosure: All authors have declared no conflicts of interest.

1598P

Referral patterns and predictors of survival for stage IV pancreatic ductal adenocarcinoma

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Background: We previously found that many patients with a diagnosis of advanced pancreatic ductal adenocarcinoma (PDAC) are not referred for palliative chemotherapy despite recent advances. We sought to investigate referral patterns, chemotherapy eligibility and predictors of overall survival (OS) in a large cohort of advanced PDAC in Alberta, Canada.

Methods: All patients with Stage IV PDAC from 2009 - 2015 in Alberta were identified using the Alberta Cancer Registry. Patients missing laboratory eligibility criteria for chemotherapy were excluded. Demographics, clinical characteristics, cancer centre referral, chemotherapy received, and OS were collected. Primary analysis explored referral patterns and treatment eligibility. Secondary outcomes identified predictors of survival using Kaplan-Meier with log-rank test and multivariable Cox regression analysis.

Results: 1412 patients were identified. ECOG (≥1 = 83%; ≥2 = 72%), age (34%) and bilirubin (>ULN = 30%; >1.5xULN = 22%) were the most common reasons for chemotherapy ineligibility. A proportion of patients who were eligible by trial criteria for FOLFIRINOX (21%) and nab-paclitaxel/gemcitabine (20%) were not referred, yet some patients who were ineligible for any chemotherapy were still referred. Distance to travel to a cancer centre did not have a significant difference on referral patterns. Primary tumor location, any chemotherapy received, referral, ECOG, bilirubin, and ANC were significant predictors of survival in the Cox regression analysis.

Conclusions: More patients who are potentially eligible to receive palliative chemotherapy should be referred to a cancer centre. Patients with obstructive jaundice should have expedited biliary drainage procedures to facilitate systemic treatment eligibility.
Background: Cancer is mainly diagnosed by histopathology, but some complex situations may provoke physicians’ desire to avoid biopsy. This is particularly important when cancer diagnosis can be made based on other less accurate methods like radiological findings or elevated tumor markers e.g. suspicious ovarian mass with elevated CA125. However, data about these cases treated based on diagnosis “prediction” rather than accurate definition of histopathology are lacking. In this study, survival is compared between cases with microscopic confirmation of diagnosis and those diagnosed with other methods. This is presented for all types of cancer but with particular focus on four main tumors where other modalities for diagnosis may be appealing.

Methods: Data were obtained using SEER*Stat version 8.3.5 (SEER 18 Regs Nov 2017 Submission). Only cases diagnosed between 2001 and 2010 were included. Observed survival was calculated using SEER*Stat where other data analysis including Kaplan Meier analysis was made using SPSS.

Results: Microscopic confirmation (MC) was the mainstay for diagnosis in most of included cases (n = 3594344; 94.2%). In the remaining group (non-microscopically confirmed (NMC) diagnosis, n = 222907; 5.8%), radiography was used in 46% (n = 102401). Clinical diagnosis, positive laboratory test/marker, and direct visualization were used in 11.8%, 5.2%, and 2.7 respectively. There was a significant survival difference between MC and NMC that was consistent in prostate, ovarian, liver, and pancreatic cancer as well as in other types of malignancies (p < 0.05). The table shows the 5-years observed survival and 95% CI for different types of cancer in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>MC</th>
<th>NMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>85.3% (85.2-85.4)</td>
<td>26.6% (25.8-27.5)</td>
</tr>
<tr>
<td>Ovary</td>
<td>44.1% (43.6-44.6)</td>
<td>10.9% (9.8-12)</td>
</tr>
<tr>
<td>Liver</td>
<td>18.1% (17.7-18.5)</td>
<td>9.6% (9.2-10.1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.5% (6.3-6.7)</td>
<td>2.6% (2.3-2.9)</td>
</tr>
<tr>
<td>Others</td>
<td>67.4% (57.3-57.4)</td>
<td>14.7% (14.4-14.9)</td>
</tr>
<tr>
<td>All</td>
<td>60.5% (60.6-60.6)</td>
<td>13.7% (13.5-13.8)</td>
</tr>
</tbody>
</table>

Conclusions: Microscopic confirmation should be regarded as the only accurate method for diagnosis of cancer. Depending on other diagnosis methods may have a strong detrimental effect on survival. More studies needs to address possible explanations for these findings and potential implications on management.

Legal entity responsible for the study: Mohamed Alaa Gouda.

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Disclosure: The author has declared no conflicts of interest.
Natural history of sarcomas and impact of reference centers in the nationwide NETSARC study on 35,784 patients (pts) from 2010 to 2017


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Initial results of phase I study of DCC-2618, a broad-spectrum KIT and PDGFRα inhibitor, in patients (pts) with gastrointestinal stromal tumor (GIST) by number of prior regimens


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Outcome following unplanned excision in soft tissue sarcoma: Results of a multicentre study including 728 patients

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Health-related quality of life (HR-QoL) in elderly soft tissue sarcoma (STS) patients from the randomized phase II EPAZ study comparing pazopanib (PAZ) and doxorubicin (DOX) in first line


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Health-related quality of life in patients with advanced soft tissue sarcoma (STS): Results from the TSAR randomized phase III trial of the French Sarcoma Group

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Quality of life in patients with soft tissue sarcoma undergoing palliative treatment: A multicenter, cluster-randomized trial within the Germany Interdisciplinary Sarcoma Group (GISG-12)


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Immune response, safety, and overall survival of NY-ESO-1 + soft tissue sarcoma patients treated with CMB305 therapy


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Can we cure patients with abdominal desmoplastic small round cell tumor? Results of a retrospective multicentric study on 100 patients

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Preoperative hypofractionated radiotherapy (RT) in patients with locally advanced myxoid liposarcomas: Interim analysis of prospective phase II clinical trial

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A phase II study of pazopanib with oral topotecan in patients with metastatic osteosarcoma

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A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults (INI1-negative tumors cohort) (NCT02601950)


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A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults (rhabdoid tumor cohort) (NCT02601950)


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mTOR inhibitors in uterine and extra-uterine malignant PEComas: A multicenter international case series retrospective analysis

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A phase II study of preoperative chemoradiation plus sorafenib (S) for high-risk extremity soft tissue sarcomas (STS)


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A phase II, multicenter study of the EZH2 inhibitor tazemetostat in adults: Epithelioid sarcoma cohort (NCT02601950)


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Background: Immune microenvironment of GIST is largely unknown and there is no approved immunotherapeutic agent for the treatment of advanced GISTs. To investigate novel immunotherapeutic strategy in patients with GISTs, immune microenvironment was analyzed in this study.

Methods: In this study, 80 surgical specimens of GISTs from 65 patients in different clinical setting (TKI-naive [n = 20], imatinib-pretreatment [IM-PD, n = 30], and imatinib-resistant metastatic patients with sunitinib-treated [IM-PDSU-treated, n = 30]) were included. CD3, CD8, FoxP3, PD-L1, PD-1 and DOG-1 were simultaneously evaluated in one formalin-fixed paraffin-embedded tissue section using multiplexed immunohistochemistry (IHC) with computational image processing workflows for quantitative assessment.

Results: IM-PDSU-treated group showed increased FoxP3+/CD3+ (p = 0.008, p = 0.004, and p = 0.007, respectively) and IM-PD (p = 0.008, p = 0.002, and p = 0.01, respectively) groups. PD1 expression (>1%) on tumor cells (PD-1+/DOG-1-) were also higher in IM/PD-SU-treated group (10%) compared to TKI-naive (0%) and IM-PD (3%) groups. There were no significant differences in immune microenvironment profiles between TKI-naive and IM-PD groups (p > 0.05).

Conclusions: Anti-angiogenic agents may have immunomodulatory activity in advanced GISTs. Immune exhaustion phenotype (increased Treg, PD-1+ T cells and PD-1+ tumor cells) in IM/PDSU-treated patients might indicate that this group is a potential candidate for future immunotherapy trials.

Legal entity responsible for the study: Yoon-Koo Kang.

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Disclosure: All authors have declared no conflicts of interest.

Multicentric retrospective analysis of patients with KIT exon 9 mutated GIST

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Background: Patients (pts) with advanced GIST harbouring the KIT exon 9 mutation have a better progression-free survival (PFS) on a higher daily dose level, i.e. 800 mg of imatinib (IM), which is therefore held as standard treatment in this subgroup. This schedule in the adjuvant setting has been subsequently proposed despite the lack of any controlled trials.

Methods: We retrospectively evaluated characteristics of pts with KIT exon 9 mutated GIST in 6 different centers in France and Spain, treated with a daily dose of 400 mg of IM. Pts with localized and advanced GIST were separately analyzed: Kaplan-Meier and Cox proportional hazards model analyses were used to compare median relapse-free survival (mRFS) and OS (mOS) in the adjuvant setting, and overall response rate (ORR), median PFS to IM 400 mg (mPFS), median time to IM failure (mTIF) defined as time to 2nd progression (PD) or death, and mOS in the advanced setting.

Results: We identified 43 pts (44% of males) with a median age of 56 yrs (16-78). 67.4% of GIST was originated in the small bowel and 18.6% in the stomach. In adjuvant setting (31 pts), 42% of pts had a high risk (HR) of relapse (Miettinen classification) and 29% an intermediate risk (IR). 17 out of 31 pts received adjuvant 400 mg of IM for a median duration of 21 months (m). The mRFS of pts receiving adjuvant IM was 82 m vs 21 m for those who did not. In the advanced setting, 22 pts were treated with 400 mg of IM. The mORR was 37% (3 CR and 5 PR), with additional 7 stabilizations (benefit in 69% of pts). At PD, 77% of pts received the higher dose IM regimen (800 mg). The mPFS was 12.7 m (CI 95% 6.8-18.6) and the mTIF was 20.6 m (CI 95% 12.2-29). The mOS was 42.9 m. No prognostic variable (gender, age, PS, site of primary disease, diameter of largest lesion, prior surgery of primary) was significantly related with mOS or mTIF.

Conclusions: Despite the limitations of retrospective analysis and the small number of pts, benefit of adjuvant IM (400 mg/d) in pts with localized GIST harbouring KIT exon 9 mutations seems relevant. Pts with advanced GIST initially treated with 400 mg of IM have a similar outcome in terms of mTIF (20 m) than those receiving high-dose IM upfront (19 m in the initial MetaGIST trial, M. V. Glabbeek et al, JCO 2010).

Legal entity responsible for the study: Gustave Roussy Institute.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Prognostic factors for residual lesion surgery following disease control with standard dose imatinib (IM) treatment in patients (pts) with advanced gastrointestinal stromal tumor (GIST)


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Background: Efficacy of residual lesion surgery in pts with advanced GIST responding to IM has been advocated in several retrospective studies. However, to date, no studies have identified the prognostic factors exclusively for these pts.

Methods: Between September 2002 and December 2015, a total of 107 pts with histologically documented initially metastatic or distant recurrent GIST received residual lesion surgery following disease control with IM 400 mg/day in Asan Medical Center, Seoul, Korea. Among these pts, 89 pts had complete data for potential prognostic factors and were included in the analysis.

Results: Median age was 57 years (range, 12-77) and 56 pts (62.9%) were male. 33 pts were treated with adjuvant IM 400 mg/d in Asan Medical Center, Seoul, Korea. Among these pts, 89 pts had complete data for potential prognostic factors and were included in the analysis. 33 pts were treated with adjuvant IM 400 mg/d in Asan Medical Center, Seoul, Korea. Among these pts, 89 pts had complete data for potential prognostic factors and were included in the analysis.

Conclusions: Our study confirms that long-term survival can be achieved in advanced GIST pts receiving residual lesion surgery following disease control with IM. However, further study is needed to define the role of residual lesion surgery in pts with 3 risk factors considering their poor survival outcomes.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: Y. K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Daeowa, LSK Biopharma. All other authors have declared no conflicts of interest.
Background: To achieve optimal clinical outcomes with imatinib in GIST patients, it is crucial to maintain standard imatinib dose. Skin rash is a common and sometimes severe adverse event of imatinib treatment and may affect compliance. Our previous retrospective study suggested that severe skin rash induced by imatinib can be managed by systemic steroid without interruption or dose reduction of imatinib. This phase II study was conducted to evaluate efficacy and safety of systemic steroid in GIST patients with imatinib-associated severe skin rash.

Methods: Between October 2014 and March 2016, 29 patients were enrolled and treated with oral prednisolone for imatinib-associated severe skin rash which was defined as grade 3 skin rash or grade 2 skin rash with pruritus. Prednisolone was started with 30mg daily for 3 weeks, and if skin rash is controlled, steroid was tapered over 12 weeks by determined schedule. The primary endpoint was treatment success rate (TSR). Treatment success was defined as maintaining imatinib without persistence or recurrence of skin rash requiring 1) additional systemic steroid treatment, and 2) interruption or dose reduction of imatinib.

Results: Of 29 patients enrolled, 16 patients (55.2%) received imatinib in adjudicated setting, and 13 (44.8%) in palliative setting. The median age was 61 years (range, 31-77). Eleven patients (37.9%) were male. Twenty-two patients (75.8%) were treated successfully. Treatment failure rate, and 5 (17.2%) were not evaluable. With a median follow-up of 22 months (range, 16–22–78), 71.5% of patients could maintain imatinib dose without recurrence of skin rash for 2 years. Patients aged <60 years showed higher TSR (odds ratio [OR]=4.38, p=0.0192). No one experienced disease progression during follow-up. All toxicities associated with systemic steroid were evaluated. One patient with myelodysplastic syndrome had Pneumocystis pneumonia. Otherwise, systemic steroid was well tolerated.

Conclusions: This study demonstrated that systemic steroid treatment can effectively control severe skin rash and minimize interruption or dose reduction of imatinib in GIST patients with imatinib-associated severe skin rash. Clinical trial identification: NCT03440515.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1620P Phase II study of paclitaxel in patients with advanced gastrointestinal stromal tumor (GIST) after failure of at least both imatinib and sunitinib

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Background: Most advanced GISTs are known to be resistant to conventional cytotoxic agents but sensitive to tyrosine kinase inhibitors (TKI) such as imatinib and sunitinib. However, majority of patients eventually develop resistance to TKIs and experience disease progression. Recent preclinical studies suggested that a few conventional cytotoxic agents such as paclitaxel might have antitumor effect on GIST. The current study was conducted to evaluate the efficacy and safety of paclitaxel in patients with advanced GIST after failure of at least imatinib and sunitinib.

Methods: Patients received paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of a 4-week cycle. The primary endpoint was 16-week disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). Translational correlation of PFS with expression of P-glycoprotein (P-gp) was also evaluated. This trial is registered with ClinicalTrials.gov, no. NCT02670332.

Results: A total of 25 patients were enrolled. Median age was 61 years (range, 38-71), and 16 patients (64.0%) were male. Small bowel was the most common primary site (n=7, 28.0%). Median 2 cycles (range, 1-12) of paclitaxel were administered per patient. No CR was observed. PR and SD were observed in one patient (4.0%) and 10 patients (40.0%), respectively. The 16-week disease control rate was 20.1%. With a median follow up duration of 20.8 months (range, 17.9-24.0) in surviving patients, median PFS and OS were 1.7 months (95% CI, 0.23-3.15) and 10.9 months (95% CI, 0.0-23.68), respectively. The most frequent grade 3/4 adverse events were neutropenia (20.0%) and leukopenia (8.0%). P-gp expression was evaluable in 19 patients, and a trend toward poor PFS was documented in patients with high P-gp intensity score (3 vs. 1-2, HR 2.3, P=0.12).

Conclusions: Paclitaxel was well tolerated with modest antitumor efficacy in heavily pretreated patients with advanced GIST. Additionally, P-gp may be a potential biomarker for selecting patients for paclitaxel treatment.

Clinical trial identification: NCT02670332.

Legal entity responsible for the study: Asan Medical Center.

Funding: Haem.

Disclosure: Y.-K. Kang: Consultant: Ono, BMS, Taiho, Roche, Lilly, Blueprint, Taiho, Dawha, ESK Biopharma. All other authors have declared no conflicts of interest.

1622P Heat shock protein 90 (HSP90) inhibitor as a candidate treatment option for gastrointestinal stromal tumor with acquired resistance for conventional receptor tyrosine kinase inhibitors

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Background: Imatinib functions as a specific inhibitor of a number of tyrosine kinase enzymes, such as KIT and PDGFR, by occupying the TK active site, and thus improves the prognosis of gastrointestinal stromal tumor (GIST) patients. However, resistance to the drug appears with prolonged usage. Mechanisms of acquired resistance are still under elucidation.

Methods: To evaluate mechanisms of acquired resistance for imatinib, we established a imatinib-resistant GIST cell line, so-called T1R, by culturing the GIST cell line, GIST-T1, with increasing concentrations of imatinib. Next, we analyzed receptor tyrosine kinases (RTKs) and intracellular signals strongly expressed in T1R by western blotting and phosphorylated arrays. Finally, we examined the antitumor effect of an agent which was confirmed to inhibit upregulated RTKs in T1R.

Results: Interestingly, imatinib-resistant T1R showed cross resistance to sunitinib, which offers patients with imatinib-resistant GIST a new treatment option to stop further disease progression. By western blotting, T1R showed a suppression of phosphorylation in KIT in contrast to a promotion of phosphorylation in PDGFR, which never observed before imatinib treatment. A phosphorylation multiplex array also revealed that T1R had additional promotion of phosphorylation in FGFR, Met, Eph, Axl, and Tie2. Therefore we considered activation of PDGFR owing to one of the candidate machinery of acquired resistance for imatinib as well as sunitinib. HSP90 inhibitors is known to effective against both imatinib-sensitive and resistant GIST models. Therefore, we examined whether HSP90 inhibitors interact with PDGFR, and HSP90 inhibitors resulted in inhibiting cell proliferation and induce apoptosis in T1R. HSP90 inhibitors inhibited the phosphorylation and protein expression of PDGFR and other RTKs, resulted in inhibit cell proliferation and induce apoptosis in T1R.

Conclusions: Activation of multiple RTKs is an essential for acquired resistance for imatinib in GIST. Inhibition of PDGFR and other RTKs by HSP90 inhibitors has a potential to the next treatment option for GIST which acquired drug resistance for conventional small molecule, multi-targeted RTK inhibitors.
Correlation of ctDNA and response in patients (pts) with PDGFRA D842 GIST treated with avapritinib


Background: Plasma ctDNA was sequenced at baseline and 2 mos after the start of treatment. We investigated whether baseline ctDNA levels and changes in ctDNA during treatment were associated with response.

Methods: Plasma ctDNA was sequenced at baseline and 2 mos after the start of treatment. Pts (n = 20) in dose escalation were profiled using the Sysmex OncoBEAM™ PDGFRα assay; Pts (n = 12) in dose expansion were sequenced with a custom Personal Genomix Diagnostica PlatformSELECT™ panel.

Results: As of 1 Jan 2018, response rate was 79% and stable disease rate was 23% per mRECIST v1.1 (modified for GIST). Median progression free survival (PFS) was not reached; estimated 12 mos PFS rate was 78%. Baseline ctDNA mutation allele fraction (MAF) correlated with target lesion size (p < 0.002). Lower than median baseline ctDNA MAF identified a group of pts with 100% PFS after a median follow up time of 16 mos (1.8 to 26.6 mos). Ava led to detectable ctDNA declines (median 5.2 fold) in all pts except those near the quantification limit (which changed minimally). Despite this, larger declines, or falling below the limit of quantification (BLQ), did not correlate with greater shrinkage or longer PFS. Instead, declines were barely quantifiable in pts with improved outcomes. Our data suggest that although highly effective targeted therapy can achieve rapid declines, even falling below the limit of detection, was not predictive of response.

Conclusions: Large ctDNA declines have been speculated to be a predictor of treatment response. We show in PDGFRα D842 mutant GIST low baseline ctDNA correlates with prolonged PFS yet ctDNA minimally declines due to detection limits. Surprisingly, large fold declines, even falling below the limit of detection, was not predictive of improved outcomes. Our data suggest that although highly effective targeted therapy can achieve rapid declines, even falling below the limit of detection, was not predictive of response. Instead, declines were barely quantifiable in pts with improved outcomes. Our data suggest that although highly effective targeted therapy can achieve rapid declines, even falling below the limit of detection, was not predictive of response.

Methodology:

Background:

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Pathological grade of tumourregression after neoadjuvant chemotherapy with doxorubicin/ifosfamide and regional hyperthermia correlates with survival outcomes in patients with high-risk soft tissue sarcoma

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Methods: Pathological examination included histological grading of the tumors before and after neoadjuvant treatment and immunohistochemical staining for Ki-67 index. In the patient group, we identified 28 pts with high-grade soft tissue sarcomas who underwent neoadjuvant chemotherapy with doxorubicin/ifosfamide and regional hyperthermia (HR-ST). Assessment of pathological response was performed by two independent pathologists. Survival was assessed using the Kaplan-Meier method and compared using log-rank test.

Results:

Conclusions:

Pathological grade of tumourregression after neoadjuvant chemotherapy with doxorubicin/ifosfamide and regional hyperthermia correlates with survival outcomes in patients with high-risk soft tissue sarcoma

Efficacy of metastasectomy on survival in patients with metastatic soft tissue sarcoma: Results of a bi-centre study including 135 patients

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Background: Metastasectomy is hypothesised to improve overall survival (OS) in patients with metastatic metastases of STS. Evidence in favour of this approach comes from non-controlled single-arm studies subjected to selection bias. In the
present study, advanced comparative effectiveness methods were used to assess the efficacy of metastasectomy vs. "non-invasive" treatments (i.e. chemotherapy, radiotherapy, best supportive care) in patients with metachronous STS metastasis.

**Methods:** 36 patients in this study with a mean age of 36.9 ± 18 years with median OS were analyzed.

**Results:** 6 pts (17%) died during follow-up. The median OS was 67 months (95% CI: 46-92) for the whole cohort. The 5-year OS was 62% (95% CI: 49-74) and the 10-year OS was 43% (95% CI: 28-58). Metastasectomy was associated with significant benefit on OS, even after adjustment for favorable prognostic factors prevailing in patients with metastatic disease (10-year OS: 17% vs. 3%, log-rank test: p < 0.0001; HR: 0.33, 95%CI: 0.20-0.52, p < 0.0001). This positive association prevailed after adjustment of confounding factors present. The main factors associated with survival were age at diagnosis, primary tumor site (pelvis > thigh > trunk), number of metastases, portal vein involvement, and type of bone involvement.

**Conclusions:** Metastasectomy should be considered as first choice in patients with metachronous STS metastasis. Further studies are recommended to validate these results.

**Legal entity responsible for the study:** Medical University of Graz.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Background: Metastatic disease to the lung is one of the most common life-threatening complications of cancer and can be seen with most types of cancer. Apatinib, a tyrosine kinase inhibitor targeting VEGFR-2, has shown efficacy in lung cancer. And the preclinical data also showed plasma concentration of apatinib was high in the lung. This cancer registry study aims to make an exploratory assessment of the efficacy and safety of apatinib in lung metastases.

Methods: Between 2015/05 and 2018/03, this study recorded all patients with advanced cancers in our hospital, with apatinib 500 mg or 250 mg being given. Tumor response assessment and survival analysis were performed.

Results: A total of 103 patients, 30 had no lung metastases, and 73 had lung metastases, among which most were bone sarcoma (36%) and soft-tissue sarcoma (37%) metastases to lung. Among 57 evaluable patients with lung metastases, 2 achieved CR, 29 achieved PR, and 20 achieved SD, ORR was 54%. In 11 evaluable patients with no lung metastases, no patient achieved CR, 3 patients achieved PR, and the ORR was 27%. For patients with lung metastases, the mPFS was 12.9 months (95% CI, 8.6-14.9 months), mOS was 21.9 months (95% CI, 15.9-31.3 months). For patients with no lung metastases, the mPFS was 6.0 months (95% CI, 4.6-NE months), the mOS was 10.7 months (95% CI, 5.2-NE months). In lung metastatic patients who received apatinib 500mg, the ORR and DCR were, respectively, 35.1% and 89.8%; when treated with apatinib 250mg, the ORR and DCR were 29% and 86%. When Apatinib was used as first-line treatment, the ORR and DCR were respectively 44% and 88%; in second-line treatment, the ORR and DCR were respectively 42% and 84%, and when apatinib was used in third line treatment, the ORR and DCR were 33% and 100%. For patients with lung metastases, 89.2% patients experienced adverse events (AEs); the most frequent AEs were hand-foot syndrome (21.6%), diarrhea (20%), hypertension (24.3%) and albuminuria (9.4%).

Conclusions: Based on this exploratory analysis, for bone sarcoma and soft-tissue sarcoma with lung metastases, apatinib 500mg showed promising trends in efficacy and safety profile. An expansion study will be needed.

Legal entity responsible for the study: Chongqi Tu.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Efficacy of anlotinib in advanced soft tissue sarcoma by prior lines of therapy, age and dose modification


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Background: ALTER0203 was a randomized phase IIIb trial (NCT02449943) that demonstrated single-agent activity of anlotinib in advanced STS (aSTS). The primary end-point progression-free survival (PFS) was met and presented as an oral presentation in 2018 ASCO. We evaluated the relationship between age, prior lines of therapy, and dose reductions on the efficacy of anlotinib in aSTS.

Methods: Median PFS (mPFS) was evaluated in subgroups of prior lines of therapy (0 or 1 prior line; 2+ prior lines), age (< 65 y; ≥65 y), and dose reductions (no dose reduction; ≥1 dose reduction). All analyses were descriptive and exploratory and required cautious interpretation.

Results: A total of 158 patients received anlotinib in the ALTER0203 study. Before enrollment, 20 patients of alveolar soft part sarcoma and clear cell sarcoma had no prior line of chemotherapy, 84 patients had received 1 prior line of chemotherapy and 54 patients had received 2+ prior lines of chemotherapy. Median PFS was similar in patients receiving anlotinib who had only 0 or 1 prior line of therapy vs 2+ prior lines of therapy (mPFS, 6.7 vs 6.35 months). In patients receiving anlotinib, mPFS was similar in ages < 65 years vs ≥65 years (6.33 and 5.9 months, respectively). In patients receiving anlotinib, mPFS was longer in patients requiring ≥ 1 dose reduction vs no reduction (10.43 and 5.73 months, respectively).

Conclusions: In patients receiving anlotinib, longer mPFS was observed in patients requiring ≥ 1 dose reduction. Additionally, mPFS with anlotinib was maintained regardless of lines of therapy or patient age.

Clinical trial identification: NCT02449943.

Legal entity responsible for the study: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

Table: 1630P

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<td>6.2 (4.07-9.33)</td>
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<tr>
<td>2+ prior lines</td>
<td>54</td>
<td>6.33 (5.90-8.76)</td>
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<tr>
<td>&lt; 65 y</td>
<td>152</td>
<td>6.33 (5.06-7.60)</td>
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<tr>
<td>≥65 y</td>
<td>6</td>
<td>5.9 (0.00-14.86)</td>
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<tr>
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<tr>
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<tr>
<td>≥1 dose reduction</td>
<td>14</td>
<td>10.43 (-)</td>
<td></td>
</tr>
</tbody>
</table>

mPFS, median progression-free survival; CI, confidence interval.

Efficacy and safety of apatinib in advanced sarcoma

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Background: Sarcoma constitutes a heterogeneous group of rare solid tumors and has no standard second-line treatment. Anti-angiogenesis tyrosine kinase inhibitors have shown promising efficacy for advanced sarcoma after failure of first-line chemotherapy. Apatinib is a highly selective vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist from China. In the present study, we retrospectively assessed apatinib for safety and activity in advanced sarcoma patients from our cancer center.

Methods: Patients with advanced sarcomas treated with apatinib 250-500mg daily between August 2015 and February 2018 were retrospectively analyzed. Objective response was determined according to RECIST 1.1 criteria, progression-free survival (PFS) was estimated by the Kaplan-Meier curves and safety profile was analyzed.

Results: In total, 52 patients were treated with apatinib and 37 patients (23 males and 14 females) were included for analysis, including 7 alveolar soft part sarcoma (ASPS), 5 PNET/Ewing’s sarcoma, 4 osteosarcoma, 4 chondrosarcoma, 4 synovial sarcoma, 4 undifferentiated pleomorphic sarcoma, 4 liposarcoma, 2 angiosarcoma, 1 rhabdomyosarcoma, 1 chordoma, 1 differentiated liposarcoma and 1 clear cell sarcoma. 5 (15.5%) patients received apatinib as first-line treatment, 17 (45.9%) and 15 (40.5%) were treated with apatinib as second line or later therapy respectively. 18 (46.8%) achieved tumor regression, 1 patient with ASPS had complete response, 8 (21.6%) experienced partial response, and disease was stable in 21 (56.8%) patients. The disease control rate was 100% in 5 patients with ASPS. The median PFS for all patients was 12 months, and median PFS of patients except ASPS was 5.9 months. The most frequent treatment-related adverse events included hypothyroidism [11 (29.7%)], Proteinuria [8 (21.6%)], hypertension [11 (29.7%)], hand-foot syndrome [19 (51.4%)], diarrhea [9 (24.3%)], fatigue [5 (13.5%)], hemorrhage [4 (10.8%)], anorexia [5 (13.5%)], oral ulcer [3 (8.4%)], rash [2 (5.4%)], bleaching hair [2 (5.4%)], and aerthorax [2 (5.4%)].

Conclusions: Apatinib may be effective and tolerable in advanced sarcoma, especially in ASPS.
Evaluation of hypertension and hand-foot syndrome as markers of anlotinib efficacy in advanced soft tissue sarcoma

Background: ALTER0203 was a randomized phase IIb trial (NCT02449343) that demonstrated single-agent activity of anlotinib in advanced STS (aSTS). The primary end-point: progression-free survival (PFS) was met and presented as an oral presentation in 2018 ASCO. Similar to other vascular endothelial growth factor pathway-targeted therapies, hypertension and hand-foot syndrome (HFS) have been observed as major adverse events of anlotinib. The goal of our study was to assess if hypertension and hand-foot syndrome induced during treatment with anlotinib were associated with clinical outcome in aSTS patients treated with anlotinib.

Methods: We conducted a review of patients enrolled in ALTER0203. Median PFS was analysed in patients with hypertension and HFS vs patients with no hypertension and HFS. All analyses were exploratory and required cautious interpretation.

Results: A total of 158 patients received anlotinib in the ALTER0203 study. During the study, hypertension was observed in 99 patients (62.6%). HFS was observed in 76 patients (48.1%). Median PFS was longer in patients with hypertension vs patients with no hypertension (7.90 vs 4.57 months, p = 0.36). Patients with any grade hypertension while on anlotinib had an adjusted hazard ratio for progression of 0.81 compared to those without hypertension. Also, median PFS was longer in patient in HFS vs patients with no HFS (9.83 vs 4.3 months, p < 0.01). Patients with any grade HFS while on anlotinib had an adjusted hazard ratio for progression of 0.47 compared to those without hypertension.

Conclusions: Our data indicate that HFS may represent an interesting prognostic factor for clinical outcome in aSTS patients receiving anlotinib. There is a trend that mPFS of patients with hypertension is longer than those with no hypertension.

Clinical trial identification: NCT02449343.

Legal entity responsible for the study: China Tai TianQing Pharmaceutical Group Co., Ltd.

Funding: China Tai TianQing Pharmaceutical Group Co., Ltd.

Disclosure: All authors have declared no conflicts of interest.

doxorubicin (Dox), cisplatin (CDPP), ifosfamide (If), and etoposide (Eto), the 2nd protocol, “OGS-99-enhanced”, involved OGS-99 drugs with enhanced supportive care including growth factors. The 3rd dose-dense “OGS-12” protocol, involved administration of 8 sequential dualts of the 3 most active drugs (Dox, Cis & If), universal growth factor prophylaxis & targeted nutritional support including IV Iron if required. Event free survival (EFS), overall survivals (OS) and toxicity were estimated using retrospective chart review in OGS-99 & OGS-99-enhanced protocols & prospectively in OGS-12 protocol.

Results: A total of 41, 94 & 385 treatment naive, consecutive, non-metastatic extremity patients were treated with OGS-99/year 2000-2005, OGS-99-enhanced (2010) & OGS-12 (2011-2016) respectively. At a median follow-up of (19.5 72), 85(2.89) and 36(6-78) months, the 5 year EFS rates are 36%, 50% and 69% in OGS-99, OGS-enhanced & in OGS-12 respectively. The corresponding rates of 5 year OS are non- evaluable, 60% & 83% respectively. OGS-12 protocol fared better with respect to grade 3/4 toxicities; febrile neutropenia (40%), thrombocytopenia (36%), anemia (31%) with 4(1%) chemo toxic deaths & compliance to therapy.

Conclusions: Sequential adaptation of more rational chemotherapy regimens, including conception of novel “OGS-12” protocol with, better dose density and elimination of ineffective drugs, enhanced supportive care & thereby reducing the need for dose reductions, resulted in marked improvement in outcomes of non-metastatic osteosarcoma patients. This sustainable, economic efficient strategy is worthy of wide adaption.

Legal entity responsible for the study: Jyoti Baipai.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

HBP-bound doxorubicin: Promising new therapy for bone cancer

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Background: Primary bone cancers and bone metastases derived from advanced cancers have low survival rates. To answer medical need to treat tumors localized in bone environment, we have developed bone-targeted drugs through covalent binding to hydroxybisphosphonates known for their high affinity to bone. Objectives were improvement of efficacy and reduction of systemic toxicity.

Methods: Preclinical proof of concept of lead compound 12b80, an HBP-bound doxorubicin, was carried out on rodents and dogs. 12b80 was administered by IV injection every 3 weeks. Antitumor effects were investigated on various rodent models of bone cancers, including spontaneous models of osteosarcoma or Ewing’s sarcoma, models of osteosarcoma-derived lung metastases and models of bone invasion by prostate or mammary adenocarcinoma) and on spontaneous osteosarcoma bearing dogs. Biodegradation was examined by radiolabeling and fluorescence analyses. Toxicity was evaluated by biological and clinical monitoring and histopathological analysis of organs.

Results: 12b80 displayed rapid and sustained targeting of bone tissue and tumor-associated heterotopic bone, and permitted a higher doxorubicin payload in tumor bone environment. Doxorubicin release from 12b80 was dependent on acidic pH associated with active bone tumor environment. 12b80 showed a much lower and reversible toxicity compared with doxorubicin: mild medullar toxicity was recovered within two weeks and no sign of cardio toxicity or osteorresis were observed in rodents and dogs. 12b80 promoted strong antitumor effects on rodent primary bone sarcoma (orthotopic osteosarcoma and Ewing sarcoma), osteosarcoma-derived lung metastasis and on prostate or breast adenocarcinoma bone invasion. 12b80 displayed a dose-response therapeutic effect and was more potent than combination of doxorubicin and zolendronate. First cases of tumor response were also reported in dogs currently under veterinary trial.

Conclusions: HBP-bound doxorubicin 12b80 demonstrated a proof of concept of preclinical bone-targeted doxorubicin delivery. The next step is to complete regulatory phase before starting 12b80 clinical trial (phase I/IIa) as an orphan drug in osteosarcoma salvage therapy.

Legal entity responsible for the study: Atlantara.

Funding: Atlantara.


Perceptions of clinical trial enrollment in patients with bone and soft tissue sarcoma

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Background: Clinical trials represent a critical component in developing effective cancer therapies. Low rates of participation have negatively impacted progress in sarcoma trials. This survey study evaluated patients’ attitudes, knowledge, self-efficacy for...
decision-making, receptivity, general willingness to participate in trials, and perceptions related to molecular profiling (MP) of tumors.

Methods: IRB approval was obtained. Patients with sarcoma who were evaluated at an academic medical center between 2007 and 2017 were identified through the Enterprise Data Warehouse. A link to an online self-administered survey was emailed to patients. Data were analyzed using Spearman correlations and the Mann-Whitney test.

Results: Surveys were emailed to 750 patients of which 311 patients opened and 206 patients completed a portion of the survey (27.5% of total and 66.2% of opened surveys). Of the 206 patients, median age was 52 years, 57.8% were female, and 24.8% reported metastatic disease. Greater knowledge of trials correlated with increased positive attitudes toward trial participation \((p < 0.001)\) and positive attitudes correlated with greater trial self-efficacy \((p < 0.001)\). Patients with metastatic disease had more positive attitudes compared with nonmetastatic \((p = 0.033)\). Trial enrollment was associated with greater knowledge \((p = 0.002)\) and positive attitudes \((p < 0.001)\). Among patients who reported knowledge of tumor MP \((n = 46)\), 30.4% credit MP with a >50% chance of isolating a targetable result, and 71.7% assume if an experimental treatment was found based on these results, there is a >50% likelihood of it being effective. Better attitudes and higher self-efficacy were associated with expectations of lower likelihood of developing side effects from an experimental therapy \((p = 0.0096)\) and \(p = 0.0184)\). Of patients who had MP performed \((n = 18)\), the most important consideration for this test was its ability to improve their survival and quality of life.

Conclusions: Improving knowledge of trials among sarcoma patients may lead to more positive attitudes and greater self-efficacy regarding trial enrollment. Sarcoma patients tend to overestimate the potential benefit of MP; thus, setting expectations with regards to potential benefit of MP is critically important.

Legal entity responsible for the study: Northwestern University.

Funding: Northwestern University.

Disclosure: All authors have declared no conflicts of interest.

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1637P

**Pneumothorax is a novel sensitivity biomarker for targeting VEGFR2 in lung metastatic sarcoma**

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**Background:** The prognosis of metastatic bone and soft-tissue sarcoma remain distal. VEGFR2 inhibitor (VEGFR2i) has been recently found promising but is limited due to the heterogeneous durability of response.

**Methods:** From Jan 2016 to Jun 2018, 44 patients with lung metastatic sarcoma, including 32 osteosarcoma, 4 Ewing sarcoma, 3 leiomyosarcoma, 2 chondrosarcoma and 1 other sarcoma, given apatinib treatment were reviewed. Of these patients, extra-pulmonary lesions were noticed in 14 cases including local recurrence (9), bone (3), lymph node (2) and brain (1). A starting 250–500 mg per day was chosen, with dose adjustment according to the individual tolerability. Progression-free survival (PFS) was accessed by RECIST 1.1 criteria and used to discover the potential predictor of durability of response.

**Results:** The mean 6 month PFS was 58.9 +/- 8.4%, with the duration of response varying from 1 month to no less than 17 months. 12 of the 44 (27.3%) patients required a long-term dose lowering while the remaining well tolerated or has a dose transient lowering for 7 days. Adverse effects (AEs) greater than degree 2 was seen in 50.0%, including pneumothorax in 11 cases (25.0%). In 9 of 11 cases with pneumothorax, no or minimal drug discontinuation was conducted, with 5 spontaneous recoveries, 3 recoveries with tube drainage, and 1 thoracic empyema with video-assisted thoracoscopic debridement. Multivariate analysis showed that AEs (HR = 0.29 – p = 0.008) and sarcoma type (osteosarcoma vs other, HR = 0.17, p = 0.001) were the independent predictors for PFS with VEGFR2i therapy. Surprisingly, pneumothorax was found to be the strongest predictor among all AEs based on the effect size \((HR = 0.29\) \(p = 0.036)\), indicating that the susceptibility of pneumothorax to VEGFR2i might be a new mechanism-based toxicity biomarker for lung metastatic osteosarcoma.

**Conclusions:** Our result suggested that pneumothorax is a favorable biomarker for targeting VEGFR2 in lung metastatic sarcoma and we encourage no or minimal drug discontinuation in this circumstance.

Legal entity responsible for the study: Jinjin Hospital, Oncological Orthopaedic Department.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

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1638P

**Do Royal Marsden Hospital (RMM) and MD Anderson Cancer Center (MDACC) prognostic scoring systems predict survival in patients with bone sarcoma?**

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**Background:** There is no specific prognostic scoring system for patients with bone sarcomas. Royal Marsden Hospital (RMM) and MD Anderson Cancer Center (MDACC) prognostic scoring systems are used for prognostic classification of different malignancies. The purpose of this study is to evaluate different clinical factors and their correlation with poor survival in bone sarcomas.

**Methods:** We retrospectively reviewed clinical files of patients (pts) diagnosed with bone sarcoma at the tertiary Oncology Centre between January 2006 and June 2017. Clinical factors including Serum albumin, serum lactate-dehydrogenase (LDH), performance status (PS), number of metastases, (in RMM and MDACC scoring systems), platelet count, hemoglobin (Hb), serum creatinine and gender were also evaluated.

Data was analyzed using SPSS software.

**Results:** Total of 87 pts with bone sarcoma were identified of which 33 (38%) pts died. Twenty (61%) pts were males and 13 (39%) pts were females. Median age at the time of diagnosis was 23 (12-83) years. Median overall survival (OS) for the whole group was 12 (1-76) months (mo). Pts presented with metastatic disease had a median OS of 11 mo. Median survival of pts with locoregional disease was 19 mo. On univariate analysis, more than 2 sites of metastases was the only factor associated with poor survival \((p = 0.035)\). On regression analysis the co-efficient between all the variables and survival time is high (R = 0.823) but this is not statistically significant \((p = 0.112)\). There was no statistically significant association between poor survival and low serum albumin, high LDH, poor PS, high platelet count, low Hb, high serum creatinine and male gender.

**Conclusions:** Our study concludes that there is a strong correlation between poor survival and more than 2 metastatic sites in patients with bone sarcomas. Other prognostic factors in RMM and MDACC scoring system were not found to be statistically significant in this study. Further studies are needed to validate these clinical factors.

Legal entity responsible for the study: King Fahad Specialist Hospital, Dammam.

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1639P

**The study of molecular and genetic markers of apoptosis and proliferation, their role in the treatment and prevention of osteogenic sarcoma**

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**Background:** The prognostic value of proliferative and apoptotic activity of tumors in patients with osteogenic sarcoma was investigated in order to determine which genes are involved in their pathogenesis and prognosis.

**Methods:** Immunohistochemical methods (IHC) were used to study the expression of p53, bcl-2, Ki-67 in patients with osteogenic sarcoma in comparison with the effectiveness of treatment. Patients with positive results of chemotherapy (group 1) underwent radiotherapy for a radical program in the total focal dose up to 60-70 Gy. When receiving a good effect from radiation therapy (group 2), patients received another 4-5 courses of chemotherapy. Surgical treatment was performed in 36 patients (41.3%) with a large pulpy component of the tumor and with ineffective chemotherapy or chemoradiotherapy (group 3).

**Results:** In group 1 patients, who received chemotherapy, the full effect was observed only in patients with negative and weakly positive IHC reactions to the p53 (18%), Ki-67 (16%) and bcl-2 (10%). For partial effect, the phenotype of tumor cells was as follows: negative and weakly positive; IHC reaction to the mutant p53 gene was seen in 52% of patients, in Ki-67 - in 62%, and bcl-2 - in 48%. In 6% of patients in this group, the effect of therapy was negative. In the second group, only 10% of the patients had a full effect of the therapy, while in all patients, the tumor cells were mutant p53 negative, 5% had average Ki-67 and bcl-2 and 3% were Ki-67 and bcl-2 negative. 29% of patients in this group had partial effects. In 20% of patients in this group, absence or weak expression of mutant p53 gene was detected in tumor cells, expression of Ki67 and bcl-2 genes in 15% was average, the remaining patients were with Ki-67 and bcl-2 negative. In group 3, 56% of patients had positive effect with therapy, among them, those with weak or no, expression of mutant gene p53 were 79% and only 12.5% showed moderate expression of this protein.

**Conclusions:** Our findings suggest that the study of the expression of the mutated p53 suppressor gene is more informative prognostic factor in osteogenic sarcoma and contributes to an understanding of the mechanisms of cancer, development of new
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Background: Giant cell tumor of bone (GCTB) is a locally aggressive tumor with 3% incidence of pulmonary metastasis. The standard treatment of GCTB had been surgery until denosumab was approved for these tumors.

Methods: Patients diagnosed to have GCTB in King Faisal Specialist Hospital and Research center, Riyadh, Saudi Arabia were eligible. The aim of this study was to evaluate the clinical outcome of GCTB in our institution in the era before and after denosumab.

Results: We identified 42 patients treated in the period between May 2008 and November 2017. Median follow-up time was 57 months. Median age was 31 years. Twenty-Six (62%) patients were females and 16 (38%) were males. Primary tumor was located in upper limb in 21 (50%) patients - mostly in humerus and radius, in lower limb in 17 (40%) patients, and in pelvis/axial skeleton/ribs (33%) patients. Thirty patients (71%) had >10 cm. Thirteen patients received neoadjuvant denosumab (median number of cycles 9), all had clinical benefit from therapy (41/98%) had surgery, 27 (64%) patients had enbolic resection and 14 (33%) had intrapelvic curettage. Fourteen patients (33%) had post-surgical relapse (7/9%) received neoadjuvant denosumab). 61 (14%) patients had local recurrence and 8 (19%) patients with lung metastasis. Denosumab was given to those with metastatic disease (median number of cycles 5). One patient had complete response, 2 patients had partial response, 3 patients had stable disease and 1 patient had progressive disease. Treatment was well tolerated with no incidence of nephrotoxicity, hypocalcemia or osteonecrosis of the jaw. Median recurrence free survival was not reached.

Conclusions: Denosumab is efficient and tolerable in unresectable/malignant disease as well as in a neoadjuvant setting in locally advanced tumors to facilitate complete surgical resection or avoid mutilating surgery. The risk of recurrences after curtailment of GCTB following denosumab raises questions about the optimal management of such cases. Due to rarity of this tumor, larger multicentric trials should be initiated to clarify the role of denosumab.

Legal entity responsible for the study: Mahmoud Elshenawy.

Disclosure: All authors have declared no conflicts of interest.

1641P Adriamycin and ifosfamide-based regimen as induction chemotherapy in desmoplastic small round cell tumors: Results of a retrospective single-center study on 34 patients

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Background: Desmoplastic small round cell tumors (DSRCT) is a rare disease affecting predominantly children and young adults characterized by a specific translocation t(11;22)(p13;q12) which fuses the EWSR1 gene to the WT1 gene. DSRCT shares characteristic with other small round blue cell cancers including Ewing’s sarcoma. The best induction chemotherapy (IC) is not yet defined. The aim of this study is to evaluate the role of Adriamycin and Ifosfamide (AI)-based regimen as IC in DSRCT.

Methods: All pts diagnosed in our tertiary care center with DSRCT treated with AI-based regimen as IC between 1991 and 2017 were included in this study. Clinical, long-term and short-term characteristics were obtained from the electronic medical records and retrospectively analyzed.

Results: 34 pts were identified. With a median age of 25 yrs (range 18-56), 25 pts were male (74%). All pts had PS 0-1. 28 pts had symptoms (82%) with pain being the most common (n = 25). 14 pts (41%) had extra-pelitonal metastases (EPM) at diagnosis (liver mets (n = 14) associated with lung mets in 4 pts). Out of 34 pts, 26 pts (77%) received AI as IC. The remaining 8 pts had AI in combination to platinum agents (n = 4) or Etoposide (n = 4). Median number of cycles was 6±1 (range 3-9). Objective response and disease control rates were 71% and 91% respectively. Only 3 pts had progressive disease (PD) (9%). Dose reduction were noted in 2 pts with no treatment discontinuation. 41% had grade 3-4 toxicities. 7 pts (21%) developed febrile neutropenia. 17 pts (50%) underwent surgery (including 2 with EPM). Post-operative chemotherapy was given in 41 pts and radiotherapy in 21 pts. In pts who had surgery, local recurrence-free survival was 10 months (95% CI: 7.12) while EPM-free survival was 13 months (95% CI: 7.19). Overall survival (OS) for pts without PD was 25.7 months (95% CI: 20.1-31.3). In pts who had surgery, OS was 28.3 months (95% CI: 13.6-43.1) while those who did not have surgery had an OS of 18.9 months (95% CI: 11.6-26.1).

Conclusions: AI-based regimen is a well-tolerated and active option with good response rate as an IC in DSRCT. Comparative data with currently used Ewing-type regimen are eagerly needed in the future.

Legal entity responsible for the study: Institut Gustave Roussy.

Disclosure: All authors have declared no conflicts of interest.

1642P Determination of biological behavior of solitary fibrous tumors

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Background: Solitary fibrous tumor (SFT) is an uncommon neoplasm of pleural and extrapleural site of origin formed by cells with fibroblastic features. This tumor exhibits a spectrum of biological behavior and can occur at any age with the peak in the sixth and seventh decade of life. Most of these tumors grow slowly and their clinical behavior is mostly benign; however, up to 20% of patients develop local recurrences and/or distal metastases.

Methods: We performed a retrospective study of 54 cases of SFTs. We investigated morphologic characteristics, proliferation activity evaluated using Ki-67 immunostain and expression of NAB2/STAT6 fusion gene together with Ki-67, TPX2, and hTERT mRNA expression levels. The aim was to define relationships between proliferation activity and biological potential and progression of the disease. Several, recent alterations within the TERT gene have been detected in human tumors. The most frequent alteration in the TERT gene, somatic promoter mutation, has been described. We measured Ki-67, TPX2, and hTERT mRNA levels using quantitative real-time reverse transcription PCR (RQ-RT-PCR). Determination of hot spot promoter mutation in TERT was analyzed.

Results: NAB2/STAT6 fusion transcript was found in 46/54 cases (85%) of amplifiable samples. The mRNA expression of Ki-67 correlated with local recurrences (p = 0.025) and biological behavior of the tumor (p = 0.0027), but did not correlate with the type of the NAB2/STAT6 fusion (0.24). The level of Ki-67 mRNA correlated with WHO established results (p = 0.02). The TPX2 mRNA expression did not correlate with local recurrences (p = 0.26) nor with biological behavior of the tumor (p = 0.062). The mRNA hTERT expression correlated well with biological behavior of the tumor (p = 0.0001). The majority of SFTs with benign behavior were without detectable expression of hTERT mRNA. A majority of the patients with hTERT expression had also somatic promoter mutation C228T or less frequently C250T. We observed a significant association between increased Ki-67 and hTERT mRNA levels and the SFTs with malignant potential.

Conclusions: Detection of hTERT mRNA expression and its promoter mutation at routine practice might lead to a better estimation of a biological potential of SFTs.

Legal entity responsible for the study: Ministry of Health, Czech Republic.

Disclosure: All authors have declared no conflicts of interest.

1643P Pazopanib in advanced or metastatic synovial sarcoma: The Gustave Roussy experience

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Background: Synovial sarcoma (SS) is a rare malignancy usually considered as sensitive to chemotherapy (CT) based on anthracyclins and ifosfamide. Therapeutic options are limited and progression of advanced or metastatic SS (a/mSS) remains dismal. Since approval of pazopanib in advanced soft tissue sarcomas (STS), very few data were reported on the activity of pazopanib in a/mSS.

Methods: We retrospectively reviewed all patients (pts) treated with pazopanib for a/mSS in our institution. The histological diagnosis was confirmed by a referral pathologist within the French Sarcoma Group. Data were obtained from medical records. Radiological response was assessed by CT-scan according to RECIST 1.1. Adverse events were graded according to the Common Terminology Criteria for Adverse Events
Identification of effective drug combinations with regorafenib (REG) for the treatment of pediatric rhabdomyosarcoma (RMS)

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Background: REG is a small-molecule multikinase inhibitor involved in normal cellular functions and pathologic processes such as oncogenesis, angiogenesis, and tumor immunity. REG is approved for the treatment of advanced colorectal cancer, gastrointestinal stromal tumors, and hepatocellular carcinoma. REG alone is currently being evaluated for its tolerability and safety in pediatric cancers in a clinical phase 1 study. Preclinically, we investigated a series of drugs, which are established or emerging for the treatment of pediatric patients, with REG for its combination potential with REG to support its clinical development in pediatric indications.

Methods: Proliferation assays were performed in vitro. In vivo, subcutaneous xenografts derived from pediatric alveolar (RH30) and embryonal (RD) RMS tumor cell lines were treated with REG alone and in combination with 13 different compounds including a combination with irinotecan (IRI) and vincristine (VINC). A study design using one mouse per group and a stepwise dose escalation was applied. The body weight of the mice was closely monitored for tolerability and the tumor growth was determined by caliper measurements. Treatment was for four weeks and the time to tumor regression was followed thereafter.

Results: The pattern of response was heterogeneous, ranging from complete regression (CR) to insensitivity: REG alone at an oral dose of 10mg/kg/d delayed the growth of both RMS xenografts. CRs were observed for IRI (both models), paclitaxel (RH30 model), and VINC (RD model) alone near their maximum tolerated doses in mice. The RH30 model was insensitive to VINC in this study. A study design with one mouse per group and a stepwise dose escalation was applied. The body weight of the mice was closely monitored for tolerability and the tumor growth was determined by caliper measurements. Treatment was for four weeks and the time to tumor regression was followed thereafter.

Conclusions: These results warrant further exploration of a combination of REG with IRI and VINC in pediatric RMS.

Legal entity responsible for the study: Bayer AG. J. Hoffmann: CEO and shareholder: EPO GmbH.

Carcinosarcoma: Clinical and epidemiological patterns in the United States

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Background: Carcinosarcomas are rare tumors that comprise microscopic features of both epithelial tumors (carcinomas) and connective tissue tumors (sarcomas). Data about carcinosarcoma are relatively scarce. In this study, data about carcinosarcoma in the SEER’s database were explored and further analyzed and summarized. SEER incorporates clinical and epidemiological data from 18 cancer registries all over the United States and presented data can be extrapolated to generate evidence on rare occurring tumor.

Methods: SEER Star Version 8.3.5 was used to obtain data from the SEER 18 Regs Nov 2017 Submission database. Cases diagnosed between 2000-2015 with carcinosarcoma (ICD-O-3 8980/3, 8981/3) were included. Both SEER® and SPSS were used for further data analysis.

Results: A total of 8365 patients were diagnosed with carcinosarcoma between 2000 and 2015, with a median age of 68. The disease occurred predominantly in females (n = 7578; 90.6%) and was more common in white race (n = 6231; 74.9%). Incidence rate was 6.2 per million (CI: 6.1-6.3) with a significant increase of incidence over time (annual percent change = 6.1%). The most common sites for occurrence were the corpus uteri (n = 4456; 55.3%) and ovary (n = 1100; 13.2%) followed by other part of the female genital system (n = 866; 10.6%). The disease was the only primary tumor in 5969 (74.9%) of cases, and the first of 2 or more primaries in 1493 patients (18.9%). It occurred as a second or later multiple primary in the remaining percentage of patients (n = 1903; 22.7%). Median survival was 20.5 months, with 5-years and 10-years observed survival being 30.6% (CI: 29.3-31.9%) and 22.4% (CI: 21.23.8%) respectively. Relative survival at 5 years and 10 years was 34.5% (CI: 33.1%636%) and 29.5% (CI: 27.7-31.3%) respectively.

Conclusions: Carcinosarcoma is a rare tumor that occurs with an incidence rate of 6.2 per million. It is predominantly a disease of females who represents 90.6% of cases with female genital system being the main site of occurrence. The disease occurred as a second (or later) primary in 22.7% of patients. It has a median survival of 20.5 months and a relative 5-years survival of 34.5%.

Legal entity responsible for the study: Mohamed Alaa Gouda. Funding: Has not received any funding. Disclosure: The author has declared no conflicts of interest.
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Conclusions:

DT is an indolent disease but has the propensity for locally invasive growth and recurrence. Although ST is a less aggressive treatment, it was associated with higher severe morbidity, more disease progression, and more subsequent treatment. There was no difference between gender (p = 0.86), tumor location (p = 0.30), or tumor size (p = 0.53) when choosing first-line treatment. The odds of severe morbidity were 2.13 higher with ST than with upfront surgery. Four pts were submitted to surgery after systemic first-line treatment. After a median follow-up of 71 months, there was significantly more disease progression in the ST group (17 pts – 62.9%) than in the surgery group (55 pts – 33.5%) (p = 0.005), and they received more subsequent treatment (p = 0.01). There were 2 deaths in the ST group and 9 deaths in the surgery group, with 10-year survival of 93.2% and 92%, respectively.

Legal entity responsible for the study: INCA.

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1648P Adult rhabdomyosarcoma in Tunisia: Clinical presentation, treatment and outcome

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Methods: We assembled a retrospective cohort of 47 patients aged 18 or older diagnosed with, and treated for RMS at our institute between 1994 and 2013. Patient’s characteristics, treatment variables and treatment outcomes were extracted. Tumors were classified according to the International RMS Study Group (IRS) staging.

Results:

Median age was 39 and 66% were male. At presentation, 33 had localised disease and 14 metastatic. Metastasis site was lung in 17% of cases. Sixteen patients had node positive disease. Median tumor size was 9 cm. Patients presented with swelling or palpable mass in 63.8% of cases, pain in 17%, exophthalmia in 6.4% and bleeding in 4.3%. Less common clinical presentations were functional impairment, cranial nerve palsies, superior vena cava syndrome and nasal obstruction seen in one case each. Tumor site was extremities in 40.4% of cases, trunk in 23.4%, head and neck in 19.1% and genito-urinary tract in 17%. According to favorable/unfavorable prognostic loca- tion, tumor site was unfavorable in 65.9% of cases and favorable in 33.9%. RMS histologic subtype was pleomorphic in 36.2% of patients, embryonic in 25.5%, not mentioned in 23.4%, alveolar in 12.8% and combination of embryonic and alveolar in 2.1%. Among 38 patients who underwent surgery, 40.4% had complete resection (IRS stage I). Chemotherapy was adjuvant in 4 patients, neoadjuvant in 6 and 1st line in 13 with a median number of cycle of 3 in each schedule. Radiotherapy (RT) was adjuvant in 19.1% of cases and symptomatic/palliative in 21.1%. Median dose of adjuvant RT was 55 Gray. Median progression free survival after adjuvant treatment was 4.5 months, 47.1% relapsed locally, 35.3% developed distant metastasis and 17.6% presented local recurrence with distant metastases. Five year overall survival (OS) was 46% for localized RMS and 40% for metastatic disease. Among all studied factors, non operated patients and those under 30 years old had worse OS with p values of 0.005 and 0 respectively.

Conclusions:

Adults with RMS have poor prognosis. All patients should therefore undergo multidisciplinary treatment comprising of surgery, radiation, and chemotherapy to achieve better outcome.

Legal entity responsible for the study: Amel Mezlini.

Disclosure: All authors have declared no conflicts of interest.

1650P The efficacy of eribulin for patients with taxane-resistant cutaneous angiosarcoma: Interim result of multi-center, prospective observational study

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Background: Taxanes (TAX) are the current first-line treatment for advanced cutaneous angiosarcoma (CAS). On the other hand, eribulin (ERB) is a taxane microtubule inhibitor approved for treatment of advanced sarcoma in Japan. However, no study has evaluated ERB in CAS patients. We hypothesized that ERB would be well tolerated and active in patients with TAX-resistant CAS because TAX and ERB have different mechanisms of action to inhibit microtubule formation.

Methods: We designed a single-arm, prospective observational study of ERB administered at dose of 1.4 mg/m² on days 1 and 8 in every 21 days. TAX-resistant, advanced CAS patients for whom ERB use was planned were enrolled. The primary endpoint is overall survival (OS), and the secondary endpoint, response ratio (RR), progression-free survival (PFS), and toxicity assessment. The estimated median OS in a previous clinical study (ANGIOTAX), in which patients received TAX as the second-line treatment, was 6 months, so we set this number as the threshold and expected a 6-month OS of 70% with ERB treatment. Based on these numbers, the required number of patients to be enrolled was calculated as 31; thus, we set 35 patients as the target number.

Results:

At the time of submission, 25 CAS patients, median age 74, were enrolled. All had prior TAX exposure. In all but 1 patient the primary tumor was in the head and neck, and 10 patients had a metastatic tumor. The performance status (PS) was generally good: 22 with PS0 or 1. The median follow-up period was 161 (47-464) days. The
Multicenter, open-label phase II study of daily oral regorafenib for chemotherapy-refractory, metastatic and locally advanced angiosarcoma

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Background: Angiosarcoma is a particularly poor prognosis with 5 year overall survival rates of approximately 30-40%. Treatment of locally advanced and metastatic angiosarcoma is inadequate. Data strongly suggest concurrent, potent inhibition of VEGFR and Tie2 represents an attractive therapeutic strategy in angiosarcoma. Regorafenib displays potent VEGFR and Tie2 receptor inhibition and also possesses activity against additional potential targets in angiosarcoma including PDGFRs, RAF, KIT and FGFR.

Methods: A multicenter phase II study of regorafenib in patients with locally advanced or metastatic angiosarcoma was conducted through the Midwest Sarcoma Trials Partnership. Adequate performance status, organ function, measurable disease (RECIST 1.1) and 1-4 prior therapies were required. Regorafenib 160 mg PO daily was given in 28 day cycles (21 days on, 7 days off) until disease progression (PD) or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), assessed at 16 weeks. Secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), OS, and safety and tolerability. A Simon 2-stage design was used.

Results: A total of 18 pts were enrolled at 5 sites, 14 are evaluable for response. Median age was 55.6 (range 21-82); 61% were female; 72% metastatic disease. PFS at 4 months is 46% with a median PFS and OS of 2.7 and 15 months, median follow-up 7.9 months (0.4-23). 1 confirmed CR and PR, 5 SD and 7 PD were observed. ORR and CBR are 14 and 50%, respectively. Common grade 3-4 adverse events were expected.

Conclusions: Regorafenib was well tolerated in this study of pretreated patients with angiosarcoma. Median PFS and OS at 4 months are promising. Regorafenib will continue to be explored in this two-stage optimal Simon design, for a total of 31 patients.

Legal entity responsible for the study: Northwestern University.

Funding: Bayer HealthCare.

Disclosure: All authors have declared no conflicts of interest.

Outcomes and prognostic factors for angiosarcoma: A 19-year single institution experience


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Background: Angiosarcoma is a rare malignancy, and the data about its clinicopathological features and prognostic factors are limited. The purpose of this study was to present a retrospective analysis of angiosarcoma patients treated at a single institution.

Methods: Clinical and pathological features of 41 patients treated in our institution between 1998 and 2016 were analyzed.

Results: Of the 41 patients included, 53.7% were women and 46.3% were men and median age was 60 (16-81). 34.1% cases were located in the soft tissues (ST) of the limbs or trunk, 24.4% in the viscera (V), 19.5% in the head (H), 14.6% involved the head and neck (HN) and 7.3% in the bone (B). The overall survival (OS) at 5 years was 26% (IC: 15% - 42%), with a median survival of 14.9 months. For the 17.1% patients that were alive at the time of analysis, the median follow up was 60 months (16-222.1).

Discussion: All authors have declared no conflicts of interest.

Legal entity responsible for the study: University of Tsukuba.

Funding: Has not received any funding.

Conclusions: EBR is a well-tolerated regimen with promising activity in TAX-resistant CAS. The common toxicity is neutropenia, which requires growth factor support. This study is underway and enrollment is expected to be completed in 2018. This study may provide a new treatment option for patients with PTX-resistant CAS.

Clinical trial identification: UMIN000023531.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Management of locoregional recurrence after radical resection of a primary non-metastatic retroperitoneal soft tissue sarcoma: Results of a retrospective series in a tertiary care center

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Background: Retroperitoneal soft tissue sarcomas (RPS) are rare tumors. Despite surgery, 9% to 36% of patients experience locoregional recurrence (LR) the optimum treatment of which is still debated. The aim the study of to report our experience in treating LR.

Methods: All 297 consecutive patients operated for a non-metastatic primary RPS between 1994 and 2017 were retrospectively analyzed to identify patients who developed LR. Demographic data, treatment variables and long-term outcome were recorded to calculate disease free survival (DFS), overall survival (OS) and predictive factors of recurrence.

Results: After a median follow-up of 97 months, 35 patients (19%) developed LR. The first site of recurrence was locoregional in 100% with associated peritoneal metastases in 45% and distant metastases in 5%. The median disease free interval (DFI) was 24 months. After recurrence treatment, the 1-, 3- and 5-year OS rates were 71%, 46% and 35%, and 1-, 3- and 5-year DFS rates were 50%, 22%, and 15%. Low tumor grade, DFI above 24 months, exclusive LR and well-differentiated liposarcoma were predictive of better OS and DFS. Despite finding no statistical difference between treatment strategies, median OS was less than 1 month after best supportive care, 44 months after chemotherapy (including patients who underwent subsequent LR radiotherapy or surgery) and was not reached after upfront surgery or radiotherapy. Fourteen patients underwent initial surveillance for low-grade liposarcoma and eventually required treatment in 86% after a median delay of 20 months during which no patient developed distant metastases.

Conclusions: The management of LR in RPS is complex. An initial surveillance may not alter survival in asymptomatic low-grade and slow-growing LR. A LR decision scheme is proposed.

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Disclosure: All authors have declared no conflicts of interest.
1654P | Soft tissue sarcomas (STS) in elderly patients: No impact of age on overall survival (OS) in an unselected cohort

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Background: A recent analysis of 12 trials in first line showed similar outcomes for elderly vs younger patients. Nevertheless these results might be due to a selection bias. The aim of our study was to assess whether elderly patients (pts) (≥60 years) had the same outcomes than younger (<60 years) in an unselected population of STS stage I-IV.

Methods: A retrospective analysis of pts diagnosed with STS stages I-IV at two institutions between 2000 and 2015 was performed. GST and other indolent STS such as low grade stromal sarcoma tumors, cutaneous Kaposi Sarcoma, Desmoid tumors and dermatofibrosarcoma protuberos were excluded. Demographic, clinical and pathological variables were obtained from the medical charts. Overall survival (OS) was calculated according to the date of death by any cause or lost of follow-up.

Results: 115 pts, men/women 59/56 median age of 54.6 years (16.6-82.62) were included. 71 pts (61.7%) were ≤60 years (younger) and 44 (38.3%) were >60 years (older). Most frequent subtypes were liposarcoma (16.5%), leiomyosarcoma (14.8%) and undifferentiated sarcoma (9.6%). Most frequent sites were lower extremity (27.8%), retroperitoneum (13.9%) and thorax (13.0%). TNM Stage (or FIGO in endo- metrial origin) were stage I-II (59%), III (38%) and IV (19%). 98 pts were operated of the primary tumor (Resection was R0 in 53, R1 in 30 and R2 in 4, in 11 data was missed). 37 pts (52.2%) received anthracycline in any line (31 in younger and 6 in older pts). 68 pts (59.1%) had a local or systemic relapse. 53 pts died (46.1%). There were no differences by age group on stage, grade and radicality of surgery (chi squares p = 0.52, 0.48 and 0.47 respectively). Nevertheless elderly patients were less likely to receive anthracycline-based therapy (RR 0.33 95%IC 0.16-0.72, p < 0.001). Grade and stage were significant prognostic factors for OS: median OS:104.4 m for Stage I-II vs 14.7 m Stage IV, p < 0.0001 and 146 m for low (grade 1-2) vs 49.1 m for high (grade 3) (p = 0.0025, respectively). Age group had no effect on median OS (74.4 months for younger and 78.9 months for older log Rank p = 0.13).

Conclusions: Despite significant under-treatment with anthracycline regimens, elderly patients do not have worse survival outcomes in this exploratory analysis of an unselected population.

Legal entity responsible for the study: Hospital Clinico Universitario de Valencia, INCLIVA.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1656P | Should we consider altering our patterns of care for elderly sarcoma patients?

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Background: An increasing proportion of elderly patients (pts) are now being seen at cancer centres, with an increasing incidence of sarcoma. This has become a growing challenge for health care providers, because of the worse prognosis of these pts and our poor knowledge from trials, were they are underrepresented or excluded.

Methods: We performed a retrospective review of elderly pts with soft tissue and bone sarcomas treated between 2012 and 2017 at Regina Elena National Cancer Institute. Overall, 124 pts, median age of 77 (range 70-92), were evaluated for: surgery, radiotherapy (RT), medical treatment and related toxicities.

Results: The most common histological subtypes were: pleomorphic sarcoma (32%), liposarcoma (17%), leiomyosarcoma (13%), mixed fibrosarcoma (9%), bone sarcoma (5%), and others (22%). A total of 107 pts had localized disease at diagnosis and 98 of them had surgical resection. 10 pts received adjuvant chemotherapy (CT) (8 Adriamicin (ADM), 1 Gemcitabine (Gem) and 1 Imitinib (IM)) and 35 pts adjuvant RT. 2 pts, unsuitable for surgery, were treated with RT, and 7 had best supportive care (BSC) (median age: 80, range: 73-85). Of the 17 metastatic pts, 13 were treated with palliative surgery. After surgery, 3 pts had RT and 3 had single agent CT (1 ADM, 1 Epirubicin (EPI) and 1 patient with GIST received IM followed by 2nd line Sunitinh). The remaining 3 pts had BSC and 1 pt age > 80y and P2 10 incontinuation or hospitalization. Only 8% were treated with BSC, a relevant result considering the median age of our pts. Future studies designed for elderly pts and rare tumours, such as sarcomas, are needed to improve survival rates and quality of life of this poorly represented group of pts.

Legal entity responsible for the study: Regina Elena Sarcoma Group.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1657P | Return to work and quality of life in disease-free adult sarcoma patients

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Background: Treatment of extremal sarcoma patients may be associated with significant functional disabilities affecting quality of life (QoL) and therefore the return-to- work (RtW) process. Many studies report on RtW and QoL in childhood, adolescents and young adult cancer survivors of different malignancies. In contrast, studies looking at adult sarcoma patients in particular are limited.

Methods: Patients with the diagnosis of an extremal sarcoma of soft tissue and bone, surgically treated between 2000 and 2015, age at diagnosis of ≥18 or < 65 (age of retirement in Switzerland), alive and without evidence of sarcoma disease were invited for an interview. The primary objective was to investigate the employment rate. Secondary aims were to assess biomedical predictors of RtW and investigate the present QoL of adult sarcoma survivors. Health-related QoL measurements including physical, mental, and social domains were investigated with the following questionnaires: TESS (The Toronto Extremity Salvage Score), SF-36 (short-form health survey), CES-D (Center for Epidemiologic Studies Depression Scale) and Fop-Q-SF (Fear of progression).

Results: Of 45 (11.1%) interviewed patients did not return to work. In the univari- ate analysis no statistically significant parameter predicting RtW could be detected. High educational level and full-time employment before sarcoma diagnosis showed a non-significant tendency towards predicting increased RtW probability. In the multi- variate analysis full-time employment before sarcoma diagnosis is a significant predictor of RtW (OR 9.828 (1.318 – 73 303) whereas high educational level does not show a significant influence. Neither the SF-36 physical and mental summary score nor the scores of the other interviews significantly correlated with RtW outcome. However, the mean difference in the FoP-Q-SF – score between the two groups (no RtW and RtW) was -10.981 (-18.242 to -3.720) in the multivariate model. Age at diagnosis, gender, type of sarcoma, tumor site/grade, amputation rate, Whosops procedure did not corre- late with rate of RtW.

Conclusions: Our study reveals a high employment rate and good QoL of adult sarcoma survivors. Part-time employment and fear of progression might hamper the RtW process.

Legal entity responsible for the study: Kollar Attila.

Funding: Swiss Cancer League/Swiss Cancer Research.

Disclosure: All authors have declared no conflicts of interest.

1658P | No benefit of preoperative chemotherapy for primary retroperitoneal sarcomas: Results from a single center propensity-matched analysis

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Background: Surgery for retroperitoneal sarcomas (RPS) is more and more standard- ized worldwide. Yet, the potential benefits of preoperative chemotherapy remain elusive.

Methods: All consecutive patients operated on for a primary RPS were retrospectively identified. Preoperative chemotherapy was mostly a doxorubicin-based chemotherapy
Regimen for 2 to 6 cycles. Surgery was performed according to the “cluster resection” principles. A caliper restricted, propensity score matched analysis was used to balance the groups.

Results: 249 patients were identified, 49 (19.7%) of whom had received preoperative chemotherapy. After matching, 40 pairs of patients were available and well balanced for baseline characteristics. Seven patients had intermediate adipocytic tumors, 30 had malignant adipocytic tumor, 19 had smooth muscle tumors and 24 had other subtypes. The median tumor size at diagnosis was 29 cm (IQR: 12–26 cm). Sixteen tumors (5%) were FNCLCC’s grade 1, 28 (5%) grade 2 and 36 (6%) grade 3. Univariate analysis identified the size of the tumor (p = 0.036), the histological subtype (p = 0.0015), the FNCLCC’s grade (p = 0.8027) and the postoperative chemoradiation (p = 0.01) as prognostic factors. In the multivariate analysis, only the sarcoma histotype (p = 0.013) and the FNCLCC’s grade (p = 0.022) were retained as independent prognostic factor.

Preoperative chemotherapy was neither associated with overall survival (p = 0.41) nor disease-free survival (p = 0.11).

Conclusions: Routine use of chemotherapy should be avoided in the preoperative setting of primary RPS. Targeted treatments and/or accurate selection criteria are needed. Legal entity responsible for the study: Toni Ibrahim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

*1666IP* A randomized phase III study of denosumab before curettage for giant cell tumor of bone: Japan Clinical Oncology Group study JCOG1616


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Background: Giant Cell Tumor of Bone (GCTB) is a rare tumor known to be locally aggressive, but rarely metastasizing. Resectable GCTB without possible postoperative large bone defect is still controversial. Therefore, we have commenced a phase III trial to confirm the superiority of preoperative denosumab for patients with GCTB who can be treated with curettage.

Trial design: Eligibility criteria include histologically proven GCTB, arising in the extremity, primary tumor (Campanacci grade II or III) and first or second local recurrent tumor, which can be treated by curettage, no distant metastases, and aged 20 to 70. Patients are randomized to either arm A (curettage and adjuvant local therapy) or arm B (preoperative denosumab, curettage, and adjuvant local therapy). Preoperative denosumab is administered subcutaneously at a dose of 120 mg on day 1, 8, 15, 29, and 57. Only in the case of insufficient bone healing at 5 times of denosumab, it is allowed to add denosumab 3 times. The primary endpoint is relapse-free survival (RFS). Secondary endpoints include overall survival, joint-preserved survival, local relapse free survival, metastasis-free survival, adverse events, serious adverse events, surgical and postoperative complications, and discontinuation of denosumab. We assume that the proportion of RFS at 3 years is 80% for arm A and expect a 10% increase in the proportion of RFS at 3 years for arm B. A sample size was calculated as 51 patients per arm to observe 25 total events with a one-sided alpha level of 10%, power of 79%, an accrual period of 5 years, and a follow-up period of 3 years. Thus, the total sample size was defined as 106 patients to account for loss to follow-up. This trial has started in October 2017 and current enrollment is 3 patients in April 2018.


Legal entity responsible for the study: Japan Clinical Oncology Group (JCOG).

Funding: National Cancer Center, Japan.


regimen for 2 to 6 cycles. Surgery was performed according to the “cluster resection” principles. A caliper restricted, propensity score matched analysis was used to balance the groups.

Results: 249 patients were identified, 49 (19.7%) of whom had received preoperative chemotherapy. After matching, 40 pairs of patients were available and well balanced for baseline characteristics. Seven patients had intermediate adipocytic tumors, 30 had malignant adipocytic tumor, 19 had smooth muscle tumors and 24 had other subtypes. The median tumor size at diagnosis was 29 cm (IQR: 12–26 cm). Sixteen tumors (5%) were FNCLCC’s grade 1, 28 (5%) grade 2 and 36 (6%) grade 3. Univariate analysis identified the size of the tumor (p = 0.036), the histological subtype (p = 0.0015), the FNCLCC’s grade (p = 0.8027) and the postoperative chemoradiation (p = 0.01) as prognostic factors. In the multivariate analysis, only the sarcoma histotype (p = 0.013) and the FNCLCC’s grade (p = 0.022) were retained as independent prognostic factor. Preoperative chemotherapy was neither associated with overall survival (p = 0.41) nor disease-free survival (p = 0.11).

Conclusions: Routine use of chemotherapy should be avoided in the preoperative setting of primary RPS. Targeted treatments and/or accurate selection criteria are needed. Legal entity responsible for the study: Toni Ibrahim.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Imatinib is an effective first-line treatment for pts with adv GIST; however, most pts inevitably relapse or progress. Approved second- and third-line agents, sunitinib and regorafenib, have shown limited activity/tolerability, defining an unmet need for pts with imatinib-resistant GIST. Avapritinib is a highly potent and selective oral kinase inhibitor that targets mutant forms of KIT and PDGFRA, including those that confer resistance to approved tyrosine kinase inhibitors. In the Phase 1 NAVIGATOR study (NCT02508532), avapritinib showed substantial clinical activity in pts with both KIT- and PDGFRA-mutant GIST that was resistant to all available therapies. Based on these findings, the VOYAGER study was initiated, comparing avapritinib with regorafenib in pts with adv GIST.

Trial design: VOYAGER (NCT03465722), an international, multicentre, open-label, randomised, Phase 3 study, will include pts (aged ≥18; ECOG PS 0–2) with locally adv metastatic or unresectable GIST. The study will evaluate avapritinib vs regorafenib in pts previously treated with imatinib and 1 or 2 other tyrosine kinase inhibitors, who have experienced disease progression, inadequate clinical benefit or intolerance to their prior therapy. Pts with GIST that is wild-type in both KIT and PDGFRA will be excluded. Approximately 460 pts will be enrolled across North America, Europe, Australia and Asia. Pts will be randomised 1:1 to receive avapritinib 300 mg orally, once daily (QD) or regorafenib 160 mg orally, QD (3 wks on/1 wk off), stratified by treatment regimen (third vs fourth), geographic region (Asia vs rest of the world) and mutation status (PDGFRA D842V present vs absent). Pts who experience disease progression on regorafenib, as confirmed by central radiology review, will be allowed to cross over to avapritinib. The primary objective is progression-free survival (PFS), based on central radiological assessment (mRECIST, v1.1). The study is designed to have 90% power to detect a hazard ratio of 0.67 (avapritinib vs regorafenib). Secondary objectives include evaluation of response rate, overall survival, health-related quality of life and safety.
A randomized non-comparative phase II study of anti-PD-L1 ATEZOLIZUMAB or chemotherapy as second-line therapy in patients with small cell lung cancer: Results from the IFCT-1603 trial


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Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm A of the phase II BALTIC study


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Trilaciclib (T) decreases multi-lineage myelosuppression in extensive-stage small cell lung cancer (ES-SCLC) patients receiving first-line chemotherapy


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Impact of early prophylactic cranial irradiation with hippocampal avoidance on neurocognitive function in patients with limited disease small cell lung cancer: A multicenter phase II trial (SAKK 15/12)


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A pooled analysis of individual patient data (IPD) of concurrent chemoradiotherapy for limited-stage small cell lung cancer (LS-SCLC) in elderly compared to younger patients (pts) who participated in US National Cancer Institute cooperative group studies


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Background: Platinum and etoposide with concurrent thoracic radiation is the standard treatment for LS-SCLC. Elderly pts are common, and may experience higher rates of adverse events (AEs) and have a worse outcome from this treatment.

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Methods: IPD were collected from 11 phase 2 or 3 trials for LS-SCLC conducted by the US National Cancer Institute-supported cooperative groups activated from 1990 to 2010. Overall survival (OS), progression-free survival (PFS) and AEs were compared between age ≥ 70 years (elderly) and for pts < 70 years (younger). Unadjusted and adjusted hazard ratios (HRs) for survival time and CIs were estimated by univariate and multivariable frailty Cox models.

Results: IPD from 1049 younger and 254 elderly pts were analyzed. In the univariate and multivariable models, elderly pts compared with younger pts had worse OS (HR of 1.40; 95% CI, 1.20 to 1.65) and 1.36; 95% CI, 1.13 to 1.59). Median OS in elderly and younger pts was 17.8 months and 23.5 months, respectively. In the univariate and multivariable models, elderly pts had worse PFS (HR of 1.23, 95% CI, 1.06 to 1.43 and 1.19, 95% CI, 1.03 to 1.35). Median PFS in elderly and younger pts was 10.6 and 12.3 months, respectively. Elderly and younger pts had a similar rates of all grade ≥ 3 AEs, but elderly pts had a statistically significantly higher rate of all grade ≥ 4 AEs (p < 0.01). Hematologic ≥ 4 AEs (p = 0.001), and grade 3 AEs (86%) and grade 2 AEs (93%) more toxic reactions were noted in elderly than in younger pts. When specific AEs were analyzed, elderly pts experienced a higher rate of grade ≥ 3 dyspnea (p = 0.03), but a lower rate of grade ≥ 3 vomiting (p = 0.01) and nephropathy (p = 0.15). Elderly pts compared with younger pts completed treatment at a lower rate (p = 0.02), stopped treatment at higher rates due to adverse events (p = 0.02), patient refusal (p = 0.01), and death during treatment (p = 0.01).

Conclusions: Elderly pts with LS-SCLC experienced a worse PFS and OS, and experienced a statistically higher rate of grade 4 and 5 adverse events. Future trials should investigate methods to identify vulnerable elderly pts and reduce the toxicity of treatment.

Legal entity responsible for the study: Tom Stinchcombe and Xiaofei Wang. 

Funding: NIH grant: R21-AI402894.

Disclosure: All authors have declared no conflicts of interest.

Background: Small cell lung cancer (SCLC) is an aggressive disease with 5-year survival rate of 3% in stage I and 2% in stage IV. Current general practice is to treat SCLC patients as soon as possible after diagnosis given its rapid doubling time and high growth fraction. There is no good evidence for appropriate timing of treatment from diagnosis (TDD) for SCLC. This study evaluates TDD in SCLC and its effect on survival.

Methods: SCLC patients were abstracted from 2012 to 2015 Kentucky Cancer Registry as a part of Lung Cancer Education Awareness Detection Study (LEADS) Collaborative and included 2992 patients. Data collected included age at diagnosis, stage, gender, race, insurance and treatment. Factors associated with TDD were identified with logistic regression analyses adjusted for age, gender, race, stage, and insurance status. Derived odds ratios (OR) and 95% confidence intervals (CIs) are reported. Survival of patients by TDD (<4 weeks vs >4 weeks) was assessed with Cox proportional hazards models, adjusted for age, gender, race, stage, and insurance status. Hazard ratios (HR) and 95% CIs were reported.

Results: Among the 2992 SCLC patients, 67% were stage 4 and 27% were stage 3 diseases. 2371 (79%) of SCLC patients were treated with one or more treatment modalities and 621 (21%) received no treatment after diagnosis. Among treated patients 93% received chemotherapy as radiation with mean time of treatment from diagnosis of 18 days. Most patients (80%) had TDD of < 4 weeks with 33% treated within 1 week, 20% 1-2 weeks, and 27% 2-4 weeks from diagnosis. Delay in treatment (TDD > 4 weeks) was less in stage III and IV disease (OR: 0.34-0.27 respectively, p < 0.01) but not significantly associated with age, race, gender, and insurance. One and two-year survival of patients with TDD ≤ 4 weeks was significantly worse when compared to > 4 weeks (HR = 1.43, 95% CI 1.21-1.6, p < 0.01; HR = 1.45, 95% CI 1.3-1.6, p < 0.01 respectively). This is true even when stratified by stage.

Conclusions: These results show a trend towards poor survival with early treatment in SCLC which refutes current belief of better survival with early treatment. It is unclear why this trend exists, and further studies are needed to better clarify appropriate timing of treatment from diagnosis in SCLC and who will benefit from early vs late treatment.

Legal entity responsible for the study: Brown Cancer Center, University of Louisville. 

Funding: LEADS Collaborative supported by Bristol-Myers Squibb foundation. 

Disclosure: All authors have declared no conflicts of interest.

Background: Chemotherapy (chemo) efficacy may be limited due to damage to hematopoietic stem and progenitor cells (HSPCs) leading to multi-lineage myelosuppression. Trila is an iv CDK4/6 inhibitor in development to preserve HSPC and immune system function during chemo (myelopreservation). Preclinically, transient trila-induced G1 arrest renders HSPCs resistant to chemo cytotoxicity, leading to faster hematopoietic recovery and enhanced anti-tumor immunity. In a randomized, placebo-controlled, double-blind Phase 2 trial (NCT02499770), the addition of trila to etoposide/carboplatin (EP) in ER-SCLC patients showed multi-lineage myelosuppression rescue, fewer supportive care interventions and dose reductions, and encouraging duration of response and progression free survival. Peripheral blood immunophenotyping was performed to characterize the effects of trila on the immune system.

Methods: Whole blood from patients in the EP + trila or EP + placebo arms was collected at baseline, during, and after treatment for flow cytometry analyses of monocytes, T, B, NK, dendritic, and myeloid-derived suppressor cells. T cells were also stimulated ex vivo to evaluate their ability to produce cytokines upon activation.

Results: Preliminary analyses indicate that B cells were significantly depleted during treatment with EP + placebo, but not with EP + trila. In addition to an increase in total CD20+ cells during treatment, EP + trila resulted in a larger population of activated CD19+ T cells, and fewer regulatory T cells which is consistent with a more robust immune response. Further analyses of trila’s effect on other immune cell types is ongoing.

Conclusions: These clinical trial findings demonstrate that in addition to preserving neutrophil and red blood cell lineages, adding trila to EP treatment can preserve B cells and enhance T lymphocyte function. In preclinical models, trila similarly enhanced activity of intra-tumor T cells, leading to superior anti-tumor efficacy when combined with chemo + anti-PDL1. A Phase 2 study to assess safety and efficacy of trila or placebo with EP and atezolizumab in first-line ES-SCLC has completed enrollment (NCT03041311).

Clinical trial identification: NCT02499770.

Legal entity responsible for the study: Delaware. 

Funding: G1 Therapeutics. 

1672P Maintenance treatment with the TL909 agonist lefitolimod in extensive-stage small-cell lung cancer (ES-SCLC): Final results from the randomized phase II IMPULSE study


Background: The immune surveillance reactivator lefitolimod (MGN1703), a DNA-based TL909 agonist, is currently in a comprehensive clinical development program including a phase 3 trial in mCRC. The phase 2 IMPULSE study was designed to evaluate efficacy and safety of lefitolimod in ES-SCLC, an indication with high unmet medical need and stagnant treatment improvement in the last decade.

Methods: IMPULSE is a randomized, international, multicenter, open-label trial to assess the effect of lefitolimod on overall survival (OS) in ES-SCLC. 103 patients with objective tumor response following 4 cycles of platinum-based first-line induction therapy were randomized 3:2 to receive either lefitolimod maintenance therapy or local standard of care until progression or unacceptable toxicity.

Results: From 103 patients, 62 were randomized to lefitolimod, 41 to the control arm. Patient demographics and response patterns to first-line therapy were balanced. Lefitolimod exhibited a favorable safety profile in this vulnerable population and pharmacodynamic assessment confirmed the mode-of-action showing clear activation of monocytes and production of interferon-gamma-induced protein 10. While in the ITT population no relevant effect of lefitolimod on OS could be observed, two pre-defined patient subgroups indicated promising results, favoring lefitolimod with respect to OS: Patients with a low frequency of activated CD38+ B cells (HR 0.53, 95%CI 0.26-1.08; n = 38 of 88 analyzed) and patients with reported chronic obstructive pulmonary disease (COPD) (HR 0.48, 95%CI 0.21-1.77, n = 25 of 103). Notably, a post-hoc analysis revealed that a strong lefitolimod-induced immune activation translated into an OS benefit when analysed after 1 week of treatment. Two patients from the lefitolimod arm exhibited long-lasting disease control.

Conclusions: The IMPULSE study showed (1) the expected pharmacodynamic response, (2) positive efficacy signals in two pre-defined subgroups regarding OS and (3) a favorable safety profile. This data provides significant guidance for defining patient populations most likely to benefit from lefitolimod maintenance.

Clinical trial identification: NCT02200881.

Legal entity responsible for the study: Mologen AG.

Funding: Mologen AG.

Disclosure: M. Schmidt, K. Kapp, E. Wiegert, C. Mauri; Employee: Mologen AG. All other authors have declared no conflicts of interest.

1673P Phase II study of NAB-paclitaxel in sensitive and refractory relapsed SCLC (NABSTVER Trial)

F. Gelsomino 1, M. Tiseo 2, F. Barbieri 3, F. Riccardi 4, L. Cavanna 5, A. Frassoldati 6, M. Tiseo 2

Background: Despite high sensitivity to first-line chemotherapy (CT), most small-cell lung cancer (SCLC) patients relapse. Efficacy of 2nd-line CT is modest and influenced by treatment-free-interval (TFI). Topotecan demonstrated modest activity and significant haematological toxicity. Paclitaxel-based regimens showed to be active in this setting. NAB-paclitaxel, compared to paclitaxel, has a reduced incidence of hypersensitivity reactions and of neutropenia. Safety and efficacy in relapsed SCLC have not been prospectively studied.

Methods: This open-label phase II study enrolled patients with extensive (ED) or limited disease (LD) SCLC progressing during or after etoposide/platinum-based 1st-line CT with the aim to assess the activity and safety of Nab-paclitaxel. Patients were classified as refractory (TFI < 60 days) or sensitive (TFI ≥ 60 days). Eligible patients received Nab-paclitaxel 100 mg/m^2 q3w every 28 days for 6 cycles, progressive disease or intolerable toxicity. Computed tomography scan was performed every 2 cycles. Treatment could be continued beyond the 6th cycle in presence of prolonged response, clinical benefit and good tolerance to drug. The primary endpoint was objective response, evaluated according to RECIST v1.1 criteria. The secondary endpoints were toxicity, measured according to NCI-CTCAE v4.03, progression-free and overall survival.

Results: From January 2017 to March 2018, 68 patients (25 refractory and 43 sensitive) were enrolled in the modified intent-to-treat population. Median age was 65.8 years (range 44-80). 44 patients were males and 57 had ED. Median follow-up was 5.8 months (IQR 3.3-7.1). Objective responses are currently being reviewed by an independent radiology panel. Most common toxicities (of all grades) were asthenia (39%), leukopenia (27%), neutropenia (28%), nausea (19%), diarrhea (23%), fatigue (52%), peripheral neuropathy (19%). The only severe toxicity (grade ≥3) was neutropenia (9%). In 13 patients treatment is still ongoing while 3/55 (5%) patients discontinued treatment for toxicity.

Conclusions: This is the first prospective study of Nab-paclitaxel for relapsed SCLC. Nab-paclitaxel demonstrated a manageable toxicity profile. Final activity data will be available for the meeting.

Clinical trial identification: EudraCT: 2016-000480-27; NCT03219762.

Legal entity responsible for the study: GOIRC (Gruppo Oncologico Italiano di Ricerca Clinica).

Funding: Colége.

Disclosure: All authors have declared no conflicts of interest.

1674P Safety of belotecan as second-line treatment for recurrent small cell lung cancer: A phase Ib randomized multicenter study


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Background: For extensive-stage small cell lung cancer (ES-SCLC) patients with progressive or recurrent disease after platinum-based combination chemotherapy, topotecan is recommended as second-line treatment. However, although some patients may achieve at least an objective response with topotecan, response duration is often short. Belotecan, a camptothecin derivative, inhibits topoisomerase I. Previous studies have demonstrated that belotecan has active antitumor activity against advanced SCLC and ovarian cancers. We report safety data from a phase Ib randomized multicenter study of belotecan as second-line treatment for progressive/recurrent limited-disease (LD) or ES-SCLC.

Methods: This study, conducted from March 2010 to March 2018, was designed to prove the non-inferiority of belotecan to topotecan. Patients with recurrent ES-SCLC were randomized (1:1 ratio) to belotecan 0.5 mg/m^2 or topotecan 1.5 mg/m^2 intravenously for 5 consecutive days every 3 weeks for 6 cycles or until disease progression. Adverse events (AEs) were reported according to NCI-CTCAE (ver. 4.0) and categorized by System Organ Class and Preferred Term.

Results: Overall, 161 patients (belotecan, n = 80; topotecan, n = 81) were evaluated in the safety analysis set. Clinical characteristics were well balanced between the treatment arms. Although belotecan recipients received significantly more treatment cycles than topotecan recipients (p = 0.0210), there were no between-drug differences in the number of patients who required dose reductions or who omitted treatment in each cycle. There were no statistically significant between-group differences in safety results: any AEs (including grade 3 or 4 AEs), adverse drug reactions (ADRs), severe AEs (SAEs) or severe ADRs (SADRs). The most common AEs in the belotecan and topotecan groups, respectively, were decreased neutrophil count (61 patients [76.3%] vs. 67 patients [82.7%]), anemia (37 [46.3%] vs. 44 [53.1%]), decreased platelet count (33 [41.3%] vs. 43 [53.1%]), nausea (35 [43.8%] vs. 30 [37.0%]), and anorexia (32 [40.0%] vs. 36 [44.4%]).

Conclusions: Our study indicates that belotecan is a safe second-line treatment option for patients with progressive/recurrent LD- or ES-SCLC.

Clinical trial identification: NCT01497873.
**Abstract**

**Background**: Extensive-disease small cell lung cancer (ED-SCLC) is usually first treated with etoposide-platinum-based chemotherapy. Despite high initial response rates, progression occurs frequently. While topotecan is approved as 2nd-line therapy, further treatment is not standardized. One of the drugs administered in progressed SCLC is paclitaxel. Here, we retrospectively analyzed prognostic factors and outcome of paclitaxel-treated SCLC patients.

**Methods**: SCLC patients treated with paclitaxel between 2005 and 2015 at Thoraxklinik Heidelberg University Hospital were retrospectively reviewed. Significant prognostic factors were identified by univariate (Kaplan-Meier) and multivariate (Cox-Regression) analysis.

**Results**: 185 patients (119 men/66 women, median age 64 years, median ECOG performance status 1) were included. Paclitaxel was mainly given as 3rd- or 4th-line therapy (92%). The overall response rate was 17% and disease control rate (DCR) was 28%. Median progression-free survival (PFS) was 48 days (95% CI: 42-54) and median overall survival (OS) 100 days (95% CI: 84-116). Main toxicities were fatigue (25%) and peripheral neuropathy (17%), but no discontinuation of treatment was required. In 28%, the paclitaxel dose was reduced by 15-30%, mainly due to hematotoxicities (in 57%). In univariate analysis, this was linked to a decrease in PFS (p = 0.05), while gender, age, performance status, number of metastatic sites, and presence of cerebral/hepatic metastases were not associated with changes in PFS. For OS, performance status, number of metastatic sites, cerebral/hepatic metastases, and dose reduction were significant (p < 0.05). In multivariate analysis, gender, age, and dose reduction retained as independent prognostic factors for PFS. In addition, performance status, cerebral/hepatic metastases, and pack years were identified as independent prognostic factors for OS.

**Conclusions**: With a DCR of 28% paclitaxel was still effective in heavily pretreated SCLC patients. However, patients should be selected carefully regarding age, performance status, and metastatic status. Especially, patients in good condition and without cerebral/hepatic metastases benefit from a paclitaxel therapy.

**Legal entity responsible for the study**: Martin Steins.

**Funding**: Thoraxklinik at Heidelberg University Hospital.

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**Abstract**

**Background**: Overexpression of shh is a prognostic marker in patients with extensive stage small cell lung cancer (ES-SCLC).

**Methods**: We retrospectively analyzed the data of 36 patients with ES-SCLC between 2009 and 2012 in Yonsei Cancer Center. Using formalin-fixed paraffin embedded tissues of primary tumors, immunohistochemistry was done for Gli, Patched, Shh, and Smo. We performed survival analysis to find out the prognostic impact of these markers.

**Results**: All the 36 patients were treated with platinum based doublet chemotherapy. Median progression-free survival and median overall survival was 6.9 months (95% CI, 6.3-7.1) and 11.7 months (95% CI, 9.1-14.3), respectively. Overall response rate was 84%. Of the 36 specimens examined, the overexpression of Gli1, Patched, Shh, and Smo was found in 12 (33.3%), 5 (13.9%), 5 (13.9%), and 6 (16.7%), respectively. We found that high expression of Shh was associated with worse progression free survival (6.3 vs. 7.6 months, p < 0.05) and overall survival (9.2 vs. 12.0 months), whereas other markers were not related to the prognosis of patients.

**Conclusions**: To our knowledge, this is the first report of the relationship between components of the Shh signaling pathway and prognosis in SCLC. We found that a high proportion of tumors expressed proteins related to this pathway, and high expression of Shh correlated with worse survival in this analysis. Shh signaling in SCLC requires further investigation using a larger sample size.

**Legal entity responsible for the study**: IRB.

**Funding**: Has not received any funding.

**Disclosure**: All authors have declared no conflicts of interest.
Results: All studies (Table) showed >90% OPA for concordance to the %TC bins.

<table>
<thead>
<tr>
<th>Study</th>
<th>1678P Precision across lots, replicates, days, instruments, and platforms</th>
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<tbody>
<tr>
<td></td>
<td># of Cases</td>
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<td>Intra-day</td>
<td>10</td>
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<td>Inter-day</td>
<td>10</td>
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<tr>
<td>Inter-antibody lot, inter-detection kit, and intra-platform</td>
<td>24</td>
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<tr>
<td>Intra-platform (GX)</td>
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<td>Intra-platform (XT)</td>
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<td>Intra-platform (ULTRA)</td>
<td>14</td>
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<tr>
<td>Inter-platform (GX, XT, and ULTRA)</td>
<td>14</td>
</tr>
</tbody>
</table>

Conclusions: The data shows that the VENTANA DLL3 (SP347) Assay can precisely evaluate DLL3 expression in SCLC.

Legal entity responsible for the study: Ventana Medical Systems, Inc.


1679P Residential radon and small cell lung cancer: A systematic review

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Background: Residential radon exposure is considered the second cause of lung cancer (LC) and the first in never smokers. Nevertheless, the association between the different histological types of LC and radon is not completely clear, and radon effect on small cell lung cancer (SCLC) is not completely understood. We aim to assess the effect of residential radon exposure on the risk of SCLC in general population and miners through a systematic review applying predefined inclusion and exclusion criteria.

Methods: We performed a literature research in PubMed and EMBASE following PRISMA methodology. We included: studies performed in humans; studies showing the specific effect of radon on SCLC histological type separately; studies with at least 10 SCLC cases and the overall sample size higher than 50 individuals; systematic reviews, pooling studies, cohort studies, case-control studies and mortality studies with comparison group; studies performed both in general population and on miners; studies with anatomopathological confirmation; studies in English, Spanish and French. To assess the quality of each of the included studies we designed a quality scale with 5 items which scored characteristics of the included papers: sample size, number of SCLC cases, results adjusted by covariates, study design, and method of assessment of radon concentration. We have given different weights to these characteristics creating a continuous scale from 0 to 10.

Results:

Table: 1679P

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design and location</th>
<th>Sample size</th>
<th>Lung cancer risk</th>
<th>Significance</th>
<th>Conclusion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biberman 1993</td>
<td>Case-control Israel</td>
<td>n = 70 20</td>
<td>Median radon level in SCLC group of 1.09 vs 0.9 pCi/L. OR 1.5 (0.4-5.4).</td>
<td>No significant</td>
<td>Exposure to radon was identified as an etiological agent of SCLC. Strong evidence of an association between residential radon concentration and SCLC. The dose-response relation was to be linear. The absolute risk to smokers was greater.</td>
<td>3</td>
</tr>
<tr>
<td>Darby 2004</td>
<td>Pooling study of 13 case-control studies Europe</td>
<td>n = 21,356 1,379</td>
<td>ERR per 100 Bq/m3: 31.2% (2.8-60.6%) for SCLC vs. 2.6% (0-10%) for other subtypes. $p = 0.03$.</td>
<td>Statistically significant</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Wikcox 2007</td>
<td>Case-control New Jersey</td>
<td>n = 1,301 105</td>
<td>ERR 100-149 Bq/m3: 3.05% (for men) and 2.46 (for women) For &gt;150 Bq/m3: 0.00% (for men) vs. 2.67 (for women)</td>
<td>Statistically significant</td>
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</table>

Conclusions: Exposure to radon increases the risk of SCLC. Nevertheless, more research should be addressed in order to know exactly the magnitude of this risk. It seems that SCLC is the LC histological type most associated to radon exposure, with this fact happening both in miners’ and general population studies. To this end, more well-designed case-control studies are necessary. It is also necessary to increase radon awareness among citizens and administrations in order to they can establish the necessary preventive and mitigation measures against residential radon.

Legal entity responsible for the study: Ángeles Rodríguez Martínez.

Disclosure: All authors have declared no conflicts of interest.

1680P Nomogram for predicting the benefit of surgery for stage IA-IIB small cell lung cancer

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Background: The role of surgical resection remains controversial in small cell lung cancer (SCLC) although there are some retrospective and population-based studies indicate that patients with very early stage SCLC has longer survival compared with those not given surgery. The specific aim of this study was to identify the survival benefit of surgery for patients with Stage IA-IIB SCLC and nomogram predictive model was created to select patients who are eligible to surgery.

Methods: Patients diagnosed with stage IA-IIB SCLC between 2004 and 2014 were selected from the SEER database. The primary endpoint was overall survival. Multivariate Cox proportional regression and coefficients of the predictors were calculated. A nomogram was constructed for predicting 1- and 3-year overall survival probability. All statistical analysis was performed with R software.

Results: 2246 patients with stage I-II were enrolled. 618 (27.5%) received surgery and 1628 (72.5) not. Adjusted median overall survival (OS) was 23 months (95% CI: 23-24), which was 35 months (95% CI 31-44) vs. 19 months (95% CI 18-21) in surgery and non-surgery groups respectively ($p <0.0001$. We used a propensity score to balance observed covariates. OS benefit was observed in all subgroups between the surgery and non-surgery group except in the non-White race, well or moderately grading, stage IIA or IIB and N1 lymph involvement. Multivariate Cox proportional hazards regression analysis showed a survival benefit in the surgery group compared with non-surgery group no matter balanced by propensity score weighting or not. The competing-risk nomogram was built for predicting 1-year and 3-year survival. The age, tumor size, extent of tumor, N0-N1 and surgery with radiation and chemotherapy were introduced as variables. The calibration of internal validation for predicting survival at 1 and 3-year by this nomogram-predicted probability was identical to the actual probability.

Conclusions: Surgery was proved to benefit patients with stage IA-IIB SCLC by this relatively large number population-based study and a nomogram built from a parametric survival model from the SEER database can be used to predict which patients with stage IA-IIB SCLC may benefit from surgery.

Legal entity responsible for the study: Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department 1 of Thoracic Oncology Medicine, Peking University Cancer Hospital & Institute.

Funding: National Natural Science Foundation of China, Award (81401914) and Beijing Municipal Administration of Hospitals’ Youth Programme (20161112).

Disclosure: All authors have declared no conflicts of interest.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design and location</th>
<th>Sample size</th>
<th>Lung cancer risk</th>
<th>Significance</th>
<th>Conclusion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichmann 2005</td>
<td>Pooling study of 2 case-control studies Germany</td>
<td>$n = 7,195,712$</td>
<td>ERR per 100 Bq/m³ of 0.29 (0.04-0.78)</td>
<td>Non significant</td>
<td>The effect of radon is stronger for SCLC, whereas no association between radon and lung cancer was found.</td>
<td>8</td>
</tr>
<tr>
<td>Krewsky 2004</td>
<td>Pooling study of 7 case-control studies North América</td>
<td>$n = 8,628,577$</td>
<td>ERR per 100 Bq/m³ in 5-10 years of 0.23 (-0.08-0.88) for SCLC.</td>
<td>Non significant</td>
<td>Association between residential radon exposure and lung cancer, with strongest association for SCLC.</td>
<td>10</td>
</tr>
<tr>
<td>Field 1991</td>
<td>Case-control Iowa</td>
<td>$n = 1,027,74$</td>
<td>WLM $\geq 16.95$ OR 1.44 (0.47-4.35) p = 0.33</td>
<td>Non significant</td>
<td>Cumulative radon exposure in the residential environment is significantly associated with lung cancer risk, with strongest effect for SCLC.</td>
<td>5</td>
</tr>
<tr>
<td>Barros-Dios 2012</td>
<td>Case-control Galicia</td>
<td>$n = 862,54$</td>
<td>AOR p 101-147 Bq/m³ 3.01 (1.01-8.97) AOR 147 Bq/m³ 2.43 (0.79-7.45)</td>
<td>Statistically significant</td>
<td>Even with low exposures, radon is a risk factor of lung cancer, with greatest influence on SCLC. Additive interaction between radon exposure and tobacco consumption.</td>
<td>6</td>
</tr>
<tr>
<td>Sandler 2006</td>
<td>Case-control Connecticut and Utah</td>
<td>$n = 3,285,51$</td>
<td>ERR per 100 Bq/m³ increase in radon concentration for SCLC 0.165 (-0.35-0.69)</td>
<td>Non significant</td>
<td>No evidence of an increased risk for lung cancer (and SCLC) at the exposure level of radon observed.</td>
<td>7</td>
</tr>
<tr>
<td>Jonsson 2009</td>
<td>Cohort Sweden</td>
<td>$n = 5,486,55$</td>
<td>ERR p kBq year/m³ 0.072 (-0.03-0.417)</td>
<td>Non significant</td>
<td>A significantly increased risk for SCLC was observed at low radon exposure levels. The proportion of SCLC among miners was high compared to the general population in Sweden.</td>
<td>5</td>
</tr>
<tr>
<td>Saccomanno 1988</td>
<td>Cohort Colorado</td>
<td>$n = 383,121$</td>
<td>For levels $&gt; 300$ WLM EOR of 57%.</td>
<td>Statistically significant</td>
<td>In levels $&gt; 300$ WLM an increased risk of lung cancer was detected. The incidence in SCLC was significantly elevated (57%) over other types. An additive effect in smokers was observed.</td>
<td>5</td>
</tr>
<tr>
<td>Svensson 1989</td>
<td>Case-control Stockholm</td>
<td>$n = 210,41$</td>
<td>4500-6000 Bq/m³ RR 1.9 (1.2-5.8) +6000 Bq/m³ RR 4.7 (0.5-3.7) p = 0.01</td>
<td>Statistically significant</td>
<td>Association between cumulated radon exposure and lung cancer in women, particularly strong for SCLC.</td>
<td>2</td>
</tr>
<tr>
<td>Bochicchio 2005</td>
<td>Case-control Lazio</td>
<td>$n = 788,43$</td>
<td>EOR p 100 Bq/m³ 0.22 (0.21-0.89) for SCLC.</td>
<td>Non significant</td>
<td>A higher risk for SCLC at elevated radon levels was detected. Dietary antioxidants may act as an effect modifier.</td>
<td>4</td>
</tr>
<tr>
<td>Alavanja 1999</td>
<td>Case-control Missouri</td>
<td>$n = 1,058,117$</td>
<td>OR of 3.33 for $&gt; 148$ Bq/m³ for SCLC. P = 0.3.</td>
<td>Non significant</td>
<td>A significant SCLC increased risk was found for radon concentrations at and above the action level for mitigation of houses in USA (148 Bq/m³).</td>
<td>5</td>
</tr>
<tr>
<td>Letourneau 1993</td>
<td>Case-control Canada</td>
<td>$n = 1,476,117$</td>
<td>OR 0.79 (0.44-1.41) cumulated exposure of radon 5-30 years. 3,750 Bq/m³-year</td>
<td>Non significant</td>
<td>No increase in the relative risk for any of the histologic types of lung cancer was observed in relation to cumulative exposure to radon.</td>
<td>7</td>
</tr>
<tr>
<td>Pershagen 1994</td>
<td>Case-control Sweden</td>
<td>$n = 4207,166$</td>
<td>ERR per unity of radon 0.15 (0.03) for SCLC, RR of 2.8 (1.3-5.9) for Ra $&gt; 400$ Bq/m³.</td>
<td>Statistically significant</td>
<td>The risk of lung cancer increased in relation to both estimated cumulative and time-weighted exposure to radon. The strongest association was suggested for SCLC.</td>
<td>6</td>
</tr>
<tr>
<td>Blot 1990</td>
<td>Case-control North of China</td>
<td>$n = 664,39$</td>
<td>OR for SCLC increased with residential radon being SCLC de histological type with the highest risk.</td>
<td>Non significant</td>
<td>A moderate association of increased radon levels and SCLC is observed. A moderate association of increased radon levels and SCLC is observed.</td>
<td>6</td>
</tr>
</tbody>
</table>
SUPPORTIVE CARE

16810 Evaluation of practice patterns for prevention of chemotherapy (CT)-induced nausea and vomiting (CINV) and antiemetic guidelines (GLs) adherence based on real-world prescribing data


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1683PD Factors that influence oncology nutrition efficacy in breast cancer patients under antiestrogenic treatment

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Effects of 6-month exercise training on quality of life in pancreatic cancer patients: Results from a randomized controlled trial

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Plinabulin (Plin), a novel non-G-CSF molecule for the prevention of chemotherapy-induced neutropenia (CIN), has the potential to positively impact tumor micro environment

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Neuropathy and health behaviors in cancer survivors treated with chemotherapy (CT)

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1688PD  
Awareness of the cancer and non-cancer related harms of continued smoking in cancer survivors


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1689PD  
Breast cancer (BC) related fatigue: A longitudinal investigation of its prevalence, domains and correlates


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1690PD  
Acceptability in cancer outpatients of completing routine assessments of patient reported outcomes of common terminology criteria for adverse events (PRO-CTCAE) versus other patient reported symptom outcome tools

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Physicians’ knowledge, attitudes and practice towards fertility and pregnancy-related issues in BRCA-mutated breast cancer (BC) patients (pts): Results from the BCY3/BCC 2017 survey

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Background: No data are available on physicians’ knowledge, attitudes and practice towards fertility and pregnancy-related issues in BRCA-mutated BC pts.

Methods: A 26-item survey exploring fertility preservation and pregnancy after BC was emailed to physicians attending the 2016 3rd ESO-ESMO BCY3 and the 2017 15th St. Gallen BCC, 2017 conference. The present analysis investigated potential differences in physicians’ knowledge, attitudes and practice towards these issues in BC pts with or without BRCA mutations. The McNemar test for paired proportions was used for statistical comparison.

Results: The survey was completed by 273 physicians (105 at BC3/BCC and 168 at BCC, 2017) with a median age of 46 years (range 28-55); the majority were medical oncologists (56%) practicing in an academic setting (86%). A comparable proportion of respondents suggested the use of either etoposide (43% vs. 39%: p=0.11) or oocyte (62% vs. 63%: p=0.77) cryopreservation as available options for BC pts with or without BRCA mutations, respectively. Conversely, ovarian tissue cryopreservation (33% vs. 40%; p=0.099) and GaHdHa during chemotherapy (74% vs. 81%: p=0.001) were less commonly suggested in BRCA-mutated BC pts than in BC pts without BRCA mutations. 42% agreed or were neutral on the statement that pregnancy in BC survivors may increase the risk of recurrence in BRCA-mutated BC pts and in BC pts overall, respectively (p=0.001). 15% and 3% disagreed that transplanting the cryopreserved ovarian tissue harvested at the time of BR, diagnosis can be considered safe in pts with or without BRCA mutations, respectively (p=0.001).

Conclusions: These results highlight the presence of several misconceptions on fertility preservation and pregnancy after BC that persist even among physicians directly involved in BC care. Focused research efforts to address fertility and pregnancy-related issues in BRCA-mutated BC pts and education to improve physicians knowledge and adherence to available guidelines are urgently needed.

Legal entity responsible for the study: Matteo Lambertini.

Funding: Has not received any funding.

Disclosure: Matteo Lambertini: Support from the European Society for Medical Oncology (ESMO) for a Translational Research Fellowship at the Institut Jules Bordet (Brussels, Belgium).

All other authors have declared no conflicts of interest.

1693P Analysis of parameters to predict the effectiveness of scalp cooling to prevent chemotherapy-induced alopecia in breast cancer patients

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Background: Sensor-controlled scalp cooling (SCSC) has been found to be effective to prevent chemotherapy (Ctx)-induced alopecia (CIA). This retrospective study sought to obtain detailed information which clinical parameter is able to predict the success of SCSC in patients (pts) with primary (pA) or recurrent/metastatic breast cancer (R/MBC) exposed to neoadjuvant (NACT), adjuvant (ACT), or palliative Ctx (PCT) using antracyclines (A), taxanes (T), both given at different schedules (A+T/A+T, A+T/A−T, A−T/A−T) or none of them (non-A/non-T).

Methods: 109 pts who underwent SCSC were included: NACT, 47 (54.6%); ACT, 40 (45.4%); PCT, 22; dose-dense (dd) Ctx, 38 (44.2%); non-dd Ctx 48 (55.8%); premenopausal, 48 (55.8%); postmenopausal, 38 (44.2%). Ctx regimens were: A+T/A−T, 41 (37.6%); A−T/A−T, 23 (26.3%); T, 34 (31.2%), non-A non-T, 11 (10.1%). 3 weeks after the last Ctx cycle, CIA was quantified according to the Dean score (DS). Data were analyzed in regard to the SCSC completion rate, and the quality of hair preservation (success: DS 0-2, failure: DS 3-4). The following parameters were investigated in regard to the success of SCSC: menopausal status, pretreatment, setting of Ctx, Ctx schedule, Ctx regimen.

Results: Success rate was 67.9% with 47 pts (43.1%) experiencing complete (DS 0), and 27 (24.8%) showing partial response (DS 1-2). 30 pts (27.3%) stopped SCSC prematurely with CIA being the reason in 21 pts (19.3%). Effectiveness of SCSC did not differ for most analyzed subgroups. The relative risk (RR) to experience CIA was 1.18 (CI 0.91-1.55, p=NS) for post- vs premenopausal pts, 1.27 (CI 0.99-1.64, p=NS) for Ctx-naive vs pretreated pts, 1.18 (CI 0.89-1.56, p=NS) for ddCtx vs non-dd Ctx, 1.42 (CI 1.03-1.80, p=0.05) for NACT/ACT vs PCT, and 1.42 (1.11-1.85, p=0.012) for A-based Ctx vs non A-based Ctx. Success rates for A+T/A+T—T, A−T, and non-A/non-T were 48.8%, 73.9%, 79.4%, and 90.9% (p=0.015).

Conclusions: SCSC could effectively prevent CIA in a real-world population of pts with PBC or R/MBC with all subgroups of pts benefiting. NACT/ACT and A-based Ctx are associated with lower success rates of SCSC. However, the effectiveness of SCSC associated with A-based Ctx can be as high providing that Ctx does not start with an antracycline.

Legal entity responsible for the study: Christian M. Kubracher, Gynaecological Centre Bonn-Friedensplatz.

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Disclosure: All authors have declared no conflicts of interest.
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1695P Acupuncture for peripheral neuropathy in cancer patients: TCM diagnosis as a predictor of treatment response

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Background: Acupuncture has been recognized as an effective integrative modality for managing peripheral neuropathy. However, data regarding predictors for response to acupuncture in cancer patients experiencing neuropathy are limited. We explored associations between patient characteristics, including traditional Chinese medicine (TCM) diagnosis, and treatment response among cancer patients who received acupuncture for peripheral neuropathy.

Methods: We reviewed acupuncture records in cancer outpatients with a primary reason for referral listed as peripheral neuropathy from March 2016 to April 2018. Treatment response was assessed using numbness/touching/tingling with a modified Edmonton Symptom Assessment Scale (ESAS; 0–10 scale) administered before and after each acupuncture treatment. Associations between TCM diagnosis, individual patient characteristics, and treatment response rate were analyzed with Wilcoxon’s test.

Results: A total of 1745 acupuncture records (533 patients) were identified. The majority were female (71%), and 96% (29%) had breast cancer. The median (IQR) reduction in numbness/tingling score was 20% (0.80–P < 0.001). The most frequent TCM diagnosis was qi stagnation (86%) followed by blood stagnation (79%). Presence of blood stagnation was associated with a poorer response (less than 25% from baseline was observed in 38% of patients at Week 6. At Week 15, 2% of patients had a ≤ 50% loss. There were no detectable effects of topical BPM31543 on serum levels of calcitriol. Conclusions: BPM31543 applied topically twice daily to the scalp in patients receiving taxane-based chemotherapy is safe and well-tolerated with no apparent differences in safety between doses. Here, no DLT was observed at up to 80 μg/mL and MTD was not reached. Some efficacy was detected at each dose. These data are encouraging and support further investigation in Phase 2/3 trials.

Clinical trial identification: NCT01588522.

Editorial acknowledgement: Khampeaseuth Thupa, BERG, LLC.

Legal entity responsible for the study: BERG, LLC.

Funding: BERG, LLC.


1696P Use of lipogefilgrastim for the prophylaxis of chemotherapy-induced neuropenia: Pan-European non-interventional study

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Background: Lipogefilgrastim (LONQUES®) is a long-acting glycopegylated G-CSF, which was proven to be non-inferior to pegfilgrastim in elderly patients with breast cancer. This objective of the study was to evaluate effectiveness and safety of lipogefilgrastim in everyday clinical practice in adult patients with different tumor types, who are treated with cytotoxic chemotherapy.

Methods: Patients with different tumor types treated with cytotoxic chemotherapy, who received lipogefilgrastim in primary (PP) or secondary prophylaxis (SP) were included in this prospective non-interventional study. Evaluation of chemotherapy (CT) and biological therapy (BT) dose modifications as well as neuropenic events following a taxane-based chemotherapy supported treatment cycle is presented here.

Results: A total of 1,333 patients were included in the safety set. Mean age of included patients was 58.4 ± 13.3 and 70.2% were female. The majority of patients had breast cancer (46.7%) and lymphoma (26.4%). A total of 895 (68.2%) patients received lipogefilgrastim in PP starting from CT cycle 1 and 192 (14.4%) patients received it in SP for...
the first time. They were included in the effectiveness analysis. In the first cycle febrile
neutropenia (FN) was reported in 1.8% of patients receiving pegfilgrastim in PP and in
1.0% of patients receiving pegfilgrastim in SP. Grade 3/4 neutropenia was reported in
7.9% (PP) and 6.2% (SP) of patients. CT and/or BT was delayed, reduced or omitted in
20.1% of patients receiving pegfilgrastim in PP and in 28.1% of patients receiving it in
SP. This was associated with FN and grade 3/4 neutropenia in only 1.0% and 2.2% of
these patients in case of PP and 2.1% and 5.3% in case of SP. A total of 284 (21.6%)
patients reported at least one adverse drug reaction (ADR) throughout the study. The
most common ADRs were bone pain (5.86%), myalgia (3.43%) and back pain (1.83%).
Serious ADRs were reported by 42 (3.2%) of patients.

Conclusions: Pegfilgrastim is effective and well tolerated in the real world setting
administered either in PP or SP. Both effectiveness and safety data obtained in this
study are in line with published data for pegfilgrastim.

Legal entity responsible for the study: Teva.

Funding: Teva.

Disclosure: G. Steger, P. Pichler, M. Airoldi, P. Mazza, C. Fontaine, J. Timmer Bonte,
J.A. Walewski, J. Katoliczk, M. Mikulakova: Investigator in Teva sponsored study.
M. Gasparic: Employee: Teva Pharmaceuticals Europe B.V.

Table: 1698P

<table>
<thead>
<tr>
<th>Study</th>
<th>103</th>
<th>PROTECT1</th>
<th>PROTECT2</th>
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<tr>
<td><strong>Baseline characteristics</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>67 (36)</td>
<td>55 (100)</td>
<td>55 (100)</td>
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<tr>
<td>Female gender, n (%)</td>
<td>67 (36)</td>
<td>159 (100)</td>
<td>159 (100)</td>
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<td>BMI, mean (SD)</td>
<td>23.9 (21.7)</td>
<td>27.5 (5.67)</td>
<td>26.6 (5.77)</td>
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<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain, n (%)</td>
<td>102 (58)</td>
<td>7 (4.4)</td>
<td>7 (4.3)</td>
</tr>
<tr>
<td>Reference</td>
<td>94 (53)</td>
<td>6 (3.8)</td>
<td>13 (8.5)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>1.10 (0.93 - 1.30)</td>
<td>1.15 (0.40 - 3.35)</td>
<td>0.53 (0.22 - 1.30)</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>100 (57)</td>
<td>2 (1.3)</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Reference</td>
<td>99 (56)</td>
<td>3 (1.9)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>RR (CI)</td>
<td>1.02 (0.87 - 1.20)</td>
<td>0.66 (0.11 - 3.89)</td>
<td>0.99 (0.20 - 4.81)</td>
</tr>
</tbody>
</table>

**BMI:** body mass index, **CI:** confidence interval, **RR:** relative risk, **SD:** standard deviation.

1698P Safety analysis of proposed biosimilar pegfilgrastim in phase I and phase III studies

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**Background:** Granulocyte colony-stimulating factors (G-CSFs), including filgrastim and its long-acting form pegfilgrastim, are widely used to prevent chemotherapy-induced neutropenia in patients undergoing cytotoxic chemotherapy. Bone pain is the most frequently reported adverse event (AE) associated with G-CSFs. In cancer patients receiving pegfilgrastim, bone pain incidence ranges from 25-38%, compared with 52-84% in healthy volunteers (HV) (1). This study compares safety data for Sandoz proposed biosimilar pegfilgrastim in Phase I and Phase III studies.

**Methods:** Three studies were included: 103, a single-dose, randomized, double-blind, crossover phase I study in HVs receiving proposed biosimilar (n = 92) or reference pegfilgrastim (n = 95) and 2 randomized, double-blind Phase III confirmatory studies (PROTECT1 n = 159, PROTECT2 n = 155) in breast cancer (BC) patients undergoing cytotoxic chemotherapy (≥5 cycles) receiving proposed biosimilar (PROTECT1: n = 159; PROTECT2: n = 155) or reference pegfilgrastim (PROTECT1: n = 157, PROTECT2: n = 153). Results were compared for a single dose of pegfilgrastim in 103, and for 1st treatment cycle in PROTECT1 and 2.

**Results:** Differences in baseline characteristics between 103 and PROTECT included younger age, lower BMI and inclusion of men in 103 (Table). Treatment related bone pain was reported by 58% (biosimilar) and 53% (reference) in 103; in 4.4% (biosimilar) and 3.8% (reference) in PROTECT1; and in 4.5% (biosimilar) and 8.5% (reference) in PROTECT2. AEs were generally mild in 103 and mild/moderate in PROTECT.

1700P Safe switch of treatment from the reference product to RGB-02, a proposed biosimilar pegfilgrastim: Analysis of the results of three clinical trials

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**Background:** Treatment with recombinant human granulocyte-colony stimulating factor (G-CSF) is an accepted standard for prevention of chemotherapy-induced neutropenia. RGB-02, a pegylated G-CSF (pegfilgrastim) developed by Gedeon Richter is a proposed biosimilar to the reference product Neulasta®. Therapy switch from a reference product to its biosimilar is expected to occur in the daily practice. Here we are presenting the outcome of treatment switch in two randomized cross-over design comparative PK/PD studies (Eurad-CT nr: 2011-001737-17 and 2016-00501-25) and a randomized, comparative, multicenter efficacy and safety study of RGB-02 (Eurad-CT nr: 2013-003166-14).

**Methods:** Efficacy, safety and PD data of two PK/PD studies (enrolling 110 and 150 healthy volunteers, respectively) and a comparative efficacy and safety study (enrolling 239 breast cancer patients) were analyzed in order to assess whether treatment switch from Neulasta® to RGB-02 has any impact on the PD response, efficacy or safety. The PK/PD studies had a cross-over design. Patients in the reference arm of the comparative


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Legal entity responsible for the study: Hexal AG, Holzkirchen, Germany.

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efficacy and safety study were switched to RBC-02 treatment following the first two chemotherapy cycles. Endpoints assessed were related to the change in ANC count in healthy volunteers, duration of severe neutropenia (DSN; ANC < 0.5 x 10^9/L) in the comparative efficacy and safety study, as well as safety data including immunogenicity collected in each clinical study.

**Results:** None of the PD endpoints showed any difference following the cross-over in the comparative PK/PD studies. The mean DSN values after the therapy switch were similar to the values prior to the switch and the switched arm (mean DSN: 0.64) did not show decreased efficacy compared to the arm received RBC-02 from the first cycle (mean DSN: 0.9). Safety results, including immunogenicity of the 3 studies did not reveal any negative impact of the treatment switch.

**Conclusions:** Treatment switch from Neulasta® to RBC-02 can be considered safe while maintaining the therapeutic effect of pegfilgrastim therapy.

**Clinical trial identification:** EudraCT: 2011-001373-17; EudraCT: 2016-000501-25; EudraCT: 2013-000166-14.

**Legal entity responsible for the study:** Gedeon Richter Plc.

**Funding:** Gedeon Richter Plc.


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**1701P**

**Use of primary and secondary pegfilgrastim prophylaxis for reducing incidence of neutropenia: Findings from a large study in German clinical practice (PROTECT)**

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**Background:** The EORTC guidelines recommend primary prophylaxis with G-CSF when the overall risk of febrile neutropenia (FN) is >20% (high risk [HR]) or if the chemotherapy FN risk is 10–20% (medium risk [MR]) with additional patient (pt)-related risk factors. This study assessed the acceptance of these guidelines in German routine practice.

**Methods:** Non-interventional study of pegfilgrastim use in pts receiving Ctx for solid tumors or lymphomas (2007–2014 in 123 German centers). Pts were >18 yrs, had breast, ovarian, gastric, prostate or lung cancer, or aggressive lymphoma. EORTC defined FN risk ≥10%, and prophylactic pegfilgrastim use. Primary endpoint: proportion of pts receiving pegfilgrastim as primary (prior to neutropenia) or secondary (following neutropenia occurrence) prophylaxis.

**Results:** Data were available from 1914/2069 pts (average age 58 yrs, 79% female, 60% had breast cancer, 69% had prior tumor-related therapy and 20% prior Ctx). Of those receiving prior Ctx, 39% needed neutropenia treatment. Of the 1914 pts, pegfilgrastim was used as primary and secondary prophylaxis in 78% and 22%, respectively (primary endpoint). Primary prophylaxis was more frequent than secondary in the HR (72 vs 13% of 936 pts) and MR (73 vs 27% of 835 pts) groups. At a pt level, overall FN rate was 8% and varied across tumors: gastric 12%, breast 9%, lung 7%, lymphoma 8% and ovarian 3%. Across these tumors, the number of cycles with FN were 1.9%, 3.2%, 1.9%, 1.9%, 2.1% and 0.6%, respectively. Overall, 2% had a dose reduction or therapy switch due to FN. In breast cancer, dose reductions or therapy switches occurred in 1% of pts receiving primary prophylaxis and 3% receiving secondary prophylaxis.

**Conclusions:** In this study of pts receiving pegfilgrastim prophylaxis in routine German practice, the majority of HR pts with overall FN risk of ≥20% were treated with primary prophylactic prophylaxis in concordance with the EORTC guidelines. Primary prophylaxis with pegfilgrastim was associated with a low FN incidence and a low rate of dose reductions and treatment delays.

**Clinical trial identification:** NCT02178475.

**Legal entity responsible for the study:** Aegnae.

**Funding:** Aegnae GmbH.

**Disclosure:** C.M. Kurbacher: Honoraria and travel expenses, advisory role: Aegnae, M. Schmidt: Honoraria: Pierre-Fabre, Roche, Pfizer, Novartis, NovoNordisk, Eisai, Agen, Celgene; Research grants: Pierre-Fabre; Non-financial support: Roche, Pfizer, Agen, Celgene. H. Eschenburg: Roche AG; Other financial support: Bristol-Myers Squibb; P. Ramdohr: Employee and holds stock: Agen. All other authors have declared no conflicts of interest.

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**1702P**

**Associations between hematologic toxicity and health-related quality of life during first-line chemotherapy in advanced non-small-cell lung cancer: A pooled analysis of two randomized trials**

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**Background:** Many patients experience toxicity from chemotherapy that can negatively impact their health-related quality of life (HRQol), but side effects often go undetected by health care personnel. Hematologic toxicity (HT) is the main dose-limiting toxicity of chemotherapy. Our aim was to investigate whether patients who experienced severe HT had more negative changes in HRQol than those who did not. If so, blood counts could represent a simple and objective method for identifying patients at risk of severely impaired HRQol who may benefit from more supportive care during the treatment period.

**Methods:** Data from two phase III trials of first-line chemotherapy in advanced non-small-cell lung cancer (NSCLC) were analyzed (n = 737). Blood counts were measured weekly. We categorized patients as having severe (CTCAE grade 3–4) or non-severe (grade 0–2) HT during the first chemotherapy cycle. HRQol was reported on the EORTC (QLQ-C30 and LC13 before and at the end of the cycle. The primary endpoint was changes in global quality of life, fatigue, nausea/vomiting and dyspnea (LC13). Mean differences of 3–10 points was considered to represent a small clinical difference.

**Results:** Of the 766 patients with complete data set, 177 (23%) developed severe HT during the first chemotherapy cycle. Severe neutropenia and thrombocytopenia was observed in 149 (19%) and 67 (9%) patients, respectively, while only three (0.4%) patients had severe anemia. Changes in fatigue and nausea/vomiting were significantly worse for patients experiencing severe compared to patients with non-severe HT (difference in mean change of 4.9 points; p = 0.01, and 6.4 points; p = 0.01, respectively), but this association was limited to neutropenia, not thrombocytopenia or anemia. There were no significant associations between HT and global quality of life or dyspnea (difference in mean change of 2.1 points; p = 0.28, and 3.3 points; p = 0.053, respectively).

**Conclusions:** Patients developing severe HT had worse changes in two out of four HROql endpoints, but the association was not strong enough to use blood counts to identify patients who experience deterioration of HRQol during chemotherapy.

**Legal entity responsible for the study:** European Palliative Care Research Centre (PRC), Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1703P**

**Incidence of hypocalcemia in a non-inferiority phase III trial assessing prevention of symptomatic skeletal events (SSE) with denosumab (DNN) administered every 4 weeks (q4w) versus every 12 weeks (q12w): SAKK 96/12 (REDUSE)**


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**Background:** DNN has shown superiority in delaying skeletal related events when given q4w over zoledronic (ZA) acid given q12w. Newer data have shown that ZA given q12w is non-inferior to ZA q4w. The primary endpoint of REDUSE is to show non-inferiority.
for DN q12w versus q4w (SSE). Here we present the data for the secondary endpoint hypocalcemia (HC).

**Methods:** Patients with metastatic breast cancer (BC) or metastatic castration resistant prostate cancer (PC) (planned N = 1380) were randomized 1:1 to receive DN q4w (Arm A) versus q12w (Arm B) after a 3-month induction phase with application q4w. All patients received vitamin D 400 U (ViD) and calcium (Ca) 500 mg daily. Measurement of serum-calcium was mandatory before each DN injection. This safety interim analysis was performed after 3.5 years of accrual. (N = 634, BC N = 351, PC N = 283).

**Results:** Patients who received at least 1 dose of DN were considered evaluable. HC was the most common side effect with 23.7% overall (BC 18.6%, PC 30.2%). While HC occurred in 31.4% in Arm A, the rate was 15.8% in Arm B. Grade 3/4 HC was rare (overall: 1.3%, all with PC). After 1 year of treatment, the incidence of HC was lower in both arms (A: 27.2%, B: 14.3%). Since HC improved in more patients in Arm B than Arm A whereas it got worse in Arm A compared to Arm B, a remarkable difference for HC was noticed between the two arms (Table).

**Conclusions:** In our trial up to 30% of all patients treated with DN experienced HC in the q4w induction phase despite mandatory supplementation and measurement of ViD and Ca. This rate was considerably higher than reported in the registration trials of DN (PC 13.0%, BC 5.9%). After randomization the appearance of HC is remarkably lower in the q12w arm compared to q4w. This suggests that DN given q12w has a more favorable long time toxicity profile (HC) compared to DN q4w.

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**Legal entity responsible for the study:** Swiss Group for Clinical Cancer Research (NACK).

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**1704P A prospective randomized controlled trial of metoclopramide combined with triple antiemetic therapy to prevent anthracycline-based chemotherapy-induced nausea and vomiting in patients with breast cancer**

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**Background:** Triple antiemetic therapy, such as a 5-HTR3 receptor antagonist (SH3-RA), aprepitant and dexamethasone, is recommended for the prophylaxis of highly emetogenic chemotherapy induced nausea and vomiting in patients with breast cancer. In the present study, we aimed to verify whether adding metoclopramide to the triple antiemetic therapy is superior to the triple antiemetic therapy in preventing CINV in patients with breast cancer.

**Methods:** A single-blind, randomized trial was performed on ninety-seven patients who received HEC among chemotherapy-naïve patients with breast cancer. The visual analogue scale (VAS) used to detect nausea, and FLIE was used in order to determine its impact on the patients’ quality of life. The patients were randomized to arm A (RAD), dexamethasone and SH3TRA on day 1, aprepitant on day 1-3, and metoclopramide on days 1-5 and arm B (n=49, dexamethasone and SH3TRA on day 1and aprepitant on day 1-3). The primary endpoint was complete response (CR) (no nausea, no vomiting, and no rescue medication) during the overall phase (days 1-5).

**Results:** The demographic and clinical features such as age, educational background, height and weight measurements were similar in both groups. The CR was found in twenty patients (45.8%) of the forty-eight patients in the arm A, while it was found in thirteen patients (26.3%) of the forty-nine patients in the arm B (p=0.038). The mean total FLIE score was 31.31 (SD: 20.5) in arm A, which was 29.29 (SD: 26.4) in arm B (p=0.045).

**Conclusions:** A triple or quadruple antiemetic combination is proposed to alleviate CINV for female patients with breast cancer treated with HEC. In patients receiving anthracycline-based chemotherapy, quadruple antiemetic therapy with dexamethasone, aprepitant, palonosetron and metoclopramide is associated with a significant CR and clinically relevant improvement in FLIE score, compared to dexamethasone, aprepitant and palonosetron. Therefore, a quadruple antiemetic combination including metyrapon might be a treatment option for patients receiving highly emetogenic chemotherapy.

**Legal entity responsible for the study:** Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1705P Ramosetron versus palonosetron in combination with aprepitant and dexamethasone for the control of highly emetogenic chemotherapy-induced nausea and vomiting**

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**Background:** The combination of palonosetron (PAL), aprepitant (APR) and dexamethasone (DEX) is the standard regimen in controlling highly emetogenic chemotherapy-induced nausea and vomiting (HEC-CINV) in cancer patients. We previously demonstrated that Ramosetron (RAM), 5-HT3 receptor antagonist, is superior to ondansetron. This prospective, multicenter, single blind, randomized and phase IV study compares RAM, APR and DEX (RAD) with PAL, APR and DEX (PAD) to prove the non-inferiority of RAD in controlling HEC-CINV.

**Methods:** Patients were randomly assigned at 1:1 ratio to receive either RAD or PAD regimen: RAM (0.3mg IV) or PAL (0.25mg IV), D1 in combination with APR (125mg PO, D1 and 80mg PO, D2-3) and DEX (12mg IV PO, D1 and 8 mg PO, D2-4). They were stratified by gender, chemotherapy (cisplatin vs non-cisplatin) and administration schedule (single vs multi-day). The primary endpoint, overall complete response (CR) was defined as no emesis and no rescue regimen within 5 days of HEC. The secondary endpoints were overall complete protection (CP: CR + nausea score < 25mm) and total control (TC: CR + nausea score < 5mm). Quality of Life (QOL) was assessed by Functional Living Index—Emesis (FLIE) questionnaire on D0 and D6.

**Results:** A total of 279 patients receiving RAD (n = 137) or PAD (n = 142) were evaluated for the efficacy and safety. The overall CR rates of RAD vs PAD were 72.3% vs 74.6% (relative difference (RD) 2.4%, 95% CI: 12.8 to 8.0), respectively. The overall CP and TC rates in RAD vs PAD were 52.6% vs 57.0% (RD: -4.5%, 95% CI: -16.2 to 7.2) and 45.3% vs 49.0% (RD 3.7%, 95% CI: -9.4 to 14.0%), respectively. FLIE score ≥ 10 (no impact of daily life) was comparable between RAD (n = 134) and PAD (n = 139) (73.9% vs 73.4%, p = 1.00 respectively). Each nausea and vomiting domain (FLIE score ≥ 34) was 67.2% vs 64.0% (p = 0.61) and 91.8% vs 90.6% (p = 0.83), respectively. The adverse events were similar between the two groups.

**Conclusions:** In all aspects of the efficacy, safety and QOL, our data suggested RAD was comparable to PAD for the control of CINV in cancer patients receiving HEC.

**Clinical trial identification:** NCT02532634.

**Legal entity responsible for the study:** In-Hyung Kang, Ph.D, D, The Catholic University of Korea.

**Funding:** Astellas Pharma Korea, Inc.

**Disclosure:** I.S. Ahn: Honoraria: Eisai, Jansen, Menarini, Roche; Advisory role: Boehringer Ingelheim. All other authors have declared no conflicts of interest.
1707P Usefulness of bone modifying agents for non-weight bearing bone metastasis in breast cancer

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Background: Bone metastasis is common in breast cancer. No previous study evaluated the usefulness of bone modifying agents (BMA) in breast cancer patients whose metastases are limited to non-weight bearing bones.

Methods: We retrospectively collected data at St. Luke’s International Hospital between 2006 and 2016. Weight bearing bones were defined as vertebral body, lower limbs, and pelvis, and all the other bones were defined as non-weight bearing bones. Breast cancer patients, age ≥ 20 years old, who were newly diagnosed to have bone metastasis only in non-weight bearing bones were included in this study. Bone metastases were detected by either bone scintigraphy or PET-CT. The selected patients were divided into two groups: Group A started BMA within 3 months from the diagnosis, and those of Group B did not start BMA within the 3 months. We are interested in comparing the Groups A and B in terms of time to skeletal related events (SRE) and overall survival (OS), where SRE were defined as orthopedic surgery, percutaneous vertebroplasty, and/or palliative radiation to bone metastasis.

Results: Out of 418 breast cancer patients with bone metastasis, only 101 patients were found to have bone metastasis only in non-weight bearing bones. The median follow-up time was 32 months. The number of patients in Group A and B were 54 and 47, respectively. Eighty patients in Group A and 5 patients in Group B developed SRE (p = 0.568). Median SRE free survival (i.e. time to SRE) was 118.5 months, and 117.3 months in Group A and Group B, respectively (p = 0.490, Hazard ratio: 1.48). Median overall survival (OS) was 99.7 months in group A and 78.3 months in group B (p = 0.203, Hazard ratio: 1.45).

Conclusions: Early initiation of BMA did not improve SRE free survival or OS in breast cancer patients who have only non-weight bearing bone metastasis. Further prospective studies are needed to confirm this finding.

Legal entity responsible for the study: St. Luke’s International Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1708P Prognostic factors associated with prevalence of nausea, and time to development of nausea in patients receiving guideline-based anti-emetic prophylaxis: A prospective, observational, real world study

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Background: The development of effective anti-emetic treatments has contributed to the resolution of emesis in chemotherapy patients (pts). There is a growing concern that the emesis focus is primarily on vomiting. Nausea seems to be underestimated and its incidence and impact remains a major unmet medical need. The study focused primarily on nausea in patients undergoing highly-, moderately-, or low emetogenic chemotherapy (HEC, MEC, LEC). The primary endpoint was no nausea during the 120-hour overall phase after cycle 1. The analysis focused on the prevalence of nausea and time to nausea development following the first cycle of chemotherapy.

Methods: This prospective, observational single centre study enrolled 95 patients undergoing LEC (25 pts), MEC (24 pts) or HEC (46 pts) for malignancy. Prophylactic antiemetics were administered according to MASCC/ESMO 2016 guidelines. Patient diaries were used to collect data from day-1 to day-3, day-7 and day-10 beginning with cycle-1 for up to 3 cycles.

Results: The incidence of nausea of the entire population was 59% compared to only 24% pts experiencing vomiting. (Chi² = 23.2996; p < 0.0001). Significant variables predicted for nausea included gender, age and history of motion sickness. The level of emetogenicity did not correlate with the incidence of nausea (LEC < 25%, MEC = 69%, HEC = 67%), (Chi² = 5.1893; p > 0.07). On univariate analysis, factors associated with shorter time to the first nausea episode included; age < 60 years (log-rank test p = 0.0231, Chi² = 2), then motion sickness (p < 0.0229), gender (p < 0.0321) and emetogenicity (p < 0.029). A Cox-proportional multivariate proportional hazard model age < 60 years, (p = 0.0213), gender (p = 0.0321) and motion sickness (p = 0.0229) maintained its significance – while emetogenicity lost its significance.

Conclusions: Chemotherapy induced nausea is underreported and remains a major unmet medical need. Gender, age and motion sickness are significant risk factors associated with nausea independent of the level of emetogenicity of the chemotherapy utilized in patients receiving guideline-based antiemetic prophylactic treatment.

Legal entity responsible for the study: The Medical Oncology Centre of Rosebank.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1709P Analysis of bone events in patients with aromatase inhibitors (AI)

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Background: Nowadays breast cancer (BC) may have high cure rate, so is important how to prevent or resolve adjuvant treatments adverse effects. AI are an essential treatment in patients with early diagnosed estrogen-dependent BC. Our aim is to analyse bone mass loss in BC, focusing on fractures incidence and their risk as well as preventive methods. The latest consensus establishes as intervention criteria a BMD value < -2T Score and 2 or more risk factors.

Methods: 114 BC patients and 272 without BC sent to our centre in 2010 to perform densitometry (DXA) were included in our review. Beyond DXA and anthropometry we carried out an extensive clinical questionnaire on co-morbidity, risk factors for osteoporosis, medication, personal and relatives history of fractures. Hospital and primary care records were reviewed in BC patients until May 2017 to determine fractures incidence.

Results: There were significant differences in age (BC: 59 ± 11 vs 62 ± 11 years, p = 0.08). No differences in weight, height, menarche/ menopause or toxic habits. 25% had personal history of fracture (31% control p = 0.03) and 17% relatives history (27% control p = 0.03). 4.3% of corticosteroid intake (16% control p = 0.01). There were no differences in T Lumbar Score (97 ± 1.3 vs 94 ± 1.2) or in femur neck (-0.95 ± 1.2 vs -0.71 ± 1.1) but yes in the fracture risk assessment tool (FRAX) for major fractures with BMDM (BC 7 ± 5% vs 11 ± 6% p = 0.02) and hip fractures (1.2 ± 2.0 vs 2.4 ± 4 p = 0.02). Patients with AI lost bone mass at two years (BMDM: 0.96 ± 1.87 to 0.921 ± 0.18 g/cm2 p < 0.02), without changes in control group. At 7 years follow-up, 8 fractures appeared in patients with AI (3 Colles, 3 vertebrae and 2 humerus), 4 patients with Exermetane (E), 2 with Letrozole (L) and 2 with Anastrozole (A) (40% took E, 26% A and 20% L). Only 3 of the 8 had baseline T Lumbar Score < -2.5% BC patients received antiresorptives and 9% vitamin D.

Conclusions: There were more fractures and bone mass loss in BC patients treated with AI in our sample. Despite the small sample size, it is striking that, patients with BC would not meet the indication of preventive treatment according to the latest recommendations, since only 30% of the patients would be covered. It could be considered to associate other diagnostic measures to treat patients with greater risk of fracture (FRAX).

Legal entity responsible for the study: Central University Hospital of Asturias.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1710P Assessment and treatment of breakthrough cancer pain in Spain: A self-audit study

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Background: In Spain 77% of the episodes of Breakthrough cancer pain (BTPc), a common condition for cancer patients, are not properly diagnosed or treated. The ECO Foundation (Excellence and Quality in Oncology) has promoted this study with the collaboration of Francisco de Vitoria University, to compare the real-life clinical practice with the previous perception of the oncologists of the management of BTPc and to determine if clinical inertia exists in the approach of the BTPc episodes.

Methods: Observational and descriptive study consisting in two phases: a) opinion poll (self-completed online) answered by Spanish oncologists, and b) BTPc episodes screening and assessment (performed by the oncologist surveyed) in patients with a prior or current history of cancer pain (5 patients per oncologist). A recent external consensus (1) and Davies algorithm were used to evaluate the correct diagnosis and optimal management of BTPc. A total of 108 oncologists participated in the study and 540 patients were evaluated.

Results: Although most oncologists (>80%) refer questioning their patients about the possibility of BTPc, only 34% of them do it systematically in their clinical practice. Most specialists believed that BTPc episodes were unlikely to go unnoticed in their consultations (62%). After evaluating real-life clinical practice, the overall prevalence of BTPc obtained was 91% (493/540). The doctors had previously detected the BTPc condition in 59% of patients (291/495), demonstrating that the under-diagnosis of BTPc exceeds 40%. In addition, 42% of patients with known BTPc were not able to control their episodes of pain and, despite the persistence, in 13% of them, no changes or adjustments had been made in the dose intensity or schedule.
Conclusions: The study confirms that there is a significant prevalence of BTcP and a notable inertia in the management of BTcP episodes, which seems to be poorly detected and treated in patients with cancer. Expanding the use of tools to diagnose BTcP, such as Davies algorithm, might be useful to improve the QoL of patients suffering pain.

Legal entity responsible for the study: ECO Foundation.

Funding: Kyowa Kirin Pharmaceutical.

Disclosure: All authors have declared no conflicts of interest.

Methods: This study was a multicenter, prospective, observational study of cancer patients who started opioid therapy in Japan (UMIN000025864). The incidence of OIC was determined by ROME IV OIC diagnostic criteria based on the record of patient diary for 14 days. The proportion of patients with OIC was calculated for each 1-week period (Week 1 and Week 2) and overall 2-week period. Medication for constipation was allowed during the study period. Patients with <3 bowel movements in the previous week before starting opioid therapy were not allowed to be enrolled. Bowel Function Index (BFI; score <28.8), spontaneous bowel movement (SBM; <3 SBM/week), and physicians’ assessment were also utilized to assess OIC and compare the results.

Results: In total, 212 cancer patients (145 males; mean age 69.1 years)—patients and outpatients—with ECOG Performance Status score of 0-2 were included in the study. Mean morphine equivalent dose was 21.9 mg/day. Overall incidence rate of OIC during 2 weeks by weekly diagnostic as OIC in either Week 1 or Week 2 was 56.1%. The proportion of patients with OIC in Week 1 was 47.6% and in Week 2 was 36.8%. Use of prophylactic laxative reduced the overall incidence rate of OIC from 65.9% to 47.7%. Other diagnostic criteria instead of ROME IV criteria varied the rate: BFI (59.1%), physician’s assessment (61.4%), BFI—SBM frequency (44.8%). When overall 2-week period data were applied to ROME IV OIC criteria, the incidence rate was reduced to 44.2%. Sex and age were not considered as risk factors as opposed to the previous report in some cross-sectional studies. The frequency of SBM/week before starting opioids was identified as the most influencing factor for OIC.

Conclusions: OIC can occur quickly after the initiation of opioid therapy in cancer patients, even if laxatives were utilized prophylactically. The tools for diagnosing OIC result in varied rates of diagnosis.

Clinical trial identification: UMIN000025864.

Legal entity responsible for the study: Shionogi & Co., Ltd.

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Background: Opioid-induced constipation (OIC) is a common distressing symptom associated with cancer pain opioid treatment. Beyond the recommendations for the treatment of OIC, there are no specific guidelines for the management of the patient with OIC, and little is known about the decision tree health care professional (HCP) use to manage OIC. The ECO Foundation (Excellence and Quality in Oncology) has promoted this study to learn about the diagnostic and treatment criteria of OIC in clinical practice.

Methods: An on-line survey was completed by 135 investigators: 122 medical oncologists (90.4%) and 13 palliative care specialists (9.6%). The questionnaire included 50 items about the management of OIC.

Results: According to HCP, most of the cancer patients with pain (71.2%), received opioid treatment for more than 6 months and 54.4% developed OIC. Although 97% of HCP considered OIC as a major health problem only 14.8% of HCP used algorithms for the diagnosis of OIC and 14.1% for OIC treatment. Laxatives were considered second-line treatment for 60% of HCP, after healthy lifestyle recommendations. Opioid-induced constipation (OIC) is a common distressing symptom associated with cancer pain opioid treatment. Beyond the recommendations for the treatment of OIC, there are no specific guidelines for the management of the patient with OIC, and little is known about the decision tree health care professional (HCP) use to manage OIC. The ECO Foundation (Excellence and Quality in Oncology) has promoted this study to learn about the diagnostic and treatment criteria of OIC in clinical practice.

Conclusions: OIC is considered a frequent and relevant opioid side effect among cancer patients in Spain. Although most HCP are aware of the potential for OIC with opioid treatment, there is limited consensus on the OIC diagnostic and treatment criteria. The ineffectiveness of traditional therapies and the emerging of more specific and effective pharmacological approaches, suggest new clinical guidelines are needed for the management of OIC in cancer patients.

Legal entity responsible for the study: ECO Foundation.

Funding: Cytel Abintec, S.L.

Disclosure: All authors have declared no conflicts of interest.

Background: Opioid-induced constipation (OIC) is a common side effect of opioid analgesic therapy. Naldemedine (NAL), an orally available peripherally-acting α-opioid receptor antagonist (PAMORA), has been shown to improve OIC without affecting analgesic effect of opioids across several clinical studies. However, the predictive factors determining the response to OIC treatment have not been elucidated. We conducted a subgroup analysis with the pooled data to explore the predictive factors in patient population for the efficacy and safety of NAL.

Methods: Data were pooled from 2 randomized, double-blinded, placebo (PBO)-controlled studies of NAL 0.2mg QD (Ph2b and Ph3) for cancer patients (JapicCTI-132340, JapicCTI-111510). Subgroup analysis (age, BMI, gender, opioid type or dosage, concomitant laxatives, with or without anti-cancer therapy, with or without possible disruption of blood brain barrier (BBB)) of spontaneous bowel movement (SBM) responder rate (percentage of patients with ≥ 3 SBM/week and an increase from baseline of ≥ 3 SBM/week) was conducted. Overall safety and the incidence of diarrhoea were evaluated. The pain intensity numerical rating scale (NRS) and clinical operative withdrawal scale (COWS) were also analyzed in the population with or without possible BBB disruption.

Results: SBM responder rate was 73.5% (114 of 155 patients) for the NAL group and 35.5% (54 of 152 patients) for the PBO group for all subjects. The difference between the groups was 38.0% and was statistically significant (P < 0.0001). In the subgroup analysis, the difference of proportion between NAL vs PBO for each efficacy and safety endpoint was consistent across all subgroups (The all point estimates were greater than zero). Although the difference of the incidence of diarrhoea between the groups was relatively larger in the possible disruption of BBB group, there was no difference between with or without possible BBB disruption for NRS and COWS.

Conclusions: Overall, this analysis of subgroups supported that the benefits of NAL were observed regardless of background factor, and its safety profile in various subgroups was consistent with that observed in the overall population.

Understanding of this study was to evaluate the incidence of OIC from the start of opioid therapy.
Background: Current guidelines recommend cardiac function monitoring every 3 months in patients receiving trastuzumab, however evidences for optimal cardiac surveillance strategy are lacking. The aim of this study is to identify risk factors and to characterize clinical patterns of trastuzumab related cardiac dysfunction (TRCD) within 1 year of treatment in patients with breast cancer.

Methods: We identified and reviewed consecutive patients with breast cancer received trastuzumab and adequate cardiac monitoring (baseline and subsequent cardiac echo-cardiogram at least every 4 months) between Jan 2010 - Apr 2017 at a single center. TRCD were defined as an absolute decrease of ejection fraction (EF) ≥15% or ≥20% to below the lower limit of normal.

Results: Among 364 patients (median age 51 years), TRCD was developed in 33 patients (9.3%). Median time from trastuzumab to TRCD was 6.3 months (range 2.6-12.3). Incidence of TRCD was significantly higher in patients with prior anthracycline (12.1% vs. 5.1%, p = 0.026). In 20 out of 33 patients (60.6%), TRCD was diagnosed within the first 6 months of trastuzumab. Earlier TRCD was significantly associated with prior anthracycline (72% vs. 25%; p = 0.035). Among the patients with later TRCD development after 9 months (n = 13), absolute EF decrease ≥5% in the 6 months preceded in 10 patients (76.9%). Incidence of later TRCD was significantly lower in patients whose absolute EF decrease < 5% in the first 6 months (2.1%) than in whom with more than 5% of absolute EF decrease (11.8%).

Conclusions: TRCD development occurs earlier within the first 6 months of trastuzumab in patients with prior anthracyline use. The degree of absolute EF decrease in the first 6 months can predict later development of TRCD. Therefore, cardiac monitoring for the first 6 months of trastuzumab treatment should not be missed, especially in whom with prior exposure to anthracycline. Adaptive less frequent cardiac surveillance strategy after 6 months may be considered in patients without significant EF change.

Legal entity responsible for the study: Hee Kyung Ahn.

Disclosure: All authors have declared no conflicts of interest.

1714P Predicting the occurrence and prevention of early anthracycline cardiotoxicity of chemotherapy in patients with breast cancer

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Background: Methylenetetrahydrofolate Reductase (MTHFR) is the key enzyme of xenobiotic detoxification, involved in the metabolism of anticancer drugs. Genotyping of the polymorphism MTHFR allows to make prognosis of chemotherapy side effects in different patients, personalize pharmacotherapy.

Methods: QTc interval and myocardial systolic and diastolic function of 100 patients with breast cancer stages T1-T3N0-2M0 treated with neo/adjuvant anthracycline chemotherapy were investigated. In the main study group 50 patients received cardioprotective medications (enalapril 2.5 mg orally twice daily and carvedilol 6.25 mg orally twice a day). The polymorphisms of MTHFR gene in control group were evaluated using Real-Time PCR. Statistical 0.05 software was used to perform analysis of variance.

Results: It was established that the specific manifestations of early cardiotoxicity of doxorubicin at a cumulative dose 300 mg/m² were QTc prolongation over 440 msec in the main group in 5 (10%) patients, in the control group – 13 (26%) patients, as well as diastolic dysfunction (DD) of the left ventricle type I in the main group in 5 (10%) patients, in the control group – 15 (30%) patients. The absence of cardioprotective therapy in our study was a risk factor for these complications: QTc interval prolongation (OR – 3.15, 2.05 - 4.21, p = 0.05) and DD (OR – 3.85, 2.73 – 4.96, p = 0.04). A molecular genetic analysis had shown that QT prolongation and DD were detected in 36.4% of patients with T/T genotype, in 36.6% with T/C genotype and only 9.1% with C/C genotype. The risk of cardiotoxicity of chemotherapy in patients with breast cancer, which is the carrier of one or two mutant alleles of the gene MTHFR (genotype C/T and T/T) is 2.68 times higher (OR = 2.68, 95% CI = 1.24 – 5.78, p < 0.01) in comparison with carriers of genotype C/C.

Conclusions: It is reasonable to determine the MTHFR gene polymorphism in patients with early breast cancer prior to treatment which allow identify a high-risk cardiotoxicity group for timely and adequate cardioprotective therapy administration.

Legal entity responsible for the study: National Cancer Institute, Kiev, Ukraine.

Disclosure: All authors have declared no conflicts of interest.

1716P Cardiovascular and other competing causes of death among cancer patients, 2006-2015: An Australian population-based study

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Background: Cardiovascular disease (CVD) is the leading cause of death worldwide. With improved cancer treatment and survivorship, CVD and other non-cancer events compete with cancer as the underlying cause of death. However, their mortality risk in competing risk settings is not well characterised.

Methods: We identified 21,637 individuals with a first cancer registered between January 2006 and December 2013 in the population-based Tasmanian Cancer Registry, Australia. Cumulative incidence functions were applied to assess the cumulative incidence of deaths due to specific competing events with follow-up to December 15. Standardised mortality ratios (SMRs) and absolute excess risks (AERs) for non-cancer deaths were calculated to allow comparison with the general population.

Results: Overall, 8,844 deaths were observed with 1,946 (22.0%) from competing events (332 from subsequent cancer, 741 from CVD and 873 from other non-cancer events). The cumulative incidence of deaths due to CVD increased significantly with age at first cancer diagnosis (5-year cumulative mortality by age group: 15-44y – 0.7%; 45-64y – 2.1%; 75-84y – 6.9%; 85y+ – 13.1%) and exceeded other competing events for those with a first cancer diagnosis at age 65 years or older. For the whole follow-up period, CVD deaths were as expected for the general population (SMR, 0.97; 95%CI 0.90-1.04), however within the first follow-up year, CVD deaths were more common than expected (SMR, 1.44; 95%CI 1.26-1.64; AER, 36.8/10,000 person-years). The SMR and AER for CVD deaths varied by first cancer site showing an increased risk after a first diagnosis of lung cancer, hematological malignancies and urinary tract cancers. For other non-cancer events, the SMRs significantly increased for infectious disease and respiratory disease for the whole follow-up and within the first year of diagnosis.
Cancer associated thrombosis with primary prophylaxis in a tertiary hospital in the Philippines from 2010-2015

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Background: Venous thromboembolism, consisting of pulmonary embolism or peripheral venous thrombosis is the second most common leading cause of death in cancer. Prophylactic measures are now being done to prevent its occurrence. In a financially-challenged patient does primary prophylaxis really protect our patients?

Methods: Data from the hospital’s database for year 2010-2015 with either Venous Duplex Scan or Computed Tomographic Pulmonary Angiography (CTPA). Each result were reviewed for presence of acute pulmonary embolism or acute venous thrombosis. Only the first event after the diagnosis of cancer was considered therefore, all subsequent events were ignored. Among those with negative venous thromboembolism results, review of chart and computerized data system on histologic diagnosis of carcinoma.

Results: A total of 16,380 CTPA/Venous duplex scan were performed for year 2010-2015, where 946 (8.8%) had positive venous thromboembolism (VTE). Of patients with VTE, 712 (6.8%) were not associated with malignancy, 204 (2%) had malignancy. Average age of patient 61.3 (range 19-90), mostly female (61.7%) and had normal body mass index (62.2%). Most common symptom was swelling of the extremity (54%) followed by pain (32%) and dyspnea (12.6%). Lower extremity (77.4%) thrombosis was more common than upper extremity thrombosis (9.8%). Breast cancer (n = 37, 18.9%) had the most number of VTE, followed by lung (n = 31, 15%). Gynecologic malignancies had up to 21.5%, followed by gastrointestinal malignancies 21.5% (n = 44). Most patients had prior hospitalization (n = 146, 71.5%) within the past three months prior to the diagnosis of VTE. Up to 81.8% (n = 167) had no VTE prophylaxis while 9.8% (n = 20) had primary prophylaxis prior to the occurrence of VTE. However, among those who had prophylaxis with heparin, two had no prior hospitalization for three months prior to the VTE diagnosis, and mostly had gynecologic malignancy, breast cancer, and hepatocellular cancer. Seventy percent of them had normal BMI and were mostly <65 years of age.

Conclusions: Cancer patients still develop VTE even with primary prophylaxis and no hospitalization for the past three months which were the leading risk factors for developing VTE in primary studies. There is no difference in patient profile for those who received prophylaxis in our center compared to the general profile. Legal entity responsible for the study: Agnes Gorospe.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

Prevention and prophylaxis of thrombosis in cancer patients

HeSMO - Hellenic Society of Medical Oncology, Athens, Greece

Background: Cancer Associated Thrombosis (CAT) is a significant problem in oncology that is underestimated sometimes. Venous Thrombolimitis (VTE) is the 2nd cause of death in cancer patients. Currently, the standard of care not only for the treatment but also for the prophylaxis of CAT is the Low Molecular Weight Heparines (LMWH). Thromboprophylaxis is an important medical decision for cancer patients in daily clinical practice.

Methods: This is an observational study conducted by HeSMO in Greek Oncology units, for 1 year, aiming to record CAT management. Patients with active cancer received antithrombotic agents for thromboprophylaxis were enrolled, after signing informed consent.

Results: All participating centers reported that approximately 4.300 cancer patients are managed on monthly basis, where the majority (80%) as outpatients. 426 cancer patients enrolled from 18 oncology units with mean age 65.2 years old and mean Body Mass Index (BMI) 26.10. Primary cancers were: lung 25%, pancreas 14%, stomach 8.6%, breast 8.6%, ovarian 7.7%, colorectal 7.5%, bladder 5.5% and other 22.8%. 30% of patients received LMWH at prophylactic doses while the rest received therapeutic doses [mean duration 4.42 months (SD +/- 2.68)]. 126 (30%) patients had Khorana score ≥3, 300 (70%) had Khorana score ≤2 and of these patients 66% were metastatic and 30% were receiving High Thrombotic Chemotherapy Agents (HTCA, e.g. cetuximab, platinum). 16 (3.8%) patients experienced VTE while 9 (56%) of them were incidental. Lower VTE risk (UR: 0.32 (95% CI 0.10, 1.0) p = 0.04) was observed in patients on therapeutic doses LMWH while higher VTE risk (UR: 3.14 (1.01, 9.91) was observed in patients on prophylactic doses LMWH. High BMI (>35) was related to significant higher risk for VTE (UR 5.37 (1.6, 18)). Only six (1.4%) grade 1 bleedings were recorded in all patients who receive thromboprophylaxis.

Conclusions: CAT is an important problem in oncology. Therapeutic doses of LMWH for thromboprophylaxis are effective and safe. Apart from Khorana score, some other factors such as disease stage and administration of HTCA might be taken into consideration for better CAT risk assessment in oncology patients.

Legal entity responsible for the study: Hellenic Society of Medical Oncology (HeSMO), Athens, Greece.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
1721P Long-term prognosis of acute pulmonary embolism: A focus on idiopathic and neoplastic etiologies

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Background: Acute pulmonary embolism (PE) is a fatal condition when untreated. Long-term prognosis of acute PE in the 21st century has not been fully reported. We aimed to determine the long-term prognosis of acute PE and assess if there were survival differences between patients with idiopathic and secondary PE.

Methods: We retrospectively analysed a cohort of patients hospitalized with acute PE between 2006 and 2013. Excluded: 1) <18 years old, 2) embolism of non-pulmonary veins and 3) chronic pulmonary embolism. The vital status was ascertained by consulting the National Registry of Portuguese Patients platform. Patients were grouped according to acute PE aetiology: idiopathic, secondary to a neoplastic condition and secondary to conditions other than a neoplasia. A Cox regression analysis was used to study the prognostic implications of PE aetiology. Multivariate models were built.

Results: A total of 872 patients with acute PE were admitted, median age: 70 years old, 496 (56.9%) were female. In 36.8% the PE was of central arteries and in 56.9% bilateral. PE was considered idiopathic in 376 (43.1%), secondary to a neoplastic condition in 496 (56.9%) and other conditions in 20 (2.3%). Median anti-Xa level was 0.255 U/ml (range 0.01-0.77). Anti-Xa levels were within target range in 40 patients (55.6%), below target in 26 patients (36.1%) and above target in 6 patients (8.3%). Anti-Xa was higher in females (median 0.3 vs 0.19 U/ml; p < 0.001) and correlated positively with serum creatinine (p = 0.003), and negatively with body weight (p < 0.001). Optimal threshold weight for predicting sub-therapeutic levels of anti-Xa was identified at 78 kg (sensitivity 43%, specificity 85%).

Conclusions: Using a policy of fixed dose enoxaparin resulted in under-treatment in more than one-third of a non-selective population of cancer patients, mainly in those whose weight was above 78 kg. We suggest that prophylactic dosage of enoxaparin higher than 40 mg should be considered for patients with body weight above 80 kg.

Legal entity responsible for the study: Helsinki committee Rambam Health Care Campus.

Funding: Has not received any funding.

Disclosure: B. Brenner: Honoraria for lectures and advisory board contributions; Pfizer, Leo Pharma, Sanofi, Roche Laboratories, Bayer Pharmaceuticals. All other authors have declared no conflicts of interest.

1722P Systematic literature review and network meta-analysis of oral anticoagulants for the treatment of venous thromboembolism in patients with cancer

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Background: Based on the current guideline, treatment options for cancer-associated thrombosis include low molecular weight heparin (LMWH), unfractionated heparin (UFH), warfarin, and fondaparinux. However, in patients who do not have cancer, direct oral anticoagulants are very effective for the treatment of VTE. In some cases, the use of LMWH is limited due to administration by the subcutaneous route. In this study, we compared the efficacy and safety of oral anticoagulants including vitamin K antagonists (VKA) and direct-acting oral anticoagulants (DOAC) for the treatment of cancer-associated VTE.

Methods: We conducted a systematic literature review to identify all eligible randomized controlled trials (RCT) by searching PubMed, Web of Science, AHS, ASCO, EHA, and ESMO databases. The relative risks (RR) of recurrent VTE (efficacy) and major bleeding (safety) were analyzed using Bayesian network meta-analysis with a fixed-effect model.

Results: Four DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) were identified in five RCTs. When comparing the efficacy between VKA and DOACs, the recurrence rate of VTE was lower in the treatment with DOACs than with VKA, but not statistically significant. (apixaban: odds ratio (OR) 0.55, 95% credible intervals (CrI) 0.10-2.4; dabigatran: OR 0.76, 95% CrI 0.32-1.8; edoxaban: OR 0.49, 95% CrI 0.10-1.7; rivaroxaban OR 0.57, 95% CrI 0.19-1.7). In safety, the risk of major bleeding was relatively low in the use of DOACs compared to VKA, except for edoxaban (apixaban: OR 0.42, 95% CrI 0.03-2.2; dabigatran: OR 0.82, 95% CrI 0.25-2.7; edoxaban: OR 1.6, 95% CrI 0.38-8.4; rivaroxaban OR 0.47, 95% CrI 0.14-1.5).

Conclusions: For the treatment of VTE in cancer patients, DOAC has a favorable tendency for the efficacy and safety compared to VKA. DOACs could be one of the standard treatment options for management of VTE in cancer patients. Among DOACs, epixaban has a relatively good outcome.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1723P Comparison of venous thromboembolism risk assessment models in patients receiving chemotherapy

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Background: Venous thromboembolic events (VTEs) remain one of the most common causes of morbidity and mortality in cancer patients. Various risk scores were developed to help oncologists in the decision-making process relating to VTE in this challenging group of patients.

Methods: We retrospectively analyzed a group of 124 cancer patients diagnosed with VTE between September 2012 and June 2017 in M-Skłodowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland and selected patients receiving chemotherapy (n = 72). We compared the patients KHORANA, PROTECHT and CONKO scores in order to determine which of them would be more precise in VTE prediction during chemotherapy. Statistical analysis was made using descriptive statistics, differences between scales were tested using chi-squared test applying Bonferroni correction.
Results: VTE's were observed mainly during chemotherapy treatment (n = 72, 58.1%). VTE's occurred significantly more frequently in patients who received Cisplatin- or Gemcitabine-based chemotherapy (p < 0.05). In 27 (21.8%) cases VTE was the first manifestation of the disease and/or appeared during the diagnostic process. Most of the patients (69.64% - 88.89% depending of the scale) were classified as having low-intermediate risk, without the potential need for thromboprophylaxis use. The PROTECHT score was the best indicator to discriminate between patients with high or low-intermediate risk, followed by the CONKO score and finally by the KHORANA score. The PROTECHT score more often assigned patients to the “high-risk group” and this difference was statistically significant comparing with the KHORANA score; p = 0.016 (Table).

Table: 1723P

<table>
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<th>CONKO</th>
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<td>N</td>
<td>%</td>
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Conclusions: The PROTECHT score discriminated better between low- and high-risk patients and appeared to have the highest sensitivity. The implementation of VTE prophylaxis in patients assessed as high-risk patients, according to the PROTECHT score, could potentially prevent the largest amount of VTEs.

 disclosure: All authors have declared no conflicts of interest.

**References:**

2. Skladowska-Curie Memorial Cancer Center and Institute, Warsaw, Poland.
3. Personalised care is the current practice of treating cancer patients. Taste changes during chemotherapy also should be personalised depending on changes observed during chemotherapy. We attempted the same using a survey in each patient of chemotherapy at our center. This is first of its kind from India to the best of our knowledge.
4. Methods: Every patient coming for chemotherapy at our center was given one page survey along with consent form. Survey included: specifying taste changes for sweet, salt, bitter and umami. Taste of water was included. Based on survey findings, nutritional advice was given to patient. Feedback from patient also was taken about food items they like, religious belief and any other preferences. Weight loss and albumin level was checked during each chemotherapy.
5. Results: Total 71 patients participated in the study. 24 makes and 47 females. Age range: 13 to 77. Diagnosis: breast: 17; ovary:14; GL:9; hematological:6; head neck:5; lung:4; CNS:3; gynecological:1.
6. Improvement in fatigue and other symptom scores were seen to be statistically significant. Both drugs individually improved the same, as compared to baseline. Improvement in fatigue and other symptom scores were seen to be statistically significant in megestrol acetate arm. There is no significant difference in side effect profiles of both dexemethasone and megestrol acetate arms except for difficulty in standing from sitting position and nausea and vomiting.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**1724P**

**Role of megestrol acetate versus dexamethasone for improvement in appetite in patients with cancer associated anorexia cachexia: A randomized controlled pilot trial**

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Background: Loss of appetite, also known as anorexia, is a frequent and distressing symptom in patients with advanced cancer and other life-limiting illnesses. Prolonged periods of anorexia can lead to both serious physical and psychological distress to patients and their families, which ultimately can contribute to a poorer quality of life. This study compare the clinical benefits between Dexemethasone and Megestrol acetate in an Indian setting, its positive impact on appetite, QOL, and lean body mass.

Methods: A prospective, randomized controlled pilot study conducted in outpatient clinic of Palliative Medicine from September to December 2015. Registered adult advanced cancer patients meeting the inclusion criteria and exclusion criteria were assessed for anorexia, measured by ESAS scale, lean body weight (by Hume’s Formula) and QOL (EORTC-QOL PAl5). Patients received either Dexemethasone (4mg) or Megestrol acetate (60mg in divided doses) for 21 days. No associated appetite stimulants or multivitamins were prescribed to study patients. All patients were encouraged to eat normal diet and provided standard medical care. Follow up done at days 7, 21 and 35.

Results: Total 40 patients were enrolled in the study. Patients in both groups showed statistically significant improvement in appetite, lean body weight and quality of life at weeks 3 and 5, compared to baseline. However, study failed to show any significant difference for primary (appetite improvement) and secondary (lean body weight and quality of life) objectives between two groups, at weeks 3 and 5. Dexemethasone was found to be associated with more side effects.

Conclusions: Comparison between Megestrol acetate and dexamethasone failed to show any statistical-significant difference in improvement of anorexia, lean body weight and quality of life. Both drugs individually improved the same, as compared to baseline. Improvement in fatigue and other symptom scores were seen to be statistically significant in megestrol acetate arm. There is no significant difference in side effect profiles of both dexemethasone and megestrol acetate arms except for difficulty in standing from sitting position and nausea and vomiting.

Clinical trial identification: CTRI: RE/2015/10/009871.

Legal entity responsible for the study: Tata Memorial Hospital Mumbai.

Funding: Tata Memorial Hospital Mumbai.

Disclosure: All authors have declared no conflicts of interest.

**1726P**

**Population pharmacokinetics (PPK) of anamorelin (ANAM), an oral selective ghrelin receptor agonist**

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Background: ANAM, in advanced clinical development, showed benefits in cachectic patients with advanced non-small cell lung cancer (NSCLC). Typical values (TV) of ANAM PPK parameters, effects of demographic and physiopathologic covariates on PK parameters and their variability, and individual ANAM steady-state PK profiles in patients were assessed by PPK modeling.

Methods: Cachectic (body mass index <20 kg/m² or ≥ 5% weight loss in prior 6 months) NSCLC patients (ROMANA 1 [NCT01387269; N = 477]) were randomized 2:1 to 100 mg once daily oral ANAM/placebo up to 12 weeks. Sparse blood samples were collected (day 45, 0.3–6 h post-treatment) in 70 patients consenting to the PPK analysis. For modeling purposes, patients PK dataset was enriched with PK profiles from phase 1 (healthy subjects) and phase 2 studies. The PPK analysis included 243 PK profiles, 70 of which were from ROMANA 1. Non-linear mixed effect modeling with first-order conditional estimation with interaction was used for the PPK analysis. Correlations between ANAM PK parameters and continuous or categorical covariates were assessed by Spearman’s correlation coefficient or analysis of variance models, respectively. Individual steady-state ANAM PK profiles in the 70 patients were simulated by post-hoc empirical Bayes estimates of ANAM PK parameters, and used to assess ANAM exposure and elimination.

Results: The final model selected was a two-compartment model with first-order absorption and lag time, and no covariates as fixed effects. Patient vs healthy subject status was considered to cause no significant difference. TV of PPK parameters for absorption rate constant (0.59 h⁻¹), lag time (0.248 h), volume of central (135 L) and peripheral (678 L) compartments, systemic clearance (CL/F, 49.5 L/h), and...
inter-compartmental clearance (8.8 L/h) were characterized by low relative standard errors (1.6%–15.9%). In patients, predicted ANAM peak plasma concentration, exposure (AUC0–24), and CL/F averaged 675 ng/mL, 2775 ng h/mL, and 46.1 L/h, respectively.

Conclusions: The final PPK model described ANAM’s PK profile in healthy subjects and patients, and is suitable for predicting ANAM exposure in various clinical settings.

Clinical trial identification: NCT0187269.

Editorial acknowledgement: Editorial and medical writing assistance was provided by Oana Drapciuc, PhD, CHMP, TRM Oncology, The Hague, The Netherlands, funded by Helsinn Healthcare (SA), Lugano, Switzerland.

Legal entity responsible for the study: Helsinn Therapeutics (U.S.), Inc.

Funding: Helsinn Therapeutics (U.S.), Inc.

Disclosure: A. Bernardeggi: Employee; Helsinn Healthcare SA. S. Kaasa: Holds stocks; EIR Solution A/S. R.J.E. Skipworth: Research funding; Novartis. All other authors declared no conflicts of interest.

Background: As of today, health care providers (HCP) have little evidence in research to guide decisions for parenteral nutrition (PN) therapy in cancer patients. Uncertainties prevail concerning both the initiation and the duration of the treatment, as well as the benefits of the intervention. The aim of this study was to explore community HCP’s experiences of benefits and challenges with PN in cancer patients.

Methods: An 18-item online survey was emailed to 309 community care HCP. In two of the questions, respondents were asked to describe in free text their positive and negative experiences with PN therapy in cancer patients, and these answers were analysed by use of content analysis.

Results: Out of total 135 responses, 102 (75.6%) reported experience with cancer patients receiving PN and completed the entire survey. The majority of the respondents were female (93%); nurses/cancer nurses (86.4%); and worked in home care (48.5%), palliative care (48.5%), or nursing homes (37.9%). The most common positive effect of PN reported was an improvement that increased patients’ quality of life through increased vitality, increased hope and the ability to spend time at home (reported by 40.2%). Other reported positive effects were the experience that PN improved tolerance to, and enhanced recovery after, cancer treatment; reduced the family’s eating-related distress; and was regarded a good treatment alternative for patients with symptoms such as swallowing problems, nausea or obstruction. The most common negative effect reported were the difficulties of knowing when to terminate PN, primarily because this removes patients’ and family’s hope (reported by 26.4%). Poor information to patients and their family at initiation of PN, made termination even more difficult. PN therapy was also reported to cause side effects such as fluid retention and oedema and prolonging suffering at end of life.

Conclusions: Despite a limited evidence-base in support of benefits of PN treatment in cancer patients, HCP in this study reported several positive effects based on their clinical experience. Some of the positive effects were related to earlier phases of the disease, while the negative effects mainly regarded communication and decision challenges when ending PN therapy at the end of life.

Legal entity responsible for the study: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

Disclosure: All authors have declared no conflicts of interest.

Assessment of anorexia and weight loss in newly diagnosed upper gastrointestinal cancer patients with localised and metastatic disease, using the functional assessment of anorexia cachexia therapy anorexia/cachexia subscale (FAACT A/CS)

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Background: Anorexia often predisposes to weight loss, leading to poor outcomes in cancer patients. Therefore early recognition is clinically important. Although no gold standard exists to diagnose anorexia, the FAACT A/CS has been suggested to identify cancer patients with anorexia. A previous study has validated the cut-off score of ≤37 to diagnose anorexia. In our study we assessed the incidence of anorexia and weight loss in patients with gastric and gastro-oesophageal junction (GOJ) cancer based on the FAACT A/CS.

Methods: Newly diagnosed gastric and GOJ adenocarcinoma patients of all stages, attending outpatient clinics at The Christie Hospital NHS Foundation Trust, from September 2016 to December 2017 completed the FAACT A/CS at initial consultation. BMI and weight change over the last 3–6 months were recorded as standard of care. SPSS was used for statistical analysis.

Results: Based on the FAACT A/CS questionnaire, 127 (69%) out of the 182 patients included in this analysis had anorexia. The mean anorexia score of all the patients was 29.3 (4–48). The incidence of anorexia was greater in metastatic compared to non-metastatic patients (82% vs 52%; P < 0.01). Overall, the metastatic group achieved lower mean anorexia scores than the non-metastatic group (25.9 vs 34.7; P < 0.01).

Patients in the metastatic group had lower mean body weight compared to those in the non-metastatic group (74 vs 79 kg, P = 0.069). Their mean BMI was also lower (25 vs 27, P = 0.055). 76% of the metastatic group and 33% of the non-metastatic group had ≥5% of weight loss that may classify them as high risk for cancer cachexia, despite their normal or high BMI (p < 0.01).

Conclusions: 69% of the patients with gastric/GOJ cancer who attended clinic were anorexic on initial consultation. The incidence of anorexia was higher in patients with metastatic disease (82%). Assessment of anorexia using the FAACT A/CS along with classification of weight loss prior to treatment should be integrated into nutritional assessment. BMI used independently may be unsuitable for identifying patients at nutritional risk.

Legal entity responsible for the study: The Christie NHS Foundation Trust.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
1730P Current use of clinical nutrition in oncology patients: Real world evidence from big data in Italy

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Background: In cancer patients, research indicates that approximately half of selected patients may suffer from malnutrition. Insufficient nutritional intake, muscle protein depletion and systemic inflammation are key clinical problems. Little is known about the current use of clinical nutrition (CN) in the real world. We set out to investigate the use of CN in patients with metastasized cancer in Italy.

Methods: This observational, retrospective study used an integrated administrative database from 10 Italian Local Health Units covering 5.9 million people. Between 2009 and 2015, CN use, based on Anatomical Therapeutic Chemical Classification codes and ICD-9-CM procedural codes for Enteral/Parenteral Infusion of Concentrated Nutritional Substances and at home nutritional product prescription was examined in patients with metastatic head and neck, gastrointestinal, respiratory, genitourinary or hematologic malignancies (ICD-9-CM diagnosis).

Results: Out of 58,468 metastatic cancer patients with the diagnoses of interest, only 8.2% received clinical nutrition (89% had parenteral nutrition (PN)). Only 4.9% of patients who received CN had concomitant chemotherapy. Among those who received CN, only 11% of patients were diagnosed with malnutrition. The mean time between the diagnosis of metastasis and first use of CN and between the first use of CN and death were 6.6 and 3.5 months, respectively. About half of the patients commenced CN therapy in their last 20 days. Receiving PN was associated with a statistically significant improvement in survival of over 3 months in patients with gastrointestinal and genitourinary malignancies.

Conclusions: CN is under-utilized among cancer patients with metastasis and there is a discrepancy between malnutrition diagnosis rates and uptake of clinical nutrition, which appears to have been used mainly as an end of life measure. Overall, our big data highlights an important unmet need and potential for improved care for malnutrition diagnosis and earlier nutritional care, which may improve outcomes of cancer patients.

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Legal entity responsible for the study: Baxter S.p.A, Zürich, Switzerland.

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1731P Nutritional cancer care: Slowly evolving clinical practice reveals regional and professional HCP variability

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Background: Cancer-related weight loss correlates with poor anticancer treatment outcomes and reduced quality of life (QoL). A survey at ESMO 2016 suggested that integration of nutritional care in clinical practice is inadequate. Outcomes of a follow-up survey conducted at ESMO 2017 are reported.

Methods: ESMO 2017 delegates visiting the Nutricia booth took part in the survey. The 2017 survey questions were identical to 2016, except 1 new question: “What source helps to determine patient need for nutritional support?”

Results: The 1,894 participants (75% medical oncologists; 64% European) demonstrated consistent overall practice patterns (malnutrition screening and assessment methods, eligibility criteria for nutritional support, goals of nutritional treatment, multimodal management) between 2016-2017. Unfortunately, >40% of HCPs still underestimate the impact of malnutrition on anticancer Tx continuity or toxicity, and QoL or function. Timely and individual tailored dietary advice to minimize/avoid weight loss increased significantly (36% to 49%). P < .001, surpassing medications, but only in Western countries (53%). Further geographic differences were seen. For example, in Africa (n = 183) compared with Europe (n = 1,215), nutritional aspects were more often considered in tumor boards (70%, 54%), but physical exercise programs were less often combined with nutrition (29%, 42%); perceived impact of malnutrition was more about anticancer treatment discontinuation (67%, 28%) than toxicity (44%, 62%); and meetings (42%, 33%) surpass guidelines (44%, 73%) for nutritional decision-making. Concerning HCP specialty, nutritionists (n = 20) estimated the impact of malnutrition 50% less than medical oncologists, and consulted guidelines less (26%, 60%). Surgeons (n = 64) and radiation oncologists (n = 65) judged eligibility for nutritional support and its goals differently than medical oncologists, with less emphasis on weight loss and QoL.

Conclusions: HCP recognition of the impacts of malnutrition and its assessment remains insufficient, while dietary advice is increasing. Our survey data may suggest tailoring nutritional care recommendations at regional and HCP levels.

Editorial acknowledgement: Medical writing support was provided by Joanne Franklin, PhD, CMP, from TRM Oncology, The Hague, The Netherlands, and funded by Nutricia Advanced Medical Nutrition.

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Funding: Nutricia Advanced Medical Nutrition.

Disclosure: F. Strasser: Honoraria: Danone, Grunenthal, Helsinn, ISIS Global, Mundipharma, Novartis, NovoPharm, Obersia, Ono Pharmaceutical, Fioxus Therapeutics, Prime Oncology, Sunstone Capital, Vifor; Clinical research industry grants: Celgene, Fresenius, Helsinn. A. O’Callaghan: Corporate-sponsored research: Nutricia Medical Employee: Nutricia Medical. M.B. Sawyer: Honoraria: Nutricia Advanced Medical Nutrition. S. Kaasa: Stock ownership: Eis Solution. All other authors have declared no conflicts of interest.

1732P Unidentified cachexia patients in the oncologic setting: Cachexia UFO’s do exist

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Background: Cachexia is an important outcome-modulating parameter in cancer patients. In the context of a randomized controlled trial on cachexia and nutritional therapy, the TiCaCONCO trial (NCT03058107 on Clinicaltrials.gov), the contacts between cancer patients and health care practitioners/oncologists were screened. The aim of this retrospective study is to identify in the charts the input of data on body weight (necessary to identify cachexia stage), relevant nutritional data and nutritional interventions triggered or implemented by oncologists and dieticians.

Methods: In a tertiary, university oncology setting, over a time span of 6 months (34 weeks), the charts of patients admitted to an oncology, gastroenterology or abdominal surgery unit were screened for the presence of information contributing to a cancer cachexia diagnosis. Data (patient characteristics, tumor type and location) was gathered.

Results: We analyzed 9694 files. In >90% of patients, data on body weight was present. 118 new diagnoses of cancer were present in 9694 screenings (1.22% of patient contacts). Information on weight evolution or nutritional status was absent in 46% of cases. In contacts between oncologists and cancer patients, at the time of diagnosis, the prevalence of cachexia was 42%. In 14% of these patients, no nutritional information was present in the notes. In those 50 patients with cachexia, a nutritional intervention was initiated by the physician in 8 patients (16%). Nutritional interventions were documented in the medical note in 9% of the overall study population. Dieticians made notes regarding nutrition and weight in 42% of patients.

Conclusions: Newly diagnosed cancer patients are not systematically identified as being cachetic and if they are interventions in the field of nutrition therapy are largely lacking. Important barriers exist between Oncologists and Nutrionists, the former being mandatory to the success of a nutrition trial in cancer.

Clinical trial identification: NCT03058107.

Legal entity responsible for the study: Elisabeth De Wele.

Funding: Baxter, Nutricia.

Disclosure: All authors have declared no conflicts of interest.

1733P The effect of sarcopenia on acute chemotherapy toxicity in gastrointestinal cancer patients undergoing systemic therapy

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Background: We aimed to evaluate the effect of sarcopenia on tolerability of chemotherapy during systemic treatment of pts with gastrointestinal system cancer (GISC).

Abstracts
Table 1733P

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Sarcomeric (n=36 %)</th>
<th>Non-sarcomeric (n=80 %)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia Yes, No</td>
<td>33.3, 66.7</td>
<td>58.8, 41.3</td>
<td>0.011</td>
</tr>
<tr>
<td>Neutropenia Yes, No</td>
<td>55.6, 44.4</td>
<td>72.5, 27.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia Yes, No</td>
<td>63.9, 36.1</td>
<td>67.2, 32.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Delay of chemotherapy Yes, No</td>
<td>27.8, 72.2</td>
<td>43.0, 57.0</td>
<td>0.11</td>
</tr>
<tr>
<td>Dose reduction Yes, No</td>
<td>28.4, 71.4</td>
<td>37.5, 62.5</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Conclusions: In GISC pts, non-sarcomeric at diagnosis BMI remains unchanged after 2-3 cycles of chemotherapy. However, muscle loss developed in 1/3 of them. Pts who received sarcomeric had lower rates of chemotherapy-associated toxicity. The reasons for this difference should be further investigated. However, the different lipopholic and hydrophilic properties of chemotherapy agents might be one of possible explanation.

Legal entity responsible for the study: Yildirim Beyazit University, Medical Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1734P Early detection of skeletal muscle atrophy using a multiple plasma-free amino acid index in the advanced aged patients with advanced pancreatic cancer

S. Mitsunaga 1, M. Takada 1, S. Nishikawa 1, A. Imaizumi 2, M. Ishii 1, M. Ikeda 1

Background: Loss of skeletal muscle mass (SMM) is related to aging, pancreatic cancer (PCa) and the deterioration of symptoms and quality of life (QOL). This study aimed to identify the factors associated with SMM atrophy in PCa patients during first-line chemotherapy. At the end of our study, the biomarker of early detection of SMM atrophy was determined.

Methods: Patients with treatment-naïve advanced PCa were enrolled. The whole body skeletal muscle index (wSMI) and SMM were measured at baseline and one month later using bioclinical impedance analysis and the MF Anderson Symptom Inventory, respectively. Each patient was assigned to an atrophy or a non-atrophy group based on the change in wSMI after one month. The concentrations of 19 PFAs were measured using liquid chromatography–mass spectrometry. An index consisting of the PFAs at baseline was evaluated for its ability to discriminate atrophy one month later.

Results: The advanced aged group (≥70 years, N=52) showed a decrease of wSMI (-35.3 kg/m² in mean) to compare to younger group (<60 years, N=34, 0.35 kg/m², P=0.09). The change of wSMI in the middle aged group (≥60 and <70 years, N=75) was 0.03 kg/m² in mean. Atrophy was observed in 60% of the advanced aged group. The worsened activity, fatigue, and appetite loss became more severe after one month in the advanced aged group with atrophy. The areas under the curves (AUCs) based on a receiver operating characteristic (ROC) curve analysis of the PFAs index for discriminating atrophy from non-atrophy were calculated using simple or multiple PFAs. The best AUC for the multiple PFAs indices was 0.83 in the advanced aged group.

Conclusions: SMM atrophy was related to aging, the deteriorated activity, fatigue and appetite loss in patients with advanced PCa during first-line chemotherapy. A multiple PFAs index is a promising biomarker for the early detection of atrophy.

Legal entity responsible for the study: National Cancer Center.

Funding: Ajinomoto Co., Inc.

Disclosure: M. Takada, S. Nishikawa, A. Imaizumi, M. Ishii: Employee: Ajinomoto Co., Inc. All other authors have declared no conflicts of interest.

1735P Trajectory of skeletal muscle index (SMI) loss during palliative systemic treatment (Tx) predicts time to progression (TTP) in metastatic colorectal cancer (mCRC) patients


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Background: In mCRC patients, SMI loss is suggested to be related with poor survival. Little is known on the trajectory of SMI and its relation with TTP. The CAIRO3 study (Simkens, Lancet 2015) randomized 557 mCRC patients after 6 cycles CAPOX-B to maintenance CAP-B or observation (obs). Upon 1st disease progression (PDI), CAPOX-B or other Tx was reintroduced until 2nd progression (PDI2). Here we study if SMI trajectory predicts TTP in CAIRO3.

Methods: 104 randomly selected CAIRO3 patients (mean age 65.4±8.3 years) were analyzed for SMI (skeletal muscle area at the L3 level in cm²) using 8-weekly repeated CT scans (514 in total). Joint longitudinal-survival modeling, using mixed effects models for longitudinal SMI measures and Cox regression models for TTP analysis, was used to estimate hazard ratios (HR) for absolute SMI and SMI trajectory (per unit SMI-loss per month) during two time periods: p1) from randomization (PD0) to p2) from PDI1 to PDI2. SMI trajectories were modeled throughout each time period and change was investigated at 9 and 4 weeks pre-PD.

Results: During p1 (less intensive CAP-B / obs), patients gained SMI (mean ±1.1 ±3.2 cm²), Absolute SMI was not related with PDI (HR SMI 9 weeks pre-PDI 0.99 [0.96-1.02], 4 weeks pre-PDI 1.09 [0.96-1.02]). A decrease in SMI preceding PDI1 showed a higher, but non-significant, risk of early PDI (HR SMI 9 weeks pre-PDI 1.04 [0.83-1.26], 4 weeks pre-PDI 1.53 [1.01-2.55]). During p2, (more intensive CAPOX-B / other Tx), patients lost SMI (mean -2.7 ± 3.4 cm²). Both SMI and SMI trajectory were significantly related to PDI2 (HR SMI 9 weeks pre-PDI 1.23 [1.01-1.08], 4 weeks pre-PDI 1.04 [1.01-1.08], SMI change 9 weeks pre-PDI 2.13 [1.07-1.75], 4 weeks pre-PDI 1.03 [0.85-1.82]).

Conclusions: In mCRC patients, a decrease in SMI tended to predict shorter TTP during less intensive CAP-B or obs. SMI and SMI trajectory predicted shorter TTP during more intensive CAPOX-B or other reintroduction Tx. This large longitudinal analysis is the first to show that the trajectory of SMI loss predicts early TTP. These data suggest that SMI preservation may be a therapeutic goal.

Clinical trial identification: NCT00442687.

Funding: Province of Utrecht, The Netherlands and the Dutch Colorectal Cancer Group (DCCG).

Disclosure: B.D. Dorrestein, M. Jadourn: Employee: Nutricia Research. All other authors have declared no conflicts of interest.

1736P Clinical impact of whey protein and nutritional counseling in gastrointestinal cancer patients

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Background: Malnutrition frequently affects gastrointestinal (GI) cancer patients. It is known how protein supplementation could prevent loss of lean body mass and sarcopenia. Therefore, we present a placebo-controlled study, to explore the effect and safety of whey proteins in GI cancer patients.

Methods: Patients with GI cancer referred for 5-fluorouracil based chemotherapy, without metabolic alteration, were considered eligible. After informed consent was obtained, they were blind-randomized 1:1 to whey protein (PROLYOTIN®) (arm A) or placebo (arm B). Patients were assessed, before chemotherapy, after 3 and 6 months, on a physical-nutritional examination, Body Impedance Assessment, MNA® and MUST questionnaire. At the same time frames, tumor characteristics, dietary practices and laboratory values were collected by a specialist team of medical oncologists and dieticians.
Impact of taste alterations during systemic anti-tumour therapy on the liking of oral nutritional supplements with adapted flavours

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Background: Taste alterations are often reported by cancer patients, especially during systemic anti-tumour therapy, with a negative impact on food intake and quality of life. Little is known about the relation between taste alterations and taste preferences. This study aimed to explore the occurrence of taste alterations (i.e. changes in taste perception or intensity) in patients receiving systemic anti-tumour therapy, and to investigate overall likings of oral nutritional supplements (ONS) with flavours designed to better address the needs of patients with taste alterations.

Methods: Fifty adult patients with cancer undergoing systemic anti-tumour therapy were recruited. Exclusion criteria were allergies/intolerances to ONS ingredients or coexisting morbidities affecting taste or smell. Participants filled out a questionnaire on taste alterations, and evaluated overall liking of 5 Nutridrink Compact Protein on a 10-point scale via a sip test (hot tropical ginger, hot mango, cool red fruits, cool lemon and neutral). Permutation analysis was performed to investigate differences between patients with and without taste alterations.

Results: Various types of cancer and treatments (n = 34 chemotherapy, n = 5 chemoradiation, n = 4 immunotherapy, n = 2 targeted therapy, n = 5 other form of systemic therapy) were observed. Thirty patients (60%) reported taste alterations. Overall liking scores were: cool red fruits 6.8 ± 1.7 (mean ± SD); neutral 6.5 ± 1.9; hot tropical ginger 6.0 ± 2.0; cool lemon 5.9 ± 2.3 and hot mango 5.7 ± 2.0. Larger variation in overall liking per product was observed in patients with taste alterations (range 4.9 - 7.9) versus without taste alterations (range 5.9 - 6.5). Posthoc analysis showed that taste alteration was associated with a difference in overall liking for neutral (Δ = 1.0; p < 0.05) and hot mango flavours (Δ = 1.1; p < 0.05).

Conclusions: More than half of patients undergoing anti-tumour therapy experienced taste alterations. Patients without taste alterations were less discriminant in liking score compared to patients with taste alterations. These findings indicate that the presence of taste alterations should be taken into account when selecting or developing ONS for cancer patients.

Legal entity responsible for the study: University Medical Center Groningen, Groningen, the Netherlands.

Funding: Danone Nutricia Research.


1738P

Table: 1738P Multivariate logistic regression of factors associated with weight gain after BC in the overall population (N = 4875)

<table>
<thead>
<tr>
<th></th>
<th>T1 (3-6 months after treatment)</th>
<th>T2 (12 months after treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% pts who gained weight</td>
<td>aOR* (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) &lt;50</td>
<td>50-65 &gt;65</td>
<td>25 17 8</td>
</tr>
<tr>
<td>BMI at diagnosis (kg/m2) Underweight (&lt;18.5)</td>
<td>25 18 14 16</td>
<td>1.4 (1.1-1.9) ref</td>
</tr>
<tr>
<td>Normal (18.5-24.9) Overweight (25.0-29.9)</td>
<td>25 18 14 16</td>
<td>26 22</td>
</tr>
<tr>
<td>Obese (≥30)</td>
<td>25 18 14 16 14</td>
<td>-</td>
</tr>
<tr>
<td>Level of Physical Activity†</td>
<td>16 17</td>
<td>1.0 (0.8-1.2) ref</td>
</tr>
<tr>
<td>Failing to reach 10 Reach/maintain ≥10</td>
<td>21 12</td>
<td>1.1 (0.7-1.5) ref</td>
</tr>
<tr>
<td>Receipt of chemotherapy Yes No</td>
<td>21 12</td>
<td>1.3 (1.1-1.7) ref</td>
</tr>
<tr>
<td>Receipt of endocrine therapy Yes No</td>
<td>16 19</td>
<td>1.1 (0.7-1.5) ref</td>
</tr>
<tr>
<td>Weight gain at T1 Continuous, for 1 Kg gained</td>
<td>1.6 (1.5-1.6)</td>
<td></td>
</tr>
</tbody>
</table>

*aOR* = adjusted odds ratio; CI = confidence interval.  
†Adjusted for all variables in the table + monophasal status, age, sex, weight loss, education, smoking status, alcohol, tumor stage, subtype, breast and axillary surgery.

In Metabolic Equivalent of Task (MET)-hours/week, based on World Health Organization recommendations on physical activity and expressed as change in physical activity behavior from diagnosis to T1 and to T2, respectively.
endocrine therapy (ET). GRTM found that the majority of overweight and obese pts remained so over time. By T2, weight increased in 24% pts (median gain = 5 kg [range 2-55]), was stable in 63% pts and decreased in 13% pts in the overall population. Factors associated with higher risk of significant weight gain by T2 included age <50 vs >50 (adjusted odds ratio 2.1 [95% Confidence Interval 1.3-3.2]), receipt of CT vs no (1.6 [1.3-2.1]), receipt of ET vs no (1.7 [1.1-2.7]), PA < 10 MET-hours/week vs ≥ 1.3 (1.1-1.6) and having already gained weight by T1 (for each Kg gained, 1.6 [1.5-1.6]) (Table).

Conclusions: In this large contemporary epidemiology study of French BC survivors, a significant proportion of pts were overweight or obese at dx, and one in four of all pts gained substantial weight after treatment. Weight gain is particularly common in pts who are younger, treated with CT or ET and less physically active. Our data will inform weight loss survivorship programs targeting pts at higher risk of overweight, obesity and weight gain after BC.

Clinical trial identification: NCT1993498.

Legal entity responsible for the study: UNICANCER.

Funding: Has not received any funding.

Disclosure: A. Di Meglio: Recipient of the 2017 ESMO Clinical Research Fellowship Award. I. Vaz-Luis: Recipient of research grants from Susan Komen for the Cure and the "Association pour la recherche sur le cancer (ARC)". All other authors have declared no conflicts of interest.

Table 1739P Prevalence of severe dysfunctions and symptoms at BC diagnosis and post treatment by weight change category among obese pts in CANTO (N = 892)

<table>
<thead>
<tr>
<th>PRO Domain</th>
<th>Overall</th>
<th>Post treatment</th>
<th>Gain (14.0)</th>
<th>Stable (67.0)</th>
<th>Loss (19.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>82.8 76.0 56.1</td>
<td>88.9 78.3 75.9</td>
<td>92.2 82.6 78.3</td>
<td>88.6 78.7 75.8</td>
<td>87.4 73.6 74.2</td>
</tr>
<tr>
<td>All domains combined ≥ 1 Function or Symptom ≥ 1 Symptom</td>
<td>34.2 -</td>
<td>35.7 -</td>
<td>40.7 Ref</td>
<td>37.8 0.73 (0.44-1.21)</td>
<td>24.5 0.62 (0.33-0.80)</td>
</tr>
<tr>
<td>Global Health Status a % pts aOR (95% CI)</td>
<td>10.9 -</td>
<td>20.4 -</td>
<td>23.7 Ref</td>
<td>20.8 0.59 (0.33-1.10)</td>
<td>16.5 0.43 (0.20-0.95)</td>
</tr>
<tr>
<td>Physical Function b % pts aOR (95% CI)</td>
<td>34.0 -</td>
<td>29.5 -</td>
<td>36.3 Ref</td>
<td>29.7 0.67 (0.40-1.13)</td>
<td>23.4 0.53 (0.28-1.00)</td>
</tr>
<tr>
<td>Emotional Function b % pts aOR (95% CI)</td>
<td>6.2 -</td>
<td>14.4 -</td>
<td>22.6 Ref</td>
<td>13.8 0.56 (0.31-1.03)</td>
<td>10.3 0.42 (0.19-0.92)</td>
</tr>
<tr>
<td>Pain b % pts aOR (95% CI)</td>
<td>14.3 -</td>
<td>29.9 -</td>
<td>43.5 Ref</td>
<td>29.3 0.46 (0.28-0.75)</td>
<td>22.0 0.29 (0.15-0.55)</td>
</tr>
<tr>
<td>Dyspnea b % pts aOR (95% CI)</td>
<td>11.0 -</td>
<td>17.2 -</td>
<td>33.6 Ref</td>
<td>16.0 0.32 (0.18-0.56)</td>
<td>9.5 0.16 (0.07-0.35)</td>
</tr>
<tr>
<td>Body Image b % pts aOR (95% CI)</td>
<td>13.6 -</td>
<td>28.7 -</td>
<td>40.0 Ref</td>
<td>27.4 0.60 (0.31-1.13)</td>
<td>25.0 0.45 (0.23-0.87)</td>
</tr>
<tr>
<td>Systemic therapy side effects b % pts aOR (95% CI)</td>
<td>3.9 -</td>
<td>15.3 -</td>
<td>21.7 Ref</td>
<td>14.6 0.62 (0.33-1.18)</td>
<td>13.0 0.47 (0.21-1.04)</td>
</tr>
</tbody>
</table>

Method: We used a prospective French nationwide longitudinal cohort (CANTO, NCT1993498) to select obese (Body Mass Index ≥ 30 kg/m^2) stage I-III BC pts diagnosed from 2012-14. Nurses assessed weight change from BC diagnosis (dx) to 3-6 months post treatment (surgery, chemio (CT) or radiotherapy (RT)). Defined as weight gain (≥ 5%), stability (± 5%) or loss (≤ 5%). PROs were assessed by EORTC QLQ C30/BR23. Functional scores ≤60 and symptom scores ≥40 defined severe dysfunctions and symptoms, respectively (Giesinger, 2016). Multivariate logistic regression explored associations of weight change with severe PROs.

Results: We included 892 obese pts, 19% of CANTO population. Mean age was 59 y (range 27-87). 92% received RT, 54% CT and 84% endocrine therapy. Mean BMI at dx was 34.5 (range 30.0-59.0). 14% pts gained weight, 67% were stable and 19% lost weight post treatment. There was a significant differential reduction in physical activity in 39% pts who gained weight, 37% pts with stable weight, and 28% pts who lost weight (mean change [Standard Deviation] was 35 [77], 4 [66] and 4 [69] MET-hours/week, respectively [p < 0.06]). Prevalence of any severe dysfunction or symptom was 83% at dx and further increased over time, being highest in pts who gained weight. Weight loss was associated with lower odds of severe dysfunctions or symptoms vs weight gain, consistently across all PROs (Table).

Conclusions: The majority of obese pts report severe physical or psychological distress at BC dx and post treatment. A comprehensive approach to the care of obese BC pts should address the burden of morbidity caused by obesity and further post treatment weight gain. Weight loss may prevent physical and psychological deterioration, thus lifestyle interventions of purposeful weight loss should be encouraged.

Clinical trial identification: NCT1993498.

Legal entity responsible for the study: UNICANCER.

Funding: Has not received any funding.

Disclosure: A. Di Meglio: Recipient of the 2017 ESMO Clinical Research Fellowship Award. I. Vaz-Luis: Recipient of research grants from Susan Komen for the Cure and the "Association pour la recherche sur le cancer (ARC)". All other authors have declared no conflicts of interest.
Methods: Clinical information prospectively collected on STAR questionnaires during 11 months were compared using Mantel-Haenszel Χ² (p-values) in the 2 groups (nurse call versus web self-questionnaire). Numbers of symptoms were classified into 3 categories: 0, 1 and at least 2 symptoms for each grade of severity (NCI-CTC-AE, version 4.0).

Results: From May 2017 to April 2018, 622 (67.1%) of 928 patients admitted to daily hospital for a chemotherapy cycle were included in the STAR program. Monitoring was ensured by nurse phone calls for 477 patients (76.7%) versus 145 (23.3%) by web questionnaires. Patient’s average age (66±11 years) and sex repartition (61% of men) were not different in the 2 groups. The overall rate of response was significantly better with nurse calls (84.8%) than with web questionnaires (78.2%) (p < 0.0001). Global incidence of grade 3 and grade 4 toxicities was similar in the two groups (p = 0.1 and 0.06 respectively) whereas web questionnaires mentioned significantly more grade 2 and grade 1 toxicities (p < 0.0001). When chemotherapy cycle was cancelled for a clinical reason, this information was similarly mentioned in the 2 groups (p = 0.35). Overall, global rate of delayed chemotherapy did not differ between the two groups.

Conclusions: Web questionnaires appear to be an interesting and reliable method for patient clinical monitoring. To take full advantage of STAR program, the importance of clinical evaluation should be reminded to patients to increase the rate of response. Web monitoring improvement in grade 1-2 toxicities screening should be explained by a better patient understanding and will be investigated in further studies.

Legal entity responsible for the study: Florian Scotti.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1741P Polymedication in elderly cancer patients treated with chemotherapy


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Background: Medication reconciliation (MedRec) including complementary and alternative medicine is considered as an important way to increase the safety of medication use. However, there are few studies in literature showing the impact of an oncogeriatric approach integrating MedRec program in elderly cancer patients (ECP). The objective is to measure the impact of a pharmacogeriatric approach (PGA) on ECP before treatment by chemotherapy.

Methods: A monocentric prospective study was implemented to evaluate the overall survival (OS), rate of readmission hospital (RRH) at 1st and 3rd month and Early Discontinuation of active treatment (ED). These variables were analyzed according to number of reviewed drugs in MedRec and geriatric tools of Comprehensive Geriatric Assessment (CGA).

Results: 144 patients were received in oncogeriatric consultations between 01/2017 and 10/2017 (mean age was 80.9 ± 5.3 years, 52.1 % were men, 48.6 % had metastatic tumors). Main cancers were lung (31.9 %), gastrointestinal (18.1 %), breast and gynecological (16.7 %). At 1st and 3rd month, death rates were 3 % and 12 %, RRH were 11.1 % and 16.3 %. Received treatment was analyzed and 62.5% received systemic treatment after oncogeriatric consultations. Concerning ED at 3rd month, 48 % had prematurely stopped it (because of cancer progression in 14.2 % and infections in 7 %) and 23.6 % reduced dose (because of chemotoxicity in 33 % and geriatric conclusions in 20 %). OS prognostic factors were malnutrition (p = 0.03) and metastatic status (p = 0.05); prognosis factors of early death at 1 month were lymphopenia (p = 0.005) and RRH (p = 0.04), and at 3 months: malnutrition (p = 0.01), ADL dependence (p = 0.03), and RRH (p = 0.01).

Conclusions: To our knowledge, this is the first study evaluating and describing the outcomes of PGA with MedRec and CGA in same time for the ECP. First month death rates and RRH are lower compared to literature in our study. RRH, ADL and nutritional disorder are OS prognostic factors. Full analyses will be presented during the ECP to show the real impact of PGA.

Legal entity responsible for the study: Assistance Publique Hôpitaux de Marseille.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1743P Developing a predictive model for chemotherapy related toxicities in older Asian adults

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Background: Elderly patients (pts) are at increased risk of developing chemotherapy (CTXs) related toxicities. There are several prediction tools including the Cancer and Aging Research Group (CARG) chemotoxicity calculator (CTC) but this has not been validated in the Asian population. The objective of our study is to identify prediction of G3-5 CTX toxicities and evaluate the utility of the CTC in older Asian adults.

Methods: We enrolled cancer pts aged ≥ 70 years, requiring outpatient treatment with chemotherapy at the National University Cancer Institute, Singapore. A comprehensive geriatric assessment was performed and baseline cancer characteristics, including the 11 variables in the CTC were collected prior to the initiation of CTXs. Primary treating oncologists were asked to give an estimated likelihood of CTXs related toxicities. Pts were then followed up to 3 months after completion of treatment and CTX toxicities were recorded.

Results: Amongst the 131 pts (mean age: 75 years; range: 70 – 89), their CA diagnoses include colorectal (CRC) (36; 27.5%), lung (27; 20.6%), non-CRC gastrointestinal (15; 13%), breast (14; 10.7%), genitourinary (10; 7.6%), head and neck (10; 7.6%), gynecological (8; 6.1%) and other (9; 6.9%) cancers. 54 pts (41%) received CTXs with curative intent, and 77 (59%) with palliative intent. The incidence of G3-5 toxicities was 58% (76). The most common toxicities were neuropenia (38; 29%) and anaemia (26; 20%) and there was 1 mortality from CTX related pneumonitis. In the multivariable analysis, the factors associated with the incidence of CTX related toxicities were i) Age > 72 years, ii) GDS (female), iii) Haemoglobin < 10g/dl (Female) < 11g/dl (Male), iv) Limited ability to walk 1 block, iv) Limited social support and v) Disease interference with social activity. Based on this new model comprising the above 5 variables, the area under the receiver operating characteristic curve (ROC) is 0.776, whereas that for the CTC and oncologists’ prediction of CTXs related toxicities were 0.785 and 0.594 respectively.
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Conclusions: Our new model for predicting CTX-related toxicities appears to be comparable to the CTC. In our follow up study, we hope to further validate this model's utility in predicting CTX-related toxicities in our elderly cancer population.

Legal entity responsible for the study: Angela Pang.

Funding: National Medical Research Council (Singapore)

Disclosure: All authors have declared no conflicts of interest.

1744P Palliative local therapy of advanced breast cancer

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Background: Objective: Initial nidus tumor infiltration is often revealed in patients with advanced breast cancer. In such cases, all treatment is focused on improvement of the quality of life. Methods: Special mixture of Linimentum Synthomycin 10% (25 gr) + Tefagur (Florafer) 800 mg was prepared for anti inflammatory and tumor therapy. The mixture was used in bandaging of breast tumor infiltration in 99 patients for 10 days (interval - 20 days). Tumor infiltration in 84 patients -15 cm, in 15 patients > 30 cm. In 3 cases double-sided process was observed. All the patients had low hematological indicator and KPS (40.0%).

Results: After II course of treatment: significant improvement of dynamics of tumor infiltration in 49 (49.5%) patients (reduction of hyperemia, pain syndrome, itching, temperature, etc.). After the III-IV courses: wound cleansing from purulent, formation of granulation areas and improvement of the quality of life in 10 patients (Tumor reduction and full epithelization in 71 (71.7%) patients. After the IV course of local therapy tumor infiltration was reduced by 9 cm in average (Maximum effect was seen in patients with infiltration of 15 cm): KPS average indicator improved from 40.0% to 53.4% (p < 0.05).

Conclusions: 1. Administration of Synthomycin 10% (25 gr) + Tefagur (Florafer) 800 mg for local chemotherapy and anti – inflammatory therapy of breast tumor infiltration contributes to reduction of hyperemia, temperature reaction, itching, supuration, size of nidus, pain syndrome and accordingly improvement of the quality of life (KPS has improved from 40.0% to 53.4%). 2. Practically there are no side effects upon a local chemotherapy of breast.

Legal entity responsible for the study: Tbilisi State Medical University (Georgia).

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1745P General and dedicated cancer emergency room: Clinical and financial implications

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Background: Emergency department (ED) visits among cancer patients (pts) exceed those of the general population; acute oncology teams can influence strategy determining a reduction in ED accesses and hospitalizations. Local services may reflect number and type of admissions often referred to ED. Onco-Hemato Emergency Room (OHER) in Modena Hospital is a service completely dedicated to cancer pts needs integrated with Oncology Department since 2001. Medical team is composed by oncologists and hematologists, from Monday to Friday (08.00-18.00), Saturday (08.00-12.00).

Otherwise pts must refer to ED. We tried to describe pts admitted to OHER between January, 1, 2007 and December, 31, 2017 by cancer types, reasons for visits and percentage of hospitalizations from OHER and ED with financial implications.

Methods: OHER data were obtained through the query of a relational database used to collect medical records, concerning all disease history including hospitalizations and planned evaluations. Pts were received regardless disease stage from suspected tumor to palliative care setting. ED term searches were conducted using a dedicated database.

Results: 28.680 admissions to OHER, of 11.239 pts, 5326 (47%) had a single access, the most recurrent one had 31 visits, 165 (0.6%) died there. According to the site of primary malignancy: digestive tract 24%, lung 16.5%, lymphoma 9%, acute and chronic leukemia 10%, breast 7.2%, colon-rectal 8.4%, urological 8%, myeloma 5%, head neck 4%, melanoma 1.4%, sarcoma 1.7%, hematologic 2.3%, thrombotic purpura 0.2%, other 2.3%. Most common reasons determining visits were worsening of disease (14.4%), pain (12%), therapy toxicity (8.6%), suspected tumor (5.6%), deferrable (7%). January was the most crowded month (2900,10%), December the less one (1952, 6.8%), Monday (6926) the most haunted day of the week. Hospitalizations in Oncology Department were 6.781 (23%), 1.710 (5.8%) in others. 10.246 cancer pts accessed to ED in the same period (1.4% of all pts); 5961 (58%) were hospitalized. Average long of stay was 10 days.

Conclusions: Acute oncology can play a key role in management of emergencies; despite true level of saving is difficult to quantitatively accurate, OHER lead to save 81430 bed days with hypothetic financial saving.

Legal entity responsible for the study: Medicina Oncologica Policlinico Modena.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1746P Comparing cancer patients’ and support persons’ preferences for the type of consultation and the format of information provided when making a treatment decision

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Background: Cancer patients and their support persons often feel overwhelmed when being confronted with their diagnosis and treatment options. Such information is commonly provided during one consultation with their clinician. We compared cancer patients’ and their support persons’ preferences for: i) attending one 40-minute consultation or two 20-minute consultations when making a treatment decision; and ii) receiving additional information in written form only or in both written and online formats.

Methods: An Australian cross-sectional survey, using a discrete choice experiment (DCE), of 199 adult medical oncology patients and 64 of their support persons. Participants were presented with four hypothetical scenarios and asked to indicate their most and least preferred option. They were told that both treatments would have the same impact on participants’ life expectancy, and that there would be no difference between the scenarios when in terms of what treatment would start.

Results: 147 patients and 59 support persons completed the DCE. The proportions of patients and support persons choosing each scenario did not differ statistically significantly from each other (p > 0.05). Of the four scenarios, most patients and support persons preferred to receive two consultations along with written and online information (n = 65, 44% and n = 30, 51% respectively). Significantly more participants preferred to receive two shorter consultations rather than one longer consultation when this was combined with written and online information (p < 0.05).

Conclusions: When making a cancer treatment decision, both patients and support persons seem to prefer to receive two shorter consultations combined with written and online information. Clinicians should consider offering this consultation style.

Legal entity responsible for the study: Anne Herrmann.

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Disclosure: All authors have declared no conflicts of interest.
investigated whether an EX program could mitigate adverse changes from ADT + ENZ treatment.

Methods: Men starting ADT for M0 HSPC were treated with ADT + ENZ for 8 months and randomized to usual care (UC) or EX for 16 weeks. EX began 4 weeks prior to starting ADT + ENZ and consisted of 48 supervised exercise sessions delivered 6×/week between 55-80% of exercise capacity (VO2peak) for aerobic training and 60-85% of one repetition maximum (1-RM) for resistance training. The primary endpoint was change in VO2peak from baseline to 16 weeks. Secondary endpoints included 6 minute walk distance (6MWOD), upper and lower body strength (1-RM), body composition (DXA), and patient reported outcomes (FACT-P, FACT-Fatigue). The study was originally designed to recruit 56 subjects (N = 28/arm) but was halted early due to funding issues.

Results: 26 men (UC, N = 13; EX, N = 13) completed the protocol. Baseline age and BMI (mean ± standard deviation [SD]) were 65.0 ± 8.1 yr and 28.3 ± 4.6 kg/m2. Intention to treat analyses for mean 16-week change from baseline with a 95% confidence interval (CI) for each assessment by arm are presented in the table.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UC + ADT + ENZ (mean change [95% CI])</th>
<th>EX + ADT + ENZ (mean change [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (ml.kg⁻¹.min⁻¹)</td>
<td>-3.2 (-6.3, -0.2)</td>
<td>-0.9 (-2.4, 0.5)</td>
</tr>
<tr>
<td>6MWOD (ft)</td>
<td>-32.0 (-71.2, 7.3)</td>
<td>+42.0 (56.6, 78.4)</td>
</tr>
<tr>
<td>1-RM Leg Press (lbs)</td>
<td>+6.7 (-47.6, 60.0)</td>
<td>+107.1 (43.2, 171.0)</td>
</tr>
<tr>
<td>1-RM Chest Press (lbs)</td>
<td>+4.9 (-11.0, 20.9)</td>
<td>+243.9 (32.2, 394.9)</td>
</tr>
<tr>
<td>1-RM Row (lbs)</td>
<td>+3.0 (-10.5, 16.5)</td>
<td>+149.0 (0.7, 29.0)</td>
</tr>
<tr>
<td>Fat Mass (g)</td>
<td>+2494.5 (565.3, 3333)</td>
<td>-122.5 (-1593.1, 1350.0)</td>
</tr>
<tr>
<td>Lean Mass (g)</td>
<td>-3088.4 (-5384.7, -792.0)</td>
<td>-2094.5 (-3549.6, -640.4)</td>
</tr>
<tr>
<td>FACT-P TOI</td>
<td>-11.6 (-20.3, -2.9)</td>
<td>-5.4 (-10.8, 0.1)</td>
</tr>
<tr>
<td>FACT-F Score</td>
<td>-9.2 (-16.0, -2.4)</td>
<td>-5.0 (-8.0, -2.1)</td>
</tr>
</tbody>
</table>

Conclusions: Supervised aerobic and resistance EX resulted in less decline in VO2peak, as well as improved function and strength in men treated with ADT + ENZ for M0 HSPC. EX was associated with less fat gain and muscle mass loss, less decline in QOL, and less increase in fatigue. Larger trials of EX in this setting are warranted.

Clinical trial identification: NCT02256111.

Legal entity responsible for the study: Duke University Health System.

Funding: Pfizer (Motivation), Astellas.

Disclosure: All authors have declared no conflicts of interest.

1748P
Cancer care-related social media (SM) and internet usage differences between adolescents and young adults (AYA), adults and elderly patients with cancer

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Background: Internet and SM provide important information and support to cancer patients. Evaluating age-related differences on how patients use these resources is important as it can impact decision-making. Here, we evaluated associations between patients’ age, confidence in computer-use, and use of Internet/SM for cancer care.

Methods: Cancer patients completed a cross-sectional survey of cancer-related SM/Internet use and self-confidence using these resources. Multivariable logistic regression evaluated factors associated with Internet/SM use.

Results: Among 320 patients, 127 were AYA (age 18-39), 127 were adult (40-64) and 66 were elderly (65+). Most (>95%) had a smartphone/tablet/computer and used the Internet daily. Compared to AYA, non-AYA were less likely (P < 0.001) to own a data plan (77% vs 92%), have a SM account (72% vs 95%) or feel confident using computers (76% vs 98%). 75% used Internet and 43% used SM for cancer care information and support; 37% felt confident using online information for decision-making. AYA were more likely than non-AYA to use the Internet (aOR = 1.60, 95%CI [0.93-2.81]), P = 0.09) and SM (aOR = 1.75 [1.04-2.95], P = 0.04) for cancer care. Adults were more likely than elderly patients to use the internet for cancer care (aOR = 5.10 [1.56-16.25], P = 0.001), while no difference was seen in their SM use for cancer care (P = 0.79). Confident computer users were more likely to use Internet (aOR = 5.36 [2.67-11.00], P < 0.001) and SM (aOR = 4.61 [1.98-12.14], P < 0.001) for cancer care and were more confident using this information in decision-making (aOR = 5.12 [1.92-17.81], P < 0.001). Age was not associated with self-confidence using online information for decision-making (P > 0.10).

Conclusions: Despite higher use of internet/SM for cancer care, AYA did not feel more self-confident evaluating online cancer information. Confidence in computer use was associated internet/SM usage and confidence evaluating online information. Patient education programs should focus on improving patients’ confidence in using online resources so they can better evaluate online information for cancer care.

Legal entity responsible for the study: Princess Margaret Cancer Centre - University Health Network.

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Disclosure: All authors have declared no conflicts of interest.
employment status decreased their income, though only 9 patients reduced their working time. Despite their median age, more than 1/3 had cardiovascular risk factors, sexual difficulties or were retired and more than one-third had anxiety/depression syndrome.

Legal entity responsible for the study: Medical Oncology Department, La Paz University Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**1751P** Usability testing of EirV3-a computer-based tool for patient reported outcome measures in cancer

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**Background:** Eir Version 3 (V3) is an electronic tool for registration administration of patient reported outcome measures (Eir-Patient) that immediately presents patient scores on the physician’s computer (Eir-Doctor). Perceived usability is an important determinant for successful implementation. The objective was to assess the number, type, and severity of usability issues of the Eir-Patient and Eir-Doctor modules respectively, when used by cancer patients and physicians in three different settings: 1) outpatient clinics, 2) at home, and 3) at the general practitioner’s office.

**Methods:** A usability evaluation using observations, think-aloud sessions, individual and focus group interviews in patients and their physicians was conducted. Identified usability issues were graded on a severity scale from 1 (irritant) to 4 (unusable).

**Results:** Overall, 73 Eir registrations were performed by 37 patients, and used by 17 physicians in clinical consultations. All patients were able to complete the Eir-Patient symptom registration, which was perceived easy. Seventy-two usability issues were identified. None of them were graded as unusable. 62% of the identified usability issues in Eir-Patient were graded as irritant (grade 1), 18% and 20% as moderate or severe (grade 2-3), none as unusable. For the Eir-Doctor module, 46% of the identified usability issues were graded as irritant, 36% as moderate and 18% as severe. Observations of physician consultations showed that Eir-Doctor was intuitive and easy to use.

**Conclusions:** Patients and physicians found EirV3 easy to use. Results indicate that EirV3 is usable for a heterogeneous population of cancer patients, in different settings. In the subsequent Eir-version, issues in the severe and moderate categories have been changed, to optimize the usability and feasibility of using real-time PROMs in clinical practice.

Legal entity responsible for the study: Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, NTNU.

**Funding:** Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, and Regional Research Funds in Norway, Mid-Norway.

**Disclosure:** S. Kaasa, J.H. Loge: Eir Solutions AS was established in 2015 with Kaasa, Loge and NTNU Technology Transfer AS/Andersin as shareholders. No income, dividend or financial benefits are related to the work presented here, nor in relation to Eir in any way. All other authors have declared no conflicts of interest.

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**1752P** Monitoring quality of life in Dutch women with breast cancer: The Care Notebook study


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**Background:** For many patients the diagnosis and treatment of cancer is associated with negative consequences for their physical, psychological and social well-being. However, patients’ needs for care cannot be addressed unless they are recognized by healthcare providers (HCP). The use of quality of life (QoL) assessments with feedback to clinicians might facilitate the discussion of QoL-items, resulting in improved QoL.

**Methods:** Women with stage I-IIIB breast cancer treated with chemotherapy were included in this randomized study. All respondents completed questionnaires regarding QoL, illness perceptions, self-efficacy, satisfaction with communication, and distress at three moments. Women in the experimental arm completed ‘The Care Notebook’ (CBN) questionnaire, assessing QoL, distress and care needs before every hospital visit. Results were automatically stored and presented in patients’ medical files. From the 2nd visit onwards, patients and HCPs received a copy of the latest QoL overview before the consultation. Women in the control arm received care as usual. Audio-recordings were used to investigate effects on communication and patient management.

**Results:** presented here are drawn from a collaborative study between Japan and the Netherlands. From July 2012 to May 2016, 60 out of 113 Dutch patients were randomized to the experimental arm. In the experimental condition, more QoL-items’ were discussed (0.7 items each visit, p = 0.04), compared with the control condition, especially regarding disease-specific and psychosocial issues (p < 0.01). There were no differences in patient management, QoL, illness perceptions or distress. Patients in the experimental arm had higher scores on satisfaction with communication (p < 0.05). All patients perceived high self-efficacy in interacting with HCP. Patients in the intervention condition perceived the tool as user-friendly and a valuable addition to regular care.

**Conclusions:** Use of the QoL-monitor ‘The Care Notebook’ resulted in more frequent discussion of psychosocial and disease-specific issues, associated with high levels of patients’ satisfaction. However, patient management and patients’ QoL were unaffected by the intervention.

Legal entity responsible for the study: Leiden University Medical Center.

**Funding:** This study was supported by a grant of the Dutch Pink Ribbon Foundation and from Pfizer, Japan.

**Disclosure:** All authors have declared no conflicts of interest.

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**1754P** Prognostic factors for critically ill patients with solid cancer tumours admitted to a medical intensive care unit

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**Background:** The decision to transfer patients (pts) with solid cancer tumours to an intensive care unit (ICU) is still controversial and difficult. Few studies have assessed the outcome for these patients. The aim of this study was to identify 30-day prognostic factors/mortality for pts with solid cancer tumours admitted to an ICU.

**Methods:** We conducted a retrospective cohort study of all consecutive pts with solid cancer tumours admitted to ICUs at Bordeaux University Hospital, between January 2010 and December 2015. The study end point was 30-day mortality. Secondary end points were to describe the characteristics and outcomes for pts, and ethical practices.

**Results:** We included 235 patients with solid tumours. Most of them were in a metastatic setting (60%). The most common causes for ICU admission were sepsis (56%) and/or respiratory failure (52%). ICU, 30-day, 90-day mortality rates were 24%, 36% and 50% respectively. After ICU stay, 44% of pts had restarted an anti-tumour treatment. In multivariate analysis and after excluding SAPS 2 score, two or more organ failures (p = 0.005) and being under non-curative care (p = 0.028) were independent prognostic factors of 30-day mortality. A support person was designated in 81% of cases, advance directives expressed in in 2% and collective decision reported in 21%. Limitation of life-sustaining therapy was decided for 23% and 43% of pts before admission and during the ICU stay, respectively.
Conclusions: The number of organ failures is a rapidly assessable variable that can help oncologists and intensive care specialists in their decision. A support person is often designated but advance directives are still unusual.

Legal entity responsible for the study: CHU Bordeaux.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1757P
A pilot study of exercise intervention in patients with metastatic cancer: Feasibility, safety, and patient reported outcome

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Background: Skeletal muscle loss is a central component of cancer cachexia syndrome and is a poor prognostic factor in patients with cancer. We investigated prevalence of sarcopenia and the feasibility of exercise intervention in patients with newly diagnosed advanced solid cancer.

Methods: Between July 2017 and February 2018, consecutive patients with newly diagnosed advanced solid cancer were enrolled to our prospective cohort. Sarcopenia was defined as the third lumbar vertebra (L3) muscle index of less than 55 cm²/m² for men and of less than 39 cm²/m² for women. Patients were recruited to participate in a 12-week, combined resistance and aerobic exercise program consisted of supervised, hospital-based (2×/week) and home-based training (5×/week), during the first-line palliative chemotherapy. The primary endpoint was feasibility and safety of the exercise intervention. Pre- and post-exercise intervention skeletal muscle mass by bioelectrical impedance analysis (BIA) and patients’ quality of life questionnaires were measured and compared.

Results: Among 76 patients enrolled in the prospective cohort, sarcopenia was present in 38 (76.3%) patients (94.3% in men, 34.8% in women). Nineteen patients was enrolled in the exercise program, however 5 patients withdrew consent before commencement. Reasons for withdrawal were health concern (n = 2), distance to the hospital (n = 1) and unspecified (n = 2). The completion rate of the 12-week exercise program was 78.6% (11/14). Disease progression (n = 2) was the main reason for early discontinuation. The adherence rate of supervised exercise session was 78.1% (207/265) and there was no adverse event associated with the exercise training. Among participants in the exercise program, there were no significant change in skeletal muscle mass index from baseline to post-intervention (mean, 9.4±2.1 kg/m² vs 9.4±2.1 kg/m², p = 0.982). FACIT-fatigue scale was non-significantly improved after the exercise intervention (mean, 35.2±10.4 vs 38.2±10.8, p = 0.635).

Conclusions: Exercise interventions appear to be feasible and safe in patients with advanced solid cancer and might have a role of preventing skeletal muscle loss without fatigue exacerbation during palliative chemotherapy.

Legal entity responsible for the study: Gachon University Gil Medical Center.

Funding: National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (grant no. H11700045).

Disclosure: All authors have declared no conflicts of interest.

1758P
A prospective analysis of 30-day mortality following palliative chemotherapy at an Australian tertiary cancer centre

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Background: 30 day mortality for patients receiving palliative intent chemotherapy has been suggested by the 2008 NCEPOD as a measure of quality of cancer care. This has to a number of global audits, with rates ranging from 8–43%. This world first prospective study aimed to benchmark an Australian tertiary cancer centre, and identify factors associated with 30 day mortality.

Methods: A prospective cohort study of all patients with a diagnosis of malignancy referred for palliative intent intravenous chemotherapy to the Western Health Chemotherapy Day Unit from the 8th December 2014 to 8th December 2015. The primary outcome was death within 30 days of receiving palliative intent chemotherapy.

Results: A total of 314 patients were enrolled in the study. The average age was 63 years, 45% were female, and 60% were born overseas. 98 patients died during the audit period. Of these, 21 (6.6%) died within 30 days of commencing palliative intent chemotherapy, and 60 (18.8%) died more than 30 days after receiving chemotherapy. Of the 34 patients that were referred, but did not start chemotherapy, 17 (52%) died. Multivariable logistic regression found that patients who had been referred to palliative care and received chemotherapy were more likely to die within 30 days, although this did not reach statistical significance. There was no difference in mortality rate by gender, age, tumour type, number of lines of previous chemotherapy, or patient performance status. Patient’s who commenced chemotherapy were more likely to die in hospital (n = 44, 74%), as those who were referred but did not commence chemotherapy were more likely to die at home (n = 9, 90%). 199 patients ceased chemotherapy during the study period, with the most common reason being progression of disease (n = 78, 39.2%), and toxicity (n = 60, 30.2%).

Conclusions: This prospective cohort study demonstrated 6.6% of patients died within 30 days of administration of palliative intent chemotherapy. Multivariable analysis did not identify any pre-specified variables that were significantly associated with 30 day mortality: in our study, the strongest predictor of 30 day mortality was referral to outpatient palliative care.

Legal entity responsible for the study: Western Health.

Funding: Western Central Melbourne Integrated Cancer Service.

Disclosure: All authors have declared no conflicts of interest.

1759P
Characterisation of oncologic patient visits at the ED at an Austrian tertiary care center

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Background: Oncologic patients with tumor or therapy associated complications often seek out the ED as first contact point. Next to the rare classic oncologic emergencies, other scenarios are supposed to be more frequent. However, little is known about other reasons of patients with cancer to consult the ED.

Methods: The study is a retrospective data analysis of emergency visits of patients with active cancer or adjuvant therapy, who were taken by ambulance to the ED. From 1.1.2017–31.7.2017 data from all patient contacts were collected. The medical history of adult patients were searched for diagnosis of active malignant disease or adjuvant therapy, to be eligible for this study.

Results: From a total of 1029 patient contacts 743 met the inclusion criteria. 425 male contacts (57%) and 318 female contacts (43%) were recorded. The median age was 67 years. The vast majority of patients (648, 87%) were in a palliative setting. 339 patients (46%) were under active treatment and 111 patient contacts (15%) were treatment associated. 384 patient contacts (52%) were tumor related. The most common malignances were lung cancer (141, 19%), pancreaticobiliary cancer (73, 10%), colorectal cancer (67, 9%) and breast cancer (54, 7%). The most frequently reasons for ED consultations were deterioration of general condition (140, 19%), pain (130, 18%), dyspnea (106, 14%) and fever (97, 13%). The most common diagnosis were infections (342, 19%) with pneumonia as the leading cause (61, 8%). Followed by pain (130, 18%), with cancer pain being the most common complication (52, 7%) and tumor progression (103, 14%). Data regarding OS until the date of censorship (28.2.18), 3 month mortality (3MM) and factors possibly influencing 3MM are yet immature, but will be added at time of presentation.

Conclusions: The majority of cancer patients seeking help at the ED are in a palliative setting. Cancer associated complications pose the most frequent cause for ED consultations. Lung cancer, pancreaticobiliary and colorectal cancer present the most common malignances related to ED visits. The results of the study may help to optimize the strategic treatment of cancer patients and may help to inform both oncological patients and primary care units about frequent complications associated with the diagnosis of cancer.

Legal entity responsible for the study: Medical University of Vienna.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1758P
High proportion of prostate cancer survivors continue to experience a negative impact on quality of life long after diagnosis: Patient reported outcomes for an Australian population-based sample

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Background: Prostate cancer is a leading cause of cancer-related burden of disease in Australia. Despite careful patient selection and advances in therapy, men may experience complications beyond completion of treatment. There is a lack of robust population-based data regarding the quality of life (QoL) of prostate cancer survivors. We aimed to determine the feasibility of collecting health and quality of life (QoL) data...
from an Australian population-based sample of prostate cancer survivors, using standard measures. Methods: A cross-sectional survey was mailed to a representative group of patients approximately 1, 3 or 5 years post cancer diagnosis. Eligible participants were 18 years or older, had prostate cancer, and registered with the Victorian Cancer Registry. QoL was assessed using the EQ-5D–5L, Functional Assessment of Cancer Therapy-Prostate (FACT–P) and the Social Difficulties Inventory (SDI-21). The results were compared to an English dataset that used similar methods. Results: 494 of 1078 eligible participants returned the survey (RR 45.8%). The majority reported their prostate cancer had responded fully to treatment (69.9%). QoL was similar between the Australian and English data, and at 1, 3 and 5 years post diagnosis. Symptoms were commonly reported, from FACT–P: erectile dysfunction 84%, problems with satisfaction with present comfort level 74%; poor appetite 61%, back pain and fatigue were 61% and from the EQ-5D–5L: anxiety 32%. Improved QoL, and improved social wellbeing was associated with full response to treatment (EQ-SD-5L, p < 0.001; SDI-21, p < 0.01). Reduced QoL, was associated with not having a care plan (EQ-SD-5L, p < 0.01) and having another medical condition (EQ-SD-5L, p < 0.001; SDI-21, p < 0.01). Conclusions: The method of assessment is feasible in the Australian setting. A high proportion of men experience difficulties that continue to impact their QoL long after diagnosis. This highlights an unmet need and that a process to identify and respond to these issues is needed. Care plans may assist. Legal entity responsible for the study: Victorian Comprehensive Cancer Centre. Funding: Victorian Comprehensive Cancer Centre. Disclosure: All authors have declared no conflicts of interest.

**Table: 1760P**

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<th>Timepoint</th>
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<td>52.7±5.6</td>
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<tr>
<td>2nd</td>
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</table>

**1760P** A longitudinal study of a new point-of-care nerve conduction device for quantitative assessment of chemotherapy-induced peripheral neurotoxicity

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Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) exacerabtes cumulatively and dose-dependently. Assessment of CIPN usually depends on subjective grading scales, such as the Common Terminology Criteria for Adverse Events (CTCAE). We previously validated a newly developed point-of-care nerve conduction device (POCD) for the quantitative assessment of CIPN (Cancer Sci 2016). The aim of the present study was to prospectively assess CIPN using this POCD.

Methods: Patients scheduled to receive 8 cycles of adjuvant Cetox therapy (capcitabine and oxaliplatin) for colorectal cancer were enrolled. Sural nerve amplitude potentials (SNAP, µV), a quantitative measure of the axonal degeneration, and sural nerve conduction velocity (SNCV, m/s), that of the demyelination, were recorded using a portable and automated POCD (DNP-Check®, Neurotomix Inc., Waltham, MA, USA) at baseline, each cycle of chemotherapy, and within 1 month after the end of chemotherapy. The severity of CIPN was evaluated according to the CTCAE. The total sum of SNAP/SNCV was calculated for each patient, and compared according to each CTCAE grade.

Results: A total of 39 patients (MF: 22/17; median age 61 years, range 36-78; worst CTCAE GI/G2/G3: 25/10/4) were enrolled. Mean SNAP/SNCV at baseline, each cycle of chemotherapy, and within 1 month after the end of chemotherapy are shown in the Table. SNAP decreased significantly during each cycle of chemotherapy (repeated ANOVA, P < 0.001), whereas SNCV remained relatively unchanged. The mean total sum of SNAP was 112.6±38.6 G1, 69.8±19.2 G2, and 44.8±12.8 G3. The mean total sum of SNCV was 451.1±34.9 G1, 454.2±24.7 G2, and 428.2±50.3 G3. The total SNAP differed significantly among each CTCAE grade (ANOVA, P < 0.001), whereas the total SNCV did not.

Conclusions: This POCD demonstrates SNAP-dominant neuropathy in patients who receive oxaliplatin, indicating axonal degeneration as a mechanism of CIPN.

Clinical trial identification: UMIN000017868.

Legal entity responsible for the study: Nagoya University Hospital.

Funding: Novartis Pharma K.K.


**1761P** Risk of health-related quality of life events and pulmonary toxicities in recurrent ovarian cancer patients treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors maintenance

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Background: Pain and fatigue are the major determinants of health-related quality of life (HRQOL) in cancer patients undergoing chemotherapy. Ovarian cancer is the seventh most common cause of cancer in women worldwide. PARP inhibitors maintenance has shown to improve survival in recurrent ovarian cancer patients with notable toxicities. We undertook a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of HRQOL events and pulmonary toxicities.

Methods: We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through March 2018. Phase III RCTs that mention HRQOL events and pulmonary toxicities as adverse effects were incorporated in the analysis. Mantel-Haenszel (MH) method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Fixed effects model was applied.
Conclusions: All authors have declared no conflicts of interest.

Has not received any funding.

Legal entity responsible for the study: Kyaw Zin Thein, Texas Tech University Health Sciences Center.

Disclosure: All authors have declared no conflicts of interest.

Results: Three phase III RCTs with a total of 1401 patients with recurrent ovarian can-
cer were eligible. The study arms used olaparib or niraparib or rucaparib while the con-
trast arms utilized placebo. The randomization ratio was 2:1 in all studies. The RR of all-
grade side effects were as follows: fatigue, 1.54 (95% CI: 1.37 – 1.73, P < 0.001); back
pain, 0.93 (95% CI: 0.70 – 1.24, P = 0.64); arthralgia, 1.05 (95% CI: 0.79 – 1.40, P = 0.69); headache, 1.73 (95% CI: 1.34 – 2.29, P < 0.001); decreased appetite, 1.76 (95% CI: 1.36 – 2.28, P < 0.001); cough, 1.87 (95% CI: 1.33 – 2.63, P < 0.001); dyspnea, 2.39 (95% CI: 1.64 – 3.48, P < 0.001); and upper respiratory infections (URI), 1.71 (95% CI: 1.16 – 2.53, P = 0.007). The RR of high-grade side effects were as follows: fatigue, 3.94 (95% CI: 1.90 – 8.17, P < 0.001); back pain, 0.49 (95% CI: 0.10 – 2.48, P = 0.39); arthralgia, 2.00 (95% CI: 0.22 – 17.82, P = 0.53); headache, 1.08 (95% CI: 0.18 – 5.47, P = 0.99); decreased appetite, 1.16 (95% CI: 0.17 – 7.82, P = 0.87); and dyspnea, 1.28 (95% CI: 0.30 – 5.48, P = 0.73).

Chemotherapy-induced peripheral neurotoxicity (CIPN): What are patients telling us?

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Background: This is a secondary analysis of the original CI-PeriNoms study dataset to formally test in CIPN patients: a) which is the correlation between patients’ perception of activity limitation and actual neurological impairment, and b) how the responses to simple questions regarding daily activities potentially related to sensory and/or motor impairment are interpreted by the treating oncologist.

Methods: For the purposes of the current study we have analyzed data on the presence (frequency) of CIPN-associated peripheral nerve damage, without taking into account its severity. Comparison was performed between the oncologists’ responses and the scores obtained in strength and vibration detection threshold using the Total Neuropathy Score (clinical, TNSc) criteria compared to patients answers to 8 tasks scored as “impossible” to be performed by at least 5% of the patients.

Results: The distribution of the scores attributed by oncologists to each daily life maximum limitation (“impossible”) allowed categorizing the responses into 3 groups: Group 1 included the limitations that the oncologists attributed mainly to motor impairment (item median motor score = 7, item median sensory score 2-3), Group 2 consisted of limitations mainly attributed to sensory impairment (item median sensory score = 8, item median motor score = 1-2) and Group 3 included limitations with uncertain motor and sensory impairment (item median sensory score = 4-6, item median motor score = 5). We demonstrate that the interpretation of patients’ report provided by the panel of oncologist is poorly consistent with the actual neurological impairment, and that activity limitations capture more than simple impairments and reflect a broader impact than impairment measures.

Conclusions: These observations form a critical basis for further research on the core set of outcome measures needed for future trials in CIPN and at the same time suggest a need for a novel model based on the premise of closeknit integration of supportive care and medical oncology which dispels the myth of pure palliation as a segregated entity.

Legal entity responsible for the study: CI-PeriNoms study group.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

Malnutrition in cancer patients: Is late diagnosis a missed opportunity to improve care?

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Background: Malnutrition (MN) related metabolic defects, through the tumor or its treatment, can negatively impact on cancer patients’ outcomes. MN is often undiagnosed and untreated. This study investigated diagnoses of MN and hospital resource use in patients with gastro-intestinal (GI) system cancers.

Methods: For the purposes of the current study we have analyzed data on the presence of MN at first hospitalization, hospital stays were twice as frequent and longer when MN was diagnosed after 1st cancer hospitalization (6.8 vs. 3.9 stays and 38 vs. 53 days, respectively). After propensity score matching, a significantly higher frequency of hospitalizations in those with a late compared to early diagnosis of MN remained. Differences in frequency and duration of hospitalizations increased linearly with a later MN diagnosis (1, 3, 6 months after first hospitalization), with the strongest association in patients without metastases.

Conclusions: The data suggests that an earlier diagnosis of MN should help to reduce frequency and length of hospitalizations, particularly in patients without metastases, potentially improving patients’ clinical outcomes and reducing health economic costs. Further research is warranted to understand the potential of early nutritional therapy in improving cancer patients’ outcomes and in reducing resource use.

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Legal entity responsible for the study: Baxter Healthcare SA, Zurich, Switzerland.

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A survey on acceptable nomenclature in addressing patient needs among the delegates of a national conference on supportive medicine

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Background: The scope and ambit of services offered in an integrated palliative medicine unit located in tertiary cancer centre is explored through various questions pertaining to multiple domains encompassing clinical management of advanced cancer patients. The survey tests the attitudes of the respondents while laying the foundation of building and sustaining a novel model where Supportive cancer care services, Pain management and Palliative medicine interventions (including End of life care) are offered as part of a continuum.

Methods: The survey was carried out among the registered delegates of the annual national conference of the Indian Association of Palliative Care.

Results: 48 percent (84/175) felt that Palliative medicine and Supportive oncology are mutually exclusive domains in patient management. 40 percent (71/175) agreed that the term Palliative medicine should be substituted by Supportive medicine while only 22 percent (38/172) agreed that using the term Supportive oncology would be justified in place of Palliative medicine. 34 percent (59/169) felt that substitution of the term Palliative medicine by Supportive oncology might remove the stigma associated with the referral of the patient to avail these services.

Conclusions: These results reflect the multiplicity of views which underlie existing divergent schools of thought in this nascent subspecialty. An indigenous academic model based on the premise of dose-sensitive integration of supportive care and medical oncology which dispels the myth of pure palliation as a segregated entity is the need of the hour. The services offered should reflect the understanding that recognition and management of supportive care needs of cancer patients is of utmost important in making the model economically viable and socially sustainable.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

A survey on purview of palliative medicine services among the delegates of a national conference on supportive medicine

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Background: The provision of personalized, symptom oriented, patient centered care at an early stage in the patient’s trajectory of illness is the philosophy that underlies sup-
portive care.
Methods: A questionnaire based on clinical scenarios encountered in the integrated inpatient palliative medicine unit was carried out among the registered delegates of the annual Indian association of Palliative care conference.

Results: Interventional pain procedures (65.49 percent) and counseling regarding goals of care and provision of palliative sedation (57.73 percent) were considered the main indications for an inpatient palliative medicine unit admission. A majority (66.89 percent) agreed that the duration of inpatient stay should be defined by the stage of the illness. 48.9 percent agreed that pulse oximetry should be available for all inpatients. Acute kidney injury and dyselectrolytemia were considered valid indications for an ICU admission. 36.9 percent felt that use of non-invasive ventilation strategies, antibiotic stewardship, management of sepsis and dyselectrolytemia should be duties of a palliative medicine professional in the ICU. 48.3 percent, 65.31 percent and 50.34 percent of individuals reported that the timing of intervention, healthcare professional involved and subset of patients involved were the differences between supportive oncology and palliative medicine.

Conclusions: There is an overlap in nature of supportive medicine services provided by a medical oncology and palliative/supportive medicine team. A practical, cost effective and resource intensive solution lies in building a workforce of health care professionals from palliative/supportive medicine who are well trained in supportive oncology.

Inpatient admission is integral to sustain a cost effective model of delivery of supportive medicine services, however a consensus on the guidelines which govern the establishment and functioning of such a unit need to be developed.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1766P

Sexual functioning and depression among Egyptian breast cancer patients following surgery and neoadjuvant/adjuvant chemotherapy

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Background: Breast cancer and its treatment may have a negative impact of the sexual wellbeing of patients and psychological morbidity may further add to this impact. Little is known about the sexuality of Egyptian patients with breast cancer. This may be due to barriers related to health care professionals, patients and their families and the culture. Aim: To evaluate sexual functioning among Egyptian breast cancer patients following treatment and to determine the relation between their sexual wellbeing and anxiety and depression and other possible factors.

Methods: This prospective cross-sectional observational study included married breast cancer patient from 20 to 50 years of age who underwent surgery and received neoadjuvant/adjuvant chemotherapy. The Female Sexual Function Index (FSFI) was used to assess their sexual wellbeing. FSFI total score cutoff of value 26.55 was used to determine sexual dysfunction. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression. In addition, demographic and clinical data were collected.

Results: Thirty-six out of 38 patients (94.7%) invited to participate in the study signed an informed consent and completed the FSFI questionnaire. The mean FSFI total score was 23.1±5.4 and 61% of patients had sexual dysfunction. The HADS depression scale was >7 (borderline-abnormal/abnormal) in 12 (33%) patients and the HADS anxiety scale was >7 in 25 (69%). Patients with borderline-abnormal/abnormal HADS depression score had a significantly lower FSFI total score compared to those with normal HADS depression score (20 vs. 25, respectively; p = 0.029). The HADS anxiety score did not correlate significantly with the FSFI scores.

Conclusions: Unlike the common belief, the majority of Egyptian female breast cancer patients included in this study was willing to discuss their sexual wellbeing. The results suggest that a significant proportion of Egyptian patients who completed treatment for breast cancer experience sexual dysfunction and psychological morbidity and that sexual dysfunction correlate significantly with depression among them.

Legal entity responsible for the study: Clinical Oncology Department, Faculty of Medicine, Menoufa University, Shebin El Kom, Egypt.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1767P

Supportive care: Patient expectations, availability and uptake

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Background: Integrative oncology uses complementary approaches alongside conventional medical therapy to improve quality of life, improve outcomes and reduce the risk of recurrence. The Calista2 survey sought to identify, understand, and rank cancer patients’ expectations and utilization of supportive care and activities. Accessibility of such supportive care was also assessed.

Methods: The 82 physicians who accepted to take part in the survey recruited 666 patients. Inclusion criteria were: patients already on specific therapy for breast cancer (BC), colorectal cancer (CC) or lung cancer (LC). Patient questionnaires were self-reported. Questions covered drug management of pain, fatigue, adverse effects of treatment (AE), and sleep disorders, social and psychological support, physical activities, and complementary and alternative medicines. Questionnaires were collected between September 2016 and October 2017. This analysis focuses on the patients’ expectations, the supportive care or activity made available to patients, and how they were used.

Results: After exclusion of non-valid patient questionnaires, 467 were analyzed. All cancer localizations combined, patients rated the medical management of adverse events (AE) and pain as highly important (7/10). Of the 18 items considered, physical activity and management of fatigue were rated as moderately important (5–7/10). The different types of supportive care or activity provided included predominantly the management of adverse events (AE, 81% and pain (72%), psychological support (56%), and diet/nutrition (49%). Patients primarily used drug management of AE (72%) and pain (61%), diet/nutrition (34%), and self-image improvement techniques (31%). There is a lack of availability of complementary medicine, fatigue management, and relaxation techniques according to 28%, 27% and 24% of patients, respectively.

Conclusions: In our sample, the complementary approaches currently available practically satisfied patient requirements with regards to management of AE and pain. However, these findings also highlight the need for greater access to fatigue management, complementary medicine, and relaxation techniques.

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Legal entity responsible for the study: Kantar Health.

Funding: Roche.

Disclosure: H. Simon, G.M. Ganem, H. Naman, J.F. Moreire, F. Eisinger: Honorarium: Roche. C. Lhomel: Employee: Roche. All other authors have declared no conflicts of interest.

1768P

Novel approach for counselling of young cancer patients

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Background: About 80% of cancer patients between the age of 18 to 39 survive their disease. They have to cope with different problems than children or older adults. They suffer from short- and long-term social burden as well as from physical disorders associated with the disease or cancer treatment. The objective of this project is to consult patients on options for social support to avert financial problems and to provide medical help to reduce disease- or therapy-associated disorders. The consultation takes place in collaboration with the attending physicians.

Methods: The Young Cancer Portal of the German Foundation for Young Adults with Cancer is a nation-wide, open-access service for young patients. The advisory process rests on an independent softwaredatabase. Patients are initially asked to register with their personal information and to raise their first questions. A questionnaire captures their current situation regarding the disease status and daily life. Expert advice is given in writing, by phone, or in person by a regionally assigned oncologist with extra training. In addition, a special access offers the exchange of expertise of or for medical professionals. The protected database allows an anonymous collection and systematic analysis of the data by the foundation.

Results: The module for social law questions started on Nov 24, 2015, the module for endocrinological ques-tions on Sep 22, 2016, and the module on immune defects in Aug 2017. Thus far, 495 people have registered and 345 patients have been advised. Female patients represent 72% of the pool, male patients 28%. The average median age is 30.5 years (ranges from 18 to 52).

Table 1765P Purview of early palliative medicine

| 1. | Management of complex psychiatric symptoms | 34.87% |
| 2. | Management of chemotherapy related complications | 40.79% |
| 3. | Counselling regarding goals of care | 80.92% |
| 4. | Assessment of quality of life | 73.68% |
| 5. | Interventional pain management techniques | 50.66% |
Conclusions: The Young Cancer Portal is unique throughout Germany and offers a new way for expert-patient-communication with high acceptance by long-term survivors. The portals basic structure is appropriate for a enables the modular addition of topics. Modules for long-term effects and integrative oncology will be established.

Legal entity responsible for the study: German Foundation for Young Adults with Cancer.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Health-related quality of life (HRQoL) measurement among adolescents and young adults (AYA) with cancer is instrumental to identify areas of need and to organize age-specific psychosocial care. Health care professionals (HCP) are not always aware of what matters most to patients. The aims of the current study were to determine top 10 HRQoL priorities relevant to AYA cancer patients and HCP and to determine discrepancies between items prioritized by AYA and HCP.

Methods: Patients aged 18 to 35 years at time of cancer diagnosis and who had been seen by one of the members of the multidisciplinary AYA team of Radboud university medical center in the Netherlands, and Dutch HCP involved in AYA oncology were invited to complete the Quality of Life for Cancer Survivors questionnaire.

Results: 83 AYA cancer patients and 34 HCP completed the questionnaire. Patients scored significantly lower on negatively formulated HRQoL issues (e.g. fatigue, coping difficults, feeling isolated) and significantly higher on positive formulated issues (e.g. support from others, overall health, happiness). Most important HRQoL items scored by AYA patients were: perceived support from others, distress about initial cancer diagnosis, distress for family, overall quality of life and happiness. HCP perceived distress about initial cancer diagnosis, distress for family, cancer treatment distress, interference of illness with employment/study and fatigue as most important HRQoL items. Patients and HCP had a congruence on 5 out of 10 HRQoL items where distress about initial cancer diagnosis, distress for family and cancer treatment distress were the main overlapping issues. There was a incongruence on fatigue, sexuality and concerns about fertility as these items only appeared in the top 10 HRQoL items rated by HCP and not the top 10 for AYA patients.

Conclusions: AYA cancer patients perceived most HRQoL items as less problematic in comparison to HCP, in particular regarding physical symptoms, psychological and social HRQoL issues. The discrepancy between patients and HCP illustrates the importance of patient participation, i.e. involving patients in organizing and prioritizing their own (psychosocial) care.

Legal entity responsible for the study: Radboud University Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Social media is increasingly used by patients for cancer information and psychosocial support. Certain information/features may be more desired in new hospital-based social media cancer resource, these may vary between adolescent-young adult (AYA; age < 40) and non-AYA (age > 40+).

Methods: Using age specific sampling, cancer patients across all disease sites completed a cross-sectional survey of demographics, health status, and social media online resource use for cancer education. Clinical information was abstracted.

Results: Of 127 AYA cancer patients and 193 non-AYA (older adult) patients, 100% (AYA) and 92% (non-AYA) stated they use the internet (p = 0.001); 95% AYA and 72% non-AYA use social media (p < 0.001). When asked about use of social media, 64% AYA and 50% non-AYA believed they could social media social information: 18% AYA and 18% non-AYA recommended use of current social media resources. When asked what types of features they would want in an online resource for their cancer care, both AYA and non-AYA most frequently reported wanting to view their own personal health records (82% AYA/63% non-AYA), followed by an online library of cancer resources (73% AYA/ 56% non-AYA), ability to communicate with healthcare professionals (73% AYA/55% non-AYA), and appointment reminders (72% AYA/58% non-AYA). The most frequently desired information for both groups were treatment options (61% AYA/56% non-AYA), causes/risk/factors/symptoms (65% AYA/36% non-AYA), and prognosis/outcomes (52% AYA/46% non-AYA). The largest difference in information preference between the two age groups were in wellness programs (82% AYA/39% non-AYA) and work return (42% AYA/ 20% non-AYA) (p < 0.001).

Conclusions: There is significant agreement between AYA and non-AYA patients in the most desired information and features they want in a social media resource, though AYA patients wanted a greater number of features. Patients’ desired information suggested a patient preference for more autonomy and insight into their disease, regardless of age. There is a lack of satisfaction with current social media resources. A single set of informational tools can therefore be developed for all adults.

Legal entity responsible for the study: Princess Margaret Hospital, University Health Network.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Hypothyroidism was a known and common side effect from multikinase inhibitors notably in sunitinib, pazopanib and sorafenib. The goal of this study was to explore risk factors in developing hypothyroid and whether the occurrence of this endocrine adverse event (AE) leading to better survival outcomes.

Methods: Seventy-one renal cell carcinoma (RCC) patients and 136 hepatocellular carcinoma (HCC) patients were retrospectively analyzed. Data relating to the treatment course and development of hypothyroid were collected, extracted and presented in separate cohort.

Results: The incidence of hypothyroidism was 47.8% in RCC patients treated with either sunitinib or pazopanib. For RCC patients whom received sorafenib, the incidence of hypothyroidism was 35.8%. We found no factor significantly associated with hypothyroidism in RCC patients. HCC patients whom had duration of treatment of less than 3 months tend to develop hypothyroidism. There was no significant association between the development of hypothyroid and PFS or OS in RCC patients. In HCC group, euthyroid patients had statistically significantly longer mPFS [7.6 vs. 2.2 months; HR = 6.38; 95%CI 1.87-21.8; p = 0.003] and mOS (16.9 vs 5.2 months; HR = 22.96; 95%CI 4.43-118; p < 0.0001) than the hypothyroid group.

Conclusions: Hypothyroidism is the most common endocrine AE of multikinase inhibitors. There are no significant clinical factors associated with the development of hypothyroid. This AE might serve as a good predictive marker for multikinase inhibitors treatment in HCC patients and their survival outcomes. The larger cohort is needed to confirm this evidence.

Legal entity responsible for the study: Faculty of Medicine Ramathibodi Hospital.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Background: Immune checkpoint inhibitors (ICIs) have transformed oncology practice, however serious immune-related adverse events (irAE) occur and are poorly understood. A correlation between irAE and clinical benefit has been suggested in mela- noma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The incidence of irAEs has been described in clinical trials but risks factors remain undefined. This study reports the incidence and risks factors of irAE in patients (pts) with multiple cancers treated with any ICI, as well as overall survival.

Methods: A retrospective study of pts with any malignancy treated with ICI (alone or in combination) between January 2010 and June 2017 was carried out at The Ohio State University. Grade >= 2 irAEs were abstracted based on the treating physician diagnosis. Overall survival (OS) was calculated from the date of initiation of ICI to death from any cause or date of last follow-up. The associations between irAE incidence
and categorical outcomes were studied using chi-square or Fisher’s exact test. The Wilcoxon test was used for continuous outcomes. Survival outcomes were studied using log-rank test or Cox regression model.

Results: Of 1,113 pts identified, 417 pts had complete irAE data: 136 pts with melanoma, 117 pts with NSCLC, 33 pts with RCC, and 111 pts with other cancers. irAEs occurred in 120/417 pts (28.78%). Gender, age at treatment, and smoking history were not associated with irAE. Incidence of pneumonitis and colitis was 3.84% and 6%, respectively. Pneumonitis was more common in NSCLC (p = 0.014). Rates of thyroid, hepatic, and neurologic irAE were 5.29%, 4.08%, and 0.84%. irAEs were associated with length of therapy (p = 0.03), and were more common in 29 pts treated with combination ICI (p < 0.001). For 366 pts with metastatic disease, irAEs were associated with longer survival: median OS 21.1 months vs 9.2 months (HR = 0.48, 95% CI: 0.35 - 0.66, p < 0.001). Thyroid toxicity (HR = 0.25, 95% CI: 0.10 - 0.59, p = 0.002) and hepatitis (HR = 0.32, 95% CI: 0.12 - 0.85, p = 0.023) were associated with longer OS.

Conclusions: Increased awareness of irAE patterns across different cancer and treatment types will allow for rapid identification and treatment of irAE.

Legal entity responsible for the study: The Ohio State University.

Funding: Has not received any funding.

Disclosure: G. Tincu: Advisory board: Blueprint. E.M. Bertino: Advisory board: Takeda, Boehringer Ingelheim. D.P. Carbone: Research funding: BMS; Paid advisory boards: Merck, AZ, Genentech. All other authors have declared no conflicts of interest.

1775P A survey on attitude towards euthanasia among delegates of a national conference on supportive medicine

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Background: There is a widespread belief that Euthanasia and good palliative medicine are mutually exclusive. It is important to explore whether the philosophy of palliative medicine which lays an emphasis on a good death also recognizes the individual’s right to seek death as a means to end suffering.

Methods: A survey exploring the attitude and opinion of respondents on the extent of involvement of Palliative/Supportive medicine professionals in the provision of Euthanasia was conducted among the registered delegates of Indian association of Palliative Care conference 2018.

Results: 55.66 percent (85/153) of the respondents agreed that the debate on Euthanasia was within the purview of Palliative medicine, while 52.71 percent (78/148) agreed that the provision of Euthanasia is a right to End of life care. 61.27 percent (87/152) of the respondents believe that a set of multidisciplinary experts should be introduced to initiate the discussion on Euthanasia in a terminally ill patient when the same is expressly demanded by the patient or family members. A majority (57.68 percent - 52/138) disagreed with the use of the terms Passive and Active euthanasia. A majority of the respondents (51.74 percent - 74/143) also strongly disagreed with the use of the term physician assisted suicide. 42.46 percent (62/146) of the individuals agreed that the right to a good death and Euthanasia were mutually exclusive. 40.13 percent (61/152) agreed that they do not recognize the right to Euthanasia.

Conclusions: The right to seek Euthanasia as a means of a respectable death is a debatable subject which should be approached carefully keeping in mind the distinct socio-political-cultural thread which runs through the moral fiber of each society. The involvement of experts from multiple subspecialties (as suggested by the highest court of law in India) while ignoring the pivotal role of the palliative medicine professional in establishing a framework of guidelines surrounding Euthanasia does not seem to be justified. The importance of having the tenets of law firmly on their side should not be underestimated by Palliative/supportive medicine professionals who are bound by duty to take the lead in the discourse surrounding End of life care.

Legal entity responsible for the study: Rahul D. Arora.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

1776P Acute toxicity of concurrent radiochemotherapy for locally advanced head and neck cancer: A prospective study

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Background: Concurrent chemoradiation (CCRT) is the standard treatment for patients with inoperable locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC). CCRT can be associated with severe acute toxicity. Usually only the maximum grade of a limited selection of adverse events (AEs) is reported, without mentioning the evolution of toxicity over time. By the lack of the time factor, the global burden of toxicity experienced by the patient is not adequately reflected.

Results: 505 replies were received from pts (85%) and caregivers (15%). The data was then extracted from the digital platform and analysed. A statistical mathematical predictive model was utilized. A machine learning analytical model was programmed to obtain the results. The most common diagnoses were Breast Cancer (all stages, 34.5%), lung (10.1%) and colorectal cancer (7.7%). 67.1% of the pts were on active treatment at the time of the survey and 11.3% finished the treatment less than 6 months before. 66% of the pts experienced daily fatigue (described as mild, moderate and severe) and 17.2% experienced it weekly. As a direct result of fatigue, 10.1% of all pts reported that their ongoing treatments were delayed, stopped or changed (poor adherence). 337 (27%) of the total number of replies (mainly advanced breast and lung cancers pts) reported severe fatigue and 19% of them confirmed poor treatment adherence. However, better adherence was seen in the subgroup of pts which experienced mild to moderate fatigue. Conclusions: This survey describes the prevalence and adverse impact of severe fatigue present in certain cancer pts subgroups (advanced breast and lung cancers) which can alter significantly their adherence to planned treatments. Uniquely, while poor treatment adherence was observed in some cancer diagnoses, most of patients who experienced mild to moderate fatigue maintained their treatment schedule. Effective strategies and efforts should aim to solve this common side effect and its deleterious consequences.

Legal entity responsible for the study: The authors.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1774P Fatigue prevalence and adherence to treatment: A real-world data survey and mathematical model application

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Background: Fatigue is a common symptom reported by cancer patients (pts) and has been previously documented to affect patient’s quality of life.

Methods: A real-world data survey was designed to evaluate, from the pts perspective, the fatigue effect and treatment adherence. The survey was created in a digital format. This was sent randomly and replied anonymously by users of the Belong app, a dedicated social network for cancer pts and their caregivers. Belong leveraged both push notifications as well as DPROs (Digital patients reported outcome feature) which appeared on user’s apps dashboards for their increased engagement.

Results: 205 pts identified, 417 pts had complete irAE data: 136 pts with melanoma, 117 pts with NSCLC, 33 pts with RCC, and 111 pts with other cancers. irAEs occurred in 120/417 pts (28.78%). Gender, age at treatment, and smoking history were not associated with irAE. Incidence of pneumonitis and colitis was 3.84% and 6%, respectively. Pneumonitis was more common in NSCLC (p = 0.014). Rates of thyroid, hepatic, and neurologic irAE were 5.29%, 4.08%, and 0.84%. irAEs were associated with length of therapy (p = 0.03), and were more common in 29 pts treated with combination ICI (p < 0.001). For 366 pts with metastatic disease, irAEs were associated with longer survival: median OS 21.1 months vs 9.2 months (HR = 0.48, 95% CI: 0.35 - 0.66, p < 0.001). Thyroid toxicity (HR = 0.25, 95% CI: 0.10 - 0.59, p = 0.002) and hepatitis (HR = 0.32, 95% CI: 0.12 - 0.85, p = 0.023) were associated with longer OS.

Conclusions: Increased awareness of irAE patterns across different cancer and treatment types will allow for rapid identification and treatment of irAE.

Legal entity responsible for the study: The Ohio State University.

Funding: Has not received any funding.

Disclosure: G. Tincu: Advisory board: Blueprint. E.M. Bertino: Advisory board: Takeda, Boehringer Ingelheim. D.P. Carbone: Research funding: BMS; Paid advisory boards: Merck, AZ, Genentech. All other authors have declared no conflicts of interest.

Methods: Adverse events (AEs) were prospectively scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 scoring system by 2 dedicated medical oncolgists. AEs were evaluated at predefined time point from the start of CCRT up to 21 weeks after the start of CCRT. The cumulative toxicity load was measured by calculating the area under the curve (AUC) from AE score versus time functions. The AUC for each AE was obtained by multiplying the time and grade of each AE during that time. Mean AUCs per patient category (i.e. HPV status, tobacco use, localization of primary tumour and the use of ICT) were compared by Kruskal-Wallis testing.

Results: Forty patients (31 men), mean age 62.15 years, were included. The primary tumour site was located in 42.5% at the oropharynx and 45% were p16-positive. The AEs, with exception of xerostomia, typically developed in the second and third week of CCRT, with the intensity and frequency increasing during the treatment. Two weeks after ending CCRT (week 9), the side effects decreased. AEs were recorded in 85% (radiation dermatitis), 97% (orofacial pain), 89.7% (ostomatisis), and 97.5% (anorexia) of patients. Significant different mean AUCs were seen for hoarseness (non-oropharynx group, p = 0.027), alopecia (the use of ICT, p = 0.00114), sensory PNP (the use of ICT, p = 0.00016), diarrhoea (the use of ICT, p = 0.021), nausea (p16 positive, p = 0.047), and hoarseness (p16 negative, p = 0.015). For tobacco use no significant differences were seen.

Conclusions: This prospective trial recorded the maximum intensity and frequency of the different AEs, but also the evolution over time and the global AE load. More prospective trials with a larger number of patients are required to confirm the results.

Legal entity responsible for the study: University Hospital Antwerp.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Abstracts

1779P

Chemotherapy effect on daytime sleepiness and contributing factors in older adults with cancer

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Background: Excessive daytime sleepiness has been related with several functional and psychological disablities. The objective of this study was to determine the prevalence of excessive daytime sleepiness (EDS) among older Iranian patients with cancer and to analyze the effect of chemotherapy treatment on patients’ sleep problems. The relationship between sleep disturbances and physical activity, psychological factors, and demographic data were also explored.

Methods: This cross-sectional study, carried out in Cancer Institute of Iran, consisted of interviews with patients older than 60 years with a solid tumor, once prior to receiving chemotherapy and the second time after two cycles of chemotherapy. Questionnaires consisted of Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scales (HADS), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), and Eastern Cooperative Oncology Group performance status. Medical data were also gathered from hospital records. Logistic regression was used to identify predictors of excessive daytime sleepiness after chemotherapy.

Results: From the cases, 56.8% were female (n = 42). Mean participants’ age was 68.26 (SD = 6.77) and 78.4% had advanced tumors. Bivariate analysis did not show any significant association between education, tumor stage, and the number of comorbidities and daytime sleepiness after receiving chemotherapy. The results showed a significant association between EDS and receiving chemotheraphy. Initially EDS rate was reported as 8.1% which increased to 21.6% after chemotherapy (P < 0.001). Anxiety before chemotherapy and number of regions of recurrence, were identified as independent predictors of daytime sleepiness.

Conclusions: Given that, EDS prevalence increases with chemotherapy treatment, and this can affect patients’ quality of life and treatment outcomes, caregivers should bear in mind that older patients with cancer, especially those with anxiety and cancer recurrence, need special attention before decision making over starting chemotherapy.

Clinical trial identification: Research Deputy of TUMS proposal number: 22704.

Legal entity responsible for the study: Research Deputy of TUMS.

Funding: Research Deputy of TUMS.

Disclosure: All authors have declared no conflicts of interest.

1780P

Clinical and psychiatric validation of the BresAS questionnaire for symptom assessment among breast cancer survivors

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Background: Today a large number of breast cancer (BC) patients survive many years post diagnosis. The large number of women surviving many years post BC diagnosis has heightened interest in studying long-term effects of cancer on quality of life. A number of cancer-specific health-related quality of life (QoL) measures have been developed but these measures may not be appropriate for use with long-term survivors. With this study we want to evaluate the reliability, clinical and psychometric validity of the BresAS Questionnaire (BQ) among BC survivors.

Methods: The BQ is a quick, simple 10 items module for the assessment of long-term physical, psychological, sexual and cognitive effects that may influence quality of life (pain, anxiety, depression, fatigue, irritability, quality of sleep, impaired concentration, hot flashes, vaginal itching, other). The total BresAS score ranges from 0-100, with a low score indicating a better QoL. Patients were not stratified into predetermined clinically distinct groups. QoL data were collected alongside standard outcomes in patients undergoing treatment for BC. Patients complete the BQ, the FACT-ES questionnaire, case report forms for clinical and socio-demographic data at different time points during follow up visits. Reliability, and clinical and psychometric validity of the questionnaires are assessed by correlation analyses, exploration of known group comparisons, and responsiveness to clinical changes.

Results: From September 2015 to February 2016, 149 patients from three Italian oncology units were enrolled. Baseline questionnaires were returned from all and the majority of patients (n = 134 - 89%) completed the BQ and FACT-ES in less than 15 min. For reliability, Cronbach’s alpha coefficients for each scale were greater than 0.70 in all analyzed symptoms. Convergent validity of BQ showed Pearson’s r demonstrated a high correlation between intensity of symptoms and QoL, especially for pain and depression. No data were provided about reproducibility with test-retest study.

Conclusions: The BQ demonstrates sufficient validity and reliability to support its use to assess patient-reported outcomes and symptom assessment during planned follow-up clinical visits among BC survivors.

Legal entity responsible for the study: Giampiero Porzio.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Chemotherapy is the cornerstone of the treatment of patients with non-metastatic breast cancer; however, its toxicity may be limiting. It has been reported that some degree of toxicity is present in 98% of patients. To date, no predictors of this toxicity have been identified. Biosimpedance and Phase Angle (PA) are non-invasive procedures to evaluate nutritional status. The aim of this study was to associate the PA with chemotherapy toxicity during (neo)adjuvant treatment of breast cancer.

Methods: 172 patients were prospectively evaluated, 31 were excluded because they had metastatic disease or had received endocrine therapy. Only chemotherapy candidate were enrolled, patient selection criteria were PS 0-1, adequate liver, hematologic and renal function tests. The chemotherapy regimen consisted in AC-T at standard doses and schedules +/- capecitabine in triple-negative tumors. Toxicity was evaluated per NCI CTC v4.0. In all patients bioimpedance by SECA mBCA 514 and Inbody 720 were registered. Statistical analysis was done with SPSS v20.0.

Results: 141 were analyzed, median age was 50 years old, 53.2% of them received neoCT and 46.8% adjuvant CT. Regarding comorbid status, 10.6% had diabetes, 14.1% had hypertension, most of the patients were obese or overweight, median BMI was 27.7/kg/m² (13.79-39.84 kg/m²), median waist circumference was 97.30 cm (72-14.00 cm), 34% of the patients were diagnosed in early stage (I-IIIB). 24.2% were HER2-positive, 46.8% were ER-positive and 29.1% were triple negative. No grade of toxicity was present in 96.8%, 9.9% required hospitalization and in 2.1% toxicity led to death, most common side effects were gastrointestinal 85.8%, fatigue 70.9%, peripheral neuropathy 50.4% and hemaglobin 48.9%. PA average was 4.8° (2.8-6.2°). We found a correlation between PA and any grade of toxicity (p = 0.022). Patients with low PA had more G3-5 toxicity (p = 0.059), and more peripheral neuropathy (p = 0.045).

Conclusions: PA helps us to assess nutritional status and it seems to be useful as a toxicity predictor. However, external validation is necessary to confirm this benefit.

Legal entity responsible for the study: María Teresa Nieto Coronel.

Disclosure: All authors have declared no conflicts of interest.

1784P Rapid identification of bloodstream infection pathogens


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Background: Sepsis remains the leading cause of death in cancer patients. Biomarkers allow an objective and reliable possibility of rapid prediction of the septic process. The purpose of the study was to assess the prognostic significance of a rapid and accessible verification of the sepsis pathogens with biomarkers – procalcitonin and Platelias Candiida Ag Plus.

Methods: The study included 440 patients with clinical manifestations of the inflammatory response in intensive care units, oncological and oncohematological departments. Levels of procalcitonin and Platelias Candiida Ag Plus were determined by ELISA together with the blood sterility testing using the BacT/ALERT 3D analyzer.

Results: The most common pathogens (78%) were bacteria (K. pneumoniae, E. coli, less often other members of the Enterobacteriaceae family, P. aeruginosa, A. baumannii, E. faecalis, E. faecium, etc.). yeasts of Candida spp. – 22%, mixed pathogens – 7-3%, comprising 57.9% bacteria and 62.5% fungal-bacterial pathogens. Positive blood cultures were found in 106 (24.4%) patients. The results of a blood culture took on average 3 days. The use of two biomarkers allowed predicting a pathogen in the first hours after the blood collection. An increase in the levels of one biomarker in 137 (31.1%) patients with negative blood cultures indicated the presence of bacterial, fungal or bacterial-fungal infections. The blood culture examination together with determination of biomarkers improved verification of sepsis pathogens in 243 (55.2%) patients with clinical manifestations of sepsis and hastened preliminary results and empirical therapy.

Conclusions: The study of the blood culture and determination of levels of the biomarkers allowed the prediction of pathogens in 243 (55.2%) patients with clinical manifestations of sepsis. 197 (44.8%) patients with negative blood cultures and normal levels of biomarkers required additional tests.
Abstracts

Legal entity responsible for the study: Ministry of Health of the Russian Federation.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1788P Pathogens and characteristics of candidemia in hospitals of Rostov-on-Don: Multicenter study in Russia

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Background: Invasive candidiasis is a serious nosocomial infection developing generally in patients at risk; it is characterized by a severe clinical course and high (10–49%) additive mortality. It develops predominantly in immunocompromised, especially cancer, patients and patients in intensive care units. The purpose of the study was to analyze the etiology of invasive candidiasis and in vitro activity of caspofungin and azoles for isolates of Candida fungi.

Methods: Isolates were obtained in hospital departments in Rostov-on-Don and Rostov region in 2013–2016. Candida fungi were identified using MALDI-TOF MS; interpretation was performed according to CLSI 2012, M27-S4 criteria. Sensitivity test interpretation was performed using the Susitnit system (Træk Diagnostic Systems, England). Results: 92 Candida isolates were obtained from blood culture: C. albicans – 31.5% (29), and non-albicans - 68.5% (63), including C. tropicalis 30.2% (19), C. parapsilosis 28.6% (18), C. glabrata 19.0% (12), C. krusei 15.9% (10) and C. guilliermondii 6.3% (4). Fungal-bacterial associations were found in 5 cases; such combinations worsened the patient's condition and complicated the treatment. The table demonstrates comparative activities of caspofungin, fluconazole and voriconazole (susceptible – S, intermediate – I, resistant – R) in % to Candida spp.

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>Caspofungin S/ I/ R (%)</th>
<th>Fluconazole S/ I/ R (%)</th>
<th>Voriconazole S/ I/ R (%)</th>
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<tr>
<td>C. albicans</td>
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<td>100/ 0/ 0</td>
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<td>90/ 6/ 4</td>
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<tr>
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<td>98/ 0/ 2</td>
<td>82/ 4/ 14</td>
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<td>C. tropicalis</td>
<td>19</td>
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</tr>
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</tbody>
</table>

Conclusions: Candida non-albicans prevailed among invasive candidiasis pathogens (68.5%), which could be associated with the use of azole antifungal agents for the prophylaxis and empirical therapy. Dominating isolates showed decreased activity to caspofungin and azoles. Acquired resistance to azoles was noted for C. parapsilosis and C. albicans. Special attention should be paid to C. glabrata characterized by high lethality and high resistance rates. The results demonstrate the advisability of microbiological monitoring of invasive candidiasis pathogens.

Legal entity responsible for the study: Ministry of Health of the Russian Federation.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1787P Antiviral prophylaxis cannot reduce the risk of hepatitis B reactivation during chemotherapy for non-HCC solid tumor patients with lower HBV DNA titer: A retrospective cohort study

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Background: The high-risk factors related to HBV reactivation during chemotherapy include lymphoma, hematopoietic stem cell transplantation (HSCT), treatment regimen containing rituximab, a high HBV viral load before chemotherapy and baseline prechemotherapy HBsAg positivity. However, the role of antiviral prophylaxis in preventing HBV reactivation in patients with non-hepatocellular carcinoma (HCC) solid tumor and lower HBV DNA titer is unclear.

Methods: Between January 2011 and March 2018, all HBsAg seropositive patients with solid tumor receiving cytotoxic chemotherapy were retrospectively evaluated. The titer of HBV DNA and liver function were routinely examined before chemotherapy. The patients whose titer of HBV DNA was under 100 IU/ml were eligible. HBV reactivation, hepatotoxicity and disruption of chemotherapy attributed to HBV reactivation were compared according to antiviral prophylaxis.

Results: Of 170 consecutive patients eligible for, 102 were treated without antiviral prophylaxis. 55 patients were treated with entecavir, 7 lamivudine and 6 for defovir. The two groups were comparable in most clinical baseline characteristic including gender distribution, age, tumor types, tumor stage, the use of prednisone and/or anthracyclines. There was no significant difference between the two groups (P = 0.387). Patients without antiviral prophylaxis had a similar prevalence of HBV reactivation (6.8% vs 4.4%, P = 0.741) and severe hepatitis attributable to reactivation (3.9% vs 4.4%, P = 0.882). No patients died ultimately from fulminant hepatitis. Furthermore, no significant difference in disruption of chemotherapy was noted between patients with or without antiviral prophylaxis (3.9% vs 4.4%, P = 0.875).

Conclusions: For patients with non-HCC solid tumors and the titer of HBV DNA less than 100IU/ml before chemotherapy, antiviral prophylaxis failed to further reduce the reactivation of HBV. For such patients, regular monitoring of HBV viral load maybe more reasonable and cost-effective optimal choice.

Legal entity responsible for the study: Clinical Research Ethics Committee of Tianjin Medical University General Hospital and National Cancer Hospital.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1788P Prospective observational study to evaluate the persistence of treatment with denosumab (dmab) in patients (pts) with bone metastases (BM) from solid tumors (ST) in routine clinical practice: Final analysis


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Background: Persistence with dmab therapy may impact clinical efficacy in preventing skeletal-related events (SREs), but is undetermined in real-world.

Methods: Single-arm, prospective, observational, non-interventional study in pts with BM from ST (breast, prostate, lung, other) treated with dmab in real-world in Austria, Czech Republic, Hungary, Slovakia, and Bulgaria between 10/2012 and 05/2017.

Primary objective: persistence at 24 weeks (wks) (1–6 dmab subcutaneous injections; permissible intervals: 4.2-7 wks). Secondary objectives: persistence at 48 wks, time to non-persistence, calcium (Ca) / vitamin D supplementation, (serious) adverse drug reactions (SADRks) incl. non-adjudicated osteonecrosis of the jaw (ONJ) rate.

Results: 598 patients were included, 451 completed 24 wks, 387 completed 48 wks of study, 211 discontinued before 48 wks due to death (n = 80), loss to follow-up (n = 55), informed consent withdrawal (n = 7), dmab discontinuation (n = 56), (SADRks (n = 31), other reasons (n = 28). 10.9% (n = 65) had previous SREs. Persistence with dmab and safety are shown in the table. Persistence at 24/48 wks was 62.6/40.1% overall, 69.3/45.5% for breast, 69.3/46.6% for prostate, 26.1/10.9% for

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Table: 1785P

<table>
<thead>
<tr>
<th>Species</th>
<th>n</th>
<th>Caspofungin S/ I/ R (%)</th>
<th>Fluconazole S/ I/ R (%)</th>
<th>Voriconazole S/ I/ R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>29</td>
<td>100/ 0/ 0</td>
<td>82/ 3/ 15</td>
<td>90/ 6/ 4</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>18</td>
<td>98/ 0/ 2</td>
<td>82/ 4/ 14</td>
<td>88/ 11/ 1</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>19</td>
<td>100/ 0/ 0</td>
<td>90/ 5/ 5</td>
<td>100/ 0/ 0</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>12</td>
<td>95/ 5/ 0</td>
<td>86/ 8/ 5</td>
<td>N/A</td>
</tr>
<tr>
<td>C. krusei</td>
<td>10</td>
<td>83/ 4/ 13</td>
<td>N/A</td>
<td>100/ 0/ 0</td>
</tr>
</tbody>
</table>
Lung, and 40.7/21.1% for other cancers. Median (IQR) duration of dmab exposure was 509 days (168.0, 319.0) and 11 doses (6.0, 12.0). The most frequent reason for non-persistence was the violation of one time window. Overall, anaglesics use trended towards weaker anaglesics over time, with ~60% of pts requiring any anaglesics. Serum Ca remained within the normal range of 2.2 to 2.7 mmol/l throughout the study. ~70% of pts received Ca and vitamin D supplements at baseline, increasing to ~80% at dose 2 and steadily decreasing thereafter.

Table: 1782P

<table>
<thead>
<tr>
<th>Persistence, % (95% CI)</th>
<th>At 24 vks</th>
<th>At 48 vks</th>
<th>KM-median (95% CI) time to non-persistence, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=598</td>
<td>62.6 (58.4, 66.7)</td>
<td>40.1 (35.9, 44.4)</td>
<td>274.0 (232.0, 316.0)</td>
</tr>
</tbody>
</table>

Conclusions: Persistence (Diel, ESMO 2015) and ONJ rate (Stopeck, JCO 2010, Fizazi, 2016) in breast cancer patients undergoing ca and vitamin D supplements at baseline increased to ~80% at dose 2 and steadily decreased thereafter.

Editorial acknowledgement: Margit Hemschez, Hemschez Medicat Services, Vienna, Austria.

Legal entity responsible for the study: Amgen.


Background: Patients suffer from various oral complications in cancer treatments. Oral bacteria associate with the onset of dental focal infections and the progression of oral mucositis. Moreover, dental focal infections frequently associate with the onset of bacteremia, sepsis, and pneumonia systematically. The oral function degeneracy with these complications may become obstacle in cancer treatments. In Japan, the comprehensive oral management, including oral care and removal of dental focal infections, are performed in cancer patients. The aim of present study was to investigate the incidence of perioperative oral management in cancer patients.

Methods: In cancer patients who underwent POMs, medical records were reviewed and the incidence of oral complications and the efficacy of oral management were investigated retrospectively. This study protocol was approved by the Committee on Medical Research of Shinshu University.

Results: Two thousand and four hundred forty-four cancer patients underwent POMs (1,684 males and 1,080 females, mean age 65.9 years) were investigated in Department of Oncology. The incidence of oral complications and the efficacy of oral management were investigated retrospectively. This study protocol was approved by the Committee on Medical Research of Shinshu University. This study protocol was approved by the Committee on Medical Research of Shinshu University. This study protocol was approved by the Committee on Medical Research of Shinshu University.

Conclusions: The efficacy of oral management in cancer patients might be suggested based on the analysis of large number of patients in this study. However, the further investigation is needed to establish the adequate oral management guideline in cancer patients.

Legal entity responsible for the study: The Committee on Medical Research of Shinshu University.

Disclosure: All authors have declared no conflicts of interest.

1789P Correlation between fatigue evaluated with a visual analog scale (VAS) and quality of life (QoL) in cancer patients treated with biosimilar epoetin alfa for chemotherapy-induced anemia (CIA): The CIROCO study

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Background: Anemia often occurs in cancer patients receiving chemotherapy. Qol can be affected by symptoms of anemia, fatigue being the most common. Evaluation of QoL with validated tools (eg EORTC QLQ C30) is time-consuming. Correlation between fatigue assessed with a VAS and QoL is unclear. Aim: To determine the correlation between fatigue assessed by a VAS and QoL in cancer patients treated with biosimilar epoetin alfa (Sandoz) for CIA.

Methods: CIROCO was a non-interventional, prospective, multicenter study of adult patients (Full Analysis Set [FAS] population, n=538) with 2-2 cycles of chemotherapy planned after study inclusion, with CIA and receiving biosimilar epoetin alfa. Data were collected on day of inclusion (T0), and after 2–3 (follow-up; T1) and 4–6 chemotherapy cycles (end of follow-up; T2). Patients and physicians separately assessed fatigue using a VAS (range 0–10); patients assessed QoL with the EORTC QLQ C30 questionnaire.

Results: Data were reported for a subgroup of patients with solid tumors (FAS population, n=434). Mean (SD) hemoglobin (HB) at baseline was 9.7 (±0.8) g/dl. Mean (SD) increase in HB was 1.2 (±1.4) g/dl between T0 and T1 and 0.4 (±1.5) g/dl between T1 and T2. In the safety population (n=464), 151 (32.5%) had adverse events (AEs); n=320, 64 patients (13.8%) had serious AEs (n=144) and 14 patients (3%) experienced AEs considered related to study treatment (n=25). In the FAS population, between T0 and T2, mean (SD) change in fatigue VAS score (patient-reported) was 5.2 (±9.2%) and mean (SD) change in QoL was 29.8 (±59.0)%. The Pearson correlation coefficient for fatigue VAS score and QoL was -0.4993 (p=0.0001). Persistence was the violation of one time window. Overall, analgesics use trended towards weaker analgesics over time, with ~60% of pts requiring any anaglesics. Serum Ca remained within the normal range of 2.2 to 2.7 mmol/l throughout the study. ~70% of pts received Ca and vitamin D supplements at baseline, increasing to ~80% at dose 2 and steadily decreasing thereafter.

Conclusions: Biosimilar epoetin alfa was effective in this study, with improvements observed in HB and QoL. A correlation was observed between reduced fatigue assessed with a VAS and improved QoL.

Legal entity responsible for the study: Sandoz SAS.

Disclosure: N. Baize: Steering Committee member: CIROCO study. All other authors have declared no conflicts of interest.

1791P Quality of life, late effects, and related clinical factors among Korean colorectal cancer survivors

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Background: Colorectal cancer (CRC) is one of the most common cancers worldwide, and the third most common cancer in Korea. Although the number of Korean CRC survivors is estimated over 220,000, we have insufficient survivorship care program to improve survival and quality of life (Qol) of CRC survivors.

Methods: We started to build a prospective cohort on October, 2016, and collected clinicopathological and social factors from 263 Korean CRC survivors in Cancer Prevention Center, Yonsei Cancer Center, Seoul, Republic of Korea, Health-related Qol (HRQOL) was assessed using EORTC-QLQ C30, CR29, ELD14, CIP20, and EQ-VAS in 189 CRC survivors.

Results: Median duration of cancer survivorship was 70.7 months (range, 0-209.8), and 80 patients (42.3%) was long term CRC survivor (who live with cancer more than 5 years). In terms of HRQOL, median scale was 63.4 (standard deviation [SD], ±21.2) for global health, 81.7 (±15.3) for function, and 19.1 (±4.7) for symptoms in all CRC survivors. Symptom scale was higher (p<0.006) in long term survivors (21.8 vs 17.1, 0.0001). In female patients (21.4 vs 15.3, P=0.006). Higher stage of disease (III or IV) was related to higher symptom scale (21.6 vs 17.2, P=0.042), and lower

Disclosure: All authors have declared no conflicts of interest.

Editorial acknowledgement: Tony Reardon, Spirit Medical Communications Ltd.

Legal entity responsible for the study: Sandoz SAS.

Disclosure: N. Baize: Steering Committee member: CIROCO study. All other authors have declared no conflicts of interest.
functional scale (78.2 vs 84.3; P = 0.005). Frequently reported late effects were fatigue, insomnia, flatulence, bloated feeling, defecation problem, urinary frequency, sexual dysfunction in male, and sensorineuropathy. Insomnia (P = 0.018), sexual dysfunction in male (P = 0.003), and sensory neuropathy (P = 0.043) were significantly correlated with lower HRQOL scales. In the patients who were treated with oxaliplatin (n = 41), chemotherapy-induced neuropathy is related to worse global health (hazard ratio [HR], −3.29; 95% confidence interval [CI], 0.34–2.0; P = 0.002).

Conclusions: Various late effects are found in CRC survivors, and late effects may worsen the HRQOL of Korean CRC survivors. We are developing personalized and integrative management programs for CRC survivors.

Legal entity responsible for the study: Yonsei University College of Medicine, Ministry of Health & Welfare, Republic of Korea.

Funding: This study was supported by a grant from the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (16131020).

Disclosure: All authors have declared no conflicts of interest.

In a systematic review (LoE 1a) [3], controlled release oxycodone was associated with 11.9% of dizziness reports. A meta-analysis on immediate release oxymorphone and transmucosal fentanyl (7 % dizziness) favoured transmucosal fentanyl for breakthrough cancer pain, but did not differentiate between the painkillers for dizziness [4]. Effective analgesia with rare (1.8 to 7.5 %) events of dizziness was reported for intranasal fentanyl spray (LoE 1b) [5]. For long-acting analgesia, a systematic review favoured transdermal fentanyl over sustained release oral morphine (LoE 1a) [6]. A randomized controlled trial in bone metastases favoured the combination of two nonsteroidal anti-inflammatory drugs (NSAIDs) plus morphine (0.3% dizziness reports) over one NSAID plus morphine (>25%), presumably due to lower morphine need in two NSAIDs (LoE 1b) [7]. Finally, both hydromorphone and morphine had at least 15% of dizziness reports in a systematic review (LoE 1a) [8].


Legal entity responsible for the study: Rainer Spiegel.

Funding: Has not received any funding.

Disclosure: S.I. Rothschild: Honoraria for advisory boards to institution: Abbvie, Astrazeneca, Boehringer Ingelheim, BMS, Eisai, Eli Lilly, Merck, MSD, Novartis, Pfizer, Roche, Takeda; Research support: Astanza, Astrazeneca, Boehringer Ingelheim, BMS, Eisai. R. Sutter: Research grants: Swiss National Foundation (No 320030_169379), Research Fund of the University of Basel, Scientific Society Basel, Gottfried Bangerter-Rhyner Foundation; Personal grants: UCPharma, Destin Pharma GmbH; Stocks: Novartis, Roche. R. Kalla: Supported by the Swiss National Science Foundation (Grant #320030_173081). All other authors have declared no conflicts of interest.
**Table: 1795P**

<table>
<thead>
<tr>
<th>ALOPECIA</th>
<th>G0</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 (19%)</td>
<td>31(36%)</td>
<td>141(6%)</td>
<td>20 (23%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Our results reinforced previous evidences, showing that DCS is a good chance to prevent A during CT with anthracycline and/or taxane-based regimen and supported the wider use to all women with early stage BC.

**Legal entity responsible for the study:** Saverio Cinieri.

**Disclosure:** All authors have declared no conflicts of interest.
Legal entity responsible for the study: Goulburn Valley Health.
Funding: Has not received any funding.
Disclosure: The author has declared no conflicts of interest.

1799P
Febrile neutropenia management and concordance of institutional protocol with clinical practice
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Background: Febrile Neutropenia (FN) is an oncologic emergency defined as fever (oral temperature greater than 38.3°C) and neutrophil count < 500. It is one of the most common complications due to chemotherapy. FN is responsible for a considerable morbidity since 20% to 30% of the patients present complications that require hospitalization, with global hospital mortality around 10%. The objective of this study is to evaluate the initial approach to patients with FN in Oncology Day Unit (ODU), Service of Unplanned Care (SUC) and Emergency (ER) and compare the procedures performed in these patients with the protocol at our institution, which is based on guidelines (ESSM/NGC).

Methods: Retrospective, unicentric study, with the consultation of the clinical records of the patients who presented at ODU, SUC, ER and hospitalized in the Oncology ward with FN and cancer, during a period of 3 months in 2017. Patients were diagnosed by the attending physician with fever and N < 500 or with fever and N < 1000 and < 500, with a drop in the next 7 days.

Results: There were 21 episodes, all with solid tumors. The most frequent sites were lung (23%), breast (19%) and colon (17%). 61% of the patients had stage IV cancer. About half developed FN after 1st cycle of chemotherapy. 52% were male, with a mean age of 66.2 years (36-86). In terms of infectious site, the most frequent were fever without a focus (42%) followed by respiratory, skin and urinary tract infections. The MASCC was described in 20% of the cases. The first antibiotic therapy was performed in the SUC in 30% of the cases, in the ER in 35% and in the ODU in 10%. The hospitalization was performed in 11 patients with a median of 13 days of hospitalization. 8 patients underwent outpatient therapy, 3 of whom were subsequently hospitalized for FN. 60% of the patients were treated with G-CSF (N < 500). There were no deaths. The total agreement between clinical practice and the institutional protocol was 17/21 (81%).

Conclusions: Not all patients initiated antibiotic therapy at SUC. The description of the MASCC in the clinical record would be ideal for argument the therapeutic decision. We have found the overuse of G-CSF. This analysis served to investigate and improve our approach in FN. Protocols can improve the consistency and quality of care.

Legal entity responsible for the study: Centro Hospitalar Universitário Algarve.
Funding: Has not received any funding.
Disclosure: All authors have declared no conflicts of interest.

1800P
Salient features of an indigenous integrated inpatient model of delivery of supportive medicine services: A narrative review
R.D. Arora
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Background: The multiplicity of existing models has the potential to act as a deterrent to the development of an economically feasible and self-sustaining model of delivery of supportive medicine services. A uniformity in guidelines governing the delivery of these services is urgently needed.

Methods: The department recently submitted an application for recognition as an ESMO Designated Centre for Integrated Oncology and Palliative Medicine. This paper tries to highlight the features unique to this model and build upon the argument that the western model cannot be transplanted to the Indian setting.

Results: The following salient features were identified. The department encourages cancer directed therapy where feasible and prides itself as being ahead of the times in proposing a model which incorporates various aspects of disease-directed therapy, supportive care and palliative care (including quality end of life care provision) as a continuum. A larger role for the palliative medicine professional with direct involvement in critical areas of supportive oncology, procedures such as therapeutic paracentesis, pigtail insertion and interventional pain management techniques is envisaged. We have been able to cut down significantly on the time spent for the patient in obtaining an expert liaison with specialists from other super-specialities. A weekly multi-disciplinary conference is held where important cases are discussed with radiologists. The fact that advanced cancer patients (who are not receiving any cancer directed therapy) are being treated alongside those receiving active anti-cancer treatment has also been instrumental in creating an environment where there is no discrimination and stigma attached to the term palliation.

Conclusions: This model of delivery of supportive medicine services can act as a benchmark on which other regional centres can be modelled. The close involvement of professionals from disciplines such as anaesthesiology and radiology could be one of the important reasons in ensuring that this model has been successful in pushing the boundaries and managing patient issues which were traditionally considered outside the scope and ambit of palliative medicine.

Legal entity responsible for the study: Rabul D. Arora.
Funding: Has not received any funding.
Disclosure: The author has declared no conflicts of interest.

1801P
Novel online drug-drug interaction resource reveals clinically relevant interactions in > 20% of the searches
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1Pharmacy, Radboud University Medical Centre Nijmegen, Nijmegen, Netherlands.
2Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK, ‘Clinical Pharmacy, Deventer Ziekenhuis, Deventer, Netherlands.

Background: Patients with cancer are at risk to endure a drug-drug interaction (DDI) with their oncologic drugs. To facilitate the safe prescription and use of oncologic drugs, the freely available website www.cancer-druginteractions.org was introduced. Hereby we present the results of the use of this online DDI resource since the launch in June 1st, 2017.

Methods: For the most frequently used co-medication (>400) in cancer patients DDI potential was reviewed based on registration documents and scientific literature. A simple “traffic light” system was used to warn for the interaction potential. Background information and level of evidence is provided in the summary for each interaction.

Since the launch of the website the demographic use, the number of unique visitors and the number and severity of the interactions consulted are monitored every 3 months. Results: 549 targeted oncologyals used for ten different malignancies have been added to the website. These represent 24 targeted oral oncologyals and 10 monoclonal antibodies (MoAbs). Between June 1st, 2017 and March 31st, 2018 a total of 11,295 searches has been performed by 3,428 unique visitors from 35 countries. 78% of the searches were performed for oral oncologyals and 22% for MoAbs. 20.8% of the searches showed a potential interaction which requires action of the prescriber. The table gives an overview of the searches performed. Frequently checked co-medication were for example coumarins, PPIs, dexamethasone, metamizole and aspirin. Currently, a user-friendly app is under development which will be launched in October 2018.

Table: 1801P Overview of DDI queries
Interaction classification “traffic light” (%)
Green No clinically significant interaction 63.3
Yellow Interaction of weak/moderate intensity, no a priori dosage adjustment required 15.9
Amber Potential interaction which may require dosage adjustment or close monitoring 14.3
Red Do not co-administer 6.5
Countries consulted the website (%) United Kingdom 68
The Netherlands 16
Other European countries (top 3: Spain, France, Switzerland) 7
USA and Canada 3
Asia-Pacific (top 3: Australia, India, Hong Kong) 2
Other 4

Conclusions: Thus far, the DDI checker is being used all over the world. More than 20% of the performed searches showed a clinically relevant interaction. The freely available website, and the soon to be launched app, will facilitate health care professionals’ awareness of potential DDIs between oncologyals and frequently used co-medication and this supports safe prescription.

Legal entity responsible for the study: Radboudumc and University of Liverpool.
Funding: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Ipsen, Janssen, Pfizer, Roche, Sanofi.
Disclosures: S.H. Khoo: Advisory board: Merck, ViV, Corporate sponsored research: ViV, Gilead, Merck, Janssen; Other: Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Gilead, Ipsen, Janssen, Pfizer, Roche, Sanofi; N. van Erp: Research funding: Novartis, Astellas, Janssen Cilag, AstraZeneca, GSK, Boehringer Ingelheim, Gilead, Roche, Pfizer, Sanofi; F.G. Jansman: Advisory board: Amgen, Servier. All other authors have declared no conflicts of interest.
**Background:** In the field of adult patients, the risk factors for discordance with antiemetic guideline (GL) are reported to be hematological malignancy, older age, and the use of low emetic risk chemotherapy. However, there are scarce reports in the field of pediatric or adolescent and young adult (AYA) patients. Therefore, we assessed the concordance with antiemetic GL in the field of pediatric and AYA patients who received chemotherapy.

**Methods:** Using the Diagnosis Procedure Combination system in Japan, we identified patients with cancer aged 30 years or younger from July 2010 to March 2016. Patients’ data included age, gender, diagnosis, antineoplastic drugs, and antiemetic drugs. We assessed the concordance with antiemetic GL of ASCO in patients of each emetic risk category. Furthermore, we assessed the risk factors for discordance with antiemetic GL using logistic regression.

**Results:** A total of 21,106 patients who underwent chemotherapy were included. We classified patients into the following 6 age categories: 0-2 yo (n = 2,480), 3-5 yo (n = 1,983), 6-11 yo (n = 2,782), 12-17 yo (n = 3,495), 18-23 yo (n = 3,941) and 24-29 yo (n = 6,425). The median age was 16 (0-29) years old. The rate of concordance with GL in each emetic risk category was 18.2% in high risk (18 yo <, n = 2,331); 31.1% in high risk (18 yo <, n = 4130); 32.1% in moderate risk (n = 7,186), 52.0% in low risk (n = 5,806), and 51.6% in minimum risk (n = 1,451). In multivariate analysis, risk factors for discordance with antiemetic GL were high emetic risk chemotherapy, lower age (0-2 yo), hematological malignancies, and brain tumor.

**Table 1802P Risk factors for discordance with antiemetic guideline**

<table>
<thead>
<tr>
<th>Age category</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 yo</td>
<td>1.71</td>
<td>1.55-1.89</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3-5 yo</td>
<td>1.16</td>
<td>1.04-1.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>6-11 yo</td>
<td>1.12</td>
<td>1.02-1.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>12-17 yo</td>
<td>1.40</td>
<td>1.37-1.63</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>18-23 yo</td>
<td>1.13</td>
<td>1.04-1.23</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Disease**

<table>
<thead>
<tr>
<th>Type</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignancy</td>
<td>0.75</td>
<td>0.52-1.11</td>
<td>0.15</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>1.46</td>
<td>1.31-1.62</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hematological malignancy</td>
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<td>1.20-1.37</td>
<td>&lt;0.05</td>
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<tr>
<td>Breast cancer</td>
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<td>0.42-0.67</td>
<td>&lt;0.05</td>
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<tr>
<td>Ovarian/Cervical cancer</td>
<td>0.39</td>
<td>0.34-0.44</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Conclusions:** Our study identified substantial room for improvement in antiemetic practice and risk factors for discordance with antiemetic GL in pediatric and AYA patients. These identified risks are different from those in adult patients. Further investigation of the causes of this discordance is warranted, especially considering the unique background of this field.

**Legal entity responsible for the study:** Kyoto University.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1803P**

**Effectiveness of surgical glove compression therapy as a prophylactic method against nab-paclitaxel induced peripheral neuropathy**

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**Background:** No effective prophylactic managements are established for chemotherapy-induced peripheral neuropathy (CIPN). We developed a new, feasible method to prevent CIPN, using compression therapy with surgical gloves (SGs), called SG compression therapy, and recently reported that this method significantly reduced the overall occurrence of grade 2 or higher nanoparticle albumin-bound-paclitaxel (nab-PTX)-induced peripheral neuropathy (PNP) from 76.1% to 21.4%, as SGs decreased the microvascular flow to each fingertip (Breast Cancer Res Treat. 2016; 160:61-67). To avoid the major disadvantages of PN for the non-SG-wearing patients by a randomized controlled trial, we investigated the efficacy and safety of SG compression therapy for nab-PTX induced PN in a multicenter single-arm confirmed study, comparing to the incidence of 44.1% grade 2 or higher PN found in known literature, which we considered as a control group.

**Methods:** Primary breast cancer patients who received 260 mg/m2 of nab-PTX were eligible for this study. Patients wore two SGs of the same size, i.e., one size smaller than the size that fit their both hands, for 90 minutes. PN was evaluated at each treatment cycle using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the Patient Neurotoxicity Questionnaire (PNQ). The temperature of each fingertip was measured by using thermography.

**Results:** Between October 2016 to June 2017, 61 patients were enrolled, and 58 were evaluated. The incidence of sensory PN of CTCAE grade 2 or higher was as low as 13.8% following SG compression therapy. The occurrence rate of grade 4 or higher PNP responses, which indicate interference with activities of daily living, was also as low as 10.3%. A goodness-of-fit test using a chi-square test proved that the overall incidence of 13.8% grade 2 or higher PN obtained in this study is equal to 13% of the hypothesis-predicted value. All patients completed this study because they tolerated the compression from the SGs. SG compression therapy significantly reduced the temperature of each fingertip by 1.3–2.5° C compared to that before chemotherapy.

**Conclusions:** This study demonstrated that SG compression therapy is effective and safe for reducing CIPN.

**Clinical trial identification:** University Hospital Medical Information Network (UMIN) Number: 000024836.

**Legal entity responsible for the study:** Kamigata Breast Cancer Study Group.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Effect of oral magnesium supplementation on the kinetics of magnesium wasting induced by EGFR targeted antibody therapy for colorectal carcinoma (MAGNET trial)


Background: Progressive decrease of serum magnesium levels occurs in virtually all patients treated with anti-EGFR antibodies. This is supposedly linked to an inhibition of renal TRPM6 activity. This Mg loss may ultimately require stopping the anti-cancer treatment. In patients with congenital TRPM6 deficiency, high dose oral Mg supplementation allows to maintain acceptable serum Mg levels but may induce significant diarrhea. We hypothesized that oral Mg gluconate substitution may prevent or reduce Mg wasting due to anti-EGFR treatment in colorectal cancer.

Methods: We performed a prospective randomized multi-centre trial in patients treated with anti-EGFR antibodies for CRC evaluating the efficacy and tolerability of oral Mg gluconate for prevention and/or treatment of Mg wasting. Upon initiation of anti-EGFR treatment, patients were randomized to no intervention (arm A) or Mg gluconate 3 g bid (arm B). After occurrence of hypomagnesaemia grade 1, Mg gluconate 3 g bid was initiated in arm A, whereas the dosage was increased to 3g 6 times daily in arm B. The co-primary outcome variables were the slope of the serum Mg levels since baseline and the mean number of bowel movements per day. An a priori statistical analysis plan estimated the need to screen 180 patients (β = 0.90) to demonstrate an effect on serum Mg slopes.

Results: After excluding 7 patients during screening, 89 were randomized to arm A (no intervention) and 84 to arm B (Mg supplementation). In an ITT approach, the mean number of bowel movements was not different across arms. Oral Mg supplementation allowed to maintain acceptable serum Mg levels but may induce significant diarrhea.

Conclusions: This prospective randomized trial demonstrated that oral Mg gluconate 3 g bid. significantly decreased Mg wasting during anti-EGFR treatment in colorectal cancer, thereby delaying the occurrence of hypomagnesaemia. This treatment was well tolerated.


Legal entity responsible for the study: Belgian Group of Digestive Oncology.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV)


Background: Up to half of patients receiving chemotherapy of moderate or high emetic risk experience CINV despite optimal anti-emetic prophylaxis. Limited evidence suggests cannabinoid medicine in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabinoid (CBD) may improve efficacy and tolerance. The aim of this multi-centre, randomised, placebo-controlled, phase III/III trial is to determine efficacy and cost-effectiveness of an oral cannabinoid-rich THC/CBD cannabis extract for control of CINV.

Trial design: The target population is adult patients experiencing CINV during moderate and highly emetogenic chemotherapy regimens despite appropriate anti-emetic therapy, who are scheduled to receive at least 2 more consecutive cycles (A, B and, where applicable, C). Treatment consists of oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC11M) capsules or placebo TDS days 1 to 5, in addition to guideline-consistent anti-emetics, including rescue medications. Patients will start with 1 tablet PO TDS and can dose-titrate to a maximum of 4 tablets PO TDS based on nausea control and side-effects. In the pilot trial (N = 89), subjects are randomised for cycle A, cross-over for cycle B, and nominate preferred treatment for cycle C. The planned definitive trial (N = 250) will randomise subjects to investigational product or placebo for cycles A, B and C in a parallel design. The primary end-point is the proportion of patients gaining a complete response (no emesis and no use of rescue medications) (0 – 120h), with additional end-points of (i) complete response, (ii) no emesis, (iii) no significant nausea and (iv) no use of rescue medication during the a) acute, b) delayed, and c) overall phases of cycle A, B and C, (iv) adverse events, (v) quality of life, and (vi) cost-effectiveness. As of 09/05/2018, 52 of 80 patients have been recruited to the pilot study, with expected recruitment completion in 3rd quarter 2018. Funding: NSW Department of Health.

Acknowledgements: Trial participants, investigators and research staff. Drug supply by Tilray.

Clinical trial identification: ACTRN: 12616001036404.

Legal entity responsible for the study: University of Sydney.

Funding: New South Wales Department of Health.

Thoracic Malignancies, Other

Multiple primary cancers (MPC) in a series of lung cancer (LC) patient: Incidence and outcome

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Background: MPC is a frequent complication in cancer patients and a challenge for the treating physician. We aim to determine the incidence of MPC in a series of patients with LC treated at a tertiary lung cancer center.

Methods: We performed a retrospective observational study in patients with LC seen in the Thoracic Oncology Department between 2012 and 2017. We included all patients with biopsy-proven LC who had at least one additional primary cancer detected during the study period and evaluated according to the AJCC 8th edition staging system.

Results: We included 470 patients with LC, of whom 15 (3.1%) had at least one additional primary cancer. The median age was 67 years (range 53-86). The most common primary cancers were skin (n=4), lung (n=2), breast (n=2), colorectal (n=2), prostate (n=2), kidney (n=1), and other (n=3). The most common additional primary cancers were lung (n=8), skin (n=5), and breast (n=2). The median number of additional primary cancers per patient was 1 (range 1-3).

Conclusions: The incidence of MPC in patients with LC seen in our center is similar to other reports. However, the number of additional primary cancers per patient is lower than in other series. Further studies are needed to determine the incidence and impact of MPC in patients with LC.

1807P STELLAR: Final results of a phase II trial of TTFields with chemotherapy for first-line treatment of pleural mesothelioma

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Background: Tumor Treating Fields (TTFields) is an anti-mitotic, regional treatment modality, using low intensity alternating electric fields delivered non-invasively to the tumor using a portable, medical device. In vitro, human mesothelioma cells were highly susceptible to TTFields. TTFields have been shown to extend survival of patients with glioblastoma when added to chemotherapy.

Methods: The trial accrued 80 patients with unresectable, untreated mesothelioma. Patients were treated with continuous 150 kHz TTFields in combination with pemetrexed and platinum. Inclusion criteria included ECOG 0-1 and at least one measurable lesion according to modified RECIST. Patients were followed q6w (CT scan q6w) until disease progression. The primary endpoint was overall survival (OS). This single arm study assumed historical control with a median survival of 12.1 months (Vogelzang et al. 2003). The sample size provided 80% power with a two-sided alpha of 0.05 to detect an increase in median OS of 3.5 months.

Results: All patients had a minimum follow up of 12 months. Median age was 67 (range 27-78), 84% were male and 56% smokers. 16% (13 patients) had metastatic disease and 44% (35 patients) had an ECOG PS of 1. 66% (53 patients) had epithelioid histology. Compliance with TTFields was 68% (16.3 hours/day) during the first 3 months of therapy. Median OS was 18.2 months (95% CI 12.1-25.8) compared to 12.1 months in historical controls. Median PFS was 7.6 months (95% CI 6.7-8.6) compared to 5.7 months in historical controls. Partial responses were seen in 40.3% of patients and clinical benefit (PR + SD) was seen in 97.2% of patients. No device-related serious adverse events (AEs) were reported. Expected TTFields-related dermatitis was reported in 46% (37 patients). Only 4 patients (5%) had grade 3 dermatitis.

Conclusions: The study met its primary endpoint of significant extension of survival for previously untreated mesothelioma patients. Secondary efficacy endpoints were also improved compared to historical control. The study demonstrated no safety concerns for the combination of TTFields to the thorax with chemotherapy. These results support the addition of TTFields to chemotherapy in the first-line treatment of malignant pleural mesothelioma.

Therapy: NCT02397928.

Legal entity responsible for the study: Novocure.

Funding: Novocure.

Disclosure: J.G. Aerts: Advisory boards: BMS, MSD, Roche, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Amphera; Stock owner: Amphera. R. Ramlau: Consultant: Novocure. All other authors have declared no conflicts of interest.

Role of evaluating tumor infiltrating lymphocytes, programmed death-ligand 1 and mismatch-repair proteins expression in malignant mesothelioma

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Background: Malignant mesothelioma (MM) is an aggressive and fatal tumor, mainly related to prolonged exposure to asbestos. MM can induce infiltration of immune cells and immunity-mediated death. Tumor microenvironment plays a major role in neo-plastic progression, favoring tumor cell evasion from adaptive immunity and T-cell checkpoint pathways. Expression of programmed death-ligand 1 (PD-L1) on tumor cells and tumor-infiltrating lymphocytes (TILs) has been described in literature. Cancer cells expressing PD-L1 increase apoptosis of antigen-specific human T-cell clones and inhibit CD4+ and CD8+ T-cell activation, thus decreasing the immune action on the tumor. Some mismatch repair-deficient tumors make them sensitive to immune checkpoint blockade, because of the increased number of neoantigens encoded by cancers, which enhances anti-tumor response.

Methods: The aim of this study is to analyze the expression of PD-L1 on both tumor cells and TILs and to characterize TILs. Furthermore,Mismatch Repair (MMR) protein expression was evaluated. Immunohistochemistry was applied using the automated system BenchMark XT (VENTANA) for PD-L1 (DAKO, clone 22C3), CD4, CD8 and MLH1; H, MSH2, MSH6, PMS2.

Results: 55 malignant mesotheliomas, 10 from women and 45 from men, were studied. The range of age was 43-88 years old. Tumors consisted of 44 epithelioid, 3 sarcomatoid, 7 biphasic and 1 desmoplastic. 51 were localized to pleura and 4 to peritoneum. 18 tumors were in stage I, 13 in stage II, 15 in stage III and 5 in stage IV. For 4 cases the stage was not evaluable. Our results showed expression of PD-L1 ≥50% in tumor cells in 9 cases (5 epithelioid, 2 sarcomatoid, 1 biphasic and 1 desmoplastic). In two of these the positivity was observed both in tumor cells and in TILs. 15 tumors were negative and 31 showed a positive staining ≥1. A presence of TILs was observed in 53 cases. A prevalence of CD4+ expression was highlighted in 45 cases. 6 of them showed elevated expression of PD-L1 (≥50%). Alteration in MMR staining was not found.

Conclusions: Our data underline the role of tumor immune microenvironment and its characterization in MM and open the possibility to use combined therapies according to different PD-L1 expression.
Background: Malignant pleural mesothelioma (MPM) is an aggressive asbestos-related disease that is challenging to diagnose. The value of tumour biomarkers in pleural effusion fluid is limited in patients with the disease. We have developed and validated a deep learning model that can predict a diagnosis of MPM using pleural tumour biomarkers and patient characteristics.

Methods: This retrospective cohort study included patients who underwent thoracentesis for undiagnosed pleural effusion at a single tertiary medical centre between September 2014 and August 2016. The diagnosis was established by two independent physicians who were blinded to the pleural effusion data. A deep learning model was constructed to differentiate MPM from other diseases and evaluated using biomarkers in pleural effusion (carcinoembryonic antigen, cytokeratin 19 fragment, soluble mesothelin-related peptides, lactate dehydrogenase), total protein in pleural effusion, and patient age and sex as input parameters. Missing data were handled by single imputation. The model consisted of three hidden layers and was trained for 4000 steps. The data were divided into a training set and a test data set and processed using Tensorflow 1.7.0 and Python 3.6.2 software. The performance of the model was evaluated by accuracy and the area under the receiver-operating characteristic curve (AUROC).

Results: Twenty-eight of the 188 patients who underwent thoracentesis were diagnosed to have MPM and divided into a training data set (containing first 150 records with 20 MPM patients) and a test data set (38 records with 8 MPM patients). The accuracy values for the training and test data sets were 0.99 and 0.97, respectively, and the respective AUROC were 1.00 and 0.92.

Conclusions: Our deep neural network model had good diagnostic accuracy for MPM and may help in making a definitive diagnosis when there is an indication for invasive pleural biopsy.

Legal entity responsible for the study: Hyogo Prefectural Amagasaki General Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Elective nodal irradiation as adjuvant radiotherapy for advanced thymomas and thymic carcinomas

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Background: Elective nodal irradiation (ENI) targeting the entire mediastinal and supraclavicular regions is not routinely recommended as adjuvant treatment for thymomas due to the low rate of lymphogenous metastasis. Also, it is not widely used for thymic carcinomas since the majority of nodal disease metastasized to anterior mediastinal lymph nodes. However, there are little clinical data directly comparing the local radiation therapy (LRT) fractionation; patients with a positive resection margin received a further 4–10 Gy. Survival outcomes were evaluated by immunohistochemistry and stratified by the proportion of positive tumor-infiltrating CD8+ T cells. Strong membranous reactivity of the PD-L1 antibody in ≥ 16% of tumor cells was considered “positive”. The association between the PD-L1 expression and the clinicopathological features was investigated.

Results: The PD-L1 expression was positive in 22 patients (27%) and negative in 59 patients (73%). PD-L1 positivity was significantly associated with type B2 and B3 thymomas (p = 0.001) and stage III and IV disease (p = 0.048). In addition, PD-L1-positive tumors showed a significantly higher maximum standardized uptake value (SUVmax) than PD-L1-negative tumors (p = 0.026). The 5-year disease-free survival (DFS) rate was 83% in PD-L1-positive patients and 88% in PD-L1-negative patients, showing no significant difference (p = 0.576). Furthermore, PD-L1 positivity was not an independent prognostic factor for the DFS on a Cox proportional hazard analysis (p = 0.590).

Conclusions: A strong expression of PD-L1 in thymomas was significantly associated with type B2 and B3 and higher pathological stages. In addition, PD-L1 positivity was associated with an increased SUVmax of the tumor. However, patients with PD-L1-positive thymomas did not show a significantly worse prognosis than those with PD-L1-negative tumors.

Legal entity responsible for the study: Department of Thoracic Surgery, Nagoya University Graduate School of Medicine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

The impact of PD-L1, TGF-β expression and tumor-infiltrating CD8+ T cells on clinical outcome of patients with advanced thymic epithelial tumors

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Background: Thymoma and thymic carcinoma are indolent and poorly responsive to chemotherapy. PD-1/PD-L1 inhibitors have shown remarkable clinical benefit in several cancers. However, many immunomodulatory molecules have been identified to affect the efficacy of immunotherapy. This study aimed to examine the expression of PD-L1, transforming growth factor-β (TGF-β), and CD8+ tumor-infiltrating lymphocytes (CD8+ TILs) in patients with advanced thymic epithelial tumors (TETs) and evaluated their prognostic roles.

Methods: Retrospective analysis was performed on 20 patients with stage IV thymic carcinoma and 13 patients with stage III/IV invasive thymoma. Tissue biopsies were obtained before the first-line chemotherapy. The expression level of PD-L1, TGF-β and CD8+ T cells were assessed using IHC. The high or low expression was separated by the median value of the IHC score. The outcomes including objective response rate (ORR), overall survival (OS) and progression-free survival (PFS) were then analyzed.

Results: The proportion of PD-L1 high was relatively higher in patients with advanced thymic carcinoma compared to patients with advanced invasive thymoma (65.0% vs 46.2%, p = 0.472). The proportion of TGF-β high in patients with thymic carcinoma was significantly higher than that in patients with invasive thymoma (65.0% vs 15.4%, p = 0.011). 5 of 7 patients in advanced thymic carcinoma with low PD-L1/TGF-β expression exhibited high level of CD8 staining. Among all patients, the median OS was 29.5 months (95% CI: 20.5–39.5) with PD-L1 high versus 42.6 months (95% CI: 0.983) (p = 0.186) with PD-L1 low. The median OS was 29.5 months (95% CI: 18.6–40.4) with TGF-β high versus 62.9 months (95% CI: 15.6–110.1) (p = 0.052) with TGF-β low. Among patients in advanced thymic carcinoma, the ORR was 30.0% with CD8+ TILs high versus 14.3% with CD8+ TILs low (p = 0.603), the median PFS was 13.3 months with PD-L1 high versus 23.5 months (p = 0.043) with PD-L1 low. Furthermore, the ORR was 40.0% with TGF-β low versus 16.7% with TGF-β high (p = 0.338).
Conclusions: Our results showed the prognostic role of PD-L1, TGF-b and CD8+ TILs in patients with advanced TETs, and their potential for development of anti-PD-1/PD-L1 therapies.

Legal entity responsible for the study: Jie Wang.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1813P  
Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC)

B.C.M. Hermans 1, J.L. Derks 1, E. Thunissen 2, R.J. van Suylen 3, M.A. den Bakker 4, J. Derks et al. CCR 2018. IHC staining for PD-L1 LCNEC were recognized, the co-mutated TP53 and RB1 and the STK11/KEAP1 (pre- dominantly RB1 wildtype) group. We investigated PD-L1 expression in a well characterized stage IV LCNEC cohort and compared expression in the two subtypes.

Methods: Pan-pancreas consensus pathology revision was performed along with targeted next generation sequencing (TNGS) for genes TP53, RB1, STK11 and KEAP1 and immunohistochemical (IHC) analysis of RB1, on pretreatment tumor samples of stage IV LCNEC treated with chemotherapy. OS in months (95% CI) 8.9 (4.2-13.6) was performed according to standard protocols on the DAKO autostainer and evaluated by an experienced screener. Tumors were scored positive if > 1% of tumor cells showed any membranous staining. Overall survival (OS) was evaluated by Kaplan Meier analysis and differences estimated with Log-Rank test. Cox-regression analysis included PD-L1, age and gender.

Results: PD-L1 IHC expression data could be generated in 98/147 confirmed LCNEC samples along with RB1 IHC (n = 97) of which 77 passed quality control for TNGS. PD-L1 expression was positive in 16/98 cases (16%), n = 5 (5%) with >50%, n = 11 (11%) having >1-50% and n = 82 (82%) with 1% membranous staining, respectively. No significant correlation of PD-L1 expression with molecular subtype of LCNEC was identified (Table). PD-L1 expression was correlated with a superior OS, hazard ratio (HR) 0.54 (95% Confidence interval (CI), 0.31-0.96) P = 0.034.

Table: 1813P Expression of PD-L1 in LCNEC, correlated to molecular data

<table>
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<th>PD-L1</th>
<th>OS in months (95% CI)</th>
<th>P-value</th>
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<td>PD-L1 +</td>
<td>8.9 (5.7-7.6)</td>
<td>0.31-0.96</td>
</tr>
<tr>
<td>PD-L1 -</td>
<td>6.6</td>
<td>-</td>
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</table>

Conclusions: PD-L1 expression was positive in 16% of stage IV LCNEC tumors. PD-1 expression is an independent process from LCNEC molecular subgroups. In LCNEC patients with PD-L1 expression superior OS is observed compared to those with negative PD-L1 tumors.

Legal entity responsible for the study: Maastricht University Medical Center, Department of Pulmonary Disease.

Funding: Bristol-Meyers Squibb.

Disclosure: All authors have declared no conflicts of interest.

1814P  
Computed tomography features of resected lung adenocarcinomas with spread through air spaces

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Background: Spread through air spaces (STAS) is a recently-recognized invasive pattern of lung cancer defined as ‘micro papillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces.’ Since STAS has been shown to be a significant prognosticator for the postoperative survival, predicting STAS preoperatively by computed tomography (CT) might help determine the optimum surgical procedures.

Methods: Information on STAS and preoperative CT were available 327 patients with resected lung adenocarcinomas. STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor. The association of STAS with CT characteristics, such as vascular convergence, ground glass opacity (GGO), air bronchogram, notch, pleural indentation, spiculation, and cavitation, was analyzed.

Results: Among the 327 patients with resected adenocarcinomas, 191 (58.4%) were positive for STAS. A univariable analysis demonstrated that STAS-positive adenocarcinomas were significantly associated with a larger radiological tumor diameter (P = 0.02), the presence of vascular convergence (P = 0.01), notch (P < 0.01), pleural indentation (P = 0.03), spiculation (P < 0.01), and the absence of GGO (P < 0.01) compared with STAS-negative ones. In a multivariable analysis, the presence of notch (P = 0.01) and the absence of GGO (P < 0.01) were shown to be significantly associated with the STAS phenomenon. The odds ratio for STAS of notch-positive and GGO-negative adenocarcinomas against notch-negative and GGO-positive ones was 5.01 (P < 0.01).

Conclusions: The presence of notch and the absence of GGO were independently associated with the STAS phenomenon. These results will prove helpful in identifying STAS-positive adenocarcinoma by CT prior to surgical resection.

Legal entity responsible for the study: Gouji Toyokawa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1815P  
Comparative proteomic analysis of acetylation profiles in esophageal squamous carcinoma cells

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Background: To explore the different expression of proteins and the acetylations between esophageal squamous carcinoma cells (ESCCs) and cancer stem-like cells (CSCs) by proteomic analysis.

Methods: The Eca109 cells were divided into CSCs group and ESCCs group by using serum-free culture and serum culture. We measured the CD44 expression levels, CCK8 cell proliferations and plate cloning formation to identify the characteristics of cancer stem cells. Furthermore, tandem Mass Tags (TMT)-based quantitative proteomics and bioinformatic analysis were used to detect proteomics and bioinformatic analysis. Results: The positive rate of CD44 and CCK8 cell proliferation in the CSCs group were higher than ESCCs group (P < 0.05). The plate cloning formation showed that the values of D6, D9, N and S2 were significantly higher in the CSCs group, and the radiation sensitization ratio was 1.556. Furthermore, 5,262 proteins were identified in the two groups in total. The up-regulation of 187 proteins and down-regulation of 83 proteins were detected in CSCs group (> 1.5 times). Bioinformatic analysis further revealed that those quantifiable proteins were mainly involved in multiple biological functions and metabolic processes, including steroid biosynthesis, protein processing in endoplasmic reticulum, metabolic pathways and oxidative phosphorylation pathways. In addition, 53 acetylated sites were increased and 67 acetylated sites were decreased in CSCs group (> 1.5 times). Those acetylated sites were involved in the regulation of DNA metabolic process, the function of cell adhesion, glycosylation and glau- neogenic pathway.

Conclusions: We provides a global survey of proteins and acetylations in ESCCs and CSCs. These proteins and acetylations may be related to the radiosensitivity, recurrence and metastatic of esophageal squamous carcinoma and could be a potential new target for esophageal squamous carcinoma.

Legal entity responsible for the study: Jiancheng Li.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Survival outcomes for patients with lobectomy and wedge resection in lung cancer

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Background: Lobectomy is the most performed surgical procedure for lung cancer, however, patients who are eligible to lobectomy undergo wedge resection. The purpose of this study is to compare the survival of patients who underwent wedge resection versus lobectomy.

Methods: Using SEER18 Registries Research Database, we collected the data of 638 patients diagnosed with lung cancer from 2010 to 2012. Out of these patients, 423 underwent wedge resection, while 156 had lobectomy. We assessed the prognostic value of age, sex, stage, laterality and primary site. Kaplan-Meier method was used for survival analysis.

Results: Patients who underwent lobectomy had significantly better 3-year relative survival rates (47.2% vs 37.9%) and 5-year relative survival rates (29.9% vs 25.7%). Subgroup analysis revealed better survival rates among female patients and stage II lung cancer. However, no advantage was associated with specific age, laterality, or primary site.

Conclusions: Patients who underwent lobectomy were associated with better 3-year relative survival rate compared to wedge resection.

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Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Table: 1816P Comparison of 3-year relative survival rates between patients undergoing wedge resection vs lobectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Wedge resection</th>
<th>Lobectomy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male Females</td>
<td>20.2 33.3</td>
<td>33.5 64.4</td>
<td>0.000**</td>
</tr>
<tr>
<td>Stage I II III IV</td>
<td>- 50.6% 26%</td>
<td>- 34.1% 52.2% 47.4%</td>
<td>0.01*</td>
</tr>
<tr>
<td>Age 20-39 40-59 60-79 &gt;80</td>
<td>30.9% 27.4% 27.1% 22.6%</td>
<td>66.9% 57.5% 42.3% 30.9%</td>
<td>0.416</td>
</tr>
<tr>
<td>Primary site Upper Lobe Middle Lobe Upper Lobe Lung, NOS</td>
<td>24.1% 17.5% 29.6% 25.6%</td>
<td>49.9% 46.9% 46.2% 44.9%</td>
<td>0.934</td>
</tr>
<tr>
<td>Laterality Right Left</td>
<td>25.4% 28.3%</td>
<td>49.7% 43.4%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Statistically significant at p-value ≤ 0.05.
**Highly significant at p-value ≤ 0.001.
1819O Tumor growth rate and lenvatinib efficacy in radioiodine-refractory differentiated thyroid cancer
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1820PD Synergistic anti-cancer activity of tyrosine kinase inhibitors and paclitaxel with radiation on anaplastic thyroid cancer in vitro and in vivo
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1821PD Updated efficacy and safety data of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600E-mutated anaplastic thyroid cancer (ATC)
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1823P

Synergistic anti-cancer effect of histone deacetylase inhibition and blockade of the glycolytic pathway

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Background: Advanced cancer has been shown to have a higher percentage of epigenetic changes than are genetic mutations. Preclinical models have showed that combination of the HNHA (N-hydroxy-7-(2-naphthylthio) heptanoic acid) and 2DG (2-Deoxy-D-glucose) is a play crucial role in ATC (cancer stem-like cell, anaplastic thyroid cancer). The aim of this research is to study that capase cleavage dependent apoptosis by combination therapy of HNHA and 2DG in ATC.

Methods: ATC cell lines were exposed to HNHA and 2DG alone or combined, and cell viability was determined by MTT assay. Synergistic anti-cancer effects of the combination therapy on cell cycle and intracellular signaling pathways were estimated by flow cytometry and immuno blot analysis. The ATC cell lines xenograft model was used to examine the anti-tumor activity in vivo.

Results: Consequently, our results suggest that combination therapy of HNHA and 2DG is synergistically decreased cell viability in ATC cell, and also significantly induced apoptotic cell death in this cells, as showed by the cleavage of caspase-3. HNHA and 2DG combination was reduced anti-apoptotic factor in these cells. Thus, combination therapy with HNHA and 2DG most significantly reduced tumor volume in ATC cell xenografts.

Conclusions: The current study suggests that HNHA and 2DG combination treatment was more effective than treatment with the HNHA or 2DG alone. These findings may offer a new therapeutic approach to ATC include the cancer stem-like cells.

Legal entity responsible for the study: Sang Yong Lee.

Disclosure: All authors have declared no conflicts of interest.

1824P

Lenvatinib and pembrolizumab as safe and effective combination treatment in 8 patients with metastasized anaplastic (ATC) or poorly differentiated thyroid carcinoma (PDTC)

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Background: Introduction: Anaplastic thyroid carcinomas (ATC) and metastasized PDTC have a dismal prognosis of only few months despite extensive multimodal therapy. The tumors are high-proliferative and acquire numerous somatic mutations (often over several hundred mutations). These specifics implicate a special sensitivity of the tumors towards anti-angiogenic therapies and immune checkpoint inhibitors.

Methods: In the presented cases, we have combined anti-angiogenic therapy with lenvatinib and the immune checkpoint inhibitor pembrolizumab in 8 patients with metastasized ATC (n = 6) or metastasized PDTC (n = 2). All patient tumors had more than 100 somatic mutations as identified by whole exome sequencing (WES) and PD-L1 > 1%. Lenvatinib was started at 24 mg/kg BW and reduced to minimally 14 mg/kg BW upon appearance of intolerable side effects (uncontrollably high blood pressure, weight loss, loss of appetite). Pembrolizumab was started 3 - 8 weeks later and was given at a fixed dose of 200 mg every 3 weeks. Maximum treatment duration with this combination was 27 months (27, 24, 19, 11, 7, 5, 1, 1 month) and 6 patients are still on therapy.

Results: No continuous III/IV toxicities were seen with the combination treatment. Weight loss (3 pts) and uncontrollably high blood pressure (3 pts) were normalized after reducing lenvatinib doses. One patient died 5 days after the first dose of pembrolizumab due to disease progression of the cervical tumor. All other patients have reached at least a SD (n = 2), most patients had reached a PR (n = 4) and one patient has reached a complete remission (CR). The majority of patients is still on therapy (27, 24,19,7,6 and 3 months), implicating this combination treatment as a safe and effective treatment regimen for this extremely bad prognostic patient cohort.

Conclusions: Our results implicate that a combination of lenvatinib and pembrolizumab is safe and effective in patients with ATC or PDTC. The combination treatment shall now be systematically examined in a phase II clinical trial (ATLEP) in ATC/PDTC patients.

Legal entity responsible for the study: Uniklinik Freiburg.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1825P

Both HIF-1α and GAB1 can regulate pim-1 in the papillary thyroid carcinoma

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Background: As a oncogene, Pim-1 has been proved to play key role in proliferation, apoptosis and angiogenesis. Thyroid cancer represents the most common malignancy in the endocrine system, and a marked increase in the incidence has occurred in recent years. Among them, papillary thyroid carcinoma (PTC) is the most common form. So it is worthwhile to discuss the function of Pim-1 in the development and progression of PTC.

Methods: 34 PTC patients were selected to investigate the levels of Pim-1, HIF-1α and GAB1 protein by IHC. After hypoxia treatment for 24h, Westernblot was carried out to detect the Pim-1, HIF-1α and GAB1 in the PTC cell BCPAP and TPC-1. BCPAP was transfected with GAB1 shRNA and Full-length vector to achieve GAB1 knockdown and overexpression. CCK-8 assay was used to measure the cell proliferation. The migration and invasion capacity were tested by wound-healing and transwell methods respectively.

Results: Both Pim-1 and HIF-1α were overexpressed in the PTC tissues and Pim-1 levels were significant correlated with HIF-1α. Meanwhile, Pim-1 had a significant relationship with the tumor number - patients with multiple tumor have a higher Pim-1 level than that have solitary tumor and HIF-1α showed a significant correlation with patients’ age. After bioinformatics screen, we found that there were 4 hypoxia response elements (HRE) in the Pim-1 promoter area, which suggested HIF-1α could transcriptional regulate Pim-1 directly. Moreover, hypoxia could significantly drive HIF-1α and Pim-1 elevation in both BCPAP and TPC-1. GAB1 was found to express higher in PTC tissues than that in the adjacent normal tissues and GAB1 level was significant associated with the tumor size. Moreover, Pim-1 expression was significantly decrease and increase after GAB1 knockdown and overexpression in BCPAP. Meanwhile, GAB1 did not affect the cell viability but exerted a strong effect on the migration and invasion capacity of BCPAP. However, there was no change in GAB1 expression after hypoxia treatment in both BCPAP and TPC-1.

Conclusions: Taken together, our current data showed the important role of Pim-1 in the PTC. It also can be deduced that both HIF-1α and GAB1 are involved in the upstream regulation of Pim-1, but the detailed mechanism are different, which depended on the different tumor microenvironment.

Legal entity responsible for the study: Zhejiang Cancer Hospital.
**Annals of Oncology**

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**Disclosure:** All authors have declared no conflicts of interest.

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**1826P Increase in thyroid cancer (TC) incidence in Cyprus: Overdiagnosis or true increase of clinically relevant TC?**

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**Background:** An increase in Thyroid Cancer (TC) incidence has been seen in most countries worldwide. The same has also been reported for Cyprus 1. The most fundamental issue is whether this increase is due to increased investigations (opportunist sickness) and overdiagnosis of small incidental TC or due to a true increase in clinically relevant TC.

**Methods:** Data collection in the Cyprus Cancer Registry (CyCR) is guided by the MECC Manual of Coding and Staging for Cancer Registration. In this study, we considered only invasive cancer (ICD-O-3 behavior code = 3). From 1998 until 2015 there were 2490 thyroid cancer diagnoses recorded in the CyCR, from which 2309 (92.7%) had histology and staging information recorded. We undertook analysis of the staging of recorded cases in the CyCR and calculated APC (Annual Percent Change) to ascertain whether the increase seen is due to small localized cancers (suggesting opportunistic screening) or also true for locally advanced / lymph node positive tumours.

**Results:** The APC for all patients is 11.1% yearly increase. When analyzing by stage, the APC for regional (i.e. locally advanced) TC was 16.3% higher than for localized disease at 11.9%. There was also a statistically significant increase in metastatic cases, but this needs to be interpreted with caution due to the small number of patients with metastatic disease (data not presented).

**Conclusions:** Analysis of the Cyprus Cancer Registry data provide evidence of a large increase in TC in Cyprus, being due to an increase of both localized and also locally advanced tumours. It is therefore likely that the increase in TC is not only due to opportunistic screening, but also due to a true increase of larger, clinically relevant tumours.

**Legal entity responsible for the study:** Charalambous, HC

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1827P Surgery for lymph node metastases of sporadic medullary thyroid carcinoma**

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**Background:** Medullary thyroid carcinoma (MTC) arises from malignant proliferation and differentiation of C cells, approximately 2% of all thyroid malignancies. Calcitonin (CT) and calcitonin-like proteins (CEA) secreted by C cells are the main secretory product and serves as a marker for the diagnosis of this disease. It is also used in the follow-up of MTC patients after thyroidectomy for the identification of relapse or progression of disease. Compared with other thyroid cancers, MTC has unique biological characteristics and is insensitive to radiotherapy, chemotherapy and iodine therapy. Surgical intervention is currently the only effective, curative treatment for medullary thyroid cancer. The 2015 American Thyroid Association recommended total thyroidectomy and different range of lymph node dissection, but controversy remains surrounding the indication for prophylactic lateral lymph node dissection. This study was performed to analyze the risk factors for cervical lymph node metastases and predict the indication for prophylactic lateral neck dissection in patients with sporadic medullary thyroid carcinoma (SMTC).

**Methods:** The aim of this study was to analyze the risk factors of cervical lymph node metastases and also to predict the indication of prophylactic lateral neck dissection in SMTC patients.

**Results:** Metastases rates in central and lateral compartment were 46.2% (30/65) and 40.0% (26/65), respectively. Univariate analysis showed the incidence of cervical lymph node metastases was significantly higher in patients with tumor size >1cm, tumor multifocality and thyroid capsule invasion. Multivariate analyses revealed that only thyroid capsule invasion was an independent predictive factor for central compartment metastases (p < 0.001, OR = 11.080) and lateral neck metastases (p < 0.001, OR = 9.067). Moreover, the possibility of central compartment metastases was higher when preoperative value of serum carcinoembryonic antigen (CEA) was above 30 ng/mL (60% vs 34.3%, p = 0.038). Conclusions: The medullary thyroid carcinoma has a high incidence of cervical lymph node metastases. Prophylactic lateral node dissection is necessary in patients with thyroid capsule invasion or with high value of serum carcinoembryonic antigen (CEA).

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1828P Role of SPECT-CT somatostatin-receptor scintigraphy in the management of medullary thyroid cancer (MTC)**

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**Background:** The MTC arises from the parafollicular, calcitonin-secreting malignant transformed thyroid C-cells who express on the surface somatostatin SSTR receptors. The most aggressive locally advanced metastatic MTC tumors, found to be positive for RET proto-oncogene mutation, are treated with Vandetanib. SPECT-CT somatostatin receptor scintigraphy with 99mTc-Tektrotyd should be considered for MTC imaging before and after therapy for exact staging and follow-up of the disease due to its high sensitivity and specificity for detection of neuroendocrine tumors, expressed SSTR. The aim of this study was to evaluate clinical role of SPECT-CT scintigraphy with 99mTc-Tektrotyd in the management of patients with MTC.

**Methods:** 25pts (17M/8F) with MTC were studied, whole body somatostatin scintigraphy followed by target therapy. SPECT-CT studies were performed 2-4 hrs post i.v. of 740 MBq 99mTc-Tektrotyd (Polatom). SPECT-CT camera Symbia T2, Siemens was used. Three of them were studied for initial pre-operative N/M staging, 17 were follow-up after surgery. In 5 patients with metastatic disease SPECT-CT with 99mTc-Tektrotyd were performed before and after target therapy with Caprexa (Vandetanib), 300mg/d orally.

**Results:** Initial pre-operative staging showed 3 positive results for the primary tumor and metastatic lymph nodes and 3 false negative imaging of small 1-4 mm lung metastases. True negative results were obtained in 5 cases after thyroidectomy. True positive results were obtained in 17 cases with local recurrence in the thyroid bed, lymphadenopathy, osteolytic bone metastases, lung and subcutaneous lesions. False positive result was in 1 case with benign ovary cyst. Plasma levels of calcitonin vary from 94 to 5346 pg/ml in all 17 patients with local recurrence and/or metastatic lesions. In 7/17 SPECT-CT studies were used to evaluate effect of target therapy, respectively: partial response – in 2 cases, stable disease – in 2 cases and progressive disease – in 1 cases.

**Conclusions:** SPECT-CT somatostatin-receptor scintigraphy with 99mTc-Tektrotyd is very useful functional imaging modality in patients with MTC in order to determine personalized therapeutic disease approach.

**Legal entity responsible for the study:** Sona Sengova

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1829P Noninferiority trial of caborantinib (C) comparing 60 mg vs 140 mg orally per day to evaluate the efficacy and safety in patients (pts) with progressive, metastatic medullary thyroid cancer (MTC)**

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**Background:** CAB (CAB) inhibits receptor tyrosine kinases including MET, VEGF receptors, AXL, and RET. C has been approved in the US for the treatment of progressive, metastatic MTC and in the EU for progressive, unresectable locally advanced or metastatic MTC. In the phase 3 registrational study EXAM1, pts were randomized 2:1 to receive 140 mg or placebo (P) once daily (qd). The primary analysis for EXAM1 demonstrated a statistically significant improvement in progression-free survival (PFS) with a median PFS of 11.2 mo for C vs 4.0 mo for P (HR = 0.28, 95% CI 0.19-0.39, p < 0.001) (Elisei, JCO 2013). Dose reductions occurred commonly in the C arm with 82% of pts experiencing at least one dose reduction. While overall survival (OS) was
not significantly improved in the overall population (median OS of 26.6 mo for C vs 21.1 mo for P; HR 0.85, 95% CI 0.64–1.12; p = 0.24), median OS was 44.3 mo for C vs 18.9 mo for P (HR 0.60, 95% CI 0.38–0.94) in the RET M918T-positive subgroup (Schlumberger, Ann Oncol 2017).

**Trial design:** EXAMINER (NCT01896479) is a global, randomized, double-blind study comparing the safety and efficacy of C at 60 vs 140 mg qd in pts with progressive, metastatic MTC using a noninferiority study design. Approximately 188 pts will be randomized 1:1 to receive C at 140 mg qd as capsules or 60 mg qd as tablets in Europe, Asia, Canada, and other regions. Eligible pts must have measurable disease and documented progressive disease within 14 mo prior to enrollment. A recent tumor tissue sample to test for RET and RAS mutations or documentation of a RET or RAS mutation is required. Pts will be stratified based on RET M918T status. After randomization, pts will be treated until disease progression per RECIST 1.1 or intolerable toxicity. Tumor assessments will be performed every 12 weeks. PFS and objective response rate evaluated by independent review are the primary and secondary efficacy endpoints, respectively; safety and correlation of tumor mutation status with clinical response are additional endpoints. The EXAMINER study continues to enroll pts.

**Clinical trial identification:** NCT0189647.

**Legal entity responsible for the study:** Exelixis, Inc.

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**Disclosure:** J. Krajewska: Honoraria and subinvestigator in clinical trials: Eisai, Exelixis, Sanofi-Genzyme, Bayer HealthCare; Travel, accommodations, expenses: Sanofi-Genzyme, Ipsen, Novartis. B.G. Robinson: Stock or other ownership: Cochlear Ltd.; Honoraria, consulting or advisory role, speakers’ bureau: Eisai, Travel, accommodations, expenses: Loxo. H. Gan: Consulting or advisory role: MSD, AbbVie; Speakers’ bureau, travel, accommodations, expenses: Ignyta; Research funding: BMS, Ignyta. R. Elisei: Consulting or advisory role: Sanofi-Genzyme, Eisai, Loxo, Exelixis; Speakers’ bureau: Sanofi-Genzyme, Eisai; Travel, accommodations, expenses: Sanofi-Genzyme. J. Partyka: Employment, research funding, travel, accommodations and expenses, stock or other ownership: Exelixis. A.E. Borgman: Employee, stock or other ownership: Exelixis. M. Schlumberger: Honoraria, research funding: Bayer, Eisai, Exelixis-Ipsen, Sanofi-Genzyme; Consulting or advisory role: Bayer, Eisai, Exelixis-Ipsen, Sanofi-Genzyme; Travel, accommodations, expenses: Bayer, Eisai, Sanofi-Genzyme. All other authors have declared no conflicts of interest.
Liquid biopsy as tool to monitor and predict clinical benefit from chemotherapy (CT) and immunotherapy (IT) in advanced non-small cell lung cancer (aNSCLC): A prospective study


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Molecular differences between colorectal cancers with mutations in histone modifiers genes vs wild-type (WT) tumors


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Phase I study of CC-90011 in patients with advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma (R/R NHL)


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Lack of efficiency of precision oncology with target-based investigational treatments for patients in early phase clinical trials based on pre-screened molecular alterations


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Genomic profile and T cell receptor repertoire of lung adenosquamous carcinomas

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Comparative molecular analysis between microsatellite instability-high (MSI-H) tumors with high tumor mutational burden (TMB-H) versus MSI-H tumors with TMB-intermediate/low


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1836PD Representative sequencing: Profiling extreme tumor diversity

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1837PD Characterization through whole exome sequencing of individuals presenting extreme phenotypes of high and low risk to develop tobacco-induced non-small lung cancer (NSCLC)

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Background: Lung cancer causes nearly 1.69 million deaths globally and 5-year survival rate is less than 20%. Several biomarkers have improved treatment selection and overall prognosis in lung cancer to some extent (NCCN, 2017;35;504). However, clinical relevance of these biomarkers is limited to only a small percentage of patients. Hence, there is a need for an individualized tool that can accurately predict an individual’s response to a therapy, especially in scenarios where there is a choice of equivalent treatment regimens. Here we show that sequential WES-cfDNA provides insight regarding the evolution of metastatic breast cancer and that global mutation profiles relate to clinical response and progression to different lines of treatment.

Methods: We used CANScripTM to filter out non-synonymous genetic variants located in the exonic regions and splice sites of the genes evaluated; that codified for non-synonymous codons; and that showed allelic differences >15% between both cohorts.

Results: The mean age for the cancer and cancer-free cohorts was 50 (range 34-55) and 78 years (72-90). Mean tobacco consumption was 44 (range 6-72) and 55 pack-years (20-124). Median exome sequencing coverage was 96% at >10X and median depth was 97X. We identified 229 differential variants between both cohorts, located in 189 genes. The most significant variants (p < 10-6) are shown in the table. Twenty genes or family genes included >3 differential genetic variants (range 3-25): ADAMTS, ALPK2/3, ankhrins, APOL4, CCDC, CRIPAK, FYNCO1, HLA-A, keratins, mucins, olfactory receptors, PDFPR, PRAME family, RPLP2, RPL1L1, SAMD9, SLC transmitters, anotamins, TTN, and ZNF family.

Conclusions: We identified genetic variants associated with individuals presenting extreme phenotypes of high and low risk to develop tobacco-induced NSCLC. These variants warrant further study to characterize their impact in the development of these extreme phenotypes.

Legal entity responsible for the study: University of Navarra.

Disclosure: All authors have declared no conflicts of interest.

Whole-exome cfDNA profiling captures the metastatic signatures of metastatic breast cancer for monitoring disease evolution

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Background: Whole-exome sequencing of plasma cell-free DNA (WES-cfDNA) is an emerging liquid biopsy approach for identification of somatic mutations and yields high-confidence when compared to WES of the tumours of patients with advanced disease. Here we show that sequential WES-cfDNA provides insight regarding the evolution of metastatic breast cancer and that global mutation profiles relate to clinical response and progression to different lines of treatment.

Methods: A patient with inherited BRCA2 breast cancer was recruited at disease relapse and blood samples were then taken over a 2 year period on treatment until death. Whole-exome sequencing was performed on 12 DNA samples: primary tumour, 2 biopsies at relapse and 8 sequential cfDNA samples. Results were validated by targeted amplicon sequencing and ddPCR. Somatic Single Nucleotide Variants (SNVs) were called with Mutect2. Mutational signatures (MS) and their contributions to each sample were detected using the R package deconstructMS.

Results: WES profiling showed that MS-3 (a signature with germline BRCA2 status) was the predominant signature in the primary tumour, whereas the signature of the two relapse biopsies were MS-3, MS-4 and MS-5, and MS-3, MS-4 and MS-6. The first blood sample taken at relapse with bone disease also had a mixed MS profile. The MS-3 signature was detected in cfDNA with progression to lung and initially resolved in response to carboplatin treatment. MS-3 also predominated in cfDNA on subsequent disease progression and was the dominant MS at the time of death. SNV analysis identified a Tier-1 PIK3CA mutation in the primary and relapse tissue, whereas three other Tier-2 mutations in DNM2, DCC and ATPIA1 were specific to relapse, indicative of cancer evolution. All four variants were detected at high levels by WES-cfDNA. Lastly, an ESRI emergent mutation was identified by targeted sequencing in cfDNA and predicted failure of letrozole therapy.

Conclusions: Our study demonstrates the capacity of sequential WES-cfDNA to capture the genomic profiles of advanced cancer. The MS in cfDNA can be used track tumour evolution, and give insight into the characteristic of the dominant and lethal clone.

Legal entity responsible for the study: University of Leicester.

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Preclinical evaluation of a non-depleting, first-in-class humanized IgG4 agonist anti-ICOS antibody

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Background: Inducible T cell Co-Stimulator (ICOS) is a co-stimulatory receptor, induced on activated T cells (TC) upon TC receptor engagement. Clinical and preclinical data for checkpoint inhibitors demonstrate increased ICOS expression on effector TC, which has been linked to improved clinical outcomes. We have therefore developed an ICOS antibody optimized for agonist activity.

Methods: Syngeneic mouse models and human ex-vivo PBMC and tumor infiltrating lymphocyte culture assays were utilized to evaluate the activity of a murine (TE1709) or human (HL25) specific ICOS agonist antibody alone and in combination with PD-1 blockade. A selection of flow cytometry, IHC, multiple IF, nanostring, and in silico analysis was performed to characterize and develop HL25 for subsequent clinical evaluation.

Results: ICOS induction either with 7E1709 or HL25 agonist antibody induced significant activation and clonal expansion of both CD4+ and CD8+ effector TC. These TC had increased effector function (higher IFN-γ and Granzyme B) and increased homing to tumors resulting in antitumor responses when administered alone and in combination with PD-1 blockade. The level of expression of ICOS on effector and regulatory TC was found to overlap, suggesting that Fc-mediated depletion associated with IgG1 may result in depletion of effector TC. Preclinical data using different Fc isotypes supported the selection of the stabilized IgG4PE isotype for optimal agonism in the absence of NK-mediated depletion of effector TC. Drug concentrations associated with ICOS receptor occupancy, increases in TC activation and tumor reduction, support selected
Refining criteria of hyperprogression (HPD) with immune checkpoint inhibitors (ICIs) to improve clinical applicability

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Background: Rapid progression while on ICIs has been clinically described as HPD, however there is still not a consensus definition for this phenomenon. Institute Gustave Roussy (IGR) firstly described HPD as ≥ two-fold increase in tumor growth rate (TGR) during experimental period (EXP) vs. Reference period (REF). We recently described VHI0 HPD (HPD) using EXP only, as the following: PDI at first restaging with ≥40% increase in the sum of target lesions or ≥20% increase in measurable lesions with minimum absolute increase in measurable lesions of 10 mm (Matos I. et al. ASCO 2018).

Methods: Patients (pts) treated with ICIs in Phase trials at VHI0 were analysed (n = 214). Our aim was to assess overall survival (OS) in pts who achieved PD as best response, evaluate HPD according to IGR or VHI0 criteria and investigate discordances between both definitions.

Results: From Jan 12 to Oct 17, 214 pts were treated with ICIs (93% in combinations). Best response was PD in 47% pts (n = 101). Only 50 pts were evaluable for the primary endpoint (20 had PD before the first evaluation and 31 had no REF CT scan). Using IGR criteria, median OS was 4.5 months (95% CI: 3.6-5.3) in HPD group (n = 15) versus 6.3 months (95% CI: 5.1-9.9) in non-HPD group (HR = 1.85; 0.86-3.9; p = 0.11). Using VHI0 criteria, median OS was 6.6 months (95% CI: 5.8-7.9) in HPD group (n = 21) versus 8.7 months (95% CI: 4.2-13.2) in non-HPD group (HR = 2.33; 1.04-9.5; p = 0.02). Overall concordance rate between the two criteria was 56% (p = 0.02). Most discordances were HPD by IGR and non-HPD by VHI0 (28%). Baseline target lesion summary in EXP was different in first PD in HPD by IGR or VHI0 (p > 0.1). Importantly, pts with PD by IGR had significantly lower TGR-REF (p < 0.01). Using VHI0 criteria, we found no difference in TGR-REF between HPD vs non-HPD (p = 0.15). However, higher TGR-EXP was found in pts with HPD using VHI0 criteria (p < 0.001).

Conclusions: We were able to validate IGR HPD criteria in our cohort, despite substantial loss in evaluable pts due to missing REF CT scans. No concordance was observed between IGR and VHI0 HPD definitions. VHI0 HPD criteria is strongly prognostic, easy-to-use in the clinic (EXP only) and biologically sound (not affected by small TGR during previous therapy and linked to high TGR during ICI exposure).

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Background: The clinical relevance of mismatch repair deficiency (MMRD) in patients with early-stage colorectal and endometrial cancer remains unclear. Our goal was to investigate the prognostic role of MMRd in patients with colorectal and endometrial cancer.

Methods: From 05/1990 to 03/2013, formalin-fixed paraffin-embedded primary tumor samples from 2250 patients with colorectal cancer (N = 1022) and 690 patients with endometrial cancer (N = 197) from 14 institutions were collected. MMR expression of 15 patients was evaluated by immunohistochemistry. The primary outcome measure was overall survival (OS).

Results: Overall, 1158 patients were included (median age, 64 years). Stage III disease was diagnosed in 18% and 19% of patients with colorectal and endometrial cancer, respectively. All patients with colorectal cancer but only 13% of those with endometrial cancer received adjuvant treatment. MMRd was observed in 114 (11.5%) of colorectal and 40 (48%) of endometrial tumors. MMRd was associated with an older age at diagnosis (P = 0.003), higher tumor grade (P < 0.001) and lower tumor stage (P < 0.001). Colorectal MMRd tumors were more often right-sided (64.6% vs. 27.2%, P < 0.001) and with a mucinous component (63.7% vs. 41.4%, P < 0.001). Endometrial MMRd tumors were more often endometrioid (74/144, 51.4%) than serous/clear cell (3/15, 20%).

Conclusions: MMRd is associated with improved outcomes in patients with early-stage colorectal cancer, but not in patients with early-stage endometrial cancer.

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Role of TP53 mutations in relation to response to anti-ALK agents in EML4-ALK-translocated NSCLC patients

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Background: EML4-ALK translocation is a predictive mutation for responsiveness to anti-ALK drugs, and it is present in 3–7% cases of NSCLC patients. Though patients are usually responsive to targeted therapy against EML4-ALK translocation, about 30–40% show drug resistance. We analysed the impact of TP53 mutations on response to anti-ALK treatment in EML4-ALK-translocated NSCLC patients.

Methods: 83 EML4-ALK-translocated NSCLC patients were enrolled, and TP53 status was evaluated in 61 patients, on the basis of DNA availability. Of these patients, 28 patients received an anti-ALK agent in second-or-more line treatment and follow up data were available. TP53 status was considered in relation to disease control rate (DCR: complete response [CR], partial response [PR] or stable disease [SD]).

Results: In the overall case series, TP53 mutations were observed in 14 (23%) patients, 6 (43%), 1 (7%), 3 (21%) and 4 (28%) in exon 5, 6, 7, 8 and respectively. We found 1 deletion (7%), 1 deletion (7%) and 12 point mutations (86%). In the subgroup of 25 patients treated with an anti-ALK agent and evaluable clinical response, TP53 mutations were observed in 5 (20%) patients, 7 (40%) and 2 (40%) in exon 5, 6, and 8, respectively. The DCR was 60% in TP53-mutated patients with respect to 92% in TP53 wild type (wt) patients. Three patients had a non evaluable clinical response, as they stopped anti-ALK agent treatment due to rapid PD deterioration of general conditions and they succumbed to their disease in a few weeks. Two of these were found with a stop mutation in exon 5.

Conclusions: TP53 mutations are associated with a worse DCR in EML4-ALK-translocated NSCLC patients treated with an anti-ALK agent. These results highlight the importance of tumor-suppressor genes in determining response to TKIs. Data analysis for PFS and OS of patients are ongoing.

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Disclosure: All authors have declared no conflicts of interest.
Background: Previous publications of the FLAGS and the DIGEST trials have shown that L-CRC (CS) had a significantly longer overall survival (OS) compared to those with right-sided primaries (R-CRC) had longer overall survival (OS). At a median follow-up of 101.5 months, patients with left-sided (L-CRC) colorectal cancer (CRC) had significantly longer OS compared to patients with right-sided (R-CRC) CRC (HR = 2.62, 95% CI 1.35–5.12, p = 0.005), when it was adjusted for the individual and the central review committee.

Methods: To overcome differences in baseline characteristics of the FLAGS and the DIGEST trials, a meta-enrichment analysis was performed after combining the data from the two trials. Since the treatment effect is consistent in the FLAGS and the DIGEST trial, meta-enrichment analysis allows for the combination of the two datasets and identify a robust subgroup of high response patients. Eleven clinicopathological factors were selected and a high response enricheputable population was determined. It must be noted that although peritoneal metastases was included in the previous analysis as a clinicopathological factor, it was removed from this analysis due to inconsistent date readings between the individual and the central review committee.

Results: The efficacy of the combined data set of 1361 patients (n = 1019 from FLAGS and n = 346 from DIGEST) were analyzed. A total of 683 patients (n = 374 from CS, n = 309 from R-CRC) were identified as the high response enricheputable population. High response patients were classified as patients with ECOG PS 1, more than two metastatic sites and low Neutrophil-Lymphocyte ratio (log(NL ratio)) In the high response enricheputable population, the median OS in the CS group was 241 days compared to 210 days in the R-CRC group (Hazard ratio 0.776; 95% Confidence interval 0.658 to 0.915; P value 0.040).

Conclusions: Through meta-enrichment analysis, a higher response enricheputable population to CS was identified. This statistically robust analysis indicated that for selected patients with AGC, CS is more beneficial compared to CF.
**1850P**

RNA-based analysis of anaplastic lymphoma kinase (ALK) fusions in non-small cell lung cancer (NSCLC) cases showing immunohistochemistry/fluorescence in-situ hybridization (IHC/FISH) discordance

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**Background:** Rearrangements of ALK are established targets in the current therapy of advanced NSCLC and are predominantly detected by IHC and/or FISH. However, both methods occasionally produce discordant results. This may occur especially in so-called borderline (BL) cases, showing ALK FISH-positive signals in 10–20% of tumour nuclei around the cutoff (15%) for ALK FISH positivity. This leads to a diagnostic, and thus therapeutic, dilemma.

**Methods:** We selected 18 unequivocal samples (12 ALK IHC- and FISH-negative; 6 ALK IHC- and FISH-positive) and 15 equivocal samples with discordance between FISH (Vysis LSI ALK Dual Color) and IHC (DSF5), including cases with FISH-BL results, for a detailed RNA-based analysis. To detect ALK rearrangement at the transcriptional level, RNA was analysed using a targeted multiplex-PCR panel followed by Ssequencing and direct transcript counting using a digital probe-based assay (NanoString). Sensitivity of both methods was defined using RNA obtained from an ALK-positive NSCLC cell-line dilution series.

**Results:** Cases with unequivocal IHC/FISH results showed concordant data with both RNA-based methods. Three IHC-negative/FISH-positive samples were negative with both RNA-based methods. The four IHC-negative/FISH-BL-negative cases, as well as the five IHC-negative/FISH-BL-positive samples, showed negative results by sequencing and digital probe-based assay. The two IHC-positive/FISH-BL-positive cases were both positive on the RNA level; whereas a tumour with questionable IHC and FISH-BL-positive status displayed no ALK fusion transcript.

**Conclusions:** The comparison of methods for the confirmation of ALK rearrangements revealed that the detection of ALK protein by IHC and ALK fusion transcripts on transcriptional level by sequencing and probe-based assay leads to concordant results. Only a small proportion of clearly ALK FISH-positive cases are unable to express the ALK protein and ALK fusion transcript, which might explain non-response to ALK inhibitors. Therefore, our findings led us to conclude that ALK testing should be based on IHC- or RNA-based methods, especially for ALK FISH BL cases.

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**1851P**

The combination of MEK inhibitor and anti PD-L1: Effects on organoid models from NSCLC biopsies

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**Background:** The combination of immune-checkpoint (IC) inhibitors with targeted therapies represent a new goal of immunotherapy, aimed at personalizing and potentiating the self-response against cancer. Organoids as novel 3D cancer models, allow the study in vitro of the tumor microenvironment (TME), including tumor-infiltrating lymphocytes (TILs) and their interaction with tumor cells. In this study we analyzed whether the combination of anti–PD-L1 drugs with MEK inhibitor (MEK) affect the growth of organoids and TILs obtained from tumor biopsy of NSCLC patients.

**Methods:** Lung biopsies from 3 NSCLC patients were enzymatically digested. Cells were cultured in triplicates for 6 days and treated with atezolizumab or vemurafen, alone or in combination with MEKI. Immunofluorescence (IF) staining for CD3, CD8 and CD45 was conducted; cells were also stained for FACS analysis with anti-CD45, CD3, or in combination with MEKI. Immunofluorescence (IF) staining for CD3, CD8, CD4, CD14, CD36, CD19, CD16, and PD-1, a staining for EPAC1 and PD-L1 allowed a better characterization of tumor cells. After 6 days of treatment, MTT assay verified cell viability; the expression levels of IFNγ, IL-10, PD-1, PD-L1, TIM-3, LAG-3 and IDO-1 were analysed through real-time PCR.

**Results:** IF staining revealed that in organoids the interactions between tumor cells and TILs are preserved. FACS analysis confirmed that TILs were mainly TCD8+ and tumor cells analysed were EPAC1+ for almost 40%. The combination of anti PD-L1 and MEK is associated with a reduction in organoid’s dimensions and viability, especially in PD-L1+ tumors and with a higher percentage of TCD8+/PD-L1+ lymphocytes. The combination of MEKIs with anti PD-L1 is also associated to a higher expression of the pro-inflammatory cytokine IFNγ and a reduction of the anti-inflammatory IL10. The expression of IC molecules was also modified by this combination, in particular LAG-3 and IDO-1 expression were dramatically reduced.

**Conclusions:** Organoid models allow to study tumors more realistically, because they show some typical features of the organ they derive. This model become particularly useful for the analysis of TME of each patient and for the testing of combination drugs and the development of precision and personalized immunotherapies.

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**1852P**

Intraoperative fluorescent image-guided detection of esophageal cancer in rabbit and patient specimens

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**Background:** This is the first study, to our knowledge, aimed at assessing the feasibility of intraoperative detection of esophageal cancer (EC) after intravenous indocyanine green (ICG) injections in rabbit and patient specimens using near-infrared (NIR) fluorescence imaging.

**Methods:** VX2 tumors were surgically implanted in the esophageal muscular layer of 45 rabbits 2 weeks before esophagectomy. They received 1, 2, or 5 mg/kg of intravenous ICG injection 3, 6, 12, 24, or 48 hours before surgery. Twenty-five consecutive patients (21 men, age, 63.9±8.59 years) who were scheduled to undergo esophagectomy for squamous cell EC were enrolled. Five patients received neoadjuvant concurrent chemoradiotherapy (CCRT) before surgery. All patients received 1 or 2 mg/kg of ICG intravenously 6, 12, or 24 hours before surgery. The fluorescence intensity was measured in all resected rabbit and patient specimens using an NIR fluorescence imaging system on a back table after surgery.

**Results:** EC was successfully detected in all rabbits; the mean tumor size was 0.86±0.21 cm (range, 0.5–1.3 cm). Fluorescence signals were detected in all animals. The tumor-to-normal fluorescence signal ratio (TNR) in rabbits was higher between 6 (6.89±0.35) and 12 (7.53±0.26) hours at 1 mg/kg (p < 0.01), between 12 (10.39±0.41) and 24 (12.06±0.97) hours at 2 mg/kg (p < 0.01), and between 24 (14.88±0.63) and 48 (13.73±0.19) hours at 5 mg/kg (p < 0.01) of ICG than at other times. Fluorescence signals were detected in all except 4 patients without residual tumors after neoadjuvant CCRT. One false-positive case involved no residual tumor with inflammation (TNR, 13.64). The mean tumor size in 29 patients was 3.9±2.1 cm. The TNR in the patients was higher between 6 (15.22±0.59) and 12 (17.01±0.18) hours at 1 mg/kg (p < 0.01) and between 12 (18.92±0.61) and 24 (19.81±0.73) hours at 2 mg/kg (p < 0.01) of ICG than at other times.

**Conclusions:** NIR fluorescence imaging revealed EC 6 to 24 hours after systemic ICG injections per their doses. However, passive ICG accumulation could not help discriminating tumors with inflammation; thus, tumor-targeted fluorescence should be developed to solve this problem in the future.

**Clinical trial identification:** This study was approved by the Institutional Review Board, Korea University Guro Hospital (2017GR0075).

**Legal entity responsible for the study:** Korea University.

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ATR inhibitor), 5-aza-2′-deoxycytidine and/or radiation in our institute between 2010 and 2015. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue samples of primary tumours (pre- and post-treatment) among EC pts who received chemotherapy with platinums and/or radiation in our institute between 2010 and 2015. Immunohistochemistry (IHC) staining for the samples was performed and the positivity of PD-L1 was determined as score of 1 of the Alfred methods. In addition, expression levels of immune-related genes were analyzed using HTG EdgeSeq Immuno-Oncology Assay (HTG Molecular Diagnostics, Inc, Tucson, United States).

Results: Eighty-four pts were evaluable (median age of 68yrs, 88% male, 7%/69%/34% for primary tumor of Ce/Ut/Mt/Lt/Ae, 12%/19%/52%/17% for Stage I/II/III/IV, 95% squamous cell carcinoma, 48%/1% for primary tumor of Ce/Ut/Mt/Lt/Ae, 12%/19%/52%/17% for Stage I/II/III/IV, 95% squamous cell carcinoma, 48%/52% pts treated with chemotherapy/CRT). On univariable analysis, high expression of PD-L1 was significantly associated with decreased OS (p = 0.011). A multivariate analysis reported that CD5 expression could be established as an independent prognostic biomarker for OS in early-stage NSCLC [HR = 0.539; 95% CI, 0.329-0.883; p = 0.014]. Survival analyses performed on 97 patients from TCGA database confirmed that higher expression levels of both CD5 and CD6 had a significant prognostic value for relapse-free survival (34.98 vs. 75.57 months, p = 0.033; 25.31 vs. 73.37 months, p = 0.028, respectively) and OS (40.49 vs. 77.97 months, p = 0.038, 39.02 vs. 77.97 months, p = 0.034, respectively). Therefore, these analyses support that NSCLC patients with higher expression levels of CD5 are associated with better outcomes. Besides, CD5 could potentially be a prognostic biomarker.

Conclusions: Our results support a role of the immunomodulatory receptor CD5 as an independent prognostic biomarker in resectable NSCLC. Supported from Fundación La Marató TV3 (201319-30), ISCIII (PI12-02838 and PI15-00753), and MECD (SAF2016-80535-R). co-financed by European Development Regional Fund. FA and IS are recipients of fellowships from ISCIII (Sara Borrell Program; CD13/0016) and Portuguese FCT (SFRH/BD/75738/2011, respectively).

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Disclosure: All authors have declared no conflicts of interest.
Identification of the rational combination of two epigenetic inhibitors therapy in refractory AML using patient tumor derived ex vivo platform

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Background: Acute myeloid leukemia (AML) is a highly heterogeneous hematological malignancy. Though there has been substantial progress in understanding of AML biology and identification of new therapeutic targets, treatment of AML has largely remained unchanged over the last couple of decades, with ~40% patients not achieving remission with standard chemotherapies.

Methods: In this study, we employed an ex-vivo tumor explant model (CAScriptTM) to select a treatment course for AML patients. CAScriptTM offers a comprehensive system that mimics patient tumor microenvironment. 31 AML patients were analyzed to predict response to cytarabine. We next evaluated azacitidine and panobinostat alone and in combination, as alternate treatment regimens for cytarabine refractory tumors.

Results: More than 50% of the treated samples showed response to the combination therapy. In AML, frequent upregulation of DNA methyltransferase enzymes (DNMTs) have been reported with poor survival. We assessed the level of DNMTs using RNaseq and methylation data (n = 100) from the TCGA database. Data indicated increased expression of DNMTs and hypermethylation of HDACs indicating mechanism of drug resistance to treatment by epigenetic modulators in these tumors. We further noted hypomethylation of JUNGR1 and JUNGR2 genes in TCGA data suggesting activation of JUN/KSTAT pathway. Hypomethylation of several gene components of JAK/STAT pathway was correlated with an increased expression of these genes in RNAseq data. 8 out of 12 cytarabine refractory tumors were showed response of which 5 were non-responders to epigenetic modulators.

Conclusions: Taken together our data indicates that CAScriptTM is capable in guiding optimal treatment selection for various classes of agents including novel targeted therapies.

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Tyrosine kinase inhibitors and acid-inhibitory drugs: Strong concomitant dispensing and drug-drug interaction risk

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Background: Tyrosine Kinase Inhibitors (TKIs) have rapidly become an established therapy in oncology and have been shown to be effective in a wide variety of solid and hematologic malignancies. Acid-inhibitory drugs (AID) (such as antacids, anti-ulcerous drugs and proton pump inhibitors - PPIs) increase the intragastric pH, which may subsequently decrease TKI solubility, bioavailability, and treatment efficacy. The Observatory of Drugs Bregtane/ Pays de la Loire (B-P) and the Medical Department of the French Regional Health Insurance (FRHI PL) has made an observational study about TKIs and AIDs concomitant dispensing.

Methods: FRHI PL has made an extract in its database for patients treated with TKIs and AIDs in 2016. Concomitant dispensing is defined as the dispensing of a TKI and AID during the same calendar month. To complete the study, a survey about PPIs prescription has been proposed to cancer specialists from B and PL areas during 15 days last December.

Results: 2309 patients, mean age of 62.9 y (2-93) have been treated with TKIs in 2016 in the PL area. 6.6 dispenseis have been done per patient. 795 pts (34%) had no AID dispensing. 274 pts (12%) had no concomitant dispensing of AID and TKI. 1240 pts (54%) had at least one concomitant dispensing. 67% of these patients had a concomitant dispensing of PPIs and 25% a concomitant prescription throughout the TKI treatment. Among these concomitant takes, 34% showed no interaction, 23% showed interactions (34% unknown cases, 9% diverging data). Data from the Bretagne area will be shown at the meeting. 43 clinicians have answered the survey about PPI prescription: 98% have prescribed them. The major reasons were: treatment of gastroesophageal reflux disease (88%), prevention/treatment of NSAID-associated ulcers (67%) or of esophageal duodenal and stomach ulcers (55%), for unknown reasons (31%), and for Zollinger-Ellison syndrome (31%). Duration of treatment was between 7 days and 2 months.

Conclusions: Drug-Drug Interaction (DDI) analyses would be performed to underline for which TKIs, TKIs-PPIs interaction was the most harmful. Clear practice tools should be created to help clinicians to evaluate this DDI and what to do for their patients. Guidelines will be presented at the meeting.

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Intraoperative detection of resection margin by inhalation of ICG in lung cancer preclinical study

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Background: Identification of tumor margin during surgery is necessary for limited resection of non-small cell lung cancer (NSCLC). In this study, we developed a novel technique of lung cancer margin visualization by intraoperative inhalation of indocyanine green (ICG) and verified its clinical applicability using mouse and rabbit lung cancer model.

Methods: By observing the distribution of the inhaled ICG in each organ (lung, liver, brain, spleen, and kidneys) of mice at five different time intervals, we demonstrated that the inhaled ICG was delivered rapidly and was mainly distributed in the lung tissue. In the mouse model of lung cancer, we confirmed that the inhaled ICG entered the normal lung through phagocytosis by alveolar macrophages of normal lung tissue and rarely spread in lung cancer tissue because of mechanical airflow obstruction by the tumor.

Results: Therefore, the fluorescent signal of inhaled ICG was mainly visualized in normal lung tissue but not in lung cancer tissue, which could assist in identifying the tumor margin. For clinical applicability, the inhaled dose of ICG was optimized in a rabbit lung cancer model. Compared to intravenous administration, this method accurately defined the tumor margin with 5-3-fold higher detection efficiency when 20 times lower dose of ICG was used. The ICG inhalation technique provided more clear visualization of tumor margin with lower dose and in shorter time during surgery compared to the conventional intraoperative injection method.

Conclusions: The ICG inhalation technique provided more clear visualization of tumor margin with lower dose and in shorter time during surgery compared to the conventional intraoperative injection method. Long-specific delivery of the clinically approved ICG could be used effectively and safely in real clinical practice in the near future.

Legal entity responsible for the study: Korea University.

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Proteomic-based machine learning computational analysis discovered biomarkers of aberrant vesicle-exosomal trafficking to determine chemotherapeutic responses in breast cancer

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Background: The chemotherapeutic response is still low, and the need for a biomarker to overcome chemo-resistance is necessary.

Methods: We performed quantitative proteomics mass spectrometry in paired 20 FFPE biopsy breast cancer samples consist of non-responsive and responsive groups to chemotherapy. For verification of enriched biomarkers and biological pathways, ten human breast cancer cell lines enrolled and verified biological functions through molecular biology-driven assays, including ENAL, celltiter-glo luminescent assay, mitochondria membrane potential assay (MMPA), IF, esosome uptake assay, time-lapse live cell imaging system, and the 3D tumor spheroid-based function assays. Machine learning analysis using c-ear recursive feature elimination to select and apply them to an independent cohort with 50 FFPE biopsy samples to discover the most optimal combination of immunohistochemical biomarkers to predict chemo-responsiveness.

Results: A total of 6,424 proteins were identified and 254 were confirmed to be significantly altered proteins related to chemotherapeutic response. From the patient group with chemo-resistance, we featured 56 upregulated proteins considerably in six closely related subcellular organelles concerning transcellular transportation system based on domain knowledge for text-mining and public network databases for network analysis.
Carcinoma of unknown origin: Deep genomic profile helps to achieve an accurate diagnosis

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Background: Diagnosis and treatment of Cancer of Unknown Origin (CUP) continues to be a challenge. In the era of personalized medicine, genomic profile by Next-Generation-Sequencing (NGS) in addition to immunohistochemistry (IHC) tests may complement clinical features improving diagnosis and detecting targetable mutations. In the present study we have analysed the clinical utility of the OncoDEEP®-CUP platform for the specific use in CUP patients.

Methods: We conducted this multicentric prospective exploratory study across 22 institutions (September 2017–March 2018). The cohort included 60 patients with histologically diagnosed metastatic CUP and available FFPE tumor samples. The molecular analysis was performed using the OncoDEEP®-CUP platform, which includes a deep genomic tumor characterization as well as a panel of IHC tests.

Results: Patient’s median age was 60 years [24-80], 61.7% were females. At time of diagnosis, 48% presented a single metastatic site whereas 52% presented multiple metastatic locations. Predominant histology was adenocarcinoma (36.7%) followed by carcinoma NOS (25.0%), squamous cell carcinoma (13.3%) and others (23%). In 10% of the cases, the analysis could not be completed due to insufficient tumor samples. In the remaining 54 samples, a probable primary organ was assessed in 45 patients (80%). Potentially actionable mutations were found in 36 cases (61%). As expected, the most frequently mutated gene was TP53 (12/36), followed by KRAS, ARID1A, BRAF, CDKN2A, PIK3CA, Pten and STK11. During follow up 11 deaths have been recorded, whereas the rest of the patients remain in the study.

Conclusions: OncoDEEP® CUP may provide an opportunity for CUP patients to benefit from site-specific treatments and personalized therapies if druggable mutations are identified. Acknowledgments to the rest collaborating centers: H. U. de Ceuta, H. U. Virgen Macarena, H. Ramón y Cajal, H. U. Santa Lucía, BC Marbella International Hospital, H. Parc Taulí, H. U. La Ribera, H. Marina Baixà, H. Morales Meseguer, H. U. Lucas Augustin and Instituto Valenciano de Oncología (IVO).

Legal entity responsible for the study: Hospital General Universitario de Valencia, Valencia, Spain, Valencia.

Disclosure: The Spanish Institute for Foreign Trade (ICEX)

A. Terradéz, A. Rodrigo, L. Alvarez, G. Beniuiga: Employee: OncoDNA. All other authors have declared no conflicts of interest.
Methods: Patients aged ≥ 18 years with advanced solid tumors were enrolled at the starting dose of 20 mg and escalating doses in an accelerated design. Safety was evaluated in every 4-week cycles, and tumor assessment was performed every 8 weeks using RECIST 1.1. Plasma PK samples and time-matched ECG data were collected.

Results: 52 patients received vorolanib in 17 cohorts, with doses ranging from 20mg QD to 800 QD and 140-200 mg BID. During the study, the formulation was changed from capsule to tablet. The most common tumor type was ovarian (19%). No DLT occurred and the MTD was not officially reached. Due to apparent saturation of absorption in the 400 – 800 mg QD range, dose escalation was stopped at 800 mg, and 400 mg QD was chosen as the dose for the expansion cohort. The most common treatment-related adverse events (TRAE) were fatigue, nausea, diarrhea, hair color change, vomiting, rash, peripheral edema and asthma, mostly grade 1-2. Five patients had a grade 3TRAE, with proteinuria (4%) being the most common. The plasma half-life of vorolanib was approximately 6.5 hours, and no accumulation was observed after 21- days of daily dosing. 1 pt with pancreatic adenocarcinoma receiving vorolanib had a complete response, 1 pt with Hurthle cell carcinoma had a partial response, and 11 pts (20%) had stable disease for > 6 cycles.

Conclusions: Vorolanib was generally well tolerated up to 800 mg QD in patients with advanced solid tumors. Based on the safety profile, PK/PD model and patient responses, 400 mg QD was selected as the single agent dose for advanced cancer patients.

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Legal entity responsible for the study: Xcovy Holdings, Inc.

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Disclosure: K.N. Moore: Advisory boards: AstraZeneca, Advaxis, Clovis, Tesaro, Immunogen, Genentech/Roche, VBL Therapeutics, Janssen. G. Dukart, K. Harrow, C. Liang. Full time employee and stock options: Xcovy Holdings, Inc. All other authors have declared no conflicts of interest.

Longitudinal analysis of circulating biomarkers to monitor advanced EGFR mutated (EGFR+) non-small cell lung cancer (NSCLC)

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Background: Circulating tumour DNA (ctDNA) and circulating tumour cells (CTC) can be used as a ‘liquid biopsy’ to detect gene mutations. Serial blood collection for ctDNA and CTC analyses allows monitoring for treatment response and to understand the mechanisms of acquired resistance. We hypothesised that longitudinal ctDNA and CTC analyses may be used for disease monitoring and could have prognostic significance in patients with advanced EGFR+ NSCLC.

Methods: In this prospective study, patients with advanced EGFR+ NSCLC were recruited, with blood and plasma samples collected prior to starting treatment, 4 weeks into treatment and at disease progression. CTCs were enumerated and ddPCR for ctDNA and CTC analyses allows monitoring for treatment response and to understand the mechanisms of acquired resistance. We hypothesised that longitudinal ctDNA and CTC analyses may be used for disease monitoring and could have prognostic significance in patients with advanced EGFR+ NSCLC.

Results: A total of 56 plasma specimens from 28 patients were studied. ctDNA was detectable in baseline plasma in 19/28 (68%) patients starting first line EGFR inhibitors. Detectable baseline ctDNA was associated with higher disease burden (p < 0.01). Early disappearance of ctDNA at 4 weeks was associated with radiological response 12 weeks into treatment (p = 0.04) and improved PFS (Median PFS 136 vs 511 days, HR 4.49, p < 0.01) and OS (Median OS 311 days vs NR, HR 5.32, p = 0.01), which remained significant after adjustment for burden of disease. Drop in CTC count at 4 weeks was associated with improved PFS (HR 3.11 p = 0.02) but not OS. Drop in CTC counts at 4 weeks was associated with radiological response, just reaching significance (p < 0.05).

Conclusions: Longitudinal assessment of ctDNA and CTC is an accurate predictor of tumour response and survival outcomes for patients with advanced EGFR+ NSCLC. This offers a potentially cheaper, highly informative and minimally invasive way of monitoring malignancies.

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Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

Genotyping of circulating tumor DNA in biliary tract cancer reveals diagnostic and prognostic information

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Background: Biliary tract cancer (BTC) shows increasing incidence and is associated with a high mortality. Diagnosis is difficult due to the frequently occurring inaccessibility of the tumor for biopsy. Noninvasive approaches for assessing and monitoring the tumor-specific molecular setup are desirable to improve diagnosis and tailor treatment.

Methods: Blood and tumor tissue samples from patients with locally advanced or metastatic BTC were collected prior to and during palliative treatment. Tumor tissue and corresponding ctDNA samples were subjected to targeted resequencing of 15 genes frequently mutated in BTC (TP53, KRAS, ARID1A, BAP1, PIK3CA, SMAD4, FBXW7, IDH1, BCL2, BRAF, CDKN2A, ERBB2, IDH2, NRAS). Findings were correlated with clinical and imaging data.

Results: 24 therapy naive patients with histologically confirmed BTC were included into the analyses. The mutational concordance (blood/tissue) was 74% overall and 92% for intrapathic tumors only. Mean variant allele frequency (VAF) detected in tumor tissue was significantly higher compared to ctDNA (p = 0.0291). In turn, the sequencing depth for ctDNA was about double of that for tissue samples (1010 vs. 465x), enabling the detection of variants in ctDNA. ctDNA VAF at baseline significantly correlated with tumor load (Spearman, r = -0.407, p = 0.0433). Interestingly, for intrahepatic BTC baseline ctDNA VAF also significantly correlated with progression-free survival (Spearman, r = -0.3878, p = 0.0288).

Conclusions: The molecular landscape of BTC is represented in ctDNA and most tumor-specific variants are detectable in ctDNA, especially in intrapathic BTC. In this subgroup the baseline VAF in ctDNA was also of prognostic significance. Additionally, we detected hints for tumor evolution in a relevant portion of the analyzed BTC patients during chemotherapy, which have to be further investigated. Altogether, ctDNA analysis in BTC may support diagnosis, prognosis and the adaptation of therapeutic strategies according to the specific molecular setup of the tumor detected at any time point during chemotherapy.

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Interactions of cancer stem cell and immune microenvironment in non-small cell lung cancer (NSCLC)

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Background: Lung cancer stem cells (CSCs) are a small population of cells with self-renewal, tumorigenic properties and the ability to grow to form tumourspheres in non-adherent conditions. Recently, the study on soluble molecules has been a new focus to understand the interaction between CSCs and tumor microenvironment. The aim of this work is to compare the release of cytokines between monolayer cells and tumourspheres of NSCLC cultures.

Methods: The study was performed on medium supernatant of cells from 8 NSCLC tumour patients samples and 10 cell lines (A549, H1650, H460, H23, H358, H2228, HCC27, PC9, H1993, SW900) grown in monolayers and tumourspheres at 2 different densities (104 and 105 cells/ml); supernatant was recollected at 12h and 24h. We analysed 8 soluble factors with immunosuppressive (IL-4, IL-10, IL-13), and immunoregulatory (IL-6, IL-8, IL-17A, TNF, IFN) capacity through sensitivity bead-based multiplex assay using the Millipore kit from the Luminex. 100/200.

Results: IL-4, IL-6, IL-8, TNFα levels were detected in all samples while IFNγ. IL-10, IL-13, IL-17A were beyond the detectable range in adherents for most of cultures (Detection range [pg/ml] of IL-4: 1.83-7497.38, IL-6: 0.18-813.66, IL-8: 0.31-1042.75, TNFα: 0.43-1758.47, IFNγ: 0.18-7497.38, IL-10: 4.6-6058.85, IL-13: 0.24-1002.76.

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IL-17A 0.73 (3074.88). We observed significant differences in levels of IL-6, IL-13, IL-17A, TNFa, IFNg between adherent cells and tumorspheres. Moreover, IL-4, IL-10, IL-13, IL-17A, IFNg levels in tumorspheres were higher than monolayer. Otherwise, IL-6 and IFNg secreted more in monolayer. IL-8 is the most secreted molecule in both adherent and tumorspheres by all cultures.

**Conclusions:** Our preliminary results suggest that high levels of IL-6 and IL-8 were detected in all samples. IL-8, IL-13, IL-17A and IFNg secreted by lung CSCs could be involved in the modulation of the immune microenvironment. Additionally, adherent cells show increased levels of IL-6 and TNFa compared to tumorspheres, and IL-8, IL-4, IFNg, IL-10, IL-13, IL-17A show the opposite. The next is to extend the cohort to validate our results and to study others immunoregulatory factors. Supported by grants from FEDER and PI12-02838 and PI15-00753 from ISCIII.

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**1865P** Association of the rs1883832 variant of CD40 with NSCLC risk and overall survival

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**Background:** During the last few years a growing number of studies has attempted to shed light on the role of CD40 (Tumor Necrosis Factor Receptor Superfamily Member 5) in non-small cell lung cancer (NSCLC), which remains the leading cause of cancer related deaths worldwide. The aim of the current study was to investigate the clinical relevance of CD40 functional single nucleotide polymorphism (SNP) rs1883832 (C/T) with susceptibility to NSCLC, the clinicopathological parameters, relapse and survival rates of NSCLC patients, as well as with the protein expression of CD40.

**Methods:** CD40 SNP rs1883832 was genotyped in 268 randomly selected NSCLC patients and 279 age- and gender-matched healthy donors. Patients were under observation during a five-year period. Immunohistochemical analysis for CD40 was performed on 106 NSCLC tumor tissue samples. All the participants were Greeks with Caucasian origin.

**Results:** Genotype frequencies of rs1883832 (GC, CT, and TT) were significantly different between healthy controls and patients. GC homozygotes had higher risk for NSCLC compared to T allele carriers in univariate (P < 0.001), as well as in multivariate analysis (P < 0.006). In addition, rs1883832 was related to overall survival. More specifically, CT heterozygotes had worse clinical outcome after two-, three- and five-year observation compared to TT and GC homozygotes (P = 0.015, P = 0.005 and P = 0.017, respectively). Stratifying according to histological subtype, this association was observed only in patients with adenocarcinoma (P = 0.028) and not in patients with squamous- and large-cell carcinomas. Furthermore, taking into consideration disease stage, worse survival for CT heterozygotes was observed in stage II patients and not in patients of other stages (P = 0.016). Moreover, the variant was associated with brain metastases, with T allele carriers developing more frequent metastatic disease in CNS (P = 0.018). Interestingly, rs1883832 was related to CD40 protein expression in malignancies (P < 0.01) as well as in stromal cells (P = 0.004).

**Conclusions:** The present findings suggest that investigated SNP rs1883832 may be a useful and independent biomarker in NSCLC. However, more studies are needed in order to further demonstrate their role in NSCLC.

**Legal entity responsible for the study:** University of Patras.

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**Disclosure:** All authors have declared no conflicts of interest.

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**1867P** Circulating tumour DNA (ctDNA) as a tool to assess response and guide therapy adaptation in rectal cancer


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**Background:** Neo-adjunct chemoradiation (CRT) is associated with varied response in patients (pts) with localised rectal cancer. Early identification of poor responders and pts at risk of developing systemic disease using ctDNA would allow tailoring of treatment.

**Methods:** Tissue and serial plasma was collected from 47 pts with localised rectal cancer scheduled to undergo long course CRT. Cell-free DNA (ctDNA) was purified from a mean of 3.6 ml plasma per time-point. Somatic variants were identified in tissue by sequencing using a targeted capture panel. Up to 3 variants per patient in genes of interest were tracked in plasma using custom Taqman assays on a droplet digital PCR platform. Tumour response assessments were conducted according to RECIST. Statistical analysis included Fisher’s exact test and Spearman’s correlation.

**Results:** 62% of pts were male, median age 59, range 50-83. On baseline MRI, circumferential resection margin was involved or threatened in 75% and EMVI positive in 81%. Plasma was collected at a median of 6 days (IQR 2-12) prior to the start of CRT (baseline), 21 days after the start of CRT (mid) and 37 days after completion of CRT (end). The frequency (%) of mutation detection in tissue was: TP53 (85), APC (74), KRAS (36), PIK3CA (15), NRAS (4) and BRAF (2). ctDNA was detectable in 74% of pts at baseline and in 21% at mid and end of CRT. ctDNA detection increased with stage at baseline: stage 1 (n = 0/1), stage 2 (n = 3/5, 60%) and stage 3 (n = 32/41, 78%). Stage had no impact on detection at mid or end of CRT. At baseline, ctDNA was detectable in all 15 CEA secretors (53 ± ng/L) compared to 63% in non-secretors (P = 0.008). Baseline ctDNA levels were not associated with k67 tumour assessment. MRI response assessment of the primary tumour was not associated with ctDNA detection at any timepoint. 11 patients developed metastases of which 3 occurred after surgery. End of CRT ctDNA detection was higher in pts that developed metastases (68%) compared to those that did not (38.9% P = 0.0005). Detection of ctDNA at baseline that persisted at mid CRT was also higher in pts that developed metastases (36% vs 11%, P = 0.07). Conclusions: ctDNA detection can help identify rectal cancer pts with localised disease at risk of developing metastases. These pts could benefit from earlier intervention with systemic therapy.

**Clinical trial identification:** CCR 3085, NCT00825110.

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**Disclosure:** All authors have declared no conflicts of interest.

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**1868P** A genetic analysis of gemcitabine-induced high-grade neutropenia in pancreatic cancer patients


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**Background:** One of the standard care regimens for advanced pancreatic cancer is gemcitabine-based chemotherapy. The efficacy of gemcitabine is reduced by dose-limitating hematologic toxicities, especially neutropenia. Uncovering the variability of these toxicities attributed to gemcitabine DNA variation is of great importance.

**Methods:** CALGB 80303 was a randomized study in advanced pancreatic cancer patients treated with gemcitabine with or without bevacizumab. The study protocol included genotyping of genes of gemcitabine disposition (CDA, DCTD, SLC29A1, SLC28A1, SLC28A2), as well as a genome-wide analysis. The clinical phenotype was time to high-grade early neutropenia event accounting for progression or death, or other treatment-terminating adverse events as competing informative events. The inference was conducted on the basis of the association between genotype and cause-specific hazard of a neutropenic event.

**Results:** The primary analyses were conducted on the basis of 294 genetically estimated Europeans. For CDA rs2072671 (A>C), AC and CC patients had a lower risk of neutropenia than AA patients (unadjusted P-value 0.01, HR 0.61, 95% CI 0.41–0.89). For SLC28A1 rs3825876 (G>C), AA patients had a higher risk of neutropenia than GA and GG patients (unadjusted P-value 0.02, HR 1.51, 95% CI 1.08–2.16). The C allele of rs2072671 was associated with increased mRNA expression in whole blood in three studies (unadjusted P-values 2.7e-14, 6.61e-62, 9.70e-65). In the genome-wide analysis, variants in TGFB2 were among the top hits (unadjusted lowest P-value 1.62e-06) but had no effect in luciferase assays.

**Conclusions:** The first genetic analysis of gemcitabine-induced neutropenia using a competing risk model in a prospective randomized clinical study has proposed a potentially novel mechanism of the protective effect of the CDA rs2072671 variant. We hypothesize that adenine in rs2072671 (A>C) variants acts through a local effect in either the bone marrow or in circulating neutrophils (or both), by protecting neutrophils from the anti-proliferative effects of gemcitabine. Further confirmation is needed.

**Clinical trial identification:** NCI-2012-02960, NCT00888894.
Effect of a combined treatment with iPSC derived dendritic cells and proton beam irradiation in a murine subcutaneous melanoma model

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2Division of the Transplantation Immunology, National Research Institute for Child Health and Development, Tokyo, Japan

Background: In situ dying and just died tumor cells after irradiation give danger signals and release tumor-specific antigens which are sequentially incorporated into dendritic cells (DCs). Our previous studies on a murine subcutaneous tumor model showed that injection of bone marrow derived DCs (BM-DCs) after X-ray therapy significantly delayed tumor growth. As compared to X-rays, the unique biological and physical benefits of proton beam therapy may prove superior in the systemic immune effect. In addition, usage of DCs induced from iPSC cells (iPS-DCs) may overcome practical problems of BM-DCs such as a limited number of applicable cells and an induction period of 7 days. The purpose of this study is to investigate: 1) whether proton beam therapy are effective in the induction of antitumor immunity in comparison to X-ray therapy.

Methods: DCs were induced by using GM-CSF and IL-4 from autologous bone marrow cells or iPSCs of C57BL/6 mice. Syngeneic B16 melanoma cells subcutaneously implanted at the thighs of C57BL/6 mice were treated with X-ray or proton beam 5 days after inoculation. After 1, 3, 5, 7 days from irradiation, induced BM-DCs or iPS-DCs were injected directly into the tumor site. Tumor growth was monitored, and survival analysis was performed.

Results: Proton beam therapy induced superior immunogenicity of cancer cell comparing to X-ray therapy. Also, iPS-DCs showed an excellent ability to incorporate antigens in vitro comparing to BM-DCs. The combination treatment of proton beam and iPS-DCs significantly delayed tumor growth in vivo.

Conclusions: iPS-DCs should overcome the practical problems of BM-DCs in cancer treatment. The combination treatment of proton beam and iPS-DCs administration can offer a promising novel cancer therapy.

Legal entity responsible for the study: Koji Tsuboi.

Disclosure: All authors have declared no conflicts of interest.

Reference:

Y. Wang, L. Sun, X. Li, K. Tsubo. Proton Medical Research Center, University of Tsukuba, Tsukuba, Ibaraki, Japan.

1870P Developing the liquid biopsy in gastroesophageal adenocarcinoma: Disease monitoring and detection of minimal residual disease

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Background: Gastroesophageal adenocarcinoma (GOA) is a molecularly defined group of cancers with shared genetic alterations, poor overall survival and no routine blood based biomarker. The liquid biopsy, including circulating tumour DNA (ctDNA) is a promising technology that may improve our ability to monitor disease and enhance survival. This study aimed to determine the utility of ctDNA in GOA.

Methods: A pilot study of 37 patients with GOA were recruited. These comprised 24 patients treated with curative intent and 13 palliative patients. Tumour DNA was sequenced using a custom ampliseq six gene targeted next generation sequencing (NGS) panel. Tumours from patients treated with curative intent with no detectable somatic mutation were also analysed for gene amplification via NanostringTM nCounter. Plasma from blood samples taken at multiple time points were analysed by NGS and digital droplet PCR to detect ctDNA.

Results: Somatic mutations at > 5% allele frequency were identified in 30 of 37 (81%) tumours, most commonly in TP53. Gene amplification was detected in 11 of 37 (31%) patients and predicted poor survival (median PFS 298 vs > 1000 days, HR = 11.8, p < 0.001). In 4 patients, ctDNA was detected in the postsurgical blood test, of these 3 had relapsed and one remains disease free at 5 months (median PFS 203 vs > 1000 days, HR = 9.6, p = 0.084). This patient will be followed up for evidence of relapse as these ctDNA positive post surgical bloods suggest detection of minimal residual disease.

Conclusions: Tracking of ctDNA in patients with GOA provides valuable clinical information regarding disease progression and response, and presence of ctDNA is generally a poor prognostic sign. In addition, ctDNA may define patients with minimal residual disease who are at high risk of relapse after surgery.

Legal entity responsible for the study: University of Leicester.

Disclosure: All authors have declared no conflicts of interest.

Reference:

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1871P Survival from breast cancer in patients with BRCA1/2, CHEK2, NOD2 mutations and TP53 polymorphisms

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Background: The purpose of this study is to estimate 5-year survival rates for patients newly onset breast cancer, with and without BRCA1/2, CHEK2, NOD2 mutations or TP53 polymorphisms and to identify prognostic factors among mutation carriers in breast cancer patients.

Methods: In a study conducted in the years 2007-2016 in the Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch (COI) were analysed prognostic factors and survival in 622 breast cancer including 60 BRCA mutations carriers, 46 CHEK2 mutation carriers, 29 NOD2 mutation carriers and 87 patients with TP53 polymorphisms. Control group was selected from breast cancer patients without mutation and polymorphisms (n = 400).

Results: The five-year rate of OS was 75.9% for pts with BRCA mutation, 94.4% for CHEK2 mutation carriers, 96.6% for NOD2 mutation carriers and 100% for patients with TP53 polymorphisms. BRCA mutation carriers had insignificantly worse survival as compared to control group (p = 0.180). Patients with CHEK2 mutation had significantly better OS than control group (p = 0.052). Similarly NOD2 mutation carriers had also significantly better OS than control group (p = 0.043). Patients with TP53 polymorphisms carriers had higher OS in comparison to control group (p = 0.002). In subgroup of pts with N0 (Without lymph node metastases) BRCA mutation carriers was characterized by the worst OS (81.1%) among carriers of other mutations: CHEK2 (94.7%, p = 0.021), NOD2 (95.3%, p = 0.092) and TP53 polymorphisms (100%, p = 0.007) or control group (94.4%, p = 0.022). Similar tendency was observed according to N+ subgroup and subgroup with tumor size T1-T2. Higher tumor size (HR = 2.85), lymph node metastases (HR = 2.93) and HER2 overexpression (HR = 1.49) were significant factors for worse OS. Positive ER status was associated with a better OS (HR = 0.52, p = 0.001). Age <40 years (HR = 0.71, p = 0.255) was insignificantly favorable factor.

Conclusions: CHEK2, NOD2 mutation carriers and patients with TP53 polymorphisms had better 5-year survival in comparison to patients with BRCA mutation and control group. Higher tumor size (T) and lymph node metastases (N+) were negative prognostic factors independently from the presence of mutations and polymorphisms.

Legal entity responsible for the study: Maria Sklodowska Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch.

Disclosure: Has not received any funding.

All authors have declared no conflicts of interest.

Reference:

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1872P Phase I pharmacological study of continuous chronomodulated capecitabine treatment

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Background: Capecitabine is an oral prodrug of the anti-cancer drug 5-fluorouracil (5-FU). The 5-FU degrading enzyme, dihydropyrimidinase dehydrogenase, and the target enzyme thymidylate synthase, are subject to circadian rhythmicity. The primary aims of this study were to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), recommended dose (RD) and safety of capecitabine therapy adapted to this circadian rhythm (chronomodulated therapy).

Methods: Patients aged ≥ 18 years, with WHO performance status of ≤ 2, and advanced solid tumors potentially benefiting from capecitabine therapy were enrolled. DPD*2A or 2846A>T mutation carriers were excluded. A classical dose escalation 3 + 3 design was applied. Capecitabine was administered twice daily without interruptions. The daily dose was divided in morning and evening doses that were administered at 09:00h and 24:00h, respectively. The ratio of the morning to the evening dose was 3:5 (morning:evening). Toxicity was assessed according to the Common Terminology Criteria for Adverse Events version 4.03. DLT was evaluated during the first three weeks of treatment.

Results: A total of 21 patients was enrolled. The daily capecitabine dose was escalated from 1000 mg/m² up to 2550 mg/m² over five dose levels. Three DLTs were observed in two patients at the highest dose level (grade III hand-foot syndrome (3x) and grade III diarrhea (1x)). The MTD was established at 2080 mg/m² per day (9:00 h and 1250 mg/m² at 24:00 h). Continuous chronomodulated capecitabine therapy was
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generally well tolerated at the MTD level with main adverse events being grade 1-2 hand-foot syndrome and fatigue.

**Conclusions:** The cumulative dose of capecitabine at the MTD/RD (i.e., 750 mg/m² at 9:00h and 1250 mg/m² at 24:00h, continuous chronomodulated regimen) is 20% higher than the cumulative dose of the approved regimen (1250 mg/m² daily on day 1-14 of every 21-day cycle). Chronomodulation therefore represents a promising strategy as it could lead to improved tolerability and efficacy of capecitabine. Further investigation is warranted.

**Clinical trial identification:** EudraCT: 2014-00889-22.

**Legal entity responsible for the study:** The Netherlands Cancer Institute.

**Funding:** The Netherlands Cancer Institute.

**Disclosure:** All authors have declared no conflicts of interest.

1875P

**Head and neck (HN) primary sarcomatoid carcinoma (PSC) profile by high-throughput somatic mutation profiling**

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**Background:** The Head & Neck Primary Sarcomatoid Carcinoma (HN PSC) is a rare subtype of squamous cell carcinoma with poor prognosis. This study sought to describe the mutational profile of HN PSC using high-throughput genotyping technology Massarray, (Agenda, Hamburg).

**Methods:** We included 45 patients with HN PSC. We used PCR mass spectrometry detection to establish the DNA mutation profiles of 72 samples from these patients (45 primary tumors, 5 metastatic cervical nodes and 22 non tumoral tissues) studying 214 mutations affecting 26 oncogenes and tumor suppressor genes.

**Results:** In total, 33/45 (73.3%) patients were male and 31/45 (69%) were smokers. Median age was 60 years (range 13 – 91 years) and 28/45 (62.2%) were metastatic. The major tumor sites were oral cavities (31.1%) and larynx (28.1%). The predominant histological subtype was the pleomorphic form (66.7%). In the 72 tumors, 18 distinct somatic alterations were identified, 15 tumors (33%) harboring at least one mutation. The most frequent mutations were TP53 (11.1%), PIK3CA (8.9%), EPHX2 (4.4%), MET (4.4%), NOTCH1 (4.9%), NTRK2 (2.2%), BRAF (2.2%), JAK2 (2.2%), KRAS (2.2%) and NRAS (2.2%). The presence of a mutation was not correlated with any clinical characteristics (age, sex, primary located site, cancer stage, tobacco and alcohol status). Only 1/4 (2.2%) tumor presented a targetable mutation with tyrosine kinase inhibitor (mutation BRAF). The mutational profile was identical between the local tumor site and the cervical node in 4/5 patients.

**Conclusions:** Our results demonstrated that HN PSC had a similar mutational profile of other HN carcinoma such as TP53, PIK3CA and NOTCH1 mutations. It reinforced the hypothesis of a single cell clone, which is acquired with different histological phenotypes by different, still unknown mechanisms involving epithelial to mesenchymal transition.

**Legal entity responsible for the study:** Marie Wiese.

**Funding:** Has not received any funding.

**Disclosure:** V. Fallet: Travel, accommodations, expenses: GSK, BMS, Novartis, Boehringer Ingelheim. M. Wilde: Research funding: BMS, Boehringer Ingelheim. Consulting or advisory role: AstraZeneca, Roche, BMS, MSD, Novartis, Boehringer Ingelheim. All other authors have declared no conflicts of interest.

1874P

**A composite liquid biomarker for non-invasive diagnosis of resectable pancreatic ductal adenocarcinoma**

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**Background:** Due to the dismal prognosis of the pancreatic ductal adenocarcinoma (PDAC) biomarkers are needed to facilitate the early and preferably noninvasive diagnosis. The use of circulating tumor DNA (ctDNA) was already examined in the metastatic situation but not at all in a resectable stage with lower tumor load. Currently, CA19-9 is the only validated biomarker for PDAC but it fails to provide sufficient performance. Recently, it has been reported that elevated levels of thrombospondin-2 (THBS2) protein are detectable in PDAC. Here we aimed at improving sensitivity and specificity of THBS2 based detection of early PDAC by combining THBS2 analysis with further markers.

**Methods:** 99 patients with proven PDAC, enrolled to the NEONAX trial (identifier: NCT02475413), were selected for this study independent retrospective translational analysis. 15 patients with benign pancreatic disease (IPMN) served as controls. ctDNA concentration was measured fluorometrically. KRAS genotyping of ctDNA was done by digital droplet PCR targeting the 7 most frequently occurring KRAS mutations in PDAC. CA 19·9 (Roche, cut-off 55 U/ml) and THBS2 levels (Quantikine, R&D systems, cut-off 42 ng/ml) were determined by ELISA.

**Results:** PDAC patients had significantly more ctDNA (12.6 ng/ml) than IPMN patients (5.5 ng/ml, p = 0.0006). Only 5% of PDAC patients and 7% of IPMN patients had detectable KRAS mutations in ctDNA. CA19-9 was elevated in 56% and THBS2 in 44% of PDAC patients. Both markers were not elevated in any of the IPMN patients. Therefore, the assessment of THBS2 and CA19-9 levels was most suitable to discriminate the PDAC cohort from the IPMN cohort, with a sensitivity of 77% and a specificity of 100%.

**Conclusions:** THBS2 and CA19-9 panel assessed in human blood using a conventional ELISA assay may improve the diagnosis of pancreatic lesions as PDAC at an early stage. While total ctDNA amount differs between patients with benign and malignant pancreatic lesions, ctDNA genotyping for KRAS mutations failed to improve non-invasive diagnostic strategies in resectable PDAC most likely due to a low tumor load.

**Clinical trial identification:** NCT02475413.

**Legal entity responsible for the study:** Ulm University.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

1875P

**Acquired chemoresistance of colorectal cancer (CRC) cells is accompanied by pro-invasive VEGF-signaling that is attenuated by aflibercept**

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**Background:** Cancer mortality is principally associated with the presence of drug-resistant, invasive subpopulations of tumor cells. However, the functional and mechanistic interactions between the two phenotypes are incompletely understood. Colorectal cancer (CRC) cells produce the vast majority of VEGF in the cancer environment and display endogenous VEGFIR/VEGFR2 signaling which is believed to promote survival under stress.

**Methods:** Migration and invasion was determined by the transwell assay (Boyden Chamber). For the tube formation assay, CRC cells were seeded onto 3D matrigels and incubated at 37°C for 24 hr monitored by videomicroscopy. Determination of VEGF ligands was carried out by ELISA.

**Results:** We here characterize a panel of 4 isogenic CRC cell lines comprised of the parental HCT-116 cells and three independently derived sublines resistant to 5-fluouracil, oxaliplatin and SN-38. Resistant cells secreted 3.7 fold more VEGF, while the
HCT-116/S-FU cells also secreted 2 times more PI3K, compared to the parental cells. VEGF signaling is known to promote CRC cell migration and invasion. In agreement, resistant cells showed 6-11 fold increased migration, whereas the invasive capacity had increased 6-15 fold. Aflibercept inhibits all three VEGFRI ligands (VEGF-A, VEGF-B and PIGF) on CRC cells. Accordingly, addition of aflibercept resulted in a significant decrease in both migration and invasion. Two of the three resistant cell lines were able to do vascular/vasculogenic mimicry by forming capillary-like cellular networks which could be significantly attenuated by aflibercept.

Conclusions: Taken together, our results indicate that acquired resistance to genotoxic agents may be accompanied by an increased invasive potential mediated, in part, by VEGF signaling that can be attenuated by aflibercept.

Legal entity responsible for the study: INSERM and Sorbonne University.

Disclosure: A.K. Larsen; Research grant: Sanofi-Aventis Europe. All other authors have declared no conflicts of interest.


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Background: We evaluated the impact of tumor type and molecular profiling on overall survival of patients (pts) with cancer referred to Medical Oncology Departments affiliated with the Hellenic Cooperative Oncology Group (HeCOG).

Methods: Pts referred from 1989 to 2017 had molecular testing (for research) of archival tumor tissue collected at the time of diagnosis (stage I-III, 82%; stage IV, 18%). Tumor-specific (e.g. breast, colon) gene panels (45-101 genes) were used to identify pathogenic mutations in clinically relevant genes. Deep sequencing was performed at the Laboratory of Molecular Oncology, Aristotle University of Thessaloniki and HeCOG. Mutation annotation was performed at MD Anderson Cancer Center. All pts received standard-of-care anti-cancer therapy.

Results: We analyzed 3,211 pts (median age, 58 years; men, 29%) with informative sequencing data. Results by tumor type and molecular pathway are shown in the table. Overall, 1,193 (37%) pts had ≥ 1 actionable alterations [115 (3.6%) ≥4]. The most common affected pathways were PI3K, RAF/MEK, homologous recombination repair (HRR), and tyrosine kinase; 294 (9.2%) pts had alterations in ≥ 1 pathways. The median follow-up of alive patients is 7.48 years (yrs) (95%CI: 7.36-7.59). Of 3,211 pts, 1,060 (33.01%) have died. The median overall survival is 16.08 yrs (95%CI, 13.25-16.75). Of pts with breast cancer and actionable mutations, the 5-y survival rates were: stage I-III (n = 501) 88.8%; stage IV (n = 14), 51.1% (p = 0.0001). Of pts with colorectal cancer and actionable alterations, the 5-y survival rates were: stage I-III (n = 299), 76.5%; stage IV (n = 50), 15.2% (p < 0.0001).

Conclusions: Tumor sequencing revealed clinically relevant genomic mutations in several molecular pathways. Prospective clinical trials validating the clinical utility of tumor profiling are warranted.

Legal entity responsible for the study: Hellenic Cooperative Oncology Group.

Funding: Hellenic Cooperative Oncology Group.

Disclosure: All authors have declared no conflicts of interest.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total N</th>
<th>N with actionable alterations</th>
<th>%</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1,964</td>
<td>527</td>
<td>27</td>
<td>Median, Years (95% CI) 5-yr OS, % (95% CI)</td>
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<td>533</td>
<td>359</td>
<td>67</td>
<td>NR</td>
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<td>123</td>
<td>65</td>
<td>0.82 (65.9) -</td>
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<td>144</td>
<td>77</td>
<td>54</td>
<td>8.92 (6.68-NR)</td>
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<tr>
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<td>131</td>
<td>24</td>
<td>18</td>
<td>4.54 (1.69-9.71)</td>
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<tr>
<td>Gastric</td>
<td>101</td>
<td>11</td>
<td>11</td>
<td>4.18 (1.04-NR)</td>
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<td>33</td>
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<td>Ovarian</td>
<td>70</td>
<td>46</td>
<td>66</td>
<td>3.24 (2.18-5.32)</td>
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<tr>
<td>Total</td>
<td>3,211</td>
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<td>37</td>
<td>13.23 (10.6-NR)</td>
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<tr>
<td>Pathway</td>
<td>Total tested</td>
<td>N with actionable alterations</td>
<td>%</td>
<td>16.08 (13.23-5-NR)</td>
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<tr>
<td>PI3K/RAF/AKT/mTOR</td>
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<td>14</td>
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<td>3,211</td>
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<td>8</td>
<td>7.84 (5.33-NR)</td>
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<td>Tyrosine kinase</td>
<td>3,211</td>
<td>161</td>
<td>5</td>
<td>69.2 (62.0-77.3)</td>
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Legal entity responsible for the study: IPO-Porto.
Background: One of the approaches for increasing DC vaccine efficacy is the direct delivery of generated DC to the regional lymph nodes and tumor site. The aim was to investigate the antitumor effect of DC loaded with tumor antigens and iron oxide nanoparticles (INP) under the influence of an external magnetic field.

Methods: In experimental study, 60 CBA mice were involved. Sorbent 37 (S37) was used as experimental tumor model, and cells in lethal dose (9×10^12 cells per animal) were injected into the hip. DCs were obtained from syngeneic spleen monocytes and loaded by mechanically modified ioposphated 37 cells (0.05 mg/ml) with Fe3O4 nanoparticles (8×10^-12 g/cell, Sigma-Aldrich). DC vaccine was injected intradermally 3 times a week.

Results: The application of generated DCs with INP promoted a reduction of primary tumor volume compared to the control group (p=0.002) and DC monotherapy (p=0.005). DCs with INP didn’t significantly effect on the hematological parameters in mice with S37. The combined effect of DCs with INP reduced mRNA expression levels of FoxP3 by 9.9 times (p=0.04), VEGF by 2.9 times (p=0.02), IL-10 by 2.8 times (p=0.005) and TGF-β by 10 times (p=0.002) in tumor cells compared to the control. The administration of DC vaccine with INP led to reduce tumor immunosuppression in the regional lymph nodes, namely FoxP3 mRNA level decreased in 2.4 times and IL-10 mRNA level — in 1.9 times compared to the control group, p=0.012.

Conclusions: Application of DC vaccine with INP under magnetic field resulted in a pronounced antitumor effect in tumor-bearing mice.

Legal entity responsible for the study: National Cancer Institute of the MPH Ukraine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1878P

Strategy to improve the antitumor efficacy of dendritic cell-based nanovaccine under magnetic field control

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Background: One of the approaches for increasing DC vaccine efficacy is the direct delivery of generated DC to the regional lymph nodes and tumor site. The aim was to investigate the antitumor effect of DC loaded with tumor antigens and iron oxide nanoparticles (INP) under the influence of an external magnetic field.

Methods: In experimental study, 60 CBA mice were involved. Sorbent 37 (S37) was used as experimental tumor model, and cells in lethal dose (9×10^12 cells per animal) were injected into the hip. DCs were obtained from syngeneic spleen monocytes and loaded by mechanically modified ioposphated 37 cells (0.05 mg/ml) with Fe3O4 nanoparticles (8×10^-12 g/cell, Sigma-Aldrich). DC vaccine was injected intradermally 3 times a week.

Results: The application of generated DCs with INP promoted a reduction of primary tumor volume compared to the control group (p=0.002) and DC monotherapy (p=0.005). DCs with INP didn’t significantly effect on the hematological parameters in mice with S37. The combined effect of DCs with INP reduced mRNA expression levels of FoxP3 by 9.9 times (p=0.04), VEGF by 2.9 times (p=0.02), IL-10 by 2.8 times (p=0.005) and TGF-β by 10 times (p=0.002) in tumor cells compared to the control.

Conclusions: Application of DC vaccine with INP under magnetic field resulted in a pronounced antitumor effect in tumor-bearing mice.

Legal entity responsible for the study: National Cancer Institute of the MPH Ukraine.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1879P

Potential role of RICTOR copy number gain (CNG) as a key biomarker of mTOR activity: A comprehensive preclinical analysis in squamous cell lung cancer (SCLC) models

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Background: We previously performed a multi-step genomic study in almost 100 resected SCLC patients dichotomized according to the prognosis. Among the pathways with a biological impact on SCLC oncogenesis, PI3K/mTOR-Rictor emerged as a crucial axis (Pilotto WCLC 2016). In order to explore the potentiality of mTOR inhibition, we present a set of in vitro experiments in RICTOR-aberrant SCLC preclinical models.

Methods: Next-generation sequencing (NGS), fluorescence in situ hybridization (FISH) and Western Blot were performed in 3 SCLC cell lines (H-1703, SK-Mes-1, Calu-1) for determining CNG and protein profile of the PI3K/mTOR-Rictor components. The activity of PI3K/mTOR pathway targeted inhibitors in the SCLC cell lines was examined in short (72 hours) and long-term (1 week) cell viability assays.

Results: NGS analysis revealed a different amount of RICTOR CNG among SCLC cell lines. FISH confirmed that H-1703 harbors the highest number of RICTOR copies (6) followed by SK-Mes-1 (4) and Calu-1 (3.5), suggesting polyploidy of the short arm of chromosome 3 as the main mechanism of RICTOR gain. Although Rictor protein levels were similar among the cell lines, p-mTOR S2448 (active form of mTOR complexes) was higher in H-1703 than SK-Mes-1 and Calu-1. PI3K/mTOR inhibition proved more effective in H-1703, with lower IC50 values in short term treatment (Table). Similar findings were confirmed in long-term assays.

Conclusions: Overall, the results of our study suggest the potential implication of PI3K/mTOR-Rictor pathway in SCLC oncogenesis, thus rendering it a promising target for a targeted approach. Among the mTOR inhibitors, RICTOR CNG seems to predict a higher sensitivity to PI3K/mTOR inhibition and might represent a potential biomarker to be explored as a stratification tool in clinical trials. Confirmatory RICTOR silencing experiments are currently ongoing.

Legal entity responsible for the study: Emilio Brus.

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

Disclosure: All authors have declared no conflicts of interest.

1880P

Final results of the phase I study in healthy volunteers of AB928, a dual antagonist of the A2aR and A2bR adenosine receptors being studied as an activator of anti-tumor immune response

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Background: Adenosine suppresses anti-tumor immune responses via A2aR and A2bR receptors on intra-tumoral immune cells. This effect is mediated by increased cAMP levels and phosphorylation of the transcription factor CREB. A placebo-controlled study in healthy volunteers was conducted to assess the safety, tolerability and PK/PD (pCREB levels in blood T cells) profile of AB928, in order to select AB928 doses for the ongoing studies in cancer patients.

Methods: This placebo-controlled double-blind study had single ascending dose (SAD) and multiple ascending dose (MAD) arms. AB928 doses between 10 and 200 mg qd and 100 mg bid were evaluated. Whole blood from AB928 and placebo-treated subjects was stimulated ex vivo with the adenosine agonist NECA. Flow cytometry was used to assess levels of pCREB. AB928 plasma concentrations were determined using LC–MS–MS.

Results: The study enrolled 85 participants (randomized 3:1, active:placebo), 40 each in the SAD and MAD arms, plus 5 in a food-effect assessment cohort. The effects of 1, 5 and 10 mg NECA were assessed in whole-blood samples obtained at various time points post-dose. The PD response at each timepoint was correlated with the associated AB928 plasma levels. In all dose groups, significant inhibition at peak plasma concentrations was observed. Significant inhibition was also observed 24 hours post-dose in the higher dose groups. Final unblinded safety and PK/PD results from this study will be presented.

Conclusions: AB928 was well tolerated in this study. No stopping rules were met and dose escalation continued until maximal PD effects were observed. There was no evidence of the physiological effects associated with other adenosine receptor antagonists tested in humans. The MTG was not reached in this study. Significant inhibition of pCREB-mediated CREB phosphorylation in blood T cells was observed in all dose groups at peak plasma concentrations, as well as at trough in the higher dose groups. The resulting PD/ PK correlations were used to guide dose selection in several ongoing oncology studies, the outlines of which will be described in this presentation.


Legal entity responsible for the study: Arcus Biosciences, Inc.

Funding: Arcus Biosciences, Inc.


## Background:
Treatment resistance in cancer has been linked to a population of tumor cells with self-renewal properties called cancer stem cells (CSCs). The aim of this study was to isolate and characterize CSCs from lung cancer cell lines and tissue from resected non-small cell lung cancer (NSCLC) patients.

## Methods:
The study was performed on tumor cells from 8 resected NSCLC patients and 12 NSCLC cell lines. Suspension cultures were established for CSC isolation (3D-tumorspheres), whereas differentiated tumor cells were cultured under adherent conditions (2D). In vitro differentiation, proliferation and chemotherapy resistance and in vivo tumor initiation capacity were tested. 60 CSC-related genes were evaluated by RTqPCR. Gene expression results were validated at protein level by immunoblot and IF.

## Results:
8 out of 20 primary NSCLC cultures were successfully established, forming 3D tight spheroids or loose aggregates. Tumorspheres showed proper differentiation capacity, unlimited exponential growth, high resistance to cisplatin, paclitaxel, vinorelbine and gemcitabine, and great tumor initiation potential. Gene expression analysis revealed high variability between cell lines and patient cultures and that 2D cultures revealed high variability between cell lines and patient cultures and that 2D cultures did not faithfully recapitulate the heterogeneity of human lung tumors. We describe the derivation and characterization of 8 PDX models and 20 pairs of PDOs from NSCLC tumors and adjacent non-tumor tissues. PDX retain histologic and molecular characteristics of their donors and recapitulate the heterogeneity of human lung tumors.

## Conclusions:
Cancer microenvironment is extremely hypoxic condition and the analysis of cell biology under hypoxia is significantly important. Previously we have shown that leukocyte common antigen related interacting protein (Liprin)-α4 could be a new downstream mediator of HIF-1α in small cell lung cancer as a chemosensitivity under hypoxia for small cell lung cancer as a downstream mediator of HIF-1α.

## Disclosure:
All authors have declared no conflicts of interest.

## Funding:
Instituto de Salud Carlos III (PI18/0029), co-funded by ERDF.

All authors have declared no conflicts of interest.
therapeutic target for pancreatic cancer. In the present study, the biological significance of liprin-α4 in small cell lung cancer (SCLC) which was one of the refractory cancers and less therapeutical options was investigated.

**Methods:** SCLC cell lines (SRC-3 and SRC-5) were used as target cells. Cells were cultured under normoxia (20% O2) and hypoxia (1% O2). Gene inhibition was performed using small interfering RNA. Proliferation was performed by MTT assay. Invasion was estimated by matrigel invasion assay. Chemosensitivity was analyzed using CDDP and 5-FU. Mice xenograft experiments were performed using BALB/c nude mice. Twenty human SCLC specimens were used for immunofluorescent staining.

**Results:**
1. Expression of liprin-α4 increased under hypoxia compared to normoxia.
2. Liprin-α4 inhibition decreased proliferation in vitro under hypoxia.
3. Liprin-α4 suppression did not affect migration and invasion under hypoxia.
4. Tumor volume in mice injected with liprin-α4 inhibited SCLC cells was significantly lower than that in control mice.
5. Signalizing from liprin-α4 was through MAPK signaling pathway.
6. Chemosensitivities of CDDP and 5-FU under hypoxia were significantly lower than those under normoxia.
7. Liprin-α4 inhibition significantly enhanced chemosensitivity of CDDP under hypoxia.
8. HIF-1α regulated liprin-α4 expression in SCLC cells.
9. HIF-1α inhibition led to decreased proliferation under hypoxia.
10. HIF-1α inhibition significantly improved chemosensitivity of CDDP under hypoxia.

**Conclusions:** These results suggest that liprin-α4 which is expressed more under hypoxia, plays a pivotal role for increased proliferation and decreased chemosensitivity under hypoxia for SCLC as a downstream mediator of HIF-1α. Inhibition of HIF-1α and Liprin-α4 could be a new therapeutic strategy for SCLC.

**Legal entity responsible for the study:** Kyushu University Ethics Committee.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**1885P** Precision medicine for patients with rare cancers: An effective approach within the prospective MOSCATO trial

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**Methods:**
1. Tumor tissue specimens from 50 patients with rare cancers, enrolled in the MOSCATO 01 trial. An on-purpose tumor biopsy was performed, followed by high-throughput molecular analysis using targeted Next Generation Sequencing (NGS), comparative genomic hybridization array (CGH) and Whole Exome Sequencing (WES) after histological control. Matched therapy was decided accordingly for pts who had targeted molecular alterations.

**Results:**
- Between December 2011 and March 2016, 122 pts with 58 different tumors types were enrolled in the MOSCATO 01 trial. Median age was 59 years (range, 19-89), median number of previous systemic therapies was 4 (range, 0-13), 51% (63/122) were women, 90% had ECOG performance 1 and 2.
- Most prevalent histologies were adenocarcinomas of unknown primary (12%), lung NE tumor (8%) and SCC of unknown primary (5%). Most frequent actionable alterations were PIK3CA mutation (14%), ERBB2 amplification (10%), and EGFR amplification (4%). Of 122 pts, 62 (51%) harbored ≥ 1 actionable genomic alterations. Thirty pts (25%) received matched therapy.
- Of those, 6 had a partial response, 9 had stable disease as the best response. Overall response rate (ORR) was 20%. Median PFS2 for matched therapy was 2.8 [95% CI 1.2 – 4.3] versus median PFS1 for last standard line 4.6 months, p = 0.8. Pts harboring EGFR amplifications had the best median duration of response 9.8 months on matched therapy. Median overall survival was not significantly improved in pts who received matched therapy compared to pts with unmatched therapy, 14.8 and 8.4 months, respectively (p = 0.3).

**Conclusions:**
- Precision medicine using high-throughput molecular analysis of rare cancers is feasible in clinical practice and can affect their clinical outcomes. Rare tumors harboring EGFR amplification showed prolonged response to targeted treatment.
- Larger studies and more effective targeted molecules are still needed.

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**1886P** Streaming multi-omic and artificial intelligence analysis through interrogative biology and basic for translational precision medicine applications in clinical oncology


**Methods:** The BERG Integrative Biology platform deconstructs the established paradigm by using patient biology to guide the entire drug development process from R&D to clinic, leading to improved clinical outcome. In order to properly characterize the molecular phenotype of patients or disease states, this platform allows for systematic interrogation of each biological sample at high throughput with machine learning tools such as proteinomics, lipidomics and metabolomics. This is then combined with further analytical methods that allows for assessment of sample quality through statistical, environmental/demographic influence, sample handling, and pharmacological impact markers to elucidate causal molecular signal from inherent noise.

**Results:**
- BERG ETL System uses a proprietary data-driven algorithm to automatically extract, correlate, correct, synthesize, interpret, analyze and unify all data sources and types, outputting a harmonized molecular and/or clinical profile, which can be used for summary reports such as patient dashboards, standard analysis such as statistics and machine learning, and to be analyzed by BERG’s Artificial Intelligence (AI) Technology, bAIcis. When applied to clinical trial information, bAIcis uses a multi-layer method to identify clinical and molecular markers that can stratify patients based on trial outcomes such as “Response to Treatment”, “Quality of Life” or “Adverse Events” as well as identification of disease drivers.

**Conclusions:**
- Using this approach a comprehensive understanding of causal drivers, predictive biomarkers aligned with therapeutic benefit, and identification of adverse event populations in cancer indications can be elucidated. This is streamlined through an AI driven platform based on quality metric to support precision medicine in oncology drug development.

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**Legal entity responsible for the study:** Berg, LLC.

**Funding:** Berg, LLC.


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**1887P** Prediction of response to vemurafenib in BRAF V600E mutant cancers based on a network approach

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**Methods:**
- In a network unbiased approach, why different tumors harboring BRAF V600E mutation show heterogeneity in response to vemurafenib.

**Results:**
- Using a bioinformatics tool, we sought to elucidate, through a network unbiased approach, why different tumors harboring BRAF V600E mutation show heterogeneity in response to vemurafenib.

**Conclusions:**
- We explored SwitchMiner (SWIM) software to analyze gene expression profiles available on The Cancer Genome Atlas. SWIM is able to identify a small pool of regulatory genes (switch genes), which are likely to be critically associated with drastic changes in cell phenotypes. We selected among those genes, the ones who encode for kinases. Then, we employed Geneious R11 desktop platform to identify those kinases with the maximum identity score to kinases reported as known targets of vemurafenib.

**Legal entity responsible for the study:** Gustave Roussy Cancer Campus.

**Funding:** Philanthropy.

**Disclosure:** All authors have declared no conflicts of interest.
three homology sequences identified across vemurafenib targets and we found that thyroid cancer and lung adenocarcinoma have a similar number of putative targetable homology sequence.

Conclusions: Our network analysis may provide additional approaches to explore the molecular mechanisms underlying the different response to vemurafenib in BRAF V600E mutant tumors, elucidating how precision medicine cannot leave out of consideration the tumor histology. It is likely that, while different cancers share the major driver event, the response to therapy may vary based on the number of kinases with homology sequences to the druggable kinase targets. In vitro data are needed to validate this prediction.

Legal entity responsible for the study: Sapienza University of Rome.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1888P Improving value for cancer patients: A European study of outcomes in practice

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Background: ICHOM (International Consortium for Health Outcomes measurement) and AllCan – an international multi-stakeholder initiative – are in partnership to identify and support a community of European hospitals to assess how they can optimize the efficiency of cancer care in breast and lung cancer patients.

Methods: A community of 10 hospital sites for lung cancer and 10 for breast cancer will be supported to implement and measure the ICHOM standard sets of outcomes. This community will measure clinical and patient reported outcomes and will use Time Driven Activity Based Costing to measure the cost to deliver cancer care. Guidance will also be provided to the community to support the utility of outcomes and cost data. The AllCan Patient Survey will also be deployed at the sites to obtain patient insights on sources of potential inefficiency in their care. Additional aspects of care, including intervention type and delivery of care, will also be measured based on results of an international literature review on determinants of value in the two indications.

Outcome domains for collection for lung cancer patients include survival, complications, other outcomes such as treatment delays and quality of measures at the end of life. For breast cancer, the outcome domains include survival and cancer control, distur- tility of care such as the impact of acute complications and degree of health. All data will be collected over a six month period. Outcomes data will be collected on all patients with a first diagnosis of lung or breast cancer, followed up over a 6-month period, with three data collection points: (1) immediately after diagnosis, prior to treat- ment initiation; (2) 3 months; and 6 months after treatment initiation.

Results: Risk adjusted outcomes and costing data for the lung and breast pathways will be compared to one another to identify variation and its potential drivers. Qualitative interviews and insights from the AllCan Patient Survey will be used to identify barriers and enablers to value measurement and innovative value improvement strategies.

Conclusions: Findings will guide AllCan policy recommendations to improve the efficiency of cancer care.

Legal entity responsible for the study: International Consortium for Health Outcomes Measurement (ICHOM).

Funding: Bristol-Myers Squibb (main sponsor), Amgen, MSD and Johnson & Johnson (sponsors).

Disclosure: All authors have declared no conflicts of interest.

1889P High-throughput screening of new drugs targeting lung CSCs


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Background: Non-small cell lung cancer (NSCLC), the most common subtype of lung cancer, is characterized by low response rates and a poor prognosis. The majority of patients are diagnosed in advanced stages, where chemotherapy remains the gold standard of treatment. However, the resistance has been associated to cancer stem cells (CSCs), a highly tumorigenic subpopulation of cells with the ability to grow as spheres in non-adherent conditions. The aim of this study was to discover novel therapeutic strategies through screening platforms in order to target CSCs population.

Methods: High-throughput screening with commercial chemical libraries (Prestwick and Myria) was performed, comparing cytotoxic effect in monolayer cells vs lung-tumorspheres derived from 8 resected NSCLC patients and 11 NSCLC cell lines. Compounds were added per triplicates at different concentrations (0.01 to 50 µM). Cell viability was measured after 48h using MTS Assay. Consecutively, 8 tumors were induced by inoculating resected NSCLC patient and H1650 lung-tumor-spheroids in NOD/SCID mice. Selected drugs were administered intraperitoneally (3 times a week, 100 mg/kg). Characterization of the inhibition pathway involved in the mechanism of action of these drugs was performed by RT-qPCR.

Results: Three drugs of the commercial chemical libraries (DSF, Compound 1 and Compound 2) were identified with greater cytotoxic potential against lung tumorspheres, compared to a poor or null effect on monolayer cells. These were validated in mice, which demonstrated the capability of these drugs to inhibit tumor growth in mice treated respect to the control (Table). We are currently characterizing the signaling pathways involved in the mechanism of action of these drugs.

Conclusions: Our findings reveal that these drugs can inhibit CSCs like properties, as evidenced in the lung tumorspheres in vitro and in vivo assays. Therefore, these compounds could be a promising targeted therapy as potential inhibitors of lung CSCs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tumor Volume (mm³)</th>
<th>Tumor Reduction (%)</th>
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<td>Patient Compound 2</td>
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</tr>
</tbody>
</table>

Legal entity responsible for the study: Fundación para la Investigación Hospital General Universitario de Valencia.

Funding: Supported by ISCIII (PI12-02838 / FIS PI15-00573).

Disclosure: All authors have declared no conflicts of interest.
EGFR-mut NSCLC patients benefit from EGFR-TKIs therapy. However, most patients relapse within 1 to 2 years. In 40-60% of the cases, the mechanism of resistance is the emergence of the EGFR p.T790M mutation, and third generation TKIs have shown efficacy in this setting. The availability of new biopsies at relapse to TKIs is limited and guidelines recommend testing for the p.T790M in blood at relapse to TKIs, and rebiopsy only in case of a negative result. Several blood based methodologies for EGFR-mut detection have been developed, including some NGS approaches, but comparison studies are limited. We aim to evaluate the agreement, specificity and sensitivity of methodologies available for T790M testing in liquid biopsies and to determine the best pre-analytical conditions for T790M mutation identification.

Trial design: The RING is a non-PAS, non-interventional, cross-sectional, diagnostic study that will enroll 75 patients from different Spanish institutions. Blood samples will be collected at the time of progression to first and second generation TKIs, and sent to the laboratories participating in the study. Three DNA extraction procedures will be tested; Maxwell® RSC cfDNA (Promega), the QIAamp® Circulating Nucleic Acid Kit (Qiagen) and automatic extraction using Qiasymphony® (Qiagen). The presence of the p.T790M in the purified DNA will be tested by 7 methodologies, namely cobas® EGFR Mutation Test v2 (Roche Diagnostics), Therascreen EGFR Plasma RGQ PCR Kit (Qiagen), QuantStudio® 3D Digital PCR System (Applied Biosystems), a 5'-nuclease real-time PCR (Taqman®) assay in presence of PNA, BEAMing digital PCR (Sysmex Inostics), NGS with the Oncomine® panel for Ion Torrent (Thermofisher) and NGS with the Lung Cancer Panel for GeneReader® (Qiagen). The kappa coefficient values and its corresponding 95% confidence intervals (95% CI) will be used to assess the agreement between methodologies and the Intraclass Correlation Coefficients (ICC) and Bland & Altman plots to evaluate the concordance between quantitative methodologies. Finally, we calculate that 40 patients will have a re-biopsy mutation T790M analysis, which will be considered the gold standard to estimate the sensitivity and specificity of each method.

Legal entity responsible for the study: Spanish Lung Cancer Group / Grupo Español de Cancer de Pulmón (Slcg/Gecp).

Funding: AstraZeneca.

Disclosure: All authors have declared no conflicts of interest.
TUMOUR BIOLOGY AND PATHOLOGY

1892D Molecular characterization of epithelioid sarcoma (ES) tumors derived from patients enrolled in a phase II study of tazemetostat (NCT02601950)

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1893PD A joint metabolic profile of plasma and tissue samples or discovering novel biomarkers in breast cancer

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1894PD Single-cell RNA sequencing of triple negative breast cancer patient-derived xenograft reveals distinct cellular populations spatially mapped to histological sections

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Homology-directed repair (HDR)-defective lung adenocarcinomas (LUACs) in circulating tumor DNA (ctDNA)


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Joining analysis of sarcomatoid carcinoma (SC) mutational profiles: Comparison of lung versus head and neck cancer

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Differential expression of immune checkpoints (PD-L1, HHLA2, B7x and B7TH3) and their association with driver mutations in pulmonary sarcomatoid carcinoma (PSC)

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Background: Pulmonary sarcomatoid carcinoma (PSC) is a histologically distinctive tumor arising from the bronchial epithelium with high incidence of metastasis. This aggressive tumor subtype is often associated with a poor prognosis, and little is known about the mechanisms underlying its development.

Methods: The study was conducted at the Cleveland Clinic, Cleveland, OH, USA, and included 217 PSC patients, all of whom had subtype confirmation. Tissue samples were collected for immunohistochemistry (IHC) and evaluated using the SP1 system. PD-L1 expression was determined using a validated assay kit. The association between PD-L1 expression and driver mutations was analyzed using a Fisher's exact test.

Results: The study found that PD-L1 expression was significantly associated with specific driver mutations, including EGFR, ALK, and ROS1 alterations. The expression of PD-L1 was found to be higher in tumors with driver mutations, indicating a potential role for immune checkpoint inhibition in the management of PSC.

Conclusions: The study highlights the potential role of immune checkpoint inhibitors in the treatment of PSC, particularly for tumors with specific driver mutations. Further research is needed to confirm these findings and to develop personalized treatment strategies for PSC patients.
of CT or US-guided core-needle biopsy. The TPS (50% of / 1-499 / <1% / undiag- nosed) for total cases was 31/29/37/3% respectively which was similar to the past report. In histological subtype, TPS for adenocarcinoma (n = 82) were 28/27/43/2% and squa- mous cell carcinoma (n = 49) were 35/35/27/4% respectively. TPS for TBBs using BF- P260F (thin bronchoscopy) were 20/23/43/4% and TBBs using BF-T1200 (normal bronchoscopy) were 48/22/30/0%. TPS for TBBNs were 50/25/25/0% and CT or US- guided sample showed 37/21/37/3%. Four cases were not atypical for being a TPS because we couldn’t obtain enough tumor cells (less than 100 tumor cells) for diagnosis of TPS. The concordance rate of PD-L1 expression status by biopsy and surgical materi- als was 85.3% for comparison of 24 cases.

Results: Utilizing smaller samples to evaluate PD-L1 expression, the frequencies of TPS were comparable to past clinical trials which used larger samples for evaluating TPS. In this study, the larger samples showed higher PD-L1 expression than smaller samples due to their containing more squamous cell carcinoma cases or advanced stage. The concordance rate of PD-L1 expression for surgically resected tissue and biopsy sample was relatively good in our institution.

Clinical trial identification: UMIN000027030.

Legal entity responsible for the study: Kei Morikawa.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1901P ATM as a DNA damage response protein in uveal melanoma: Association with clinicopathological factors and prognostic outcome

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Background: Uveal melanoma (UM) is an intraocular malignancy commonly arising from choroid which can cause visual loss or metastasis. Till date, there is no current study available on UM with respect to ATM (Ataxia Telangiectasia Mutated) protein that induces DNA damage response. Several studies revealed that loss of nuclear ATM (nATM) in various cancers like pancreatic, colorectal, gastric cancer leads to poor prog- nosis. This signifies ATM protein as a prognostic biomarker for cancer progression. Therefore, the aim of the study is to detect the expression/localization of ATM protein in uveal melanoma patients.

Methods: Expression of nATM was investigated on 69 formalin fixed paraffin embedded choroidal melanoma samples by immunohistochemistry and validated by western blotting. Results were then correlated with clinical and histopathological parameters. To determine the prognostic significance, Kaplan–Meier analysis and multivariate analysis by Cox’s Proportional Hazards Model was performed.

Results: There was a male predominance in our study. Histopathological high-risk fac- tors were identified in 30/69 (43.5%) cases. Loss of nATM was found in 65.2% of the cases. Loss of nATM was statistically significant with epithelioid cell type, high pigmen- tation, LTD >10mm, HRFs >1, tumour height and advanced tumour staging (p < 0.05). On multivariate analysis, advanced tumour staging found out to be an inde- pendent prognostic factor.

Conclusions: Our data suggest that loss of nATM protein might serve as a potential prognostic marker in the pathogenesis of uveal melanoma and leads to increased risk of metastasis. These findings demonstrate an important role of ATM protein and may have a therapeutic potential in uveal melanoma. However, further studies are required in a larger cohort of patients with longer follow up and translational validation needs to be performed.

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Disclosure: All authors have declared no conflicts of interest.

1902P BRCA mutation and castration-resistant prostate cancer

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Background: Mutations of BRCA genes are an independent poor prognostic factor in the development of prostate cancer. It is known that the mutations BRCA1/2 are most often associated with the AKT / m-TOR signaling cascade hyperactivation. The purpose was to study the AKT/m-TOR pathway components in castration-resistant prostate cancer patient, depending on the presence of the BRCA mutations.

Methods: 40 patients with prostate cancer, 15 patients with castration-resistant pros- tate cancer and 20 patients with benign hyperplasia are enrolled in the investigation. The expression of AKT, c-Raf, GSK-3, PI3K, and m-TOR, 70-564, E-BPI was deter- mined by real-time PCR. The BRCA-12 mutation was determined in allelic-specific PCR in real time.

Results: Activation of the AKT / m-TOR signaling cascade was detected in prostate can- cers. The high levels of AKT and m-TOR expression were revealed. The increase in the level of phosphorylated PTEN was found in benign hyperplasia and cancer tissues. The level of mRNA 4E-BPI was decreased in castration-resistant prostate cancer patients.

At the next stage of the study, the incidence of inherited BRCA1 / 2 mutations were studied in patients with castration-resistant cancer. The BRCA-15382insC mutation was detected in 3 patients (20%), BRCA1-1453delA – in 2 patients (13%), BRCA1-185delAG in 2 patients (13%), BRCA1-T380G – in 2 patients (13%) and BRCA2-6174delC – in 4 patients (27%). BRCA1-deficiency activates the AKT oncogenic path- way, one of the most common alterations associated with human malignancy. Mutation of BRCA1 gene increases the phosphorylation and the kinase activity of AKT. The decreased AKT expression in cancers was found in patients with BRCA1-15382insC mutation. Mutation of BRCA1-1453delA increased expression of 70k, m-TOR, in the presence of BRCA1-T380G - increased PTEN. The inherited BRCA2-6174delC mutation was correlated with the increased expression of AKT.

Conclusions: Therefore, the development of PCa is accompanied by activation of this signaling cascade, even more pronounced in the presence of mutations BRCA2-6174delC, BRCA1-1453delA, BRCA1-T380G. It should be noted that the frequency of occurrence of these mutations varies from 13 to 33%. At the same time, a greater accumu- lation of hereditary mutations BRCA1-1453delA and BRCA2-6174delC was noted.

Legal entity responsible for the study: Tomsk National Research Medical Center.

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Disclosure: The author has declared no conflicts of interest.

1903P Prevalence of KRAS mutation subtypes and MSI status in pancreatic cancer

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Background: KRAS is the most prevalent driver mutation in pancreatic ductal adenocarcinoma (PDAC) which impacts cell differentiation, proliferation, migration and apoptosis. KRAS subtypes may have prognostic significance but this finding remains uncertain. Microsatellite Instability / mismatch repair deficiency (MMR) has also been reported in PDAC but at a low frequency (0.8%) and these patients are eligible for immunotherapy. This study investigates the effect of KRAS subtype on survival rate and the prevalence of mismatch repair deficiency in our patient cohort.

Methods: 91 patients enrolled from 2005 to 2012 with biopsy proven PDAC of all stages. All clinical data were collected from the medical records of each patient. Next generation sequencing was performed on all 91 samples. We also evaluated MMR expression in all resection specimens who underwent adjuvant treatment. Statistical analysis: Data were summarized as descriptive analysis statistics and analyzed using unpaired t-test. Overall survival (OS) was measured from the date of diagnosis to last known follow up or date of dead from disease.

Results: The most common type of mutation in all stages is KRAS (95%). KRAS muta- tion subtypes in the order of frequency were: G12D, G12V, G12R, G12L, G12Q. Among codon 12 mutations, G12V showed the best OS at 20.12 months. Mutations in codon 12 carry better OS compared to codon 12 by 24 months (P = 0.0002, 95% CI 11.85 to 37.03). The staining for MMR status was performed on 30 of 91 specimens and all were mismatch repair protein proficient (analogous to MSI- stable [MSS]).

Conclusions: The prevalence and distribution of KRAS mutations from our study is similar to previous reports. Patients with a KRAS codon 61 mutation had better OS than with a codon 12 mutation. Interestingly, Q61 variants are far less common than the G12 variants which may explain why most of the pancreatic patients have an aggres- sive disease course. Our results support the conclusion that MMR defects are uncon- mon in PDAC. Germline mutation analysis could be considered to find other targetable mutations found in hereditary cancer syndromes such as BRCA1/2 or PALB2.

Legal entity responsible for the study: Lloyd Hutchinson.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: MPM is a highly aggressive pleural tumor associated with asbestos exposure. The ability to analyze entire genomes opens the door to identification of new treatments.

Methods: RAMES is a ongoing phase II study to evaluate the efficacy and the safety of the addition of ramucirumab to gemcitabine as the second-line treatment in 160 pts with MPM. We designed a custom panel covering 1040 amplicons spanning 33 genes frequently altered in MPM. To establish the genetic asset of MPMs we used an amplicon-based next generation sequencing approach.

Results: To date, 40 FFPE mesothelioma cancer tissues were successfully sequenced. A total of 2930 variants passing quality filters were detected. Focusing on potentially functional alterations, polymorphisms and non-coding variants were excluded, leaving 143 alterations in 23 of the analyzed genes. Of these, 59.4% (85/143) were missense mutations, 22.4% (32/143) lead to frame-shift alteration of the gene sequence, 13.3% (19/143) were splice variants, while the remaining 4.9% (7/143) were start loss, stop gain alterations and deletions. 97.5% of patients (39/40) displayed at least one mutation, while the average number of mutations per sample was 3.6 (range 0-8), confirming the high mutational load of these tumors. The most frequently altered genes identified were PIK3CA (62.5%), RDX (40%), MXRA5 (20%), BAP1 (15%), NF2 (15%).

Conclusions: This preliminary data supports the generation of a genetic signature for MPM. We observed a significant correlation between mutations in RDX tumor and MXRA5, NF2, PIK3CA, RDX, CUL1, BAP1, NF2, TAOK1 altered genes in thoracic MPM. We found the following NF2, PIK3CA, RDX altered genes in 9 biphasic MPM. Molecular analyses have been correlated with Histology and Stage (thoracic vs extra-thoracic MPM). We found the following NF2, PIK3CA, RDX altered genes in 9 biphasic MPM. We designed a custom panel covering 1040 amplicons spanning 33 genes frequently altered in MPM. We established the genetic asset of MPMs we used an amplicon-based next generation sequencing approach.

N-Myc and STAT interactor (NMI) as a key determinant of chemosensitivity in breast cancer: Proteomic-based computing network mapping and in vivo verification with a mouse model

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Background: We targeted NMI based on our previous proteomics analysis using FFPE breast cancer samples with noadjuvant settings and text-mining analytics to verify NMI as a target agent to overcome chemoresistance through in vitro and in vivo studies.

Methods: Quantitative proteomics was analyzed for three different breast cancer cell lines with NMI gene silencing. We performed computation pathway enrichment based on domain knowledge for text-mining and bioinformatics tools to identify critical pathways related to chemoresistance sensitivity. A total of 8 breast cancer cell lines with or without endogenous chemoresistance were enrolled to define the important pathways and molecules in determining chemoresistance through cell-titer glo assay, FACs, 3D spheroid and invasion assay, ROS assay by DCFDA and Mitotracker. Interaction network analyses were investigated to define the signaling pathway landscapes with public network databases and bioinformatic network evaluations. To verify the chemosensitivity roles of NMI in vivo setting, we are conducting animal tests and immunoinmunostaining in human breast cancer samples where the patients received neoadjuvant chemotherapy.

Results: A total of 972 were confirmed to be significantly altered proteins after NMI gene silencing. A vast number of cell cycle-related proteins, which were downregulated considerably in NMI suppressed group led us to verify NMI’s biological function on chemosensitivity through molecular biology-driven assays. Cell-titer glo assay and FACs revealed significantly induced cytotoxicity and apoptosis in both hormone receptor positive and negative groups without NMI gene alteration treatment with three different chemotherapeutic agents. The 3D-spheroid assay demonstrated a reduced spheroid formation in the case group. DCFDA and Mitotracker assay revealed increased intracellular and intranuclear ROS levels. We built biological network models based on in-silico and -biology-driven assays. Currently, we are conducting in vivo validation using an animal test model and human samples.

Conclusions: Our biological evidence for NMI can provide novel insights to overcome chemoresistance in breast cancer.

Lung cancer predisposition in women with previous breast cancer identified by whole exome sequencing

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Background: Women treated for breast cancer (BC) are at risk to develop a subsequent lung cancer (LC, relative risk ranging from 1.38 to 5.05), especially in case of smoking history and if adjuvant radiation (aRT) was administered for BC. We hypothesized that genetic variants might predispose patients (Ps) to develop LC after BC. Our aim was to perform whole exome sequencing (WES) to identify genes associated with such predisposition.

Methods: 28 women with diagnosis of LC after BC (Study Population, SP) were enrolled, as well as 32 women treated for BC and with no secondary cancer after a follow-up ≥10 years (control population; CP). DNA was extracted from tumors and normal tissue samples from both SP and CP. Libraries were prepared with Agilent SureSelect Human All Exon kit and sequenced on Illumina HiSeq™500/8. Variant calling was performed with Freebayes software.

Results: The median age of SP at BC diagnosis was 63-5 years (range 47-76); the median interval between diagnosis of BC and occurrence of LC was 4.5 years (range 0-11). 33 Pts (46%) were never-smokers and, among the 21 Ps who had received aRT, 13 (62%) developed ipsilateral LC. At somatic analysis, no common mutation among known driver genes was shared between each BC and LC pair in SP Pts. WES performed on BC and LC samples identified two mutational signatures (S1 and S2). S1 (C>T substitutions) was observed in all BC samples and 16/28 (57%) LC samples and was more frequent in never-smokers (11 vs. 5 Pts) and among Pts who developed ipsilateral LC after aRT (10 vs. 6 Pts). S2 (C>A transversions) was observed in 12/28 LC samples (43%) and was strongly associated with smoking habit (10 vs. 2 Pts). When compared with COSMIC libraries, S2 results were similar to COSMIC 4, common in LC samples collected from smokers. Since S1 was largely shared between paired BC and LC, samples, we explored the eventuality of a genetic predisposition to S1-related malignancies with a gene-based burden test over rare germline variants in normal tissue of S1-LC Pts compared with CP Pts. 249 candidate genes were identified (FDR<0.05).

Conclusions: Our data identified two mutational signatures underlying the LC development. Germline analysis suggests that genetic variants may contribute to increase the risk of LC after BC.

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Disclosures: F. Grossi: Honoraria: BMS, MSD, AstroZeneca, Pierre-Fabre, Boehringer Ingelheim, Pfizer, Celgene, Agen, Roche. C. Genova: Honoraria: AstraZeneca, Boehringer Ingelheim, BMS, MSD, Roche. G. Barletta: Employee: AstraZeneca. All other authors have declared no conflicts of interest.

Discordance of the PAM50 intrinsic subtypes compared with IHC-based surrogate in breast cancer patients: Potential implication of genomic alterations of discordance


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Background: In recent decades, 5 intrinsic molecular subtypes have been characterized according to variation in gene expression patterns of breast cancer. However, in real-world practice, immunohistochemistry (IHC) based classification such as estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) are routinely used. We aimed to analyze the discordance between IHC-based surrogate subtype and PAM50 intrinsic subtypes and to assess overall survival (OS) according to discordance.
Methods: A total of 607 patients were analyzed. Hormone receptor (HR) was evaluated by IHC and HER2 by IHC and/or FISH. PAM50 intrinsic subtypes were determined according to 50 cancer genes using NanoString nCounter Analysis System. In addition, we used the AmpliSeq Cancer Panel v2 to identify the genomic alteration related with discordance between IHC subtype and PAM50 intrinsic subtype. The Kaplan-Meier method was used for estimation of OS.

Results: The majority of patients were HR+ (343/607, 56.5%) by IHC and luminal A/B (283/607, 46.6%) by PAM50. We matched concordant tumor as luminal A and HR+/- HER2-, luminal B and HR-/HER2+, HR-/HER2+ and HER2-enriched, TNbc and Normal- or Basal-like. 235 patients (38.4%) were discordant between IHC-subtypes based and PAM50 intrinsic subtypes. The discordant patients were mostly HR+ (176 of 234, 75.3%) and 12.4% (28 of 234) were HER2+2. Using targeted sequencing with Ampliseq, we detected somatic mutation related discordant breast cancer including VHL gene in HR-/HER2- group (31% in concordant group, 0% in discordant group, P = 0.03) and IDH and HIN genes (7% vs. 12%, P = 0.02, 0% vs. 29%, P = 0.02, respectively) in TNbc group. In survival analysis, among the patients with HR+ - basal-like group by PAM50 showed significantly inferior OS compared with other intrinsic subtypes (P = 0.010).

Conclusions: A substantial portion of patients showed discrepancies between IHC-based subtypes and PAM50 intrinsic subtypes in our study. The survival analysis demonstrated that current IHC-based classification could misdirect treatment and result in poorer outcomes. Current guidelines of IHC for ER, PR, and HER2 would better be updated accordingly.

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Disclosure: All authors have declared no conflicts of interest.

1908P Impact of invasive lobular breast carcinoma in Latin American breast cancer patients' disease-free survival: The new paradox

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Background: Traditionally invasive lobular breast carcinoma (LBC) has been considered a good prognosis histology. However, it has a unique molecular pathogenesis and different genomic profile. Our objective was to establish whether there is a difference in disease-free survival (DFS) between LBC and ductal carcinoma.

Methods: We evaluated a cohort of 5185 breast cancer patients with lobular and ductal carcinoma (DC) treated at the National Cancer Institute Mexico between 2006 and 2016. We compared presentation variables using the chi squared test. A Cox proportional hazards regression model was constructed to evaluate disease-free survival.

Results: With a median of 60 months follow-up, patients with LBC were older (p < 0.001), more frequently patients with Ki67 <18% (40.2% vs 28.6% p < 0.001), had lower nuclear grade (p < 0.001), and predominately hormone receptor positive disease (77.9% vs 56.9% p < 0.001). Nevertheless, LBC patients had a higher recurrence rate (25.2% vs 21.1% p = 0.011). For both LBC and DC patients, factors that negatively influence DFS in the univariate analysis were stage III (71.9% vs 78.9% p < 0.010), Ki67 18% vs 95.9% (0.016), low nuclear grade (82.1% vs 95.9% p < 0.001), triple negative (46.7% vs 71.8% p = 0.002), and Her2 positive (72.4% vs 84.3% p = 0.023). In the multivariate analysis patients with stage III, (OR 10.8, 95%CI 5.9–19.9), high nuclear grade (OR 1.5, 95%CI 1.0–2.4), Ki67 >18 (OR 1.5, 95%CI 1.1–1.9), triple negative phenotype (OR 2.7, 95% CI 1.1–6.6) and lobular carcinoma (OR 1.8, 95%CI 1.1–2.7) are independent negative factors for DFS.

Conclusions: The presence of lobular invasive carcinoma is an independent negative factor for DFS. Despite the high rate of good prognosis elements in pathological reports, lobular carcinoma seems to be another disease and we need to evaluate deeply new and old treatment strategies to provide better disease control. Particularly in clinical stage III, Latin America has a challenge to be aware of it.

Legal entity responsible for the study: Instituto Nacional de Cancerología, Mexico

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Disclosure: All authors have declared no conflicts of interest.

Clinical validation of an NGS-based assay for the detection of BRCA1 and BRCA2 variants in Chinese women with breast cancer or ovarian cancer

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Background: Variation in BRCA1 and BRCA2 genes are associated with the development of hereditary breast cancer and ovarian cancer (HBOC) and sensitivity to poly ADP-ribose polymerase inhibitors (PARPi). A genetic testing assay based on next-generation sequencing (NGS) method, named AmoyDx BRCA1 and BRCA2 Mutation Detection Kit (ADx-BRCA NGS kit), has been developed for the detection of BRCA1/2 variants. The present study evaluated the clinical performance of the ADx-BRCA NGS kit in detecting BRCA variants in peripheral blood-derived DNA.

Methods: A cohort of 1,341 peripheral blood samples from Chinese patients were analyzed for BRCA1/2 variant using ADx-BRCA NGS kit, including 1,035 patients with breast cancer and 306 with ovarian cancer. BRCA MASTR Dx assay (Multiplicom) was used as a reference method to test the same cohort. ADx-BRCA NGS kit allows identification of variants in complete coding regions of BRCA1/2 genes which are also covered by the reference method, and 22 additional UTR regions beyond the coverage of the reference assay. The concordance of BRCA variant detection with ADx-BRCA NGS kit was calculated compared to the reference assay.

Results: In this study, all the 1,341 samples were successfully detected and the classification for BRCA1/2 variants identified by ADx-BRCA NGS kit in breast and ovarian cancer is listed in the table. Using BRCA MASTR Dx assay as reference, the overall concordance of BRCA variation status determined by ADx-BRCA NGS kit was 99.92% (1,286/1,287). In addition, 54 samples were excluded from the analysis due to the variation detected in the UTR regions that were not covered by reference method.

Conclusions: ADx-BRCA NGS assay has shown a high concordance rate of 99.92% compared to the BRCA MASTR Dx assay, demonstrating that it is a highly accurate method for the detection of BRCA1/2 variants and can be used to screen patients with germline BRCA mutations.

Legal entity responsible for the study: Amoy Diagnostics Co., Ltd.

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Disclosure: All authors have declared no conflicts of interest.

Correlation between the expression of androgens receptor (RA) and histopathological survival parameters of breast cancer

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Background: Clinical trials have attempted to demonstrate a correlation between the expression of androgen receptor (RA) and the prognosis of breast cancer. We have analyzed a sample of women with diagnosis of triple negative breast cancer (TN) in order to establish their prognostic value.

Methods: We retrospectively analyzed a cohort of women diagnosed of early stage TN breast cancer in the University Hospital of León from 2008 to 2013. Our first end point was to establish a correlation between RA expression, clinical parameters, immuno-histochemical characteristics and DFS.

Results: A total of 58 women with TN breast cancer were included. From the total number of biopsies, 20% expressed RA, and the 80% of this subgroup had an apocrine histology. The RA expression was associated to a favourable grade (G) GIT (RA + G3: 45.5% vs RA - G3 79%, p = 0.05), smaller size (11.1% T1, 77% T2, 11% T3-4), and lower percentage of Ki-67: (mean in RA + = 23.6% ± 5 vs 41.4% ± 3, p = 0.005). There was also a trend towards association with premenopausal status (60% vs 40% postmenopausal p = 0.02) and axillary involvement at the time of diagnosis (65% N1-2 vs. 35% N0 p = 0.045). Regarding OS and DFS, we did not find statistical significant differences between RA positive and negative tumors (p = 0.89 and p = 0.34 respectively).

Conclusions: The RA expression in TN breast cancer is associated with more favourable histopathological characteristics except the axillary involvement. Although most of our cases were N1-2, we did not find a worse prognosis in these patients. It is possible that with the antiandrogen therapy a better survival could be obtained, which justify the design of clinical trials.

Table: 1909P Classification for BRCA1/2 variants detected by ADx-BRCA NGS kit

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Variant amount in breast cancer</th>
<th>Variant amount in ovarian cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Definitely pathogenic</td>
<td>63 (6.09%)</td>
<td>73 (23.86%)</td>
<td>136 (10.14%)</td>
</tr>
<tr>
<td>4</td>
<td>Likely pathogenic</td>
<td>33 (3.19%)</td>
<td>6 (1.96%)</td>
<td>39 (2.91%)</td>
</tr>
<tr>
<td>3</td>
<td>Uncertain</td>
<td>101 (9.76%)</td>
<td>40 (13.07%)</td>
<td>141 (10.51%)</td>
</tr>
<tr>
<td>2</td>
<td>Likely benign</td>
<td>213 (20.58%)</td>
<td>53 (17.32%)</td>
<td>266 (19.84%)</td>
</tr>
<tr>
<td>1</td>
<td>Benign</td>
<td>625 (60.38%)</td>
<td>134 (43.79%)</td>
<td>759 (56.6%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,035</td>
<td>306</td>
<td>1,341</td>
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</table>

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Metabolic syndrome in breast cancer patients: An observational study

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Background: With significant increase in the prevalence of overweight population in India, there might be a similar increase in the prevalence of metabolic syndrome. Positive association between metabolic syndrome in Indian subjects, if any, may translate into significant changes in the risk factors for breast cancer and may have a significant impact on the incidence and mortality related to breast cancer in India. Hence, we undertook this study to find any correlation between metabolic syndrome and breast cancer.

Methods: We did a prospective study from August, 2016 to July, 2017. Measurements of height, weight, BMI and waist circumference and fasting blood sugar, fasting triglycerides, fasting HDL and HBA1c were done. Metabolic syndrome was defined according to International Diabetes Federation consensus statement 2006. TNM staging, type and grade of tumour, hormone receptor status, Her2 neo status and Ki67 index along with other known risk factors of breast cancer like age at menarche, age at first child birth (FCB), family history of breast cancer and mammographic density were recorded. K-S test was used to check the normality of the data. Student’s t test and Mann Whitney U test, Chi Square test or Fisher exact test (whichever was applicable) was used for comparison.

Results: Total of 305 patients were recruited into the study with 191 (62.6%) patients having metabolic syndrome. The mean age was of 50.7 ± 12.4 years. There was no correlation of metabolic syndrome to any of the known risk factors (Age, age at menarche, age at first child birth (FCB), parity, no breast feeding, breast density on mammography or family history of breast cancer). Patients with metabolic syndrome were found to be less likely to have hormone receptor positive tumours (p = 0.023), more likely to have Her2 positive tumours (p = 0.011). They were also more likely to have Her2 enriched and basal like subtype and less likely to have luminal A and B subtypes (p = 0.027).

There was no correlation between metabolic syndrome and T, N, M or overall staging. It also had no relation to type of tumour (IDC vs No IDC), grade or Ki67.

Conclusions: Metabolic Syndrome may emerge as an important prognostic factor in breast cancer in the future.

Legal entity responsible for the study: Department of General Surgery, PGIMER, Chandigarh

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

The prognostic value of different molecular subtypes of breast cancer in relation to enhancer-of-zeste homologue 2 expression

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Background: Studies have shown that Enhancer-of-zeste homologue 2 (EZH2) plays an important role in carcinogenesis in the breast cancer, and invasion and progression of the disease. We aimed to assess the prognostic value of different molecular subtypes of breast cancer in relation to EZH2 expression.

Methods: We performed a cross-sectional analytical research study on 100 breast cancer women. Survival analysis was then performed using the Kaplan–Meier method, with log-rank tests to assess statistical significance between groups. To assess the effects of variables on OS and DFS, a Cox proportional-hazard model was then used to give adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: Samples were collected for 100 women with breast cancers, with follow-up data collected over a 5-year period. The mean age was 51.5 ± 9.5 years (range, 34–75 years). By molecular subgroup, 43% had luminal A tumors, 41% had luminal B tumors, 9% had Her2 tumors, and 7% had TNBC tumors. Overall, 74% had high EZH2 expression, which was most common for the luminal A subtype (43.2%) and least common for the TNBC subtype (8.1%). There was no significant correlation between subgroups by EZH2 expression (p = 0.33).

Conclusions: In conclusion, although our results provide some interesting insights, there remains controversy about the prognostic value of different molecular subtypes of breast cancer in relation to EZH2 expression. Given that there are very few studies on this topic, we advocate further research with larger sample sizes and the inclusion of molecular techniques.

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A guided and personalised treatment in metastatic breast cancer: Optimisation of gene and protein expression in tumor tissue

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Background: The better understanding of the signaling pathways involved in cancer has led to the use of targeted therapies, such as everolimus (E), a mammalian target of rapamycin (mTOR) inhibitor and palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in the treatment of metastatic breast cancer (mBC). However, treatment response is variable, and resistance occurs systematically. We hypothesised that the combination of gene sequencing and protein expression analysis could help, in a patient, to identify resistance mechanisms occurring on a specified treatment as well as to determine potential further treatments.

Methods: We studied paired-biopsies performed in a 69-year-old woman patient with mBC who achieved a durable (16 months) partial response to E-oxemestane association. Biopsy 1 was performed before E initiation and biopsy 2 at the progression on E. Analyses were realised with OncosTRATiGrOM (TM), from Oncodna company, which combines sequencing of oncogenic genes panel and expression analysis of proteins that could be targeted by current antitumoral agents.

Results: Biopsy 1 revealed PIK3CA(E542K) gene mutation and a high expression of phospho 4EBP1, an effector of mTOR, reflecting an excessive activation of the mTOR pathway that explains the E sensitivity. Biopses 1 and 2 showed a high expression of phospho-erinostomablastoma (pIRB), reflecting a continuous cell cycle activation by CDK4/6. Palbociclib was thus initiated in association with letrozole at the progression on E and resulted in a rapid and long-duration (17 months) partial response. In the paired biopsies, the tyrosine kinase receptor cMET was not detected on biopsy 1, but was highly expressed in biopsy 2, suggesting that cMET could play a role in the development of resistance to E. In this context, we are currently treating our patient with cabozenzini (cMET inhibitor) and developed a response profile will be further specified.

Conclusions: These gene and protein expressions reflect correctly the efficacy of targeted therapies this patient received. PIK3CA mutation was associated with E sensitivity and pIRB with impressive response to palbociclib. CMET could play a role in the development of resistance to E and its inhibition should be evaluated in mBC.

Legal entity responsible for the study: Centre Hospitalier de Jolimont.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
1915P Does the minimal auxiliary approach lead to loss of prognostic factors in breast cancer?

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Background: There are several factors for metastasis in breast cancer, such as tumor size (T) and lymph node involvement (N). In this study we investigated the association of T and N with breast cancer patients treated in the Oncology Sector of a public Hospital of Minas Gerais.

Methods: Observational and retrospective study. A total of 1671 medical records of women with breast cancer treated in the period of 1981-2013 were analyzed, of which 797 were excluded for lack of pathologic data or by being diagnosed in advanced stage. Fisher’s exact test or χ² were performed.

Results: As expected, the positivity of lymph node metastasis increased with tumor size: of the Tis patients, 5.55% were N+(3.7% N1, 1.85% N2); of T1, 25.29% were N+(21.01% N1, 4.28% N2); of T2, 51.45% were N+(37.21% N1, 9.88% N2, 4.36% N3); of T3, 77.05% were N+(55.74% N1; 18.03% N2; 3.28% N3); and of T4, 80% were N+(48.57% N1; 17.14% N2, 14.29% N3). When analyzed by T, decreased odds of metastasis in N+(OR=0.343; p=0.0197) and T1 (OR=0.3805; p<0.0001) were observed, while increased odds in T2 (OR=1.449; p=0.0364), T3 (OR=2.114; p=0.0081) and T4 (OR=4.222; p=0.0001). When analyzed by N, decreased odds of metastasis in N0 (OR=0.557; p<0.0001) was observed and increased odds in N1 (OR=2.56; p=0.0001), N2 (OR=3.703; p<0.0001) and N3 (OR=4.328; p=0.0002). Overall, N+ had an increased odd of metastasis when compared with N-(OR=6.312; p<0.0001). Increased odds only in T1+(OR=9.49; p<0.0001) and T2N+(OR=3.557; p<0.0001) was observed when compared with their N- counterparts. Moreover, a borderline increase in the odds (OR=3.667; p=0.0533) was observed in T2N+ compared with in T1N+, but not in T2 (p=0.9190) nor T3 (p=0.4639) patients.

Conclusions: Lymph node involvement (N) is a greater risk factor for metastasis than tumor size (T). Adjuvant therapy is based on T, N and molecular subtype. In the mini-auxiliary approach, tumor size (T) and lymph node involvement (N) are the key points of auxiliary therapy and surgical margin were obtained from anatomopathological reports. In the minimal auxiliary approach, the combination of T and N is the basis of the auxiliary therapy.

1916P The influence of the surgical approach in women diagnosed with breast neoplasia

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Background: Although recent years have seen improvement in systemic therapies and radiotherapy, the surgical approach is still a keystone in oncologic treatment. In this study we investigated the association between surgical margin status and surgical approach with disease progression and death of breast cancer patients treated in the Oncology Sector of a Public Hospital of Minas Gerais.

Methods: Observational and retrospective study: A total of 1979 medical records of women with breast cancer treated in the period of 1981 to 2013 were analyzed. The surgical approach and surgical margin were obtained from anatomopathological reports. Of the total, 987 were excluded for lack of pathologic data, being diagnosed at stage IV or pathological 0 stage.

Results: Of the subtotal, 992 medical records reported the surgery approach (radical or breast-conserving), and 905 reported surgical margins, of which 110 had positive margin (9.0%). It was observed that 49.69% (n=493) of surgeries were breast-conserving. No association between surgical approach and local relapse (p=0.2672) was observed. However, increased odds of surgical margin impairment (OR=1.531; p=0.0195) and decreased odds of distant relapse (OR=0.4068; p<0.0001) and death (OR=0.4455; p<0.0001) was observed for breast-conserving surgeries compared with radical surgeries. No association between surgical margin and local relapse was observed (p=0.1063). However, patients with positive surgical margin had greater odds of distant relapse (OR=1.940; p=0.0002) and death (OR=2.002; p=0.0494). When analyzed by pathologic stage (III-I), it was observed that positive surgical margin increased the odds of distant relapse in stage II (OR=2.280; p=0.00499) and III (OR=2.820; p=0.0132) patients.

Conclusions: Although an association between radical surgery and death was observed, factors such as tumor complexity and locally advanced tumor could be involved. However, it is noteworthy that positive surgical margin increased the odds of distant relapse, mainly in stage III patients, and death. These data corroborate the fact that the surgical approach is still a keystone in breast cancer treatment and it has a strong impact in patients with locally advanced tumors.

Legal entity responsible for the study: Grupo Luta Pela Vida.

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Disclosure: All authors have declared no conflicts of interest.

1917P Use of comparative proteomics to identify potential cisplatin-resistance mechanisms in neuroblastoma

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Background: Neuroblastoma (NB) is an embryonal tumour, originating from progenitor cells of the sympathetic nervous system, and is the most common extra-cranial solid tumour of childhood. Cisplatin is one of the most commonly used agents in the treatment of NB. Unfortunately, the development of resistance against this cytotoxic agent limits its clinical use. We aimed to gain further understanding of the mechanisms underlying development of cisplatin resistance using an in vitro cell line model.

Methods: Cytotoxicity of cisplatin, carboplatin and oxaliplatin in neuroblastoma UKF-NB-4 and UKF-NB-4CDDP cells cultured in the exponential growth was determined. Peptide separations were carried out on an Easy-nLC 1000 nano system. MS analysis was performed using a Q-Exactive MS. MS data were analyzed with Proteome Discoverer (version 1.4.1.14) using standardized workflows. The mass spectrum *raw* file was searched against the human SwissProt 57.15 database (20266 sequences protein entries) using MASCOT search engine (version 2.3, Matrix Science).

Results: The two cell lines that were used were the following: cisplatin-resistant UKF-NB-4CDDP and UKF-NB-4 cell lines. We proved decreased sensitivity of line UKF-NB-4CDDP to cisplatin and crossresistance to carboplatin and oxaliplatin. Out of a total 1802 identified proteins, 1488 were common expressed in two datasets. A total of 281 significant protein expressions were exclusively registered in the UKF-NB4CDDP cell line and 73 proteins were exclusively identified in UKF-NB-4 cell line. UKF-NB-4 and UKF-NB-4CDDP cell lines showed overexpression of trafficking of transport in two datasets: comparison between of UKF-NB-4CDDP and UKF-NB-4 cell lines and proteins exclusively identified in UKF-NB-4CDDP. Exosome vesicles assay showed increase of vesicles in UKF-NB-4CDDP cell lines.

Conclusions: The OmriTap MS results could shed some light on the proteins involved in inducing resistance to cisplatin in cancer cells. These data strongly suggest that exosomes potentially induce properties of NB cells and their chemoresistance to cisplatin and reinforces the potential benefit of trafficking of biological material across membranes in cancer.

Legal entity responsible for the study: Mendel University in Brno, Czech Republic.

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Disclosure: All authors have declared no conflicts of interest.

1918P Acquired resistance mechanism of osimertinib targeting EGFR in human lung cancer

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Background: Significant progress has been achieved by the development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) targeting EGFR mutations in non-small cell lung cancer (NSCLC), however the acquisition of resistance to these agents are always the main cause of disease progression. Osimertinib (AZD9291), an oral potent drug, has developed as 3rd generation EGFR-TKIs with activities against sensitising mutations and the EGFR Thr790Met resistance mutation, which accounts for about 50% of the mechanisms of acquired resistance to 1st or 2nd generation EGFR-TKIs.

Methods: We developed in vitro model of acquired resistance to EGFR-inhibitors by treating human NSCLC cell lines with Osimertinib. PC9 and H1975 cell lines, which were initially sensitive to Osimertinib treatment (IC50: 0.1 and 0.5 µM, PC9 and H1975, respectively), became resistant after 8 months of continuous treatment reaching an IC50 = 20 µM. This phenomenon was accompanied by visible morphological changes of the cells that acquire the typical characteristics of mesenchymal cells.

Results: We verified if this morphological change is translated into a functional change through the activation of specific pathways; protein lysates from harvested resistant cells showed higher levels of phosphorylation of EGFR, AKT and MAPK proteins than parental cell lines. We next examined whether resistant cell lines exhibit molecular changes known to occur during Epiteliali-to-Mesenchymal Transition (EMT) and we...
found a significant expression of mesenchymal protein like Vimentin, Snail and Slug in Osmertinitb-resistant cells as compared to Osmertinitb-sensitive cells.

**Conclusions:** This data, indicates the importance of EMT as a crucial event in the acquisition of resistance to third-generation EGFR-TKIs inhibitors and suggests new opportunities to design new treatment strategies in lung cancer.

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

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**1919P Interaction of oncostatin M and its receptor OSMR promotes gastric cancer progression via STAT3/FAK/Smad signaling pathway**

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**Background:** Gastric cancer (GC) is one of the deadliest cancers in the world. With its lacking of early diagnostic methods, metastasis and recurrence lead to a low 5-year survival rate. Discovering mechanisms of gastric cancer and thus developing new strategies for gastric cancer diagnosis and therapy is urgent for clinicians and scientists. OSM receptor (OSMR) is a member of the interleukin 6 (IL-6) receptor family and transduces signaling events induced by its major ligand OSM. Interaction between OSMR and OSM plays key roles in inflammation, hematopoiesis, and development, and is increasingly being recognized as an important contributor to cancer progression. However, the role of OSM-OSMR interaction on GC is still not known.

**Methods:** Expression of OSM receptor (OSMR) was performed by RT-PCR, immunochemistry and Western Blot in gastric cancer tissues and cell lines. The malignant effects of OSM-OSMR interaction on gastric cancer cells in vitro and in vivo were examined.

**Results:** OSMR is highly expressed in GC tissues and cell lines, and OSMR levels are positively associated with age, T stage, tumor size, lymph node metastasis, TNM stage, Lauren Classification and poor prognosis. In GC cells that overexpress OSMR, recombiant human OSM (rOsM) treatment promotes cell proliferation, migration, invasion, EMT in vitro, as well as tumorigenesis and peritumoral metastasis in vivo. These multiple pro-malignant effects induced by OSM-OSMR interaction are mediated by activation of STAT3/FAK/Smad signaling pathway. Specific inhibition of OSM-OSMR interaction by silencing OSMR expression significantly inhibits STAT3/FAK/Smad activation, leading to reduced cell proliferation, migration, invasion and EMT.

**Conclusions:** OSM-OSMR interaction contributes to the progression of GC through the activation of STAT3/FAK/Smad signaling pathway and OSMR could be a potential target for gastric cancer treatment.

**Legal entity responsible for the study:** Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

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**1920P Role of pioglitazone on gene/protein expression profile, bioenergetics and TGF/SMAD signaling pathway in NSCLC**

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**Background:** Pioglitazone is an antidiabetic drug of the Thiazolidinediones (TZDs) class that acts as ligand for PPAR-γ, a member of peroxisome proliferator activated receptors (PPARs), that regulates lipid and glucose cell metabolism. Prior studies in vitro and in vivo models of non-small cell lung cancer (NSCLC) showed that PPAR-γ modulation affects cancer cells proliferation and differentiation but few studied reports have investigated molecular pathways involved in the potential role of PPAR-γ agonists as anti-cancer agents.

**Methods:** NSCLC cell lines H460 and H1299, were treated with different doses of Pioglitazone. Anti-proliferative effect was determined by MTT, colony-forming assay and flow-cytometry. Protein expression was detected by Western Blot analysis while functional mitochondrial measurements were performed with Seahorse® test. Finally, cell lines samples were analyzed with a cDNA microarray assay.

**Results:** Pioglitazone significantly reduces cell proliferation and invasion with an IC50 of 1-5 μM. Analysis of apoptosis confirmed the data. Western blot analysis demonstrated a dose-related reduction of Survivin and phosphorylated proteins of MAP kinase pathway and cDNA microarray expression profiling showed a down-regulation of MAPK, Myc and RAS genes. Oxygen Consumption Rate (OCR) and proportionnal Glut1-protein expression reduction of treated cells demonstrated cell bioenergetics modulation. Interestingly cDNA microarray analysis showed that also TGFβ pathway is regulated by Pioglitazone through pTGFβRI and pSMAD3 down-regulation and consecutive up-regulation of total TGFβRI.

**Conclusions:** Pioglitazone regulates NSCLC cell lines proliferation and bioenergetics. Moreover, affecting TGFβ/SMAD signaling pathway, it could have a role in epithelial-to-mesenchymal transition (EMT) and cancer invasive phenotype development. These results encourage the study of PPAR-γ agonists as anti-cancer agents and promote research to explore the mechanisms beyond their activity in NSCLC models.

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**1921P Somatostatin receptor 2 expression and clinical significance in pulmonary lymphoepithelioma-like carcinoma**

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**Background:** Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare Epstein-Barr virus (EBV) associated cancer, histologically indistinguishable from naso-pharyngeal cancer (NPC). Somatostatin receptor type 2 (SSTR2) is a bonafide therapeutic target in neuroendocrine tumour. It is also demonstrably expressed in NPC, with autopsagographic and positron emission tomography (PET). SSTR2 expression has not been reported in PLEC. In this study, we aimed to investigate SSTR2 expression and co-localization with EBV positive PLEC cells using immunohistochemistry (IHC), and to investigate the clinical significance of SSTR2 in PLEC.

**Methods:** Clinical demographics including age, gender, TNM staging, EBV titre, smoking status, survival and treatment regime were collected. Archival formalin fixed, paraffin embedded (FFPE) tissue from patients diagnosed with PLEC between 2003 and 2016 at National Cancer Centre Singapore were retrieved and studied retrospectively. IHC staining for SSTR2 and Epstein-Barr encoding region in-situ hybridisation (EBER-ISH) were performed using a dual-staining technique.

**Results:** We report clinical data and dual staining from 20 PLEC patients. The median age at diagnosis was 56.5; 80% (16/20) of the patients were female; all non-smokers (except 3 with unknown status); 55% (11/20) of the patients had stage IV disease and the rest stage I-IIIB. High serum EBV titres were also noted in PLEC patients. Sixteen out of 20 patients (80%) stained positive for SSTR2 on IHC. SSTR2 expression co-localised with EBER positive cells. Nine out of 11 (82%) patients with stage IV PLEC stained positive for SSTR2 while 7 out of 9 (78%) stage I-III disease stained positive. Two year OS by SSTR2 status is 100% in SSTR2 negative and 65.2% (CI 35.1, 84.0) in SSTR2 positive patients, p = 0.467 by Log Rank Test. Two year OS by stage is 85.7% (CI 33.4, 85.7) for stage I-II and 63.6% (CI 29.7, 84.5) for stage IV disease, p = 0.014.

**Conclusions:** In PLEC, high levels of SSTR2 IHC expression is reported with co-localisation with EBV infected cells. A high proportion of stage IV patients have SSTR2 positive tumours. These patients have limited treatment options. This study opens up the possibility of using SSTR2 theranostics for these patients.

**Legal entity responsible for the study:** National Cancer Centre Singapore.

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**1922P The role of neurotrophic factors in nerve-cancer crosstalk**

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**Background:** ‘Nerve-cancer crosstalk’ has been suggested as an important mechanism of tumor growth and dissemination. Cells in the cancer microenvironment secrete bio-molecules which induce neurogenesis, while tumor cells utilize nerves for dissemination to other organs, thru a process of perineural invasion. The molecular basis for this crosstalk has remained unclear and no targeted approaches against these mechanisms exist. The current study evaluates the neuronal effects of cancer from the viewpoint of neurotrophic growth factors (NTFs). We screened various tumors for changes in gene expression of NTFs, in order to characterize the role of these factors in human cancers.

**Methods:** TTNF gene expression data was assessed from the Cancer Genome Atlas (TCGA) and GTEX transcriptomic databases for 33 cancers, totaling to 9736 tumor and 8587 normal samples. Data was analyzed by Gene Expression Profiling Interactive Analysis software (http://geopia.cancer-pku.cn/index.html), as transcripts per million using the log2 FC cutoff of 1 and by ANOVA, qRT-PCR for NTFs MANF and CD317 from patients with colorectal (CRC) and breast cancer (BC) was performed. Tissue and 749325273963142967092406269922468619690847208689782953729662071525763648548298332796061310210707131116739947904688125336329792340136291374492132832968246472190723952583470760811562082541482440943275749378190790754460245712419318937905643881529903951647381366186490233050444135438083

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Results: The expression levels for the 3 NTIs: mesencephalic astrocyte-derived neurotrophic factor (MANF), cerebral dopamine neurotrophic factor (CDNF) and growth differentiation factor (GDF15) were profiled from the TCGA and GTEx databases. MANF RNA was upregulated in 9 different cancers, CDNF was up-regulated in 1 in downregulated in 3 cancers and GDF15 was up in 14 and downregulated in 1 cancer. qRT-PCR for MANF and CDNF from 52 patients with CRC showed that MANF is significantly upregulated 2-fold (p < 0.001) in CRC as compared to controls from the same patients, and upregulation was already seen in tumor-near samples. The analysis of RNA samples from 38 BC patients showed significant down-regulation for CDNF (p < 0.05).

Conclusions: These results support the hypothesis that NTIs indeed play a role in tumors and provide the basis for the need for further study for these factors within the cancer paradigm.

Legal entity responsible for the study: Ana Planken.

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Disclosure: All authors have declared no conflicts of interest.

**1924P** Glutathione S-transferase M subfamily in TMZ-resistant glioblastoma cells

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**Background:** Glioblastoma multiforme (GBM), the most aggressive central nervous system cancer, is highly angiogenic and infiltrative with high potential of resistance to chemotherapy and radiotherapy. Angiogenesis is now well known for being involved in tumor progression, aggressive ness, emergence of metastases, and also resistance to cancer therapies. In this study, to better mimic tumor angiogenesis encountered in vivo, we generated TMZ-resistant glioblastoma GBM8401 cells (GBM8401-TMZ-R) over a one-day period. We compared TMZ resistance level in TMZ-sensitive cell lines U87MG, A172 and GBM8401 with TMZ-resistant cell lines GBM8401-TMZ-R, T98G and U138 through cell toxicity assays and O-6-Methylguanine-DNA Methyltransferase (MGMT) expression. Moreover, we investigated the mRNA profiles of GBM8401, GBM8401-TMZ-R, and T98G cells by using next-generation sequencing (NGS) for analyzing.

**Methods:** In our study, we generated TMZ-resistant glioblastoma GBM8401 cells (GBM8401-TMZ-R) over a one-day period. We compared TMZ resistance level in TMZ-sensitive cell lines U87MG, A172 and GBM8401 with TMZ-resistant cell lines GBM8401-TMZ-R, T98G and U138 through cell toxicity assays and O-6-Methylguanine-DNA Methyltransferase (MGMT) expression. Moreover, we investigated the mRNA profiles of GBM8401, GBM8401-TMZ-R, and T98G cells by using next-generation sequencing (NGS) for analyzing.

**Results:** We found GBM8401-TMZ-R cells with significantly higher MGMT expression and increased TMZ tolerance. GSTM subfamily proteins, which are located in human chromosome 1, showed different basal expressions in the GBM cell lines we tested. Some research results point out more than 90% of patients show no response after the second cycle of current GBM chemotherapy. Glutathione S-transferase S (GST) is an important detoxification protein family that highly correlates with drug inactivation and multi-drug resistance.

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**Disclosure:** All authors have declared no conflicts of interest.

**1925P** Combining 2D angiogenesis and 3D osteosarcoma microtissues to improve vascularization

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**Background:** The number of patients suffering from cancers worldwide is increasing, and one of the most challenging issues in oncology continues to be the problem of developing active drugs economically and in a timely manner. Considering the high cost and time-consuming nature of the clinical development of oncology drugs, better pre-clinical platforms for drug screening are urgently required. So, there is a need for high-throughput drug screening platforms to mimic the in vivo microenvironment. In pancreatic cancer whose microenvironment is extremely hypoxic, the analysis of signal transduction under hypoxia is thought to be important. Recently, we have found that the expression of TRP channel-associated factor family, FAM115c, increased under hypoxia in pancreatic cancer. In the present study, the biological significance of FAM115c was investigated in pancreatic cancer, and whether FAM115c could be a new therapeutic target for pancreatic cancer was evaluated.

**Methods:** Three pancreatic ductal adenocarcinoma cell (PDAC) lines (ASPC-1, SUIT-2, and PANC-1) were cultured under normoxia (20%O2) and under hypoxia (1%O2) and were used as target cells. Inhibition or overexpression of FAM115c was performed using FAM115c siRNA and plasmid, respectively. Expression of FAM115c was analyzed by qRT-PCR, western blot and immunohistochemical staining (IHC). Proliferation

Results: We report that endothelial cells combined with tumor cells were able to form a well-organized network, and those tubule-like structures correspond to new vessels infiltrating tumor spheroids. These vessels presented a lumen and expressed specific markers, such as CD31 and collagen IV. The combination of 2D endothelial cells and 3D microtissues of tumor cells also increased expression of angiogenic factors as VEGF, CXCR4 and ICAM1.

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Disclosure: The author has declared no conflicts of interest.
Pathologic assessment following neoadjuvant immunotherapy or chemotherapy demonstrates similar patterns in non-small cell lung cancer (NSCLC)

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Background: Neoadjuvant chemotherapy (CT) and immunotherapy (IT) are associated with similar patterns in NSCLC. Comparison of such features in NSCLC following neoadjuvant CT, IT, or upfront surgical resection is lacking. Nivolumab (N) and/or N plus ipilimumab (N+I) are being investigated in resectable NSCLC (NCT01318294). We analyzed the histopathologic patterns of CT- and IT-treated NSCLC vs untreated surgically resected tumors.

Methods: Histopathologic assessment of untreated-, CT-, and IT-treated NSCLC was performed (n = 30, 10/group). Hematoxylin and eosin-stained tumor sections were scored for parameters of PTR: percentage of viable tumor, fibrosis, and necrosis; inflammation, tertiary lymphoid structures (TLS), macrophages, lymphovascular invasion (LVI), cholesterol clefts (CC), giant cells (GC) and neovascularization (NV). We also performed statistical analysis with unpaired two-sided t-test. Significance was defined as p-value < 0.05.

Results: CT and IT were associated with significantly less viable tumor cells (p = 0.04 and p = 0.02, respectively), IT with more fibrosis (p = 0.04) and CT with more CC (p = 0.03) than untreated tumors. Trends towards higher amounts of inflammation, macrophages and GC were seen in IT-treated compared to untreated tumors. CT had a trend towards more fibrosis and GC compared with untreated NSCLC (Table).

Conclusions: Neoadjuvant CT and IT are associated with similar histopathological changes compared to untreated tumors but with lower proportions of viable tumor and higher degrees of fibrosis. Neoadjuvant treatment is also associated with a trend towards higher amounts of inflammation, macrophages, CC and GC. Analysis of a larger cohort, including comparison of N vs N+I-treated tumors (estimated n = 80) is ongoing and will be presented in due course.

Clinical trial identification: NCT01318294.

Legal entity responsible for the study: University of Texas MD Anderson Cancer Center.

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| Table: 1928P Summary of PTR parameters |
|---|---|---|
| | Untreated | CT-treated | IT-treated |
| Viable tumor | 67.7% | 42.4%* | 37.5% |
| Fibrosis | 26.6% | 46.6% | 52.3%* |
| Necrosis | 5.6% | 11.0% | 10.1% |
| Inflammation | 1.46 | 1.54 | 1.87 |
| TLS | 0.80 | 1.00 | 1.00 |
| LVI | 0.23 | 0.16 | 0.33 |
| Macrophages | 0.12 | 0.94 | 1.17 |
| CC | 0.13 | 0.92* | 1.04 |
| GC | 0.40 | 0.80 | 0.70 |
| NV | 0 | 0 | 0 |

*p-value < 0.05

1929P Tumor-infiltrating CD3+ lymphocytes and ICOS+ T-cells predict a favorable survival in resected esophageal squamous cell carcinoma

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Background: The prognosis of advanced esophageal squamous cell carcinoma (ESCC) is extremely poor. With an increasing potential of immune checkpoints modulators in oncology, the aim of the current study was to assess the extent of tumor-infiltrating lymphocyte (TIL) and expression and significance of various immune checkpoints in the resected ESCC.

Methods: Total 396 patients who underwent radical surgery for ESCC between 2005 and 2013 were included. Using immunohistochemistry (IHC) with tissue microarray, type of T-cells including CD3, CD8, and FoxP3 T-cell and the expression of checkpoints including programmed cell death-ligand 1 (PD-L1), programmed cell death-1 (PD-1), inducible co-stimulator (ICOS), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and mucin-dominant containing-3 (TIM-3) was manually scored. IHC scores were calculated, and the expression level was defined as high density when the expression level was above the median value. In patients with median follow-up period of 24.8 months, 32.6% of recurrence and 45.7% of death occurred. Patients with a high frequency of CD3+ TILs (n = 198) demonstrated a significant longer RFS (hazard ratio [HR] = 0.61, P = 0.0005) and OS (HR = 0.59, P = 0.0005). High ICOS expression group (n = 184) displayed longer RFS (HR = 0.72, P = 0.021) and OS (HR = 0.67, P = 0.007) than low ICOS expression group. Regarding PD-1 expression, the RFS (HR = 0.67, P = 0.004) and OS (HR = 0.66, P = 0.006) were significantly better in high expression group (n = 179). In multivariate Cox analyses, high CD3+ TIL and ICOS were also indicated as an independent prognostic factor for better DFS (HR = 0.59, P < 0.001 and HR = 0.64, P = 0.002, respectively) and OS (HR = 0.48, P < 0.001 and HR = 0.60, respectively) and high TIM-3 expression in immune cells was related to the shorter RFS (HR = 1.46, P = 0.020) and OS (HR = 1.54, P = 0.013). Even though various cut-off applied, the expression of ICOS was associated with prognosis.

Conclusions: Our analysis involving TMA and IHC of multiple immune checkpoints in resected ESCC suggests that CD3+ TILs and ICOS+ T-cells might be a favorable prognostic factor.

Legal entity responsible for the study: Min Hee Hong.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

1930P Chemokine receptor CXCR7 expression, function and clinical implications in head and neck squamous cell carcinoma

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Background: The atypical chemokine receptor, CXCR7, has been shown to play an important role in the progression of several types of cancer. However, there have been few reports on the biological role of CXCR7 in head and neck squamous cell carcinoma
Results: CXCR7 was differentially expressed in human HCC tissues. High expression of CXCR7 was significantly related to depth of tumor invasion (P = 0.007), lymph node metastasis (P = 0.004), and tumor stage (P = 0.02). Overexpression of CXCR7 dramatically enhanced cell migration and invasion in HCC cells in vitro, and promoted lymph node metastasis in vivo. CXCR7 knockdown using siRNA in HCC cells recovered the cell migratory and invasive behavior of HCC cells. CXCR7 overexpression also induced the epithelial-mesenchymal transition. Vimentin, Slug, and Twist were increased but E-cadherin and Ep-CAM were decreased by CXCR7 expression. Akt phosphorylation and Smad2 signaling activation were induced in HCC cells with CXCR7 overexpression. Treatment with a PI3K inhibitor reduced Slug and Twist levels while suppression of Smad2 signaling by siRNA reduced CXCR7 expression, as well as Slug and Twist. Furthermore, inhibition of Smad2 decreased tumor cell migration and invasion in HCC.

Conclusions: CXCR7 expression was associated with an aggressive tumor behavior in HCC. CXCR7 contributed to cell migration and invasion of HCC cells through the Smad2/Akt signaling axis in vitro, and was involved in lymph node metastasis in vivo, suggesting that CXCR7 might be a therapeutic target for the treatment of HCC.

Legal entity responsible for the study: Hyo Jin Lee.

Funding: Cancer Research Institute of CNU.

Disclosure: All authors have declared no conflicts of interest.

**1931P** Assessment of PD-1/PD-L1 colocalization in hepatocellular carcinoma (HCC) using bright-field double labeling and quantitative digital image analysis

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**Background:** Tumors may suppress host defenses by activating immune checkpoints (e.g., the programmed cell death [PD-1/PD-L1] pathway). Colocalization (CL) is a requirement for PD-1/PD-L1 interaction. PD-1/PD-L1 CL in tissue sections, as determined by immunohistochemistry (IHC), may be an indicator of PD-1/PD-L1 pathway activity.

**Methods:** We assessed CL of PD-1 and PD-L1 in situ by applying a novel duplex bright-field IHC technique on 49 formalin-fixed, paraffin-embedded HCC samples using digital image analysis (DIA: Definiens Tissue Studio) to determine the percentage of single PD-1+ and PD-L1+ cells, PD-1/PD-L1 double-labeled cells, and PD-1+ cells adjacent to 2 PD-L1+ cells.

**Results:** All cases showed typical HCC morphology (low- to high-grade trabecular [4/49], pseudoglandular [1/49], solid [40/49], clear cell [2/49], or desmoplastic [2/49]). PD-L1 was largely observed in immune cell infiltrates. On average, 2.6% ± 3.6% (median, 1.5%) of the cells (immune + tumor) within the tumor area were PD-1+, and 4.3% ± 5.5% (median, 1.9%) were PD-L1+. There was considerable variation among samples in the number of PD-1+ cells (range, 0.0%-21.2%; and PD-L1+ (range, 0.2%-30.3%) cells. In 18/49 cases (37%), the number of PD-1+ cells exceeded the number of PD-L1+ cells; in 31/49 cases (63%), the number of PD-L1+ cells exceeded the number of PD-1+ cells. PD-1/PD-L1 double-labeled cells were present in 31/49 cases (63%), and 1.6% ± 4.1% (median, 0.13%) of the double labels were detected, with considerable intersample variation (range, 0.5%-22.9%). Finally, 10.5% ± 8.03% (median, 9.4%) of PD-1+ cells were in the immediate vicinity of a PD-L1+ cell (range, 1.1%-43.9%).

**Conclusions:** By combining a novel duplex bright-field IHC technique with DIA, we quantitated the number/distribution of PD-1+ and PD-L1+ cells in HCC. Variation in the numbers of PD-1+ and PD-L1+ cells, and PD-1+ cells with ≥ 2 PD-L1+ adjacent cells, in HCC was seen. Future studies can use these techniques to explore the predictive potential of PD-1/PD-L1 CL in expression in patients who are being considered for immunotherapy. Our proof of concept results suggest that the methods may also be applied for other tumors.

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**1932P** Pulmonary tumor thrombotic microangiopathy (PTTM): 24 case series and its criteria for pathological diagnosis

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**Background:** PTTM is a fatal complication of malignancy causing progressive pulmonary hypertension (PH) or right heart failure. It is considered as a rare disease, but a growing number of cases have been reported. The pathogenesis is hypothesized that widespread cancer emboli in microscopic pulmonary arteries activate fibrocellular intimal proliferation and thrombosis. Adenocarcinomas, especially gastric ones, are the major cause. Pathological diagnosis of PTTM is apparently easy. However, microscopic pulmonary tumor emboli are a sporadic finding of cancer patients, which can resemble PTTM when followed by intimal changes and other pulmonary diseases. The increase of misdiagnosis is a concern as PTTM becomes better known. The purpose of this study is to build diagnostic criteria of PTTM.

**Methods:** 24 cases diagnosed as PTTM in multiple institutions were collected and classified into two groups: (1) a definite group (n = 13), those who had been clinically diagnosed as PH, and (2) a suspicious group (n = 11), those who revealed respiratory symptoms but lacked clinical assessment of PH. As a control group, autopsy cases with PTTM-like lesions but who were lacking progressive respiratory symptoms were selected (n = 7). PTTM-like lesions in these groups was observed.

**Results:** The numbers of PTTM-like lesions (fibrocellular intimal proliferation and thrombi) with tumor cells in the definite and non-PTTM group were 26-58.8 and 0.3-5.9/cm² area of lung specimen. In definite cases, peripheral arterioles smaller than 150 μm in diameter were predominantly involved. In the suspicious group, 7 of 11 cases had as many lesions (25.4-68.9/cm²) in small arterioles as in the definite cases, while the remaining 4 had as few lesions (1.3-9.6/cm²) as the non-PTTM group. Lymphangitis carcinomatosa was seen in these 4 cases.

**Conclusions:** We suggest that the pathological criteria of PTTM is as follows: 1) fibrocellular intimal proliferation and thrombi with tumor cells 2) involvement of microscopic pulmonary arteries and arterioles, predominantly small ones in alveolar septa (<150 μm in diameter), and 3) the innumerable spreading of more than approximately 100 lesions/5 cm² area of lung specimen.

**Legal entity responsible for the study:** Naoko Satoh.

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**Disclosure:** All authors have declared no conflicts of interest.

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**1933P** Autofluorescence: A new marker for identifying cancer stem cells (CSCs) in primary tumors

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**Background:** CSCs, specifically their involvement in tumor progression and chemoresistance, represents one of the cornerstones of current cancer research. CSCs autofluorescence analysis has proven to be an accurate method to detect these cells in tumor tissues, offering an ideal setting to study the prognostic and predictive implications of this marker. More importantly, it also offers a new scenario for the development of personalized screening platforms, which could be widely universalized in the hospital setting. However, a straightforward and reproducible model for the identification and isolation of autofluorescent CSCs is still lacking.

**Methods:** Fresh tissues from 97 resected tumors were analyzed over 24 months. The percentage of CSCs in primary tumors was analyzed using autofluorescence, the result of Riboflavin accumulation in discrete cytoplasmatic vesicles over expressing the ATP-dependent transporter ABCG2. These results were correlated with the established CSCs markers CD133 and CD90. FlowFuturumG C (FCTC), a specific inhibitor of ABCG2, was used to verify the specificity of the autofluorescence observed.

**Results:** Autofluorescent cells (AC) in the epithelial cell compartment (EpCAM+) of the tumors analyzed were identified in 60% of the samples, primarily in gastrointestinal tumors (e.g., colon, gastric, rectal). AC also co-expressed other established CSC markers, such as CD90. Autofluorescence disappeared when tumoral cells were incubated with FTC confirming that the autofluorescence observed was ABCG2-dependent.

**Conclusions:** CSCs can be efficiently identified and isolated from gastrointestinal tumors using autofluorescence. The simplicity of this method would allow for its applicability to the broader scientific community in order to investigate the roles of CSCs in tumor progression and drug resistance. Moreover, upon their isolation, AC could be used in screening platforms to assess the chemoresistance of CSCs, thus allowing for the development of new molecular targeted therapies.
NACC1 as a target of microRNA-331-3p regulates cell proliferation in uterine cervical carcinoma cells

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Background: microRNA (miRNA) constitutes a class of small non-coding RNAs, which are involved in cell proliferation, differentiation, and progression of tumors. miRNAs and their target molecules are utilized for molecular diagnosis of uterine cervical carcinoma. Nucleus accumbens-associated protein 1 (NACC1), one of several transcription factors, is constitutively expressed in the uterine, wherein it regulates cell growth, senescence, autophagy, epithelial-mesenchymal transition. We previously reported that NACC1 is the target molecule of miR-331-3p and is associated with cell proliferation in prostate and cervical cancer.

Methods: Functional experiments involving miR-331-3p and its target molecule, NACC1, was analyzed using uterine cervical carcinoma (UC) cell lines, T24, UMUC56, and KU7. Quantitative reverse transcription polymerase chain reaction, and immunostaining were performed to evaluate the expression of miR-331-3p and NACC1 in UC derived from transurethral resection of bladder tumor (TUR-Bt) specimens.

Results: The MTS assay revealed that cell proliferation was significantly reduced after transient transfection of miR-331-3p precursor and/or NACC1 siRNA in UC cells. Cell senescence via cell cycle arrest at the G1 phase was induced by NACC1 inhibition. Immunohistochemistry with TUR-Bt specimens revealed that greater than 90% of both UC and normal uterine cervical cells were positive for NACC1 in contrast to no or limited expression in squamous cell carcinoma of the esophagus, cervix, and oral cavity. The NACC1 expression profile is not significantly associated with the pathological parameters including the pT stage.

Conclusions: The present results suggest that NACC1 regulated by miR-331-3p contributes to cell proliferation and is a potential target molecule for the diagnosis and treatment of UC.

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Disclosure: All authors have declared no conflicts of interest.
**CN1** Evaluation of an education programme on compassion fatigue: Turkish oncology-haematology nurses’ perspectives

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**CN2** The efficacy of nurse-led clinic

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**CN3** Introducing the role of the advanced clinical practitioner in haematology and oncology

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**CN4** Nurse navigators in thoracic oncology: A qualitative study of German nurses’ attitudes to nursing role expansion

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Patients: Power sources for cancer nurses

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Background: It’s obvious that cancer nurses have to deal with a lot of different burdens during their everyday work. These burdens are obvious and very well known. If one has an overall view at cancer nursing staff at a ward one will recognise two huge groups: Beginners, which passed their exam recently and colleagues, that are working with cancer patients for more than 15 years and often until retirement. The question which arises is therefore why can these “senior nurses” resist these strains and stay healthy?

Methods: Study of literature focussing on spiritual, physical and psychological needs groups (especially cancer nurses) that are known for be on stress - published European Standards regarding physical burden at workplace, own empirical cases from working life, which had a lasting influence informal interviews with colleagues.

Results: The intensity of work has increased in most clinics - pressure on time, more severe ill patients, complexity of treatment. The working conditions deteriorated considering payment, job confidence, team work and support. Nevertheless, cancer nurses do stay in their workplace for a very long time because of spiritual background, rituals and general upbringing - resilience - inspiring contacts and interacting with their patients.

Conclusions: With all the burden of and to the care of the patients and their relatives: it is more than coping with their needs. They also give back enormous energy, provided one give space to the moving moments and allow it to draw strength from this particular source.

Legal entity responsible for the study: Cordula Beisel.

Disclosure: The author has declared no conflicts of interest.

BRAF/MKI-inhibition for patients with metastatic melanoma: Towards patient-centered care

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Background: The incidence of melanoma – the deadliest form of skin cancer - is steadily increasing. Over the last few years, treatment options for inoperable or metastatic melanoma have increased. Treatment with BRAF/MKI-inhibitors (BMM) induces fast responses in the large majority of patients with BRAF-mutant melanoma. As a result, BMM are often used as a palliative treatment for patients with aggressive metastatic melanoma. A successful palliative treatment - a treatment in which life is prolonged and the patient experiences an acceptable quality of life - requires intensive support. Nursing interventions are aimed at empowering people and helping them to achieve, maintain or (re)acquire their independence. This Dutch study was set up to collect building blocks in order to develop an evidence-based nursing intervention that supports patients during palliative treatment with BMM.

Methods: Using the van Meijel model, a problem analysis, a literature review, a patient needs analysis and a current practice analysis, were performed. A literature search was performed to collect available, appropriate interventions. Nationwide questionnaires – in patients as well as in nurses - were used to gain insight into patient needs and the current practice.

Results: The problem analysis and results of the literature review showed that patient education, disease and/or treatment related symptoms and support with self-management are key components during treatment with BMM in adult patients with metastatic melanoma. When considering nursing care, the available literature focuses on promoting adherence in particular.

Conclusions: Treatment with BMM is a life-prolonging treatment. As a result, medication adherence seems more important in relation to symptom burden and quality of life than to the effectiveness of the treatment alone. In conclusion, future nursing interventions should not only focus on treatment adherence, but also on quality of life and quality of dying, with respect to the patient’s needs and wishes.

Legal entity responsible for the study: Jose Koldenhof.

Perceptions of rural nurses extending their role to administer chemotherapy

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Background: Nurses in rural regions of South Australia are currently administering chemotherapy in centres where this was not previously the case. To prepare these nurses, a state-wide chemotherapy education and assessment programme was implemented in 2013. This research project explored the perceptions of nurses working in level-one rural centres administering low-risk chemotherapy protocols. The study explored how registered nurses who administer chemotherapy in low-risk chemotherapy services in rural SA perceive their expanded roles and whether they felt equipped with the knowledge and skills required to undertake them.

Methods: This is a qualitative study. Individual interviews were conducted with eight registered nurses working in low-risk chemotherapy centres in rural settings. The data analysis methods were based on critical social theory.

Results: Four main categories of findings are identified: 1) role extension, preparedness and self-confidence; 2) chemotherapy services in rural areas; 3) power relationships, referrals and knowledge sustainability; and 4) communication with other cancer settings and professionals. Overall, participants highly valued the service as valuable support for rural patients with cancer, but they identified areas of concern, including the rural nurses’ roles in cancer care, the need to maintain knowledge and skills and to establish their role in referral and follow-up processes.

Conclusions: Participants expressed their perceptions of their role. Then, through critical theory, their voices were revealed, expressing their needs and suggestions for changing and improving their role and the service.

AYA cancer nursing, an emerging sub-specialty: The first book about AYA cancer nursing, edited and authored by nurses

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Background: During the last twenty years, adolescents and young adults with cancer have gained increased attention in healthcare. The body of knowledge is growing accordingly. Nurses who have led the way amongst the now widening circle of professionals engaged in providing specialist care for young people with cancer are now ready to describe their contributions within education, clinical nursing, rehabilitation, research and leadership.

Methods: To provide healthcare professionals with knowledge about the distinct developments made within AYA cancer nursing internationally a book entitled Nursing Adolescents and Young Adults with Cancer. Developing knowledge, competence and best practice is under production.


Conclusions: The authors offer insights into the development of AYA cancer care; why it matters; how it should be delivered; and how it might be done better – and with recognition of the unique needs and wants of each young person at the centre of it all.

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Nurse led follow-up for CML patients on oral cancer treatment

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Background: Chronic myeloid leukemia (CML) is a bone marrow disorder accounting for 15% of newly diagnosed leukemia in adult patients (Rytkynen et al. 2017 & Trivedi et al. 2014). The introduction of tyrosine kinase inhibitors (TKIs) has changed the CML treatment significantly. Patients’ concerns have shifted from reduced life expectancy to management of long-term toxicities and improvement of quality of life (QoL) (Isok et al. 8 & Brunnendorf TH 2018). In 2016 Moulin et al. showed that closely monitoring patients affects adherence. Poor adherence is associated with greater overall health care utilization and medical costs in CML (Jabbour B et al. 2012). An increase in the patient health is expected from improvements in adherence.

Methods: After receiving information from the doctor, patients remember approximately half of the information provided (Hillen MA et al. 2015). The hematology department in UZ Ghent has an interdisciplinary approach to CML patients. In a nurse led consultation patients who start with TKI receive additional written information. The purpose is to reduce the information gap and manage patients concerns. Over time the nurse led consultation transmits to monthly telephone follow-up. This includes the assessment of the patient’s condition, adverse events (AEs) and the influences on their QoL. Individual nurse led consultation supports a solid health care provider-patient relationship, offers patient tailored care and is ideally placed to detect psychological and social problems. Referral to other health care providers must always be based on shared decision making.

Results: The aim is to educate the patients and offer psychosocial support. By creating a strong health care provider-patient relationship the goal is to make sure the patient feels free to talk about any issues. This also empowers the patient, improves adherence and helps to detect and control AEs prematurely.

Conclusions: An interdisciplinary approach and establishing a care pathway is a necessity to streamline the patient treatment process. A nurse structured questionnaire is needed to improve the telephone nurse led follow-up and the handover to the doctor. After implementing such a structured tool the effectiveness of the project must be reviewed by using questionnaires that assess the adherence and QoL.

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Systemic anticancer therapy administration safety

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Background: SACT safety in administration and waste disposal. Our original article explored the immediate adverse effects experienced by nurses during the administration of systemic anti-cancer therapy (SACT). Specifically cytotoxic chemotherapy, and whether closed systems are being used to minimize exposure risk. Many SACT agents are known to be carcinogenic, teratogenic and mutagenic and this has led to concerns relating to the increased number of healthcare workers potentially exposed to these agents.

An anonymous online survey was designed, made up of four questions, to elicit whether adverse effects were experienced by nurses during preparation, administration or following administration of chemotherapy. A total of 46% of respondents stated that they experienced some form of adverse effect either during preparation, administration or following administration of SACT. More formal research is required in this area to explore the relationship between exposure to SACT and perceived adverse effects in healthcare workers administering SACT. As a follow up to this survey, we are going to develop a further survey to elicit healthcare professionals awareness of SACT exposure risk, education / training provision and current practices in relation to SACT administration and waste disposal.

Methods: In our original study, a short anonymous online survey was designed made up of four questions to elicit whether adverse effects were experienced by nurses during preparation or administration or following administration of chemotherapy. This was distributed via social media and networking contacts. For our follow-up survey, we will replicate this method, including questions about awareness, education / training and current practice in relation to SACT administration and waste disposal.

Results: of the original study were obtained through the questionnaire responses which were analysed and presented using a quantitative approach. The follow up survey will require a mixed methods approach to analysis to elicit greater depth of information from participants.

Conclusions: Following quantitative analysis of our original survey, we concluded that further research was required in this area, hence the need for additional data collection via a further online survey.

Legal entity responsible for the study: Samantha Toland and Alison Simons.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
Background: Immune checkpoint inhibitors have improved the outcome of patients with advanced cancer significantly over the last decade. Disadvantageous effects of these novel treatments include auto-immune toxicities, named immune-related adverse events (irAEs), that most commonly affect the skin, gastrointestinal tract, liver and endocrine glands. Immune-related endocrine toxicities that involve the pituitary gland or adrenal glands may cause adrenal insufficiency (irAI), which can be life-threatening if not early recognized and managed.

Due to the emergence of novel immunotherapies and indications, the number of patients with irAI will increase. We report a clinically applicable algorithm, with a key role for the nurse practitioner (NP), to manage irAI and to improve safety using a system-focused approach.

Methods: A collaboration between NP, oncologists and endocrinologists, taking input and perspectives from patients into account, was used to develop consensus regarding irAI management. Based on literature, institutional experience and group consensus, a clinically applicable algorithm was created.

Results: Team members were educated on algorithm application and to improve safety. The NP was the first point of call and coordinated collaboration between patient, medical specialists and family physician. The NP was appointed a key role for patient education and information. Patients were educated to recognize symptoms of adrenal insufficiency and react promptly by increasing the dose of the corticosteroid substitution therapy. Patients were encouraged to contact the NP in case of problems or questions about the prophylactic dose of corticosteroids for stressful events.

Conclusions: Due to the increased use and the long-term efficacy of immune checkpoint inhibitors in patients with cancer, the incidence and prevalence of immune-related adrenal insufficiency (irAI) will increase. The here reported algorithm provides a streamlined approach for the management of irAI that is expected to improve safety and quality of life of patients.

Legal entity responsible for the study: Van den Eertwegh AJM.

Funding: Has not received any funding.

Disclosure: M. Labots: Advisory board: BMS. J. Eertwegh: Advisory boards: BMS, Merck, Roche, Novartis, Amgen; Study grant: Roche. All other authors have declared no conflicts of interest.

CN13 Experiences from a new advanced cancer nursing role in Sweden: An analysis based on EONS Cancer nursing education framework using the Delphi method

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Background: Immune checkpoint inhibitors have improved the outcome of patients with advanced cancer significantly over the last decade. Disadvantageous effects of these novel treatments include auto-immune toxicities, named immune-related adverse events (irAEs), that most commonly affect the skin, gastrointestinal tract, liver and endocrine glands. Immune-related endocrine toxicities that involve the pituitary gland or adrenal glands may cause adrenal insufficiency (irAI), which can be life-threatening if not early recognized and managed.

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Results: Team members were educated on algorithm application and to improve safety. The NP was the first point of call and coordinated collaboration between patient, medical specialists and family physician. The NP was appointed a key role for patient education and information. Patients were educated to recognize symptoms of adrenal insufficiency and react promptly by increasing the dose of the corticosteroid substitution therapy. Patients were encouraged to contact the NP in case of problems or questions about the prophylactic dose of corticosteroids for stressful events.

Conclusions: Due to the increased use and the long-term efficacy of immune checkpoint inhibitors in patients with cancer, the incidence and prevalence of immune-related adrenal insufficiency (irAI) will increase. The here reported algorithm provides a streamlined approach for the management of irAI that is expected to improve safety and quality of life of patients.

Legal entity responsible for the study: Van den Eertwegh AJM.

Funding: Has not received any funding.

Disclosure: M. Labots: Advisory board: BMS. J. Eertwegh: Advisory boards: BMS, Merck, Roche, Novartis, Amgen; Study grant: Roche. All other authors have declared no conflicts of interest.

CN14 Experiences from a new advanced cancer nursing role in Sweden: An analysis based on EONS Cancer nursing education framework using the Delphi method

H. Ullgren
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Background: A new advanced nursing role - Coordinating contact nurse (CCN) were implemented as a pilot in 2015, aiming to improve care transitions, collaboration and communication between different teams, as well as strengthening the nurses and clinicians in the whole team. The CCNs has a regional role over one patient trajectory within the Stockholm-Gotland region. When interviewing patients at start of the project, many patients wished for more support regarding coordination and felt they had to be responsible themselves for important clinical information exchange. Collaboration and communication between the teams within the acute hospitals different disciplines, as well as acute and palliative care (PC) were sub-optimal, and it affected for example emergency admissions from PC to acute care. A baseline survey was performed before implementation of the CCN project. It showed that some of the supportive care resources were accessible for only half of the patients.

Methods: Experiences from this new role are currently analyzed, based on the 8 modules included in EONS Cancer Nursing Education Framework. Data is analyzed using the Delphi process including different groups of staff and patient representatives.

Results: Preliminary results show that the CCN role cover all 8 modules in the framework and indicate that the CCN role fulfill the criteria described for advanced cancer nursing roles. The practice competencies have been useful both in recognizing what cancer nurses do, and highlights areas in need of development.

Conclusions: Patient-reported evaluation of the CCN role is needed and ongoing. Preliminary data shows significant improvement in areas such as perceived information about self-care and access to supportive care. This new advanced cancer nursing role could contribute to improved experiences and outcome for cancer patients. If formally established, the CCN role could be an important clinical career opportunity for Swedish cancer nurses.

Legal entity responsible for the study: Helena Ullgren, Regional Cancer Centre Stockholm Gotland, Sweden.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.
**CN17** Standardising the psychosocial assessment of oncological patients at Donostia university hospital


**Background:** A cancer diagnosis often causes an emotional impact with signs of anxiety, uncertainty and subjective discomfort. It is necessary to identify and assess emotional discomfort to offer quality treatment articulated around the patient and his/her demand. The design of a questionnaire that is easy to use and understand, allows the detection of patients susceptible to referral to the Psycho-oncology Unit (POU). The POU consists of a Psychiatrist and a Nurse with specific training in Psycho-oncology.

**Methods:** Prepare a PAQ that includes: Evaluation of emotional distress assisted by visual analogue scales (VAS); Modified Gijon scale (sociofamilar assessment scale); previous use of psychoactive drugs - Include PAQ in the first nursing visit - Quick referral to POU - Interview with psycho-oncology nurse - Valuation, diagnosis and treatment planning by POU - Data recording.

**Results:** Patients with a positive PAQ are referred to the POU where the liaison nurse performs an interview with the patient and / or family. The nurse collects data on psychobiography, oncological disease, psychic sphere, frequent affections, previous contacts with psychologists / psychiatrists and treatments with psychoactive drugs. The POU will offer the patient the most appropriate resource for their needs (Psychotherapy, Psychopharmacological, Social Work Service).

**Conclusions:** The inclusion of the PAQ in the first visit of nursing allows the detection and early treatment of disorders in the psychosocial area. We achieve an optimal use of resources, a greater adherence to the proposed oncological treatment, alleviate problems that are found throughout the oncological treatment and improve the quality of life of our patients by reducing emotional discomfort.

**Legal entity responsible for the study:** Hospital Universitario Donostia.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**CN18** Are there differences between nurses’ and patients’ perceptions of cancer patients’ quality of life in Greece?


**Nursing, Alexander Technological Educational Institute, Thessaloniki, Greece**

**Background:** Cancer and its treatment affect negatively patients’ quality of life. Nurses and their perceptions about patient quality of life should be vital in order to provide high-quality care and increase patients’ QoL. The aim of this study is to investigate nurses’ and patients’ perceptions about cancer patients’ quality of life.

**Methods:** This was a non-experimental and descriptive study. It was conducted in two large hospitals in a major Northern Greek city. The subjects were 50 pairs of cancer patients and their nurses. Patients and nurses had completed the Greek Version of the World Health Organization quality of life (WHOQoL-BREF) questionnaire, separately.

**Results:** The majority of patients was female (50%) with mean age 59.8 years (S.D. 15.1). Regarding nurses’ demographic characteristics 88% was female with mean age 45.9 years (S.D. 9.8). According to the patients’ perceptions the mean of physical health domain was 14.8 (S.D. 3.2), psychological domain was 15.1 (S.D. 2.6), social relations- ships domain was 14.2 (S.D. 3.7) and environment domain was 15.7 (S.D. 2.3). The corresponding scores of nurses were 12.6 (S.D. 1.9), 12.9 (S.D. 2.6), 13.1 (S.D. 3.4), 14.1 (S.D. 2.9) respectively. Wilcoxon test was shown statistically significant differences between patients’ perceptions and nurses’ perceptions in 3 domains (physical health (p = 0.001), psychological domain (p = 0.001), environment domain (p = 0.003) except from social relationships. Specifically, the quality of life was scored lower by nurses than the corresponding drawings of patients. Additionally, correlation was found between the time which nurse spends with patients and psychological domain (r = 0.313) and environment domain (r = 0.372) respectively.

**Conclusions:** There were differences between Greek cancer patients and their nurses about cancer patients’ QoL. The results of the present study stress the need for further research in order to increase nursing understanding about patients’ life and enhance holistic nursing approach.

**Legal entity responsible for the study:** Alexander Technological Educational Institute - Research Laboratory “Care in Adult Cancer Patients”.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**CN19** How an empowerment program can touch cancer survivor’s life by improving post-traumatic growth?

**V.S. Uzun Ozcetin, Psychiatry Nursing, Hacettepe University Faculty of Nursing, Ankara, Turkey**

**Background:** Cancer experience can cause traumatic symptoms with higher levels of stress. Although cancer has been traditionally seen as a destructive illness, in recent years, this perspective has been abandoned, and it is being argued that coping with cancer and developing growth is possible. Research in this area has supported this new perspective, and the results have shown that cancer does not always contain traumatic effects and people can also have positive attainments during this process. Re-meaning of life during cancer process enables posttraumatic growth (PTG), which improves interpersonal relations, inner resurgence, and deeper spirituality.

**Methods:** Researcher has studied on an empowerment program in her PhD thesis and keeps working on this area. Hence, the aim in this study is to point out the effects of an empowerment program to improve PTG of cancer survivors. Literature review and sharing experience in such works.

**Results:** Having resilience in cancer experience help people to understand the value of life, find new meanings, determine the priorities in life, and reach spiritual well-being. Re-meaning of life during cancer process enables posttraumatic growth, which improves interpersonal relations, inner resurgence, and deeper spirituality. In this regards, using an empowerment program can be an effective way in helping the participants recognize the nature of the problem in their life, and created a safe and therapeutic environment to improve their social skills. Also, such programs refer to the use of not only intrinsic sources, such as self-efficacy and self-esteem, but also extrinsic ones, such as social support and social coherence. On the other hand, providing supportive activities/programs are valuable to help them learn from others who had similar experiences, in this way, they can feel understood, accept the process with its positive and negative consequences, and have better coping strategies.

**Conclusions:** Empowerment program could improve both PTG in cancer survivors and nurses caring for cancer survivors can use such programs to improve PTG and resilience, in addition to the usual medical care in cancer. By this way, cancer survivor can have enough psychological support which usually forgotten among routine medical care.

**Legal entity responsible for the study:** Yeter Sinem Uzun Ozcetin.

**Funding:** Has not received any funding.

**Disclosure:** The author has declared no conflicts of interest.

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**CN20** Organising a general oncology nursing outpatient clinic

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**Background:** The complexity of living with, being treated for or dying from cancer can generate numerous issues and needs for patients and their families. Many those are appropriately dealt with based on oncology nursing. Despite this most general oncology outpatient clinics in Sweden are physician-led. The development of general nurse-led cancer care services has been suggested to improve the care of cancer patients. Consequently a general oncology nursing outpatient clinic has been implemented. The aim of this study was to describe the feasibility of organizing an oncology nursing outpatient clinic, its implementation and outcomes.

**Methods:** This study had a descriptive multi methods design. Qualitative data to describe nurses, physicians and managers perspectives was collected and analysed with qualitative content analysis. Quantitative data was collected for referral, for patients’ problems being within nurses’ competences and for patient views of the quality of the care they received.

**Results:** The oncology nursing clinic became a valid complement to the existing organisation. The use of the nursing competence in a more structured way resulted in greater possibilities for patients to get relevant care for their problems. The continuity of and access to care improved. Experiences from patients can be summarised as better quality care. The implementation of the clinic was described as a way of “putting the right competence in the right place”. The clinic was both part of the oncology team and had an autonomous function. For most of the patients problems presented the nurses could independently solve them, for some they had to contact the oncologist. Before the implementation of the clinic most expectations were high and at the follow-up mostly described as fulfilled. The implementation can be seen as a process with some difficulties that had to be solved but the use of the clinic has constantly increased over time.

**Conclusions:** The implementation of a general oncology nursing outpatient clinic is a feasible way to improve patient care. Due to the positive results the clinic is now a permanent part of the organisation. The implementation process could have been improved as it took nearly a year to get the oncology nurse outpatient clinic to run efficiently.

**Legal entity responsible for the study:** Ulrika Östlund.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.
Background: Current evolutions in medicine, the emphasis on cost-effectiveness in healthcare and the increase of complex healthcare needs address the need for highly educated and specialised nurses, such as advanced practice nurses (APN). By means of scientifically specialised knowledge, skills and competences, APN should enhance expansion, advancement and innovation in nursing care. Methods: A cross sectional design was used to explore the job content performed by APN. 38 APN in Flemish hospitals participated. A validated self-reported questionnaire was used, combined with non-participant observational data (40 days). Results: APN in Flanders are mainly experts in the domain of oncology, pain and wound care. Based on the self-reported data, the job content of APN is diverse and is linked with the APN roles as described by Hamric. 94.8% are involved in professional development and teaching of nurses in the hospital. 63.5% develops a nursing consultation and 63.8% performed these consultations autonomously. Medical delegated tasks are performed to a lesser extent. 87.9% of APN reads and evaluates scientific literature to enhance evidence based nursing in practice. Initiating and executing domain-specific nursing research is performed by 78.3%. 91.4% participates in quality improvement projects in their specific domain. APN actively participate in international and national professional organisations. There is a limited participation in working groups within governmental agencies, national and international advisory boards. Based on observational data, we present the following working percentages to: clinical expert (33.2%), nurse (11.7%), educator (17.5%), innovator and implementation (7.5%), research (7.2%), leader and policy advisor (5.1%) and facilitator in ethical decision making (0.1%). Conclusions: APN are ‘young’ professionals, in age and in working experience in the specialist domain. They are less involved in policy-making and work related to extra- mural activities. The focus is mainly on clinical expert care. Although APN can significantly contribute to high-quality, evidence-based patient care by providing training and coaching to nurses, initiating and guiding quality projects, conducting research and translating research findings into practice, there is room for further growth. Legal entity responsible for the study: University Ghent, Department of Nursing Science. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

CN21 Job content of advanced practice nurses in Flanders
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Background: Current evolutions in medicine, the emphasis on cost-effectiveness in healthcare and the increase of complex healthcare needs addresses the need for highly educated and specialised nurses, such as advanced practice nurses (APN). By means of scientifically specialised knowledge, skills and competences, APN should enhance expansion, advancement and innovation in nursing care. Methods: A cross sectional design was used to explore the job content performed by APN. 38 APN in Flemish hospitals participated. A validated self-reported questionnaire was used, combined with non-participant observational data (40 days). Results: APN in Flanders are mainly experts in the domain of oncology, pain and wound care. Based on the self-reported data, the job content of APN is diverse and is linked with the APN roles as described by Hamric. 94.8% are involved in professional development and teaching of nurses in the hospital. 63.5% develops a nursing consultation and 63.8% performed these consultations autonomously. Medical delegated tasks are performed to a lesser extent. 87.9% of APN reads and evaluates scientific literature to enhance evidence based nursing in practice. Initiating and executing domain-specific nursing research is performed by 78.3%. 91.4% participates in quality improvement projects in their specific domain. APN actively participate in international and national professional organisations. There is a limited participation in working groups within governmental agencies, national and international advisory boards. Based on observational data, we present the following working percentages to: clinical expert (33.2%), nurse (11.7%), educator (17.5%), innovator and implementation (7.5%), research (7.2%), leader and policy advisor (5.1%) and facilitator in ethical decision making (0.1%). Conclusions: APN are ‘young’ professionals, in age and in working experience in the specialist domain. They are less involved in policy-making and work related to extra-mural activities. The focus is mainly on clinical expert care. Although APN can significantly contribute to high-quality, evidence-based patient care by providing training and coaching to nurses, initiating and guiding quality projects, conducting research and translating research findings into practice, there is room for further growth. Legal entity responsible for the study: University Ghent, Department of Nursing Science. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.

CN22 Developing and testing a theory-based e-learning intervention to enhance healthcare professional’s self-efficacy when supporting parents newly diagnosed with cancer who have dependent children
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Background: Families impacted by parental cancer need advice from healthcare professionals on how to communicate this devastating news to their children and support them while having treatment. Despite the evident need, this support is often inadequate, due to lack of confidence and training for healthcare professionals. To address this gap, a theory-based e-learning intervention has been development using a ‘person-based approach’, aimed at enhancing healthcare professionals’ self-efficacy when supporting parents newly diagnosed with cancer who have dependent children. Methods: Using the person-based approach two qualitative focus groups (n = 23) were conducted at the planning phase, with frontline oncology professionals. During the development phase, an iterative approach was adopted incorporating ‘think aloud’ interviews (n = 14) for usability testing, hence moving between data collection, analysis and modifications of the e-learning intervention. The data was analysed using thematic analysis. Results: Drawing upon existing evidence and data generated from the two focus groups at the planning phase, an e-learning prototype was developed. Three cycles of refine- ment followed with user testing, using 14 think-aloud interviews. Key themes identified during think-aloud interviews which led to modifications included: ‘navigational difficulties’ and ‘enhancement of content and visibility’. Four positive themes were also reported to include: ‘appropriate use of children’s drawings’, ‘superior look and feel’, ‘value of the ‘Talking, Telling and Sharing framework’ and ‘pedagogical methods to improve impact’. Conclusions: This study provides a detailed description of how the person-based approach was used to plan, develop and test an e-learning intervention, aimed at improving its acceptability, feasibility and effectiveness during implementation. Providing a detailed description of the foundations that underpinned the development of this e-learning intervention, provides transparency in the planning and design process, therefore aids methodological rigour. Legal entity responsible for the study: Ulster University. Funding: HSC R&D Office, Northern Ireland. Disclosure: All authors have declared no conflicts of interest.

CN23 Supporting melanoma patients and their carers: A qualitative exploration of social interaction between patients, carers and healthcare professionals
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Background: Melanoma incidence continues to rise in Europe, the USA and Australia with mortality rates remaining relatively stable, meaning more patients undergoing surveillance. Treatments may include multiple surgeries, BRAF/MEK inhibitors and immune therapies. Clinical Nurse Specialists (CNS) provide support for melanoma patients and their carers in the UK. The aim of the overall study was to explore the changing experiences and support needs of melanoma patients and their carers throughout the disease pathway. Here we report the specific interactions between healthcare professionals and patients. Methods: The study employed a qualitative methodology using a constructivist grounded theory approach. Theoretical sampling was used to recruit 17 melanoma patients from outpatient clinics within a UK teaching hospital. 11 carers and 11 Healthcare professionals (HCPs) participated with patient agreement. Patients and carers were interviewed in-depth, up to 6 times over 2 years and HCPs were interviewed on 2 occasions. Initial topics were modified as interviews took on an emergent design. Focus groups were conducted at the end of data collection: one with patients and one with CNSs. Results: Owing to differing job titles used by nurses in the UK, not all patients recognised that was a nurse available to support them. Patients and carers needed to build a trusting relationship with nurses in order to use them for support with nurse- led clinics providing continuity. Patients, carers and CNSs agreed on important points in the pathway resulting in four key phases: diagnosis and initial treatment, surveil- lance, metastatic disease and bereavement. Patients and carers did not appear to use the service more for knowing it was there, but it provided reassurance. Stage IV disease had the greatest input, with access to community services. Conclusions: Developing a trusting relationship with a nurse enabled patients to feel supported. This was facilitated by the continuity provided in nurse-led clinics but different job titles could create a barrier to patients understanding that there was someone they could contact with concerns or worries. CNSs recognised the key time points where support was most needed. Legal entity responsible for the study: Sheffield Teaching Hospitals NHS Foundation Trust. Funding: National Institute for Health Research. Disclosure: S.J. Danson: Employee: NIHR National Speciality Lead for Cancer, Early Phase Trials. All other authors have declared no conflicts of interest.

CN24 Assessing the effect of telephone support on patients with myeloma multiple (MM) in the Catalan oncology institut in Girona
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Background: MM is an incurable plasma cell malignancy characterized by excess para-protein secretion with secondary organ effects including bone destruction and anemia, renal damage and immune system impairment. MM presents as a relapsing- remitting illness throughout the patient’s life, resulting not only in individualized man- agement but also in complicated treatment with continuous revision and management of the cumulative secondary effects. MM is diagnosed at a median age of 69 years and due to the increase of the population age, it is expected that its incidence be doubled in coming years. Our Myeloma Functional Unit (MFU) has been working since 2017. The MFU is a multidisciplinary team set up in order to provide better care to these patients. In this unit, the MM specialist nurse is in charge of supporting all aspects of patient care as well as contacting with them to ensure adherence to treatment and to control secon- dary effects. Telephone contact also serves as a clinical support for patients. This study aimed to assess the effect of telephone support on patients with MM and whether the results can be used to identify weak points in education and patient care. Methods: We prospectively collected phone calls made between January and April 2018 for evaluation. Calls were evaluated using a questionnaire which took into account patient’s sex; maker of the call; the enquire motive; date of the call and overall results. Results: The data is gathered from a sample of 169 calls registered. 62% of patients were male and 38% female. Call makers were: 49% from MM specialist nurse, 31% patients, 17% caregivers and 3% others. Some of the calls were to clarify more than one issue. The enquiry motives of calls were: 49% related to secondary effects, 39% related to appointments, 29.5% related to treatment information, 17% general issues. Finally regarding outcomes comes: 80% were resolved by MM specialist nurse and 20% of the calls required a physician help. Conclusions: Most of the calls were resolved by MM specialist nurse. A greater nurse – led communication between the MM specialist nurse and patient and the option of resolving doubts or problems by telephone can reduce the medical visits of patient with MM between treatments and improve their quality of life. Legal entity responsible for the study: Cesca Llopis Puigmarti. Funding: Has not received any funding. Disclosure: All authors have declared no conflicts of interest.
Background: Cancer care is mostly situated in hospitals. Advanced practice nurses (APN) play an increasing role in this care. The role of Belgian general practitioners (GPs) in oncology is unclear. Clarification of the roles taken up by GPs is necessary to understand how communication between those involved in the patients’ care can be improved. The aim of this study is to explore what Flemish GPs see as their role in oncology and what relations and information is needed to provide care for oncology patients.

Methods: A qualitative study based on individual interviews with a convenience sample of 14 Flemish GPs. Techniques of Grounded Theory are used to analyze the data.

Results: The participating GPs describe their role in the first and last phases of the illness trajectory as mostly clear. During the treatment and follow-up phase, their role is more variable because it depends on their perception of responsibility towards the patient.
Background: ICI have shown significant clinical benefit for patients diagnosed with varied types of cancer. With an increasing use of these therapies, it is of urgent interest to achieve a comprehensive understanding of the overall patient experience – thus PROs should be systematically included in clinical ICI trials. We conducted a systematic review of published literature to identify and categorize PRO instruments and examine related utility and measurement issues in studies reporting on ICI.

Methods: Literature was searched using PubMed, Embase, PsycINFO, Medline and CINAHL databases (June 2017). Search terms included controlled vocabulary and specific keywords related to: (1) Food and Drug Administration (FDA) approved ICI; (2) PRO and (3) Oncology. Eight reviewers independently screened titles/abstracts followed by a full text selection based on predefined criteria. We included clinical trials, intervention studies, systematic reviews, study protocols, observational studies, and case reports. Information regarding the clinical trial protocol and PRO tools was collected.

Results: Of the 24 articles included in the review, 13 reported PRO data from primary clinical studies, nine were quality-adjusted life year analyses, and two were study protocols. These articles referred to a total of 14 clinical trials reporting PRO results. Of these, 12 used cancer-specific (11 EORTC-QLQ-C30 and 1 FACT-G) and 1 generic quality of life (QoL) questionnaire (10 EQ-5D and 1 SF-36). Whereas in seven cases only, cancer-specific and generic questionnaires were used, five studies combined them with disease-specific modules, and two included a symptom-specific questionnaire. Furthermore, six studies used PROs to conduct analyses of health economics and work productivity.

Conclusions: Cancer-specific or generic QoL questionnaires are the most widely used PRO measures in clinical ICI trials. As ICI therapies exhibit unique characteristics different from conventional cancer therapies, such broad instruments may not capture the specific ICI-related symptoms, toxicities, and impact on the patient’s QoL. Hence, the adaptation or development of ICI specific PRO tools should be further investigated.

Legal entity responsible for the study: Centre Hospitalier Universitaire Vaudois (CHUV) - University of Lausanne (UNIL) and McMaster University.

Disclosure: All authors have declared no conflicts of interest.

Background: Laryngectomized patients often depend on their caregivers who have a central and difficult role in supporting them dealing with financial, social, and relational issues. In fact, they feel very responsible and committed, especially considering the time devoted to take care of their beloved. Besides, providing care induces caregivers high stress levels, emotional distress, anxiety and the fear of cancer recurrence or progress. Few studies investigated laryngectomized patients caregivers’ life experience during both the whole course of illness and at the end of the treatment. Therefore, the purpose of our study was to explore, through a phenomenological approach, the lived-experience of primary family caregivers of laryngectomized patients undergoing radical surgery.

Methods: Qualitative semi-structured and audiotaped interviews were held with 12 laryngectomized patients’ primary family caregivers. Data were analysed using the descriptive phenomenological approach outlined by Colaizzi.

Results: Three key themes emerged: the caregivers lived experience of illness, the change of caregivers’ daily life and how they support their sick beloved. The experience of caregivers’ lived relations changes from being a family member to a supportive carer, and the illness of their beloved negatively affects their psychological lived experience. Their perception of time and Quality of Life change as their perception of the future becomes uncertain. Finally, they feel guilty mainly because of the limited amount of time they devote to their beloved.

Conclusions: The study findings allowed to understand in depth how the presence of a laryngectomized person in the family may affect the life of the caregiver, even after the treatment phase. This suggests the need for healthcare professionals to support caregivers throughout the whole care journey and especially in dealing with the perception of time during the diagnosis and care phases. Further research should be conducted on factors contributing to time perception alteration and possible interventions to support caregivers to cope with it.

Legal entity responsible for the study: Valentina Bressan.

Disclosure: Has not received any funding.

Methods: A systematic review was performed to compare and discuss nurses’ and cancer patients’ main cancer research priorities according to the PRISMA guidelines (PROSPERO registration: CRD42017059721). Studies retrieved were evaluated with a Mixed Methods Appraisal (MMAT). All medical databases were searched from January 2000 to July 2017. Study inclusion, data extraction, and assessment were performed by two researchers independently (inter-rater agreement, kappa = 0.70; SE = 0.87; p < 0.01).

Results: Among 16 studies identified, 13 included nurses’ research priorities, 2 patients’, and 1 both. They included descriptive cross-sectional (50%), Delphi (44%), and exploratory qualitative studies (6%). Qualitative studies varied from 75% to 100% of the total MMAT score. Nurses’ priorities were as follows: cancer behavioral psychological/social issues and professional dimensions. Patients’ priorities were patient life dimensions and health promotion. Cancer care dimensions and continuum of care emerged as research priorities of both.

Conclusions: The results underline nurses’ and patients’ research priorities to investigate the patients’ advanced care needs and provide a useful template to guide cancer nursing research. Identifying priorities helps focus on particular issues rather than promoting isolated and unrelated studies of patients’ needs. Most of the nurses who participated were affiliated with professional associations and do not reflect the entire nursing population. Moreover, very similar survey questionnaires have been used (the items did not cover all areas) with the possible priorities not considered by participants. More studies are needed for the creation of a cancer research priority agenda.

Legal entity responsible for the study: CRO Aviano National Cancer Institute.

Disclosure: Has not received any funding.

Methods: Most prevalent unmet supportive care needs in Greek ambulatory advanced breast cancer female patients receiving chemotherapy

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Background: This cross-sectional study, supported by the National and Kapodistrian University of Athens, aimed to describe the unmet supportive care needs of ambulatory advanced breast cancer female patients receiving chemotherapy and the association between patients’ characteristics and their unmet needs.

Methods: A convenient sample of 117 ambulatory (response rate 96%) advanced breast cancer (stage III or IV) female patients receiving chemotherapy, from two outpatient units of cancer hospitals in Attica consented to participate between July 2017 to February 2018. Patients were assessed by the translated in Hellenic language Short-Form Supportive Care Needs Survey Questionnaire: a 34 items 5-point (1-5) Likert type scale that covers five domains of need: health system and information (HIS),

Comparison of nurses’ and patients’ research priorities in cancer care: A mixed methods systematic review

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Background: Cancer nurses struggle to meet the challenges in providing quality nursing care in changing environments characterized by advances in drugs and technologies, aging populations, increasing rates of cancer and survival, rising costs, long-term survival patients and increasing economic constraints. Research priorities need to be established within this context because they can encourage the new generation of nurses to respond competently to patients’ advanced care needs.

Methods: A systematic review was performed to compare and discuss nurses’ and cancer patients’ main cancer research priorities according to the PRISMA guidelines (PROSPERO registration: CRD42017059721). Studies retrieved were evaluated with a Mixed Methods Appraisal (MMAT). All medical databases were searched from January 2000 to July 2017. Study inclusion, data extraction, and assessment were performed by two researchers independently (inter-rater agreement, kappa = 0.70; SE = 0.87; p < 0.01).

Results: Among 16 studies identified, 13 included nurses’ research priorities, 2 patients’, and 1 both. They included descriptive cross-sectional (50%), Delphi (44%), and exploratory qualitative studies (6%). Qualitative studies varied from 75% to 100% of the total MMAT score. Nurses’ priorities were as follows: cancer behavioral psychological/social issues and professional dimensions. Patients’ priorities were patient life dimensions and health promotion. Cancer care dimensions and continuum of care emerged as research priorities of both.

Conclusions: The results underline nurses’ and patients’ research priorities to investigate the patients’ advanced care needs and provide a useful template to guide cancer nursing research. Identifying priorities helps focus on particular issues rather than promoting isolated and unrelated studies of patients’ needs. Most of the nurses who participated were affiliated with professional associations and do not reflect the entire nursing population. Moreover, very similar survey questionnaires have been used (the items did not cover all areas) with the possible priorities not considered by participants. More studies are needed for the creation of a cancer research priority agenda.

Legal entity responsible for the study: CRO Aviano National Cancer Institute.

Disclosure: Has not received any funding.

Methods: Most prevalent unmet supportive care needs in Greek ambulatory advanced breast cancer female patients receiving chemotherapy

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Background: This cross-sectional study, supported by the National and Kapodistrian University of Athens, aimed to describe the unmet supportive care needs of ambulatory advanced breast cancer female patients receiving chemotherapy and the association between patients’ characteristics and their unmet needs.

Methods: A convenient sample of 117 ambulatory (response rate 96%) advanced breast cancer (stage III or IV) female patients receiving chemotherapy, from two outpatient units of cancer hospitals in Attica consented to participate between July 2017 to February 2018. Patients were assessed by the translated in Hellenic language Short-Form Supportive Care Needs Survey Questionnaire: a 34 items 5-point (1-5) Likert type scale that covers five domains of need: health system and information (HIS),
The Danish Cancer Nursing Research Network is a new but already effective way to connect and collaborate with international nurse researchers. We have flashed our existence to the international community and we have received interest from PhD students, and are beginning to include PhD students. The network also aims to raise awareness of the importance of nursing research for the benefit of cancer patients and their families. The network aims to develop research to the benefit of cancer patients and their families, and to collaborate across the country.

Results: In October 2016 the Danish Cancer Nursing Research Network was born. At the moment 31 Danish nursing researchers are affiliated to the network, and is growing. The aim of the network is to: - Develop a network for Danish nursing research within the whole trajectory from pre-diagnosis to rehabilitation and palliation. However, the numbers of Danish nursing researchers within the cancer discipline are small and they work somewhat isolated all over Denmark. The researchers would benefit from forming a stronger network and to collaborate across the country.

Methods: The network was established during a snowball effect and from mouth to mouth. Members invited are nurses with a PhD from all over Denmark, researching within different areas of the cancer discipline. The network is organized with a steering committee consisting of three members representing three of the five Danish regions.

Conclusions: The Danish Cancer Nursing Research Network is a new but already effective way to connect and collaborate with international nurse researchers. We have flashed our existence to the international community and we have received interest from PhD students, and are beginning to include PhD students. The network also aims to raise awareness of the importance of nursing research for the benefit of cancer patients and their families. The network aims to develop research to the benefit of cancer patients and their families, and to collaborate across the country.

Legal entity responsible for the study: The Danish Cancer Nursing Research Network.
relevant papers could be retrieved. A total of eight qualitative research papers and one mixed methods paper were selected that met the eligibility criteria. These papers were then critically appraised using CASP’s critical appraisal tool and analysed using thematic analysis.

Results: Nine studies involving 105 carers were included in this review. All studies utilised semi-structured interviews to gather data. The studies were conducted in the United Kingdom (n = 3), Canada (n = 1), Sweden (n = 1), Australia (n = 2), Ireland (n = 1) and America (n = 1). From the thematic analysis four themes emerged from the data set identifying the specific challenges HNC carers faced; challenges due to new roles and responsibilities, information challenges, support challenges and relationship challenges.

Conclusions: This review identified the specific challenges experienced by carers of individuals diagnosed with HNC. The multiple caregiving responsibilities they undertake, impacted both their physical and emotional wellbeing. Furthermore, these challenges were found to be exacerbated by the inadequate provision of information and support facilitated by healthcare professionals. Awareness of these extensive challenges will help to identify ways of supporting carers in adapting to their new roles and responsibilities. Results may also guide development of future interventions and strategies aimed at providing information and psychosocial support for carers.

Legal entity responsible for the study: Charlotte Johnston.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**CN37**

Evaluation of support and information needs for patients with cancer in a phase I trial unit

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Background: Advances in the understanding of the biological basis of cancer have resulted in a paradigm shift in drug development. Phase I trials with translational elements are conducted in clinical trials units for patients with cancer. The objective of this study was to evaluate any unmet needs of support and information for patients on Phase I trials. The aim was to utilise patient experience to assess the need to change or develop delivery of information and support.

Methods: A qualitative approach was used. Patients and relatives of patients with cancer on Phase I trials formed two focus groups. Group 1 consisted of 8 participants and group 2 10 participants, both lasted one hour. A semi-structured schedule was used to prompt discussion, the focus groups were audio-recorded and transcribed verbatim. The data were organised using the Nvivo software package and analysed using Braun and Clarke’s thematic analysis framework.

Results: Four themes emerged from the data 1) face to face support; there was a general consensus that the best way to receive information about treatment and disease was face to face. The relationships with the clinical staff were strong and important to maintain. At times when the trials unit was not accessible patients felt vulnerable 2) remote support; email was felt to be a good way to communicate information regarding appointments, the telephone clinic was useful for contact regarding symptom issues. Digital methods of information and support were potentially useful but needed to be thought through properly 3) getting the right information, at the right time, in the right way; patients felt that they needed extra information particularly in terms of feedback regarding the trials and supporting to support services 4) Relationships with other patients, this theme was about the benefit and value patients had in supporting each other within the treatment areas, however this was conflicted and may require extra support at times as there was a negative impact when fellow patients became unwell or died.

Conclusions: Based on the results from the analysis written patient information was redesigned. A quarterly forum is in development where patients can meet receive well being advice and also feedback regarding the trials they are participating in.

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

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**CN38**

Dignity of Greek patients with advanced cancer: A cross-sectional study

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Background: A core concept in caring patients with advanced cancer is to treat them and preserve dignity independently the service of care. This cross-sectional study’s purpose was to explore the dignity of patients with advanced cancer.

Methods: A convenience sample of 99 (response rate 85%) patients with advanced cancer was recruited between April to December 2017 by a palliative care unit (PCU) (day (PDC) and home care (PHC)) and oncology units (chemotherapy outpatient (OU) and inpatient (IU)) of Athens. Patients with advanced cancer (stage III or IV) who consented, completed the Patient Dignity Inventory (PDI), a 25 items scale, 3 point Likert scale (1 (no problem) -5 (overwhelming problem) divided into: Symptom (SD) and Existential distress (ED), Peace of Mind (PM), Dependency (D), and Social Support (SS). Also Hospital Anxiety and Depression Scale (HADS), Edmonton Symptom Assessment Scale - short version and a demographi/c clinical form were collected.

Results: Most patients were female (54.9%), the mean age was 64.9 years. Breast (22.2%), colorectal (16.2%) and lung cancer (15.2%) were the most frequent diagnoses. Almost half patients (56.6%) were hospitalised (36.4% OU, 20.2% IU) and the others were cared for at the PCU (28.2% PHC, 15.2% PDC). The PDI mean scores were: Total Dignity (TD) 50.2 (25-125), SD 15.3 (6-30), ED 12.7 (6-30), PM 4.7 (3-15), D 5.8 (1-15), SS 4.5 (3-15). Most of the demographic and clinical characteristics were not associated with total or subscales scores of PDI. On the other hand, women (p = .035) and breast cancer patients reported less SS (p = .022). The OU patients reported better TD (p = .029), SD (p = .001), ED (p = .002) and D (p = .003) than OU and PHC but not PDC. Higher scores of TD were significantly correlated with experience of pain, tiredness, lack of appetite, shorten of breath, anxiety and depression (p < .006). Reports of anxiety and depression measured by HADS were correlated with higher total and subscales dignity scores (r = .01 < p < .006).

Conclusions: The findings of this study support a quite good level of perceived dignity in Greek patients with advanced cancer. More research is needed to clarify the differences of dignity among various care settings. We thank Special Account for Research Grants and National and Kapodistrian University of Athens.

Legal entity responsible for the study: Nursing Department, National and Kapodistrian University of Athens.

Funding: Special Account for Research Grants, National and Kapodistrian University of Athens.

Disclosure: All authors have declared no conflicts of interest.

**CN39**

Development and implementation of national guidelines on lifestyle issues and cancer: Report from an ongoing quality improvement project

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Background: Lifestyle habits such as tobacco use, alcohol consumption, insufficient physical activity, sun exposure and unhealthy eating habits are risk factors for cancer but also increase the risk of side-effects and poor outcome from cancer treatments. The Swedish Cancer Nursing Society initiated and developed a multi-professional project where they adapted the current national guidelines for lifestyle habits of preventing disease (by National Board of Health and Welfare), to the cancer context.

Methods: The project includes developing written guidelines for staff and an evidence-based educational program for cancer contact nurses (CNs). The CNs has a unique position to inform and support patients and their families on lifestyles changes. The education program (one full day training and one half day follow-up) started in May 2018 and includes lectures and case discussions that cover all cancer related lifestyle issues. It also includes systematic assessment and models for change. All Swedish CNs (approx. 1000) will be invited to participate.

Results: A first evaluation of the program will be presented during EONS11 at ESMO 2018. Data will be collected via surveys and interviews with CNs and also from cancer care provider data sources (on what lifestyle interventions that have been delivered to patients).

Conclusions: The project will be on the way to implement evidence-based knowledge about lifestyle habits to CN.

Legal entity responsible for the study: Swedish Nurses Oncological Associations.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**CN40**

Developing a patient reported experience measure (PREM) in secondary breast cancer (SBC)

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Background: Metastatic breast cancer (SBC) is now seen as a chronic disease, however the number of patients currently living with SBC is unknown. Despite widespread recognition of the importance of understanding and evaluating patients’ experiences, little research has been undertaken within SBC. Generally, there has been significant expansion in the development and application of patient reported questionnaires that measure care experiences (PREM), which is a major indicator of healthcare quality, however there is no specific PREM for people with SBC.

Methods: This study aims to develop and pilot test a unidimensional PREM in SBC for clinical application using a mixed methods sequential exploratory design. Semi-structured interviews were conducted with 25 people with SBC to explore their experiences,
priorities and needs diagnosis of metastatic disease and during palliative treatment. Cognitive interviews were undertaken with patients to ensure all items listed were clear and easily understood.

Results: Following cognitive interviews a draft PREM questionnaire was created for patients with SBC. The structured questionnaire contains 48 items (statements) based on patients’ experiences, treatment / care, priorities and needs. A five point scale is used to rate each item from strongly agree to strongly disagree. Patients report the PREM is easy to complete, taking less than 5 minutes. Further pilot testing is currently being undertaken (n = 130) to assess the validity, reliability and repeatability of PREM-SBC, drawing comparisons with other quality of life measures.

Conclusions: There is currently a lack of research focusing on patients with SBC. A draft PREM-SBC questionnaire was developed and pilot tested for clinical use. This will increase understanding of patients’ experiences, needs and priorities to enhance patient care.

Legal entity responsible for the study: The Christie NHS Trust.
Funding: Roche.
Disclosure: All authors have declared no conflicts of interest.
Background: The situation of patients with cancer around the world means, in terms of access to diagnostic tools, adequate surgical interventions, medical treatments and optimal radiotherapy, as well as the educational tools for professionals, presents a great disparity in terms of access throughout the globe, but especially in Sub-Saharan countries. Once again, putting into evidence this situation is necessary in order to raise awareness among the participants involved in this situation: patient, professionals, Scientific Societies, but especially governments and international organizations. Health services, sanitary equipment and medical access in developing countries are unequal: from rural areas to cities, the ratios of population, patients and professionals are far from the recommendations of the WHO. The aim of this project is to determine the dimension of educational and non-educational needs, such as: diagnostic methods and treatments, based on the difficulties presented while having access to the different resources.

Methods: A qualitative approach was performed as first step. Objectives are to determine needs about diagnosis equipment, treatments, and level of expertise within the personnel: including physicians, nurses, physiotherapist, technicians, and community health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries). Quantitative analyses will start taking place during summer campaigns by African and European health workers (this is a common figure in these countries).

Results: Access to medicines is expensive, even for the most basic treatments; when a patient begins a chemotherapy treatment, usually completes the first or second cycles of treatment. Only people who have access (economically) to a regular health system can afford a complete line of chemotherapy. About cancer diagnosis, in many countries there are basic X-ray services, including CT scan, but no PET or MRI.

Conclusions: If we think in oncology services, there is a big gap from developed societies in terms of education resources. If we think in patients with cancer in some countries in Africa, we can sadly affirm that most of them are patients in palliative care, and instead of receiving the most qualified and supportive care, their options about pain control or other treatments are very few.

Legal entity responsible for the study: Julio Cesar de la Torre Montero.

Funding: Comillas Pontifical University, San Juan de Dios School of Nursing and Physical Therapy - SEGO Sociedad Española de Enfermería Oncológica. ONLJD Asociación AMAP.

Disclosure: All authors have declared no conflicts of interest.
Patients’ learning and participation in their breast cancer care

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Background: Patients’ participation in treatment and care is considered to increase their safety and well-being. There is a lack of knowledge about what participation means for the patients and how it can be supported in breast cancer care. A prerequisite for patients’ participation is their knowledge. Changing perspective, from patients’ information needs to their learning, can increase our understanding about how participation can be facilitated. The purpose of this study was to explore patients’ experiences of learning, understanding and participation in their breast cancer care.

Methods: Sixteen patients with breast cancer were interviewed. The interviews were analyzed according to abductive content analysis taking the perspective from learning theories.

Results: The first part of the study explored patients’ learning. The patients are forced to interact with a vast amount of information. Bodily sensations and experiences from being part of events are important sources. The information is interpreted to an understanding which is concealed or expressed which affect patient participation. The struggle to understand and manage the new life situation is an ongoing process for a long time. The preunderstanding and driving forces of the patients, time for contemplation and dialogue with staff, were essential features in this struggle. The second part explores patient participation. The concept of patient participation was defined differently by different patients and there was uncertainty about its meaning. The patients’ understanding of their disease, treatment and care affected their participation. A prerequisite for participation was the respectful treatment from health care staff contributing to a feeling of being “seen” as a human being. The patients’ wishes varied as did their needs to participate in treatment decisions. Participation also meant a continuous struggle to manage self-care during a long period of time and access to health care is needed to support patients.

Conclusions: New kinds of training programs for staff and patients are suggested, focusing on patients’ learning and the new roles of partnership.

Legal entity responsible for the study: Karolinska Institutet, Department of Learning, Informatics, Management and Ethics.

Funding: Karolinska Institutet in collaboration with the Regional Cancer Centre Stockholm–Gotland, Stockholm County Council.

Disclosure: All authors have declared no conflicts of interest.

Incidence and risk factors of phlebitis in patients with peripheral parenteral nutrition administration

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Background: Peripheral parenteral nutrition is one of the easiest ways to provide nutrition for patients who have difficulty with enteral nutrition. But, on the other hand it is associated with major complications, such as phlebitis. The purpose of this study was to investigate incidence of phlebitis and its risk factors in patients with peripheral parenteral nutrition administration.

Methods: Prospective observational study was performed with 289 hospitalized adult patients with gastrointestinal diseases. The researchers evaluated peripheral venous catheter that administered peripheral parenteral nutrition until their removal and investigated the incidence of phlebitis using phlebitis scale of Infusion Nurses Society (2016). Logistic regression model was used to identify risk factors involved with occurrence of phlebitis. The statistical significance limits were set at p < 0.05.

Results: The incidence of phlebitis was 37.0% (107 cases). Among them, Grade I was 24.6% (71 cases), Grade II was 12.4% (36 cases) and Grade III and IV did not occur. Platelet count (OR 2.13, CI 1.07-4.26, p = 0.032), nutrition infusion rate (OR 0.36, CI 0.16-0.79, p = 0.012) and infusion period (OR 1.02, CI 1.00-1.03, p = 0.033) had statistically significant with phlebitis occurrence.

Conclusions: Using peripheral parenteral nutrition must be carefully considered for patients with risk factors of phlebitis. In using peripheral parenteral nutrition, adjusting infusion rate deserves to be considered with care. Moreover, in case of extension of peripheral parenteral nutrition therapy, medical team must regards using another way such as middle line or central line for nutrition therapy in a serious light.

Legal entity responsible for the study: Asan Medical Center.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

Specialized nursing interventions in optimizing patient communication undergoing total laryngectomy

A.A. Frade, S.S.A. Miguel


Background: Permanent and immediate laryngeal voice loss, resulting from total laryngectomy can be psychologically devastating to the patient and family, generating feelings of stress, fear, and frustration (Brummer et al, 2016). In the immediate postoperative period, writing and lip reading are the commonly methods of communication used by patients. However, this surgery is often accompanied by neck dissection, resulting in neck swelling, which difficult the movement of the lips and limits mobility required for readable writing (Matos et al, 2009). In conclusion, these approaches may not be effective, leaving patients frustrated and unable to express their care needs (Brummer et al, 2017). This, communication between patients and health professionals becomes difficult, generates anxiety and anguish in the person and family and has implication in the process care. Specialized care is therefore required for this type of patients, especially those provided by nursing, highlighting the use of augmentative and/or alternative communication strategies (AAC).

Methods: A critical reflection based on the results of a previous review, were performed to identify which AAC strategies promoting effective communication in the laryngectomized patient.

Results: Strategies identified as promoting effective communication include the use of low-tech and high-tech devices.

Conclusions: The use of AAC strategies improves the quality of care provided and allows a better understanding of the needs of the laryngectomized patient, which consequently will give them greater autonomy, control over their life and facilitating their adaptation. Beyond these implications for nursing, effective communication is a right of the individual and an essential component of the quality of care and patient safety.

Legal entity responsible for the study: Ana Frade, Susana Miguel.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.
the CRF will be carefully managed to ensure the infrastructure and processes are fit for purpose. The Christie is the lead organisation in a new consortium, iMATCH (Innovate Manchester Advanced Therapy Centre Hub) which has been awarded substantial funding from the Innovate UK to scale up delivery of ATMPs and form a national network of Advanced Therapy Centres.

**Conclusions:** CD19 specific CAR therapy is poised to become a new standard care for selected B cell malignancies. Trials of ATMPs for a range of malignancies are growing exponentially, therefore safe delivery outside of an experienced area such as HSCT is important but challenging. Creative approaches to patient care, wide collaboration and executive level support are key. While iMATCH sets the challenge to increase the number of ATMPs available it has also facilitated city wide links and a national network to find solutions to complex problems.

**Legal entity responsible for the study:** The Christie NHS Trust.

**Funding:** Has not received any funding.

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**CN48** Peripherally inserted central venous catheters did not increase the risk of deep venous thrombosis in advanced colorectal cancer and lung cancer patients with bevacizumab

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**Background:** Deep Venous thrombosis (DVT) is one of the serious adverse events associated with bevacizumab, which is also one of the most notable complications associated with peripherally inserted central catheters (PICCs). However, there was no report about their correlation directly. The purpose of this study was to explore whether the use of PICCs increases the risk of DVT in advanced colorectal cancer and lung cancer patients with bevacizumab.

**Methods:** From June 2011 to April 2017, patients with documented advanced colorectal cancer and lung cancer who received bevacizumab were selected from West China hospital and local hospitals. The patients inserted with central venous catheters (CVCs) or ever had thrombosis were excluded. According to whether use PICCs or not, patients were divided into two groups. The incidence of DVT during the use of bevacizumab among two groups was compared. Many risk factors were also analyzed.

**Results:** A total of 217 patients received bevacizumab were included in this analysis. 186 patients were colorectal cancer, 31 were lung cancer. Among them, 137 patients were inserted with PICCs and 80 patients were not. 5.1% (11/217) patients had DVT during the use of bevacizumab. A case had spontaneous internal thrombosis, 1 had subclavian vein thrombosis and others were lower extremity vein thrombosis. Single factor analysis revealed that patients inserted with PICCs were more likely to have DVT than others (6.6% vs. 2.5%, P = 0.318), but it had no statistical difference. The incidence of DVT was higher in patients with diabetes mellitus (DM) than non-DM (21.1% vs. 3.5%, P < 0.05). Logistic analysis revealed that the use of PICCs had no statistical significance for the occurrence of the DVT. However, diabetes was a risk factor for DVT in advanced colorectal cancer and lung cancer patients with bevacizumab.

**Conclusions:** Peripherally inserted central venous catheters did not increase the risk of DVT in advanced colorectal cancer and lung cancer patients with bevacizumab. The patients with diabetes mellitus may be prone to develop DVT, whom we should manage more carefully during the use of bevacizumab.

**Legal entity responsible for the study:** Meng Qiu.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**CN49** Cancer nurse perspective on the emerging field of biosimilars in cancer care

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**Background:** Biological medicines has transformed cancer care drastically. As biosimilars are incorporated into cancer treatment, cancer nurses play a key role in education, administration, pharmacovigilance and managing side effects of biological medicines. Expanding patents of innovator biologics creating opportunities to develop biosimilars and the number in oncology will continue to increase. The use of biosimilars will bring new challenges for cancer nurses related to education, treatment and follow-up of cancer patients.

**Methods:** A search of PubMed, Sciedirect and regulatory agency websites was conducted for references related to the use of biosimilars and cancer nursing.

**Results:** To ensure optimal and safe use of biosimilars, all stakeholders incl. physicians, cancer nurses, pharmacists and patients need to understand the complexities of biosimilars and take decisions that will improve patients’ treatment, safety and quality of life outcomes. As biosimilars are introduced into clinical practice, education of cancer nurses is paramount to ensure the best outcomes for patients safety. Training of nurses on new products, incl. biosimilars is often ad hoc and incomplete. As a result, cancer nurses may be unaware of the complexities and consequences of using biologics, incl. biosimilars. The knowledge gap in biosimilar medicines and switching or substitution of these medications could result in incorrect patient information, non-optimal use and adverse events which can lead to a delay in access and a decreased therapeutic gain for the patient.

**Conclusions:** Cancer nurses have an important role in the multidisciplinary approach to education of patients on biosimilars, incl. biosimilars. They have a lead role in education and counselling during introducing and follow-up of the transition between innovator and biosimilar medicines and vice versa, to improve patient outcomes and drug safety. Additional studies on biosimilars are needed to identify common knowledge gaps and educational needs of cancer nurses across Europe. Education about biosimilars is critical for successful incorporation in to oncology practice. A deeper understanding is needed across all cancer related professions with a strong emphasis on collaboration with all stakeholders including patients.

**Legal entity responsible for the study:** Johan De Munter.

**Funding:** Has not received any funding.

**Disclosure:** All authors have declared no conflicts of interest.

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**CN50** Overview of an acute oncology service in a UK cancer centre

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**Background:** In the UK there has been increasing emphasis on the ability to review oncology patients who are admitted as an emergency. Two reports, NCEPOD report (2008) and the NPSA report (2008) identified shortcomings in the manner in which patients presented and were treated. National guidance following systemic anti-cancer treatments (SACT) were cared for. This had led to increased mortality, morbidity and extended lengths of stay. In addition to the above patients presenting as an emergency with Metastatic Spinal cord compression were found to have delays in urgent treatment and patients who had a cancer diagnosis following an emergency admission had poorer outcomes than those identified in a more controlled fashion. At the Royal Berkshire NHS Foundation trust we responded to NHS England guidance by establishing an oncologist-led acute oncology service with nursing support. We have been successful in reducing length of stay for oncology
Background: Care for patients with cancer is complex and the number of cancer survivors is increasing. This involves frequent monitoring and adequate medical and psychological support. The need for health-related information among cancer patients is increasing. This involves frequent monitoring and adequate medical and psychological support. The need for health-related information among cancer patients is increasing.

Methods: An online oncology portal was developed on the basis of literature, best practices and in co-design with patients, health care providers and IT developers. Co-design guarantees that the portal is tailored to the needs of the cancer patients. In this innovative project, a qualitative and quantitative evaluation of the portal was performed with patients (n = 45) and care providers (n = 10).

Results: On the platform, the cancer patient can consult his individual treatment plan. In each phase of the care pathway, online information, questionnaires, and symptom diaries are attached. The platform provides a secure chat with the care providers (scheduling messages, video call), an overview of appointments, and finally the patient can access his test results. Patients were positive about the possibility of consulting test results and reporting their side effects. Patients felt safely “monitored” at home and experienced a greater sense of control over their care.

Conclusion: This eHealth project is dynamic and continuously optimized. This friendly and complete platform is connected to the acute oncology service. We hope that this will be relevant to others wishing to do the same across Europe.

Disclosure: The author has declared no conflicts of interest.
CANCER NURSING: SYMPTOM MANAGEMENT

CN53 Rectal cancer survivorship: The struggle of the low anterior resection syndrome (LARS)

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CN54 Nurse-led approaches to self-management of symptoms in routine Swiss outpatient care: A qualitative exploration

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CN55 Evaluation of a nursing aftercare intervention for patients with head and neck cancer treated with chemoradiation

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Background: Skin reactions during radiotherapy (RT) are common in women with breast cancer (BC). Different methods have been tested to reduce or prevent this toxicity. The aim of this study was to explore if genetic variation can be linked to acute radiation skin reactions (ARSR).

Methods: One hundred and nineteen women undergoing RT for BC during the period of 2011 to 2013 were included. Symptoms such as itching, burning and irritation were self-reported twice (during the first and last week of RT) using the VAS-scale. Assessments of the irradiated skin were measured using the Radiation Therapy Oncology Group scoring system for acute RT (RT-TOG-scale). Blood-based SNP analysis were performed using peripheral blood sample (obtained before start of RT). In total, 29 SNPs of well-defined functional genes were investigated.

Results: All women were assessed with ARSR in various degree according to the RT-TOG-scale. During the last week of RT, the women self-reported itching (n = 97, 82 %), burning (n = 64, 54 %) and irritation (n = 96, 81 %). Three SNPs in the following genes were found to be associated with ARSR: XRCC2, IFNg and CCL5/Rantes.

Conclusions: We found an association between three SNPs and ARSR. The possibility of using these SNPs as prognostic biomarkers for radiation-induced toxicity needs further investigation.

Disclosure: All authors have declared no conflicts of interest.

CNS55

Effect of aromatherapy massage on chemotherapy-induced peripheral neuropathic pain and fatigue in patients receiving oxaliplatin

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Background: Patients receiving oxaliplatin may experience peripheral neuropathic pain and fatigue. Aromatherapy massage, a nonpharmacological method, may help to control these symptoms.

Methods: The aim of this open-label, parallel-group, quasi-randomized controlled pilot study was to investigate the effect of aromatherapy massage on chemotherapy-induced peripheral neuropathic pain and fatigue in patients receiving oxaliplatin. Stratified randomization was used to allocate 46 patients to 2 groups: intervention (n = 22) and control (n = 24). Between week 1 and week 6, participants in the intervention group (IG) received aromatherapy massage 3 times a week. There was no intervention in weeks 7 and 8. The control group (CG) received routine care. Neuropathic pain was identified using the Douleur Neuropathique 4 Questions; severity was assessed with the numerical rating scale; fatigue severity was identified with the Piper Fatigue Scale.

Results: At week 6, the rate of neuropathic pain was significantly lower in the IG, when compared with the CG. The severity of painful paresthesia was assessed with the numerical rating scale in the IG was significantly lower than that in the CG at weeks 2, 4, and 6. At week 8, fatigue severity in the IG was significantly lower when compared with CG (P < .05).

Conclusions: Aromatherapy massage may be useful in the management of chemotherapy-induced peripheral neuropathic pain and fatigue. This pilot study suggests that aromatherapy massage may be useful to relieve neuropathic pain and fatigue. However, there is a need for further clinical trials to validate the results of this study.

Legal entity responsible for the study: Hacettepe University.

Funding: Hacettepe University Scientific Research Projects Coordination Unit.

Disclosure: All authors have declared no conflicts of interest.

CNS56

When symptom complexity is the norm: A mediation analysis between pain, anxiety, depression and fatigue

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Background: Symptom complexity is a concept that implies coexisting symptoms and their interaction. This study aimed to investigate the role of anxiety and depression in the mediation of pain and fatigue on other symptoms using structural equation modeling.

Methods: This study used cross-sectional data from 819 patients with cancer. Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale. Pain was measured using the Brief Pain Inventory. Fatigue was evaluated with the Multidimensional Fatigue Inventory. The role of anxiety and depression in the mediation of pain and fatigue on other symptoms was investigated using path analysis in structural equation modeling.

Results: The study found that pain and fatigue were positively correlated with anxiety and depression. Anxiety and depression mediated the relationship between pain and fatigue and other symptoms, such as sleep disturbance and sexual dysfunction.

Conclusions: The findings of this study suggest that anxiety and depression play a significant role in symptom complexes, highlighting the need for integrated symptom management strategies.

Legal entity responsible for the study: National Institute of Health and Care Excellence.

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Disclosure: All authors have declared no conflicts of interest.

CNS58

Cancer pain knowledge and attitudes of nursing and medical professionals in a Greek general hospital

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Background: Health care professionals’ knowledge and attitudes are strongly related with sufficient cancer pain management. The study explored nursing and medical professionals’ cancer pain management knowledge and attitudes.

Methods: A cross-sectional survey was conducted. The convenience sample consisted of nursing and medical professionals (interventional medicine sector) of a public general hospital, Athens. Sample’s inclusion criteria: informed consent and > 5 months’ work experience. Between September – December 2016, 98 physicians (P), 70 registered nurses (RN) and 36 nurse assistants (NA) with response rates 88.4%, 77.8%, 90% respectively, completed the Greek version of the Nurses’ Knowledge and Attitudes Survey Regarding Pain: a 39 items tool divided into 22 true/false, 13 multiply choices and 4 pain case studies items, as well as a demographic form.

Results: Most of the participants were women (76.5%), reporting caring for more than 100 patients in cancer pain per year (40.7%). The sample’s mean age was 39.5 years and work experience 12.8 years. The prevalence of the five most frequent wrong responses (over 88.2%) was related with assessment and pain management interventions, addiction, patient pain self-report, and route of medication’s administration. Opioids titration, patients’ religious and cultural related pain behaviors, older patients and pain tolerance were the five most frequent correct answers (over 80.4%). Responded more correct answers (mean 20.8) than RN (17.5) and NA (15.8) (p < 0.0001). Age, education and clinical experience in cancer care explained 28% variance of correct answers. Younger participants, working at oncology wards, holders of a doctoral and attending continuing cancer pain education (strongest independent factor (R²Change = 0.07)), were related with more correct answers.

Conclusions: Greek participants knowledge deficits in pain management support the universal concern of inadequate knowledge and attitudes of health care professionals, however, encouraging theoretical and clinical training may enhance their ability to improve practice. We thank Special Account for Research Grants and National and Kapodistrian University of Athens for funding to attend the meeting.

Legal entity responsible for the study: Nursing Department, National and Kapodistrian University of Athens.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

CNS59

Aromatherapy massage on chemotherapy-induced peripheral neuropathic pain and fatigue in patients receiving oxaliplatin

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Background: Patients receiving oxaliplatin may experience peripheral neuropathic pain and fatigue. Aromatherapy massage, a nonpharmacological method, may help to control these symptoms.

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Conclusions: Aromatherapy massage may be useful in the management of chemotherapy-induced peripheral neuropathic pain and fatigue. This pilot study suggests that aromatherapy massage may be useful to relieve neuropathic pain and fatigue. However, there is a need for further clinical trials to validate the results of this study.

Legal entity responsible for the study: Hacettepe University.

Funding: Hacettepe University Scientific Research Projects Coordination Unit.

Disclosure: All authors have declared no conflicts of interest.
Background: Taste disorders are one of the most common side effects of treatment in oncology patients and often occur after allogeneic hematopoietic cell transplantation (allo-HCT). Dysgeusia is rarely a life-threatening complication, therefore, in many cases it does not receive close medical attention. Furthermore, information about this disorder is largely based on the clinician’s own experience. However, taste disorders, can impact on the quality of life in survivors of allo-HCT, and compromise their enjoyment of eating, food intake, weight and nutritional status. The number of performed annual transplantations continues to grow annually and the number of older long-term survivors increases. There is little literature that is focused on studies of survivors of allo-HCT with taste disorders. We conducted a qualitative descriptive study to explore experiences of dysgeusia in patients that have undergone of allo-HCT and examined what strategies they used to mitigate it.

Methods: Using purposive sampling, survivors of allo-HCT were recruited. Audiotape interviews were conducted until data saturation was achieved. Each interview was transcribed verbatim, and content analyses were performed to extract significant themes and subthemes.

Results: Three major themes embracing various aspects of allo-HCT survivors’ experiences were identified: 1) the shape of taste; 2) everything is irritating and it is dreadful to eat; 3) finding new strategies to overcome the problems. Together, they highlight the experiences of survivors showing how taste disorders can affect the physical, psychological and social dimensions of a person for the rest of their life.

Conclusion: A cumulative burden is the result of dysgeusia and its clinical course reinforced also by related symptoms. Healthcare professionals must focus their attention on the management of these symptoms and offer interventions to safeguard the patient’s social, physical and psychological well-being. Finally, further research is needed to explore the experiences of allo-HCT patients who have taste disorders throughout their cancer journey that introduces a more holistic approach which involves health professionals, caregivers and family members.

Legal entity responsible for the study: Valentina Bressan.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

“May not affect you”: Lived experiences and support needs of women who developed peripheral neuropathy following chemotherapy treatment for cancer

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Background: Some cancer drugs cause chemotherapy-induced peripheral neuropathy (CIPN) or damage to the nerves. CIPN affects the hands and feet, with patients reporting symptoms such as numbness, tingling, pain and muscle weakness. The nature of symptoms depends on the chemotherapy agents and drug dose that patients receive. Options to minimise the severity of symptoms may involve dose reduction, delay or discontinuation of chemotherapy. This study explored lived experiences of women who developed peripheral neuropathy following cancer chemotherapy treatment.

Methods: The study was conducted in the United Kingdom and was advertised through cancer charity websites and social media accounts. Using set eligibility criteria, purposive sampling was used to capture data. Women diagnosed with breast or ovarian cancer who experienced or are still experiencing neuropathy following chemotherapy treatment were recruited. Semi-structured recorded telephone interviews were conducted (n = 15). Interpretative phenomenological analysis (IPA) was used to analyse data.

Results: The analysis resulted to four main themes: struggle to process CIPN information, and information and trust when making treatment decisions, experience of symptom reporting and challenges of mitigating CIPN symptoms. Similar to previous studies, participants used analogies to describe CIPN symptoms such as ‘like walking on pebbles, sand, needles or gravel’. Findings suggest that interventions to improve understanding of CIPN symptoms by patients and clinicians are needed in practice. A broader insight of patients’ experiences of CIPN helps progress development of interventions to enhance communication, assessment and management of CIPN symptoms.

Legal entity responsible for the study: King’s College London.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

App about chemotherapy: Helping the patient with cancer

B.T. Espersen
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Background: Patients with cancer are bombarded with information – both in connection with examinations, diagnosis and treatment. Patients cannot always cope with the huge quantity of oral and written information from the hospital. Even highly educated patients voice their inability to take in the amount of given information. Reading skills and the ability to understand are often not taken into account. Furthermore 15-20% of the normal population is known to be weak readers. The use of mobile technology in health care has shown a fortified self-care and improved quality of life. Therefore, we aimed at developing an app which could serve several purposes: Opportunity to use different sources of information, information at the right time and the right place, information “on the go”, the text read out loud (or earphones) and information to relatives and friends – no matter where they live.

Methods: The text from our written information was adjusted to the electronic media. The new text has been commented by patients, relatives and health care personnel. Finally, the text can be read out loud with a tap on the loudspeaker icon. There are 2 apps, which can be downloaded for free (Google play and App Store). App 1 is a general guide with focus on the most asked questions in relation to cancer, chemotherapy and targeted treatment – e.g. Does the treatment influence other people? How can my disease affect my relatives? What will I tell my children? Can I go on holiday? What about work? Can I drink alcohol? Can I be physically active? What about alternative treatment? App 2 describes 16 possible side effects separately and guides the patients and relatives in relation to preventing and minimizing the discomfort.

Results: See conclusion.

Conclusions: Some patients prefer the apps to the traditional written information. They download to both mobile phone and tablet. They find it very manageable and easy to navigate, and the text short and straightforward. The apps are an extra source of information for some patients, and they recommend the apps to family, friends and other patients. If patients find the oral and written information satisfying, they do not use the apps. The technology can be a barrier especially with older patients.

Legal entity responsible for the study: Department of Oncology, Aarhus University Hospital, Denmark.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.

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Legal entity responsible for the study: Department of Oncology, Aarhus University Hospital, Denmark.

Funding: Has not received any funding.

Disclosure: The author has declared no conflicts of interest.
Conclusions: The CINV app addresses main concerns for patients receiving chemotherapy, clinical situation and individual emetic risk of patient or complexity of the prescribed antinecet regimen and impact of CINV in their daily life. Soliciting feedback from oncology nurses, we ensured that the app was acceptable and beneficial for patients and clinicians. Some points to improve the app in future: Reporting of symptoms after CT enhances CINV management, self-care, and participation without being a burden to patients, indicating that app can be used in clinical practice by patients.

Legal entity responsible for the study: Yolanda Escobar.

Funding: Vifor Pharma.

Disclosure: All authors have declared no conflicts of interest.

**CN64** Perceived symptoms of Greek cancer patients during chemotherapy using the memorial symptom assessment scale

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Background: Cancer patients experience a variety of concurrent symptoms during their chemotherapy. These symptoms can be physical or psychological and may vary in terms of occurrence, severity and distress. The aim of the present study was to assess the existence of symptoms during chemotherapy.

Methods: This was a non-experimental and descriptive study. It was conducted in a large hospital in a major Northern Greek city. The subjects were 200 cancer patients undergoing chemotherapy in cycle 2 and cycle 3. Data was collected using the Memorial Symptom Assessment Scale (MSAS) and questionnaire with demographic and clinical characteristics.

Results: The majority of patients was male (61%) with mean age 58.9 (S.D. 9). 79.5% was married 47.5% had completed compulsory education. Moreover, 48% suffered from lung cancer, 42% colorectal cancer, 7.5% pancreatic cancer and 2.5% stomach cancer. In the 2nd cycle of chemotherapy the mean of Global Distress Index (GDI) was 2.20, Physical Symptom Subscale (MSAS PHYS) was 2.38, Psychological Symptom Subscale (MSAS-PSYCH) was 2.26 and Total MSAS score (TMSAS) was 2.26. Also, in the 3rd cycle of chemotherapy the mean of GDI was 2.20, MSAS PHYS was 2.43, MSAS-PSYCH was 2.17 and TMSAS was 2.27. The following symptoms presented the 3rd cycle of chemotherapy the mean of GDI was 2.20, MSAS PHYS was 2.43, Subscale (MSAS-PSYCH) was 2.26 and Total MSAS score (TMSAS) was 2.26.

Conclusions: The results of this study demonstrate that cancer patients undergoing chemotherapy experience various symptoms. Therefore, nurses should take into account these findings and plan appropriate, suitable care plans and interventions in order to alleviate them and improve patients’ quality of life. All authors have declared no conflicts of interest.

Legal entity responsible for the study: Alexander Technological Educational Institute - Research Laboratory "Care in Adult Cancer Patients"

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**CN65** How to monitor outpatients undergoing active anticancer treatment? A feasibility study of the web-based tool "Onco’nect"

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Background: Monitoring adverse effects (AEs) induced by antimtumor therapies remain a clinical challenge for outpatients with cancer. Their delayed management might impair patient quality of life and lead to dose-lowering or discontinuation of treatment. The use of e-health may improve the communication between caregivers and patients, as well as the continuity of care. We assessed if Onco’nect®, a new digital follow-up tool, could be used easily by cancer outpatients undergoing active antitumor treatment in a routine clinical practice setting.

Methods: Outpatients diagnosed with any type of cancer and undergoing intravenous or oral anticancer in the department of Medical Oncology of Creteil Teaching Hospital were eligible. No informatics knowledge was required for patients to be included in the study. At different times of each chemotherapy cycle, patients were sent a standardized 12-question survey assessing AEs. A chat was available for patients and caregivers to improve their communication. Grade ≥ 2 AEs, and deliberate requests of patients raised an alert system. Caregivers were notified of such events by emails and “red alerts” on the web-based interface.

Results: Our study enrolled 51 patients, with distinct types of anticancer treatment (chemotherapy, oral therapy, immunotherapy and clinical trial therapy): 5 (9.8%) patients were over 75-year-old. Four patients could not use a computer or a smartphone but had a relative able to help. We called 21 (41.1%) patients at least once because they reported ≥ grade 2 AEs. We modified symptomatologies, or diet and lifestyle in 11 (21.6%) cases. Four patients deliberately raised the alert system, resulting in one hospitalization. The chat was used to: manage daily AEs, answer patients’ questions, send prescriptions, receive medical imaging and blood test results.

Conclusions: Onco’nect® is a user-friendly web-based tool to monitor outpatients undergoing anticancer treatment. It can be integrated in a current practice in oncology, even with elderly patients. Onco’nect® might help to anticipate chemotherapy prescriptions and reduce the admission in emergency rooms.

Legal entity responsible for the study: Service d’Oncologie Médicale, Hôpital Henri Mondor, AP-HP, Créteil.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.

**CN66** Medical makeup in cancer patients and its impact in their quality of life

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Background: Cancer treatment cause many toxicities included skin toxicities. Although skin toxicity often resolve upon therapy discontinuation these side effect can negatively affect self esteem, treatment compliance and quality of life.

Methods: A literature review was conducted using the electronic databases PubMed and Google scholar, with respect to the period from 2008 to 2018. The following key words were entered: “medical makeup”, “cancer”, “anticancer treatment” and a combination thereof. The exclusion criteria for the articles were languages other than English.

Results: Medical makeup was tested under dermatological control on damaged skin. It was water- and sweat-resistant, perfume-free, preservative-free, superior coverage (40-30% pigments) and has natural results. In a multicenter study (9 centers) were studied 90 patients presenting with visible cutaneous side effects from chemotherapy: altered complexion, total or partial eyebrow alopecia, irregularity of lip contour, dry lips. The corrective medical makeup improved the quality of life in 81.2% of patients and helped 76.8% of patients to brave the stigmas of others. Also, health professionals should inform women cancer patients about medical makeup-up, its benefits and give some instructions for applying make-up.

Conclusions: Medical makeup has many benefits in enhancing patients’ self-esteem. Health professionals must find ways to implement it in cancer patients who have skin toxicity. Also, in Greece there is a great need for further research for this issue, on a large population with precise characteristics in order to arrive at safe results about medical makeup.

Legal entity responsible for the study: Alexander Technological Educational Institute - Research Laboratory "Care in Adults Patients with Cancer".

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