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CNS TUMOURS
P. Y. Wen (Boston, United States of America) P. French (Rotterdam, Netherlands)

337P - Molecular subtypes of gliomas defined by gene expression profiling
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Background
Gliomas are the most common primary brain tumors in adults. The heterogeneity of tumors, the lack of reliable criteria for identifying different subtypes make their histopathological diagnosis and their management complex. The molecular classification is one of the most promising approaches to better characterize gliomas. The aim of this study was to characterize molecular markers from the differential transcriptomic analysis of high and low-grade gliomas.

Methods
Tumor samples were obtained from 81 patients diagnosed with gliomas between 1998 and 2013 at Limoges and Montpellier University Hospitals. Transcripts from brain tumor frozen samples were analyzed by Taqman Low Density Array. Cluster and principal component analyses were performed on a list of 96 selected genes belonging to glioma markers, genes coding for neurotrophins and their receptors or involved in different mechanisms such as glycosylation, autophagy, RTK signaling pathways, hypoxia and angiogenesis. Protein expressions from selected genes were achieved by immunohistochemical staining on Tissue MicroArray.

Results
Firstly, variations in gene expression were noted between the primary tumor and its recurrence and between biopsy and resected surgical specimen for a same patient. To have homogeneous series, only 64 primary brain tumors obtained from resected surgical specimens and free from radiotherapy and/or chemotherapy were presented in this work. Brain tumors were diagnosed as grade II oligo-astrocytoma (n = 9), grade III oligo-astrocytoma (n = 10), grade III astrocytoma (n = 8), glioblastoma (n = 17), grade II oligodendroglioma (n = 9) and grade III oligodendroglioma (n = 11). Using the hierarchical cluster method, we identified gene expression patterns specific of low or high grades and a set of genes of interest appeared significantly overexpressed or under-expressed according to tumor grade (p < 0.05). Some of them were correlated to prognosis (p < 0.05). Immunohistochemistry analysis confirmed the changes of protein expression between low and high grades.

Conclusions
Our results showed that high and low-grade gliomas differ in their gene expression profiles and several genes might act as new biomarkers for differential diagnosis and prognosis in gliomas.
Background
Glioblastoma is a rapidly lethal cancer with a stringent need for new treatment strategies. In this study, we tested if chitosan-capped gold nanoparticles (Chit-GNPs) may overcome the limitations of drug concentrations by an increased cell internalisation in glioblastoma stem-like cells (GSCs) and if such GNPs could enhance the response to irradiation.

Methods
GSCs lines were isolated from glioblastoma tumor fragments and characterised with stemness and neural markers. Chitosan biopolymer was used as reducing and stabilizing agent to generate Chit-GNPs through an environmentally friendly synthesis procedure. The fabricated Chit-GNPs were characterized by UV-vis-NIR extinction spectroscopy, transmission electron microscopy and zeta potential measurements. GSCs and two normal cell lines were selected for in vitro investigations. The uptake and cytotoxicity of Chit-GNPs were evaluated relatively to that of citrate-capped gold nanospheres (GNPs) of similar size. Cell lines were treated with increasing concentrations of GNPs and Chit-GNPs and then irradiated with hypofractionated radiotherapy (3 consecutive fractions of 1, 2 Gy) and brachytherapy (one single fraction of 1 and 2 Gy). The effect was evaluated through the MTT cell viability test and confirmed with Trypan blue-based counting.

Results
GSCs proved to express stem-cell markers and were highly resistant to radiotherapy. Their cell viability and proliferation were impaired by chit-GNPs with an IC50 of 10μg/mL, while remaining unaffected by simple GNP used in similar concentrations. Chit-GNPs were 15 nm in size, with a positive zeta potential and proved a superior cell internalisation compared to simple GNPs. Normal cell lines remained unaffected by GNPs and Chit-GNPs. Radiotherapy at the tested doses failed to give an additional anti-cancer effect when combined with GNP treatment.

Conclusions
The enhanced internalisation within GSCs and the cytotoxic effect of Chit-GNPs make this compound a suitable backbone for drug delivery in glioblastoma treatment, particularly as it proved a selective toxicity for cancer cells. Surprisingly, Chit-GNPs were highly cytotoxic to glioma cell lines irrespective of irradiation.

Legal entity responsible for the study
Iuliu Hatieganu University of Medicine and Pharmacy

Funding
Disclosure
All authors have declared no conflicts of interest.

339P - Hypoxia, Inflammation and redox status as determinants of malignant progression of cancer stem cells
M. Papale (Roma, Italy)

Background
Transformed cells live in a hostile environment characterized by lack of oxygen. Hypoxia produces: necrosis with alarmins release; activation of HIF1a. Recent studies have shown that HIF1a controls also the expression of membrane receptors in tumor cells. These receptors are part of the inflammatory reparative response (IRR) and have the capacity to bind and be activated by alarmins. Once activated, their signaling cascades lead to NFkB. Human tumor tissues posses 1-2% of cancer stem cells (CSCs) responsible for the metastatic potential of tumors. In particular, we investigated the overall hypothesis that, in CSCs from a primary tumor, hypoxia links the expression of IRR genes to tumor progression.

Methods
Hypoxia was achieved in a hypoxic chamber, where a 1% oxygen mix was flushed in for 4 min. Hypoxic response as well as efficacy of drugs treatments on CSCs was determined by measuring HIF1a, VEGF and other markers by WB and Immunofluorescence. Inflammation-like status was reproduced by treatment with necrotic extracts. Redox status was determined by the DCFH-DA. Expression of IRR and adhesion genes was determined by RT-PCR.

Results
Initially, two cell lines of Glioblastoma CSCs from two different tumors were selected and the protein and gene expression were analyzed by WB and RT-PCR. WB analysis showed that hypoxia promotes the expression of HIF1a and change the expression of other proteins directly related to HIF1a. Moreover the gene expression by RT-PCR showed many differences among the analyzed markers. Then we used multiple concentrations of digoxin and acriflavine in the two selected cell lines and also necrotic extracts. Both the drugs promote the reduction of the expression of HIF1a and other related markers. Moreover we used the drugs and an invasion assay kit for evaluation of invasive tumor cells. Also in this case, we observed modification in the invasiveness of CSCs.

Conclusions
Hypoxia promotes cells adaptation trough the expression of HIF1a, without new genetic mutations, and modify other HIF-target proteins such as VEGF, HKII, Rage. Using different concentrations of digoxin and acriflavine it is possible to modify protein and gene expression of HIF1a and related markers, modifying the production of ROS and the invasiveness of CSCs.

Legal entity responsible for the study
Casa di cura San Raffaele Pisana - Rome

Funding
Ministero della salute
Disclosure
All authors have declared no conflicts of interest.

340P - The prognostic role of high mobility group box protein-1 in glioblastoma and its relationship with the inflammatory response

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A. Güzel (Gaziantep, Turkey)

Background
In this study, the prognostic role of HMGB expression determined with immunohistochemistry in patients with glioblastoma, and the relationship with the systemic inflammatory response indicators, NLR and PLR are studied.

Methods
This study included 30 patients who had a histopathologic diagnosis of glioblastoma and 14 patients who underwent surgery for a non-tumoural intracranial pathology in Antalya Education and Research Hospital between 2008-2012. HMGB1 expression was examined via immunohistochemical method.

Results
There were a significant difference of HMGB1 expression between the study and the control group (p = 0.002). HMGB1 expression was found positive in 23 patients (76.7%) and negative in 7 (23.3%) patients in the study group. In the control group, it was positive in 4 (28.6%) patients and negative in 10 (71.4%) patients. When NLR was used as the SIR indicator, it was determined as positive in 11 (36.7%) patients and as negative in 19 (63.3%) patients. When PLR was used as the SIR indicator, it was determined as positive in 10 (33.3%) patients and negative in 20 (66.7%) patients. Median follow up period of patients was 7.8±7.2 (Range 0.7-26.1). Median survival of the study group was 9.6±1.8 (95% Confidence Interval Range 6-13.2) (Figure 1). There wasn’t any significant difference between HMGB1 expression and survival (p = 0.692) (Figure 2). When NLR or PLR was used as the SIR indicator, there wasn’t any relation or difference determined between SIR and survival (p = 0.692, p = 0.740). A significant relation was determined between HMGB1 expression and NLR (p = 0.29). NLR was negative in 17 (73.9%) patients with positive HMGB1 expression, whereas it was negative in 2 (28.6%) patients with negative HMGB1 expression. HMGB1 expression suppresses SIR response. There wasn't any relationship between HMGB1 expression and PLR (p = 0.127).

Conclusions
Results we achieved in our study lead to the opinion that HMGB1 overexpression might have a role in the immune response to the developing tumour in patients with glioblastoma. While treatment strategies are developing in patients with glioblastoma, we believe that HMGB1 could be an important treatment goal.

Legal entity responsible for the study
Mustafa Yıldırım

Funding
None

Disclosure
All authors have declared no conflicts of interest.
341P - Impact of hyperbaric oxygenation on the expression of PKD1 protein forms in T98G glioblastoma cell line treated with selected pentabromobenzylisothiourea (ZKK-3)

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**Background**

Glioblastoma (GBM) is the most malignant brain tumour with poor prognosis and limited therapy effectiveness. Tumour hypoxia is considered as a main reason of GBM's resistance to medical treatment. It seems that improvement of therapeutic response can be achieved by the combination of chemotherapeutics application with refinement of oxygenation status of tumour tissue. One of the novel anti-tumour compounds is isothiourea derivative ZKK-3, which inhibits the activity of protein kinase D1 (PKD1). PKD1 promotes tumour growth and mediates detoxification of mitochondrial reactive oxygen species (ROS). The aim of this study was to examine the impact of hyperbaric oxygenation (HBO) on the expression of PKD1 protein as well as its phosphorylated forms - pPKD1 (Ser 916) and pPKD1 (Ser 744/748) in glioma cells treated with ZKK-3 in vitro.

**Methods**

Human glioblastoma T98G cell line was cultured in medium supplemented with ZKK-3 and exposed to the various oxygen conditions: normoxia, hypoxia, HBO, double hypoxia, hypoxia/HBO. After 24 hours of incubation cell lysis was made. The level of tested proteins in obtained lysates was examined using Western Blot technique.

**Results**

Increasing concentration of ZKK-3 caused diminution of PKD1, pPKD1 (Ser 916) and pPKD1 (Ser 744/748) levels in all tested oxygen conditions. Comparison of hypoxia and HBO conditions showed that hyperbaric oxygen administration resulted in enhancement of expressions of all PKD1 forms. Moreover, in groups preincubated in hypoxia conditions the levels of tested proteins were also markedly elevated after hyperbaric oxygenation (hypoxia/HBO) in comparison to the double hypoxia groups.

**Conclusions**

Increase of PKD1 protein expression as well as its phosphorylated forms evidenced that HBO application resulted in enhancement of oxidative stress in T98G cell line in vitro. This combined with ZKK-3 ability to inhibit activities of those kinases gives ground to consider ZKK-3/HBO therapy as a promising therapeutic strategy for patients with malignant gliomas. Acknowledgement: The research was supported by KNOW-MMRC project and Foundation for the Development of Diagnostic and Therapy.

**Legal entity responsible for the study**

Mossakowski Medical Research Centre Polish Academy of Sciences

**Funding**

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**Disclosure**

All authors have declared no conflicts of interest.

343P - The role of clinical characteristics in low grade gliomas in molecular era

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Background

Low grade gliomas (LGGs) are rare tumors. Molecular characterization has been recently integrated into diagnostic workup of low grade gliomas (LGG) defining specific prognostic features. Moreover, clinical factors, such as age and the extent of resection have a prognostic role in LGG. Here we report a comprehensive analysis on clinical and molecular features impacting on outcome in a large cohort of LGG.

Methods

We evaluated adult LGG patients (pts) which occurred from 1991 to 2015, who received surgery and had sufficient tissue to assess molecular biomarkers characterization. We assessed the status of IDH mutation (using PCR or NGS) 1p19q codeletion (FISH), MGMT methylation (detected with PCR).

Results

213 consecutive LGG were included. The median age was 38 (range:18–69). Median follow up was 98.3 months, 25 pts (11.7%) underwent biopsy, 124 pts (58.2%) subtotal resection, 64 pts (30%) g sorting resection. According to RTOG criteria 37pts (17.4%) were low-risk (<40 years with complete resection), and 176 (82.6%) were high-risk. IDH1/2 mutation was found in 93% of pts. 1p/19q codeletion was found in 50.8% of pts, MGMT methylation in 65.3% of pts. Median progression free survival (PFS) was 47.8 months. Median survival was 211.0 months (95%CI: 185.7-236.3) and 164.0 months (95%CI: 123.0-205.0) in low risk and high risk patients patients. Significant factors in univariate analysis are listed in the Table. Multivariate analysis showed that PFS was influenced by extent of resection (P < 0.001), IDH mutation (P < 0.001) and treatment. IDH mutation (P < 0.001) and extent of resection (P = 0.029) were significantly correlated with overall survival in multivariate analysis. Table:

<table>
<thead>
<tr>
<th>Variable</th>
<th>OS (months)</th>
<th>P</th>
<th>PFS (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH mutation</td>
<td>187.2 vs 32.2</td>
<td>0.001</td>
<td>50.8 vs 16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1p19q codeletion</td>
<td>189.4 vs 164.0</td>
<td>0.015</td>
<td>57.1 vs 41.1</td>
<td>0.031</td>
</tr>
<tr>
<td>MGMT methylation</td>
<td>211.0 vs 148.7</td>
<td>0.013</td>
<td>56.0 vs 44.3</td>
<td>0.024</td>
</tr>
<tr>
<td>Surgery (complete vs biopsy)</td>
<td>211.0 vs 83.0</td>
<td>0.038</td>
<td>52.9 vs 40.0</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Conclusions

The definition of LGG outcome is complex. Both clinical and molecular factors are needed to determine prognosis and treatment strategies.

Legal entity responsible for the study

N/A

Funding

None

Disclosure

All authors have declared no conflicts of interest.

344P - IDH wild type low grade gliomas: Who seeks shall find
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D. Bartolini (Cesena, Italy) E. Silini (Parma, Italy) G. Tallini (Bologna, Italy) L. Cirillo (Bologna, Italy)
C. Bortolotti (Bologna, Italy) D. Danieli (Vicenza, Italy) S. Bartolini (Bologna, Italy) A. Paccapelo (Bologna, Italy)
A. A. Brandes (Bologna, Italy)

Background
The 2016 WHO classification of CNS tumors included molecular parameters in addition to histology to redefine many tumor entities. Low-grade glioma (LGG) are divided into isocitrate dehydrogenase (IDH) wild type or mutant. Absence of IDH mutation is a rare event in LGG, and IDH wild type are considered a provisional entity. The technique used to assess IDH mutation is essential to determine the real impact of this tumor type.

Methods
The observation of a particularly favorable outcome in a group of 42 patients with a diagnosis of IDH wild type LGG (OS = 93.7 months) led us to retest IDH mutation with a more sensitive technique. Next Generation Sequencing (NGS) was used to retest IDH status in tumor samples, the results of NGS assay were compared with previous findings.

Results
Initial assessment of IDH mutation in this 42 patients had been performed using PCR in 19 cases and immunohistochemistry in 2 cases. twenty-one (50%) of the 42 initial IDH wild type LGGs were discovered to be IDH mutant when tested with NGS. Four patients had R132H mutation while in the remaining 17 cases a rare IDH mutation was detected. In particular 4 patients showed IDH2 mutation, 5 patients had IDH1 R132C mutation, 5 patient had IDH1 R132G mutation and 3 patients had IDH1 R132S mutation. Median OS of NGS confirmed IDH mutated LGG was 164.0 months vs 32.2 months for NGS IDH wild type LGG reflecting the very distinct clinical course of these two entities.

Conclusions
Repeating testing in IDH wild type LGG cases is crucial, as well as the technique used to assess this mutation. NGS is able to assess IDH mutations in 50% of patients previously misdiagnosed. IDH wild type LGG remains a rare entity with dismal prognosis.

Legal entity responsible for the study
N/A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

345P - Effect of ADM alone or combined with monoclonal anti-programmed death ligand-1 antibody on glioma cell line U251 and T lymphocytes
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Background
Glioblastoma is the most common primary brain tumor. The current standard therapy for patients with glioblastoma is surgery and combination of radiotherapy with temozolomide chemotherapy. However, the prognosis is still very poor. Much research has been done to improve patient outcomes in glioblastoma. Recently, immunotherapy with immune checkpoint inhibitors, such as ipilimumab, nivolumab, and pembrolizumab shows great clinical improvements in other advanced tumors, which make immunotherapy an attractive strategy in glioblastoma treatment.

Methods
The expression of PD-L1 was determined by flow cytometry. The concentration of adriamycin was determined by CCK-8 assay depending on the inhibition rate of U251 cells, which was set to less then 50\%(IC50). After treatment with different concentrations of adriamycin, cell proliferation of T lymphocytes was detected by CCK-8 method, cell apoptosis of T lymphocytes and PD-L1 expression were analyzed by flow cytometry. Treated with different concentrations of adriamycin alone or in combination with PD-L1 inhibitors, U251 cells and T lymphocyte proliferation in co-culture were determined by CCK-8 assay.

Results
The expression of PD-L1 was nearly 70\%. The IC50 of adriamycin was 4.298mg/L. Adriamycin could enhance the proliferation of T lymphocytes when concentration was less than 4.298mg/L and could up-regulate the expression of PD-L1. Adriamycin (4.298mg/L) combined with immunotherapy (PD-L1 inhibitor 1.5mg/L) could inhibit glioma cells growth obviously and the number of dead T lymphocytes in co-culture system was reduced.

Conclusions
Adriamycin combined with immunotherapy (PD-L1 inhibitor) is a promising strategy for glioma treatment and our research provides theoretical basis for combination of adriamycin and immunotherapy in glioma treatment.

Legal entity responsible for the study
Shiya Zheng

Funding
Laboratory for Experimental Medicine and Surgery of Southeast University

Disclosure
All authors have declared no conflicts of interest.

346P - Prognostic Impact of neutrophil to lymphocyte ratio (NLR) in patients (pts) with recurrent primary malignant brain tumours (PMBT) in phase I (Ph1) trials: The Royal Marsden (RMH) Experience

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Background
The NLR is a marker of systemic inflammatory response and elevated levels have been associated with aggressive disease and poorer outcome in multiple cancers, including prostate, lung and colon cancer. In pts with GBM, elevated NLR prior to any initial therapy is predictive for worse outcomes. For pts with refractory PMBT, the role of NLR is
uncertain. We aimed to assess the prognostic impact of NLR, and the impact of corticosteroids (CCS) in pts with PMBT referred for consideration of Ph1 trial.

**Methods**

Retrospective data were collected on treatment (tx) and tumour characteristics of pts with PMBT referred for consideration of Ph1 trial participation between 06/2004–09/2016. Survival analyses were performed using the Kaplan-Meier method, Cox proportional hazards model; chi-squared test was used to measure associations between categorical variables.

**Results**

100 pts with advanced, refractory PMBT were referred. All pts had received at least one line of prior tx; median no. of prior systemic therapies was 2; 76% had GBM; 63% required CCS on first assessment. Use of CCS was associated with shorter disease-free survival (HR 1.93, 95% CI 1.21-3.06, p = 0.005) and shorter overall survival (OS) in both univariate (HR 2.33, 95% CI 1.44-3.77, p = 0.001,) and multivariate analysis [MVA](HR 1.84, 95% CI: 1.05-3.24, p = 0.034). Pts with NLR≥4 were more likely to require CCS compared to pts with an NLR<4 (81% vs 38%). NLR≥4 was associated with poorer outcomes in all models (OS, MVA: HR 1.73, 95% CI 1.02-2.94, p-value 0.043). Use of CCS did not modify the association between NLR and outcomes. Patients with an NLR≥4 and requiring CCS had the poorest outcome (p = 0.0364); median OS(mOS) for pts with NLR≥4 on CCS was 4.1months(m)(SE 0.29, 95% CI 3.29-5.42), vs 19m mOS for pts not taking CCS (SE 8.61 95% CI.36-not reached).

**Conclusions**

In our advanced PMBT cohort, elevated NLR≥4 remained an independent prognostic indicator for poor outcome, independent of the use of CCS. Pts with elevated NLR requiring CCS demonstrated the worst outcomes – a reminder of the potential relevance of host immunity in PMBT.

**Legal entity responsible for the study**

Royal Marsden Hospital

**Funding**

None

**Disclosure**

U. Banerji: Receipt of grants/research supports: AstraZeneca, Chugai, Onyx, BTG. Receipt of honoraria or consultation fees: Astex, Karus Therapeutics, Novartis, Vernalis. All other authors have declared no conflicts of interest.

**347P - Prognostic value of pre-operative neutrophil-to-lymphocyte ratio in patients with glioblastoma multiforme**

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**Background**

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumour. GBM development is is closely associated with inflammation status and immune response. The neutrophil-to-lymphocyte ratio (NLR) is a marker of host immune response
and its elevation has recently been shown to be a poor prognostic factor in many malignancies including colon, prostate, lung, and bladder cancer. We aimed to investigate the prognostic value of preoperative NLR in GBM patients.

**Methods**
Between 2010 and 2016; 104 patients had surgery for GBM and were assessed for consideration of adjuvant therapy at our institution. Of these, 80 patients with an evaluable pre-corticosteroid full blood count result were identified and included in the final analysis.

**Results**
The mean tumor diameter was 41mm, most of them were found in the right hemisphere (56%) and in the temporal lobe (27.5%). 85% of the patients received adjuvant chemoradiotherapy (with temozolamide). Median overall survival was 13.4 months. Patients with NLR <4, had a worse median overall survival at 12.5 months versus 13.8 months in patients with NLR >4. But this difference was not statistically significant (p > 0.05).

**Conclusions**
Our results suggest that pretreatment NLR could be a useful marker for predicting prognosis in GBM patients but large scale trials are needed to confirm this.

**Legal entity responsible for the study**
Ozlem Oltulu

**Funding**
None

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

**348P - The prognostic role of gender and MGMT methylation status in glioblastoma patients: The female power**

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**Background**
Glioblastoma (GBM) remains an incurable disease. Radiotherapy and temozolomide are the backbone of the treatment. Clinical and molecular factors are essential to define prognosis.

**Methods**
Data on all new cases of primary brain tumors observed from January 1, 2009, to December 31, 2010, in adults residing within the Emilia-Romagna region were recorded in a prospective registry in the Project of Emilia Romagna on Neuro-Oncology (PERNO). We perform a prospective evaluation about prognostic factors in GBM patients treated with temozolomide concurrent with and adjuvant to radiotherapy.

**Results**
One hundred sixty-nine GBM patients (median age, 60 years; range 29 – 82) were prospectively evaluated. MGMT methylation status was available in 140 patients. Combining gender and MGMT methylation status we obtained four groups of patients: 36 male pts with methylated MGMT (25.7%), 47 male pts with unmethylated MGMT (33.6%),
32 female pts with methylated MGMT (22.9%), 25 female pts with unmethylated MGMT (17.9%). Results of univariate analysis are summarized in the Table. Overall survival (OS) was significantly different between methylated male and methylated female (p = 0.028), methylated male and unmethylated female (p = 0.031), unmethylated male and methylated female (p = 0.002), methylated female and unmethylated female (p < 0.001). In multivariate analysis, gender and MGMT methylation considered together (met female vs met male HR = 0.459; 95% CI 0.242 – 0.827; p = 0.017), age (HR 1.025; 95% CI 1.002 – 1.049; p = 0.032) and Karnofsky Performance Status (KPS) (HR 0.965; 95% CI 0.948 – 0.982; p < 0.001) were significantly correlated with OS. Table:

348P Results of univariate analysis

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>mOS</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylated male</td>
<td>31</td>
<td>16.3</td>
<td>9.2-23.4</td>
</tr>
<tr>
<td>Unmethylated male</td>
<td>41</td>
<td>15.6</td>
<td>11.8-19.5</td>
</tr>
<tr>
<td>Methylated female</td>
<td>26</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>Unmethylated female</td>
<td>21</td>
<td>17.0</td>
<td>11.8-22.2</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
<td>17.0</td>
<td>15.2-18.9</td>
</tr>
</tbody>
</table>

Conclusions

The median overall survival is consistently higher for female pts with methylated MGMT, treated with temozolomide concurrent with and adjuvant to radiotherapy. When considered simultaneously with MGMT methylation status, gender might impact on clinical outcome and should be considered as a prognostic factor.

Legal entity responsible for the study

N/A

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None

Disclosure

All authors have declared no conflicts of interest.

349P - Reduced-intensity bevacizumab in progressive glioblastoma multiforme (GBM) is associated with similar overall survival versus standard-dosing

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Background

Bevacizumab (BEV) has demonstrated activity in glioblastoma multiforme (GBM), particularly with regard to symptom control, however overall survival (OS) benefits have not been clearly defined in prospective randomised phase III trials. Most studies have used 10mg/Kg q 2wks as standard although some experts suggest a less intensive dose schedule might offer similar benefits at a lower cost and therefore better value.

Methods

We retrospectively analysed data from the prospective database of the national neuro-oncology centre in Ireland. All patients who received BEV at the time of progression
for histologically-proven de novo GBM from 2010 to 2016 were included. At our institution there is variable practice between Neuro-Oncologists in terms of BEV dosing schedule - standard BEV dosing (10mg/kg q 2wks or 15mg/kg q 3wks) vs. reduced-intensity BEV (5mg/kg q 2wks or 7.5mg/kg q 3wks). Using the Kaplan-Meier method, we assessed OS in the entire cohort and by BEV dosing schedule.

**Results**
In total, 118 patients received BEV for progressive GBM. Median OS was 5.6 months for the entire population (range: 0.5-42 months) and OS was 45%, 18% and 2% at 6-, 12- and 24-months, respectively. Patient characteristics by BEV dosing schedule were similar (Table). Median OS was similar in the reduced intensity BEV group (N = 49) at 5.5 months and the standard-dose group (N = 69) at 5.6 months, p=0.55. Quality of life analyses are ongoing. Table:

<table>
<thead>
<tr>
<th></th>
<th>Standard Dose BEV</th>
<th>Reduced Intensity BEV</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (65%)</td>
<td>32 (65%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>24 (35%)</td>
<td>17 (35%)</td>
<td></td>
</tr>
<tr>
<td><strong>AGE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45 years</td>
<td>10 (14.5%)</td>
<td>8 (16%)</td>
<td>0.92</td>
</tr>
<tr>
<td>45-65 years</td>
<td>42 (60.9%)</td>
<td>28 (57%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>17 (24.6%)</td>
<td>13 (27%)</td>
<td></td>
</tr>
<tr>
<td><strong>MGMT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td>20 (40%)</td>
<td>17 (47%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>30 (60%)</td>
<td>19 (53%)</td>
<td></td>
</tr>
<tr>
<td><strong>Time from Diagnosis to BEV start</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 months</td>
<td>36 (52%)</td>
<td>24 (49%)</td>
<td></td>
</tr>
<tr>
<td>12-18 Months</td>
<td>16 (23%)</td>
<td>12 (24%)</td>
<td>0.94</td>
</tr>
<tr>
<td>&gt; 18 months</td>
<td>17 (25%)</td>
<td>13 (27%)</td>
<td></td>
</tr>
<tr>
<td><strong>Median Overall Survival post BEV</strong></td>
<td>5.6 Months</td>
<td>5.5 Months</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**Conclusions**
In this large heterogeneous cohort of patients, OS was similar in patients who received standard or reduced intensity BEV for treatment of progressive GBM. Given the cost of BEV, these results have important implications for value in cancer care.

**Clinical trial identification**
Not applicable

**Legal entity responsible for the study**
Cancer Clinical Trials Unit (CCTU), Beaumont Hospital, Dublin, Ireland

**Funding**
None

**Disclosure**
All authors have declared no conflicts of interest.
350P - An individualized-approach to second-line systemic anti-cancer therapy for glioblastoma

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Background
The optimal second-line systemic anti-cancer therapy (SACT) for recurrent inoperable glioblastoma (GBM) is not known. Generally, patients with a recurrence within 6 months of adjuvant temozolomide (TMZ) are treated with procarbazine/lomustine/vincristine (PCV) regimen and those with a recurrence at least 6 months after completion of TMZ are re-challenged with TMZ (rTMZ). The aim of this study is to evaluate the clinical outcomes of this individualized approach.

Methods
We treated 46 patients with second-line SACT for recurrent GB between 2009 and 2015. The Response Assessment in Neuro-Oncology (RANO) criteria were used to assess treatment response. The Kaplan-Meier method was used to calculate survival. Patient- and disease-related characteristics between the groups were compared using the Fisher exact test.

Results
31 patients received PCV and 15 patients received rTMZ (Table). The median progression-free (PFS) (3.4 months each) and overall survival (OS) (5.2 months vs. 5.3 months p = 0.482) from the start of second-line SACT were similar for both groups. Compared with the PCV group, the median PFS (19.6 months vs. 8.7 months, p = 0.001) and OS (28 months vs. 13.7 months, p = 0.001) calculated from the date of diagnosis were better for the rTMZ group. Toxicity was acceptable in both treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>PCV</th>
<th>TMZ</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>57 (range 29-71)</td>
<td>63 (range 34-80)</td>
<td>0.119</td>
</tr>
<tr>
<td>Excision</td>
<td></td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td>Debulking</td>
<td>25(80.6%)</td>
<td>13(86.7%)</td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>6(19.4%)</td>
<td>2(19.4%)</td>
<td></td>
</tr>
<tr>
<td>Radiological Appearance</td>
<td></td>
<td></td>
<td>0.182</td>
</tr>
<tr>
<td>Single</td>
<td>24(77.4%)</td>
<td>14(93.3%)</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>7(22.4%)</td>
<td>1(6.7%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant Treatment</td>
<td></td>
<td></td>
<td>0.816</td>
</tr>
<tr>
<td>Radical chemo-RT</td>
<td>25(80.6%)</td>
<td>13(86.7%)</td>
<td></td>
</tr>
<tr>
<td>Radical RT alone</td>
<td>2(6.5%)</td>
<td>1(6.7%)</td>
<td></td>
</tr>
<tr>
<td>Palliative RT</td>
<td>4(12.9%)</td>
<td>1(6.7%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant treatment completed within 6 months</td>
<td>1 (3%)</td>
<td>11 (73%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median time to progression after first-line (months)</td>
<td>1.2 (range: 0.7-11.03)</td>
<td>9.8 (range: 1-24.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Conclusions
As the individualized approach of second-line SACT in recurrent GB leads to similar survival. Patients who recur more than 6 months after completion of primary chemo-radiotherapy generally have a better survival.

Legal entity responsible for the study
Department of Radiation Oncology, Norfolk & Norwich University NHS Foundation Trust

Funding
None

Disclosure
All authors have declared no conflicts of interest.

351P - Levetiracetam offers a survival advantage in patients with epilepsy related to MGMT-unmethylated glioblastoma

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Background
Epilepsy is a common symptom in patients with glioblastoma (Gb). Levetiracetam (LEV), an antiepileptic drug (AED), enhances MGMT inhibition and reduces chemotherapy mediated neuronal toxicity, offering a theoretical benefit over other AEDs.

Methods
213 Hispanic patients were included. All patients underwent surgery (if feasible) followed by chemoradiation based on temozolomide. Type of AED was selected under treating physician discretion. Recorded variables included demographics, AED, dosage, MGMT status, performance status (PS) and type of surgical intervention. The relationship between overall survival (OS), AED and MGMT methylation status was explored.

Results
Mean age was 53-yo (SD+/-14.7), 56.8% were male, 73% presented with epilepsy after diagnosis and 50.7% harbored methylated MGMT (metMGMT). 41% were treated with LEV, 26% were given another AED and 33% did not require any AED. AED indication was not associated with age (p = 0.087), PS (p = 0.78) anatomic tumor site (p = 0.34) or MGMT status (p = 0.98). Median OS was 25.8 months (95%CI 21.6-31.5), 27.9 months (95%CI 23.8-33.7) for those with metMGMT, and 11.83 months (95%CI 7.73-16.67) for non-metMGMT (p < 0.001). OS for the group of metMGMT patients treated with LEV was 33 months (95%CI 32.6-33.7) while for the unmethylated population was 36.2 months (95%CI 31.2-37.3; p = 0.45). In contrast, OS for patients treated with other AEDs was 25.8 months (95%CI 20.4-31.5) for those who have methylated MGMT and 7.6 months (95%CI 6.53-11.8) for non-methylated (p < 0.001). Patients who achieved seizure control and had metMGMT reached an OS of 25.2 months (95%CI 17.5-32.7) compared to 5.3 months (95%CI 4.3-6.2) for non-metMGMT and seizure free patients (p < 0.001). By comparing the three treatment groups, LEV in non-metMGMT offered an OS advantage to other AED and non-AED treated patients (p < 0.001) whereas this benefit was not observed in metMGMT (p = 0.639).

Conclusions
Retrospective analysis of this cohort suggests that LEV modifies OS in non-metMGMT Gb patients making it comparable to those with metMGMT. Further validation of this data in
clinical trials is warranted.

**Legal entity responsible for the study**
Leonardo Rojas

**Funding**
None

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

### 352P - The prognostic role of indicators of systemic inflammatory response in patients with glioblastoma

V. Kaya (Antalya, Turkey) M. Yıldırım (Gaziantep, Turkey) G. Yazıcı (Ankara, Turkey) A. Y. Yalçın (Isparta, Turkey) N. Orhan (Gaziantep, Turkey) A. Güzel (Gaziantep, Turkey)

**Background**
High-grade gliomas, among which glioblastomas are the most frequently observed histologic subtype, are the most common primary brain tumors in adults. The standard treatment for glioblastoma consists of maximal safe resection, followed by concomitant chemoradiotherapy. It was reported that inflammatory response plays a major role in malignancy, including tumor progression. This study aimed to determine the prognostic role of the neutrophil to lymphocyte ratio (NLR) and the thrombocyte to lymphocyte ratio (PLR)—both indicators of systemic inflammatory response (SIR)—in patients with glioblastoma.

**Methods**
This study retrospectively evaluated 90 patients that were treated for glioblastoma.

**Results**
Median follow-up time was 11.3 months (range: 1-70 months). The 1-year and 2-year overall survival rates were 55.2% and 19.5%, respectively. Univariate analysis showed that there wasn’t a correlation between overall survival and gender (p = 0.184), comorbid diseases (p = 0.30), clinical presentation (p = 0.884), or tumor lateralization (p = 0.159). The prognostic factors that affected survival—other than SIR—were Eastern Cooperative Oncology Group (ECOG) performance status (p = 0.003), and tumor localization (p = 0.006). Multivariate analysis showed that overall survival was significantly correlated with SIR based on NLR (HR: 2.41), and ECOG performance status (HR: 1.53).

**Conclusions**
These findings confirm that the NLR value obtained from peripheral blood prior to treatment can be used as a prognostic factor in patients with glioblastoma. It is known that a high NLR value (NLR ≥5) is indicative of aggressive disease with decreased survival; therefore, aggressive treatment modalities can be offered to this selected patient population.

**Legal entity responsible for the study**
Mustafa Yıldırım

**Funding**
None

**Disclosure**
All authors have declared no conflicts of interest.
353P - Which patients with recurrent glioblastoma will require a second surgery during their treatment? A machine learning solution

A. Ruiz-Patiño (Bogotá, Colombia) A. F. Cardona (Bogotá, Colombia) L. Rojas (Bogotá, Colombia) O. Arrieta (Ciudad de México, Mexico) Z. Zatarain-Barrón (Ciudad de México, Mexico)

Background
Deciding upon the therapeutic approach for patients with recurrent glioblastoma (Gb) is a challenge. Although a second surgery may provide effective palliation, it has yet to be established whether it prolongs survival and/or improves quality of life; previous reported data is scarce to demonstrate that reoperation is indicated for all patients with recurrence. The few studies investigating this issue are retrospective and have been conducted on small series with heterogeneous data sets. The aim of the present study was to analyze potential predictors of outcome in patients with recurrent Gb selected for second surgery.

Methods
A statistical learning model based on artificial neural networks was performed. 144 Hispanic patients with Gb were selected; included variables were age, performance status (PS), MGMT promoter methylation (MGMTmet), IDH1/2, and extent of primary surgical resection (ESR). The objective was to identify patients who were candidates for a second surgery considering multiple variable combination models (342). Based on the overall survival (OS) 17 comparisons were made to identify the best model for later validation.

Results
41 patients (49.7%) were female, median age was 52-years old (SD+/-14.3), 63 cases (43.8%) were older than 60 years, 125 (86.8%) had a Karnofsky Performance Index (KPS)>80%, 73 (50.7%) had methylated MGMT and 124 (86.1%) underwent total or subtotal primary resection. The best predictive variables for requiring a second surgery were age, PS, extent of surgical resection and MGMT methylation status status. With an area under the curve of 0.984, combined age plus MGMTmet had a sensitivity of 78% and a specificity of 95%. Other models including MGMTmet+IDH, age+ KPS and age+KPS+ESR yielded an AUC of 0.563, 0.861, and 0.854, respectively. All differences were statistically significant with p value <0.05.

Conclusions
The identification of patients who will require a second surgical intervention can be achieved, offering patients and clinicians an objective tool to plan and carry multiple therapeutic options.

Legal entity responsible for the study
A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

354P - The prognostic role of age in salvage re-irradiation applied patients with recurrent glioblastoma: A meta-analysis

E. Dereağzı (İstanbul, Turkey) V. Kaya (Antalya, Turkey) G. Yazıcı (Ankara, Turkey) M. Yıldırım (Gaziantep, Turkey)

Background
Glioblastoma is the most common primary malignant brain tumor in adults. Despite of postoperative adjuvant therapy, glioblastoma recurs in almost all the patients. After recurrence, chemotherapy, carmustine wafer intended for lesions, usage of anti-VEGF, re-operation, re-irradiation are the existent salvage therapy options. In this meta-analysis, the prognostic role of age in Salvage re-irradiation applied patients with recurrence glioblastoma was analyzed.

**Methods**
PubMed and EBSCOhost databases are searched for malignant glioma, high-grade glioma, recurrence, survival, re-irradiation, re-radiation. Browsing databases was done in English.

**Results**
1588 patients were included to meta-analysis. Pooled hazard ratio showed that overall survival is correlated with re-operation (HR, 1.042; 95% CI, 1.012-1.073; p:0.006). Pooled hazard ratio was calculated by using fixed effect model. The quality determinations of 4 studies were done by using Newcastle-Ottowa Scale. The studies were counted low quality with the score 1-3, average quality with the score 4-6, high quality with the score 7-9. Median score of the studies was calculated as 5.

**Conclusions**
In this meta-analysis, we showed that for re-irradiation treatment, which is a salvage therapy option for recurrent glioblastoma, the age is an important prognostic factor.

**Legal entity responsible for the study**
Mustafa Yıldırım

**Funding**
None

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

### 355P - Temozolomide combined with fractionated stereotactic radiotherapy for large brain metastases: A propensity-matched Study

**Y. Ma (Beijing, China) J. Xiao (Beijing, China) N. Bi (Beijing, China) Q. Liu (Beijing, China) Y. Zhang (Beijing, China) R. Zhao (Beijing, China) S. Yang (Beijing, China) Y. Li (Beijing, China)**

**Background**
This study was conducted to investigate the efficacy and safety of temozolomide (TMZ) with fractionated stereotactic radiotherapy (FSRT) for large brain metastases (BMIs).

**Methods**
From 2009 to 2016, 72 patients (pts) with large BMs (diameter>3cm or volume>6cc) undergoing concurrent TMZ and FSRT (Group A, n = 38) or FSRT alone (Group B, n = 34) were compared by using the propensity score matching method at the ratio of 1:1. Finally, 27 pts of each group were matched. FSRT was given by 52-52.5Gy/3.5-4Gy/13-15f, while TMZ was given by 75mg/m² concurrently. The disease control rate (DCR, CR+PR+SD) was assessed after 2-3 months from treatment. Toxicity was recorded according to CTCAE, v4.0. Local control (LC), intracranial progression-free survival (IPFS), progression-free survival (PFS) and overall survival (OS) were assessed with Kaplan–Meier method and log-rank test.

**Results**
The median GTV of Group A and B were 19.7cc (6.02-142.81cc) and 15.7cc (6.27-62.35cc), respectively. During treatment, more lesions in Group A shrank greatly and got re-contoured (39 VS 29, p = 0.005), and the median GTV shrinkage rate was 30.5% versus (VS) 23.1%. After 2-3 months of treatment, the DCR was 97.4% (37/38) in Group A and 85.3% (29/34) in Group B (p = 0.064). The median follow-up time was 20.6 months. Before matching, the LC (p = 0.037) and PFS (p = 0.025) of Group A were significantly greater than Group B. IPFS (p = 0.059) and OS (p = 0.059) were marginally longer in Group A. After matching, the median PFS time and 1-year PFS rate of Group A were significantly greater than Group B (12.7m VS 3.3m and 55.2% VS 26.4%, respectively, p = 0.041). The rate of intracranial progression death of Group A was significantly lower (18.2% VS 45.8%, p = 0.04). Both overall survival time and IPFS were also marginally longer in Group A (MST: 23.7m VS 17.5m, p = 0.064; 1y-IPFS: 61.6% VS 40.7%, p = 0.069), while there was no significant difference in 1-y LC (89.8% VS 84.2%, p = 0.23). There was no severe toxicity in both groups (p = 0.623).

Conclusions
The addition of TMZ to FSRT shows advantages in accelerating the shrinkage of large BMs and might improve intracranial control and overall survival, with no increase of toxicities. Further studies with large sample sizes are warranted.

Clinical trial identification
NCT02654106

Legal entity responsible for the study
Cancer Hospital, Chinese Academy of Medical Sciences

Funding
None

Disclosure
All authors have declared no conflicts of interest.

356P - Worsening of quality of life (QoL), cognitive functions (CF) and psychological status (PSY) can predict radiologic progressive disease (RPD) in glioblastoma (GBM) patients (PTS) treated with radiation therapy (RT) and temozolomide (TMZ): A mono-institutional prospective study

E. Bergo (Padova, Italy) G. Lombardi (Padova, Italy) P. Del Bianco (Padova, Italy) S. Dal Pos (Padova, Italy) F. Berti (Padova, Italy) L. Bellu (Padova, Italy) A. Pambuku (Padova, Italy) V. Zagonel (Padova, Italy)

Background
Almost all PTS with GBM treated with RT and TMZ relapse during or after treatment. We performed a prospective study to assess if deterioration of QoL, CF and PSY is a predictor of RPD.

Methods
PTS with newly histologically diagnosed GBM treated with RT and TMZ as first-line therapy and KPS>60 were enrolled. PTS received TMZ for 12 cycles or until unacceptable toxicity or progressive disease. All questionnaires were given to PTS for self-assessment before performing MRI. Macdonald criteria were used for radiological evaluation. We assessed QoL, CF and PSY before starting treatment, at the end of RT, and every 3 months until 9 months after the end of RT using EORTC-C30, BN-20, MMSE and HADS questionnaires. Brain MRI were performed at the same timepoints.
Results
We prospectively enrolled 111 consecutive PTS at our oncological center, Veneto Institute of Oncology, between January 2013 and December 2015. Median age was 59; 69 PTS were male and 36 PTS aged ≥65. PTS showing a RPD reported lower physical functioning (p = 0.018), minor role function (p = 0.0007) and a lower global health status (p = 0.01) than patients without RPD. In addition, they reported greater uncertainty in the future (p = 0.007), increased drowsiness (p = 0.013), increased itchy skin (p = 0.005) and greater weakness in the legs (p = 0.027) compared to PTS without RPD. PTS with RPD were more anxious (p = 0.0021) and depressed (p = 0.0001) than PTS without RPD. The two groups significantly differed in CF (p = 0.0007), especially 1 and 6 months after RT, with worse results in the MMSE for PTS with RPD.

Conclusions
Worsening of QoL, CF and PSY can predict RPD in GBM PTS treated with RT and TMZ.

Legal entity responsible for the study
Veneto Institute of Oncology

Funding
None

Disclosure
All authors have declared no conflicts of interest.

357P - Dose distribution after tumor cavity injection in brain glioma patients
M. Zhao (Beijing, China) X. Fu (Beijing, China)

Background
The local delivery of drug into brain has not been widely used because the unpredictable dose distribution and dose-toxicity effects that drug may carry. This study is to investigate the efficacy of drug delivery by intra-cerebral injection.

Methods
3 patients with deep-seated glioma underwent stereotactic biopsy and Ommaya reservoir implantation. Radioactive agent (\(^{131}\)I-chTNT) was injected at a dose of (0.8mCi/cm\(^3\)) through Ommaya reservoir. Patients were carefully observed and Post-operational PET was performed to reveal the body distribution of 131I and evaluate the distribution of drugs in whole body.

Results
After the intratumoral injection, most of the drug stayed in the brain tumor and decayed gradually for more than 4 weeks. Although the accumulation of 131I was also found in thyroid and urinary system as well as stomach and large intestine, it disappeared within 2 weeks while strong radioactivity was still seen in the brain tumor.

Conclusions
These images demonstrated excellent localization of the radiolabel in the tumor with little diffusion over time. Intra-tumoral injection of chemical or radioactive drugs is recommendable in the local treatment.

Legal entity responsible for the study
Ming Zhao

Funding
Beijing Capital Developmental Fund (2014-2-5021)
Disclosure
All authors have declared no conflicts of interest.

358P - Retrospective analysis to ascertain whether thromboembolic events, patient gender and tumour size have prognostic implications for glioblastoma multiforme
D. Parslow (Plymouth, United Kingdom) S. Pascoe (Plymouth, United Kingdom)

Background
Glioblastoma multiforme is a rare grade 4 incurable brain malignancy. Well established prognostic indicators for this disease include performance status, age and cognitive function at diagnosis. Presenting with a seizure is also known to predict a better prognosis. Patient gender, tumour size and thromboembolic events have not been previously known to have prognostic significance. The rationale of this study is to identify alternative features which could be used as additional prognostic indicators.

Methods
We conducted a retrospective analysis of all patients diagnosed with glioblastoma multiforme at Derriford Hospital, Plymouth, UK between 2009 and 2016. We analysed factors such as survival time since diagnosis, patient demographics, tumour size at diagnosis, performance status at diagnosis, presenting symptom, treatment undergone and the occurrence of venous thromboembolic events since diagnosis.

Results
92 patients were included. The occurrence of venous thromboembolism had no impact on survival time (p = 0.386). Male sex appeared to predict a better prognosis than female sex, however, this did not quite achieve statistical significance with a p value of 0.09. Cox regression analysis revealed tumour size on diagnosis to be significantly negatively correlated with survival time, with a p value of 0.012. Our analysis agreed with previous findings that multifocal disease and increased age are poor prognostic indicators, and presenting with seizures is a good prognostic indicator. Patients who underwent radical debulking surgery followed by concomitant chemoiradation had a significantly longer survival time than patients who had best supportive care alone.

Conclusions
Our analysis has shown that increasing tumour size is negatively correlated with survival duration. This link has not been previously established. Female sex may also be a poor prognostic indicator, but our data did not achieve statistical significance so further research investigating this potential link may be warranted. Venous thromboembolic events had no impact on prognosis.

Legal entity responsible for the study
Research Office, Plymouth Hospitals NHS Trust

Funding
None

Disclosure
All authors have declared no conflicts of interest.

359P - The standard and high dose chemotherapy dose intensity and their effect on the survival of medulloblastoma using nation-wide treatment protocol
J. Lim (SEOUL, Korea, Republic of) L. Cha (SEOUL, Korea, Republic of) S. Hahn (SEOUL, Korea, Republic of)
Background
Medulloblastoma is the most common type of childhood brain tumors. We conducted Korea’s nation-wide protocol based treatment for medulloblastoma, and adopted tandem high dose chemotherapy for high risk disease. Here we present the result of treatment in Yonsei Cancer Center using the protocol and elucidate dose-response relationship.

Methods
The patient diagnosed and treated in Yonsei Cancer Center were reviewed retrospectively, from 2006 to 2015. We excluded the patients less than 3 years old and over 30 years old. Dose intensity (DI) was calculated as actual dose level/planned dose level divided by chemotherapy treatment duration. Ind-DI was defined as induction chemotherapy DI and HDCT-DI was as high dose chemotherapy DI. The protocol was composed of 2 cycles of neoadjuvant chemotherapy and 32.4Gy of craniospinal radiotherapy (CSRT) and 50.4 Gy of total tumor dose. After the radiotherapy, 4 cycles of chemotherapy and tandem high dose chemotherapy was done.

Results
Among total 39 patients, 16 were standard risk (SR) and 23 were high risk (HR). The 5 year overall survival (OS) was 92% for SR, and 67% for HR. Disease specific survival (DSS) for HR was 75%, and therefore 8% was treatment related mortality (TRM). The 5Y OS between M0 and M1 status was not statistically different in HR. The ind-DI did not affect in 5Y OS for SR and HR. Ind-DI was strongly correlated with HDCT-DI. The 5Y-OS for HDCT-DI<70% was statistically inferior to HDCT-DI>70%. All TRMs developed in HDCT-DI>90%. Therefore, the reduction of HDCT-DI in the protocol was suggested from this analysis. The responsiveness of induction chemotherapy (complete remission and partial remission) was predictive marker for 5Y-OS (P = 0.026). The complete response at the first HDCT was also predictive for 5Y-OS (P = 0.009).

Conclusions
The result from the nation-wide protocol was acceptable but high dose intensity was the cause of treatment related mortality. Now the dose of HDCT was reduced to achieve the ideal survival rate from the protocol.

Legal entity responsible for the study
Jung Woo Han

Funding
None

Disclosure
All authors have declared no conflicts of interest.

360P - Primary central nervous system germ cell tumours: A single institution retrospective study

J. P. Silva (Lisbon, Portugal) M. Ramos (Lisbon, Portugal) A. Azevedo (Lisbon, Portugal) D. Salgado (Lisbon, Portugal) I. Costa (Lisbon, Portugal) J. Marques (Lisbon, Portugal)

Background
Germ Cell Tumors (GCTs) are 2% of intracranial neoplasms, mainly in the pineal/suprasellar region and in young ages. The overall prognosis, in tumors containing a
non-germinomatous component, is poor with a median 5 year overall survival (OS) of under 30%. Treatment recommendations suggest a multimodal approach.

**Methods**

We performed a retrospective review of all consecutive primary intracranial GCT patients (pts) diagnosed and treated at our Institution from 1988 to 2015. Primary aim: to characterize the clinical, demographic and treatment data. Secondary aim: to evaluate overall survival (OS) at 5 and 10 years using the Kaplan-Meier method and related prognostic factors.

**Results**

From a total of 45 pts, 30 were males, median age 11 years (P10-90: 5,75–20). The main symptoms were cephalalgia (45%), diabetes insipidus (31%) and vomiting (20%). 53% had endocrinologic disturbances, 44% visual field limitations and 20% pts Parinaud Syndrome. Sixty percent presented with intracranial hypertension. Primary location was the pineal and suprasellar in 56% and 29% of cases. Cranial and Neuroaxial Magnetic Ressonance Imaging (MRI) was the preferred imaging method used in 91 and 53% pts, respectively. The diagnosis was reached by tumour markers in 22,2%, tumour biopsy in 26,6% and surgery in 51,1% pts. Tumour markers were elevated in 69% pts. Forty-nine percent of pts had pure germinoma, 15,5% pts had mixed germinoma and 31% pts non-germinoma. Sixty-nine percent of pts underwent intracranial decompression techniques. Sixty-nine percent of pts had chemotherapy regimens (PEI in 18 pts) and 82,2% pts had cranial radiotherapy (with simultaneous neuroaxial irradiation in 17 pts). Complete response was achieved in 91,1% of pts with 22,2% pts recurring. The 5 and 10 OS rate was 88 and 85% respectively (98 and 98% for Germinomas and 82 and 75% for non-germinoma). OS values differences between histologies did not reach statistical significance. In the multivariate analysis only cranial radiotherapy and absence of recurrence were associated with improved survival (p = 0.003 and p = 0.016, respectively).

**Conclusions**

First line multimodality treatment achieves good clinical outcomes, with focus on cranial radiotherapy. Disease recurrence is associated with worse outcomes.

**Legal entity responsible for the study**

Instituto Portugues de Oncologia de Lisboa

**Funding**

None

**Disclosure**

J.P. Silva: Travel grants to Oncology congresses by Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

361P - Effect of silibinin nutraceutical supplementation in brain metastases of patients with advanced lung cancer

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**Background**
Silibinin is a bioactive flavonolignan extracted from milk thistle (Silybum marianum). We are currently evaluating the pre-clinical activity of silibinin on reactive astrocytes, a major component of the brain metastasis microenvironment shown to play important pro-metastatic functions.

**Methods**

We present data of patients with lung cancer and brain metastases that have received compassionate use of nutraceutical supplementation with Legasil®, a commercially available silibinin-based nutraceutical, in addition to standard oncologic treatment. We have compared our observed results with the brain GPA index of each patient calculated by Lung-molGPA tool (brain GPA Index).

**Results**

Eighteen patients have been treated: median age 62 y (range: 35–80); male: 11 (61%); median number of brain metastases: 4 (range: 1-20); median size of the bigger brain metastasis: 26 mm (range: 10-65 mm). Histology: Adenocarcinoma: 14, Large cell: 1, Small cell: 2, Squamous: 1. All patients have received whole brain radiotherapy. Observed overall survival (OS) was significantly superior compared with expected OS calculated by Lung-molGPA (median 22.2 months [95% CI 13.0-32.6] vs 6.9 months [4.2-9.5]; p = 0.001). Time to central nervous system treatment failure of silibinin was 26.9 months (95% CI 11.7-42.1 months). Brain tumor progression was observed in 6 patients (33%). Overall response rate at brain disease was 75% (Complete Response:3 patients (20%) and Partial Response: 10 patients (55%)). Only one patient presented brain tumor progression as best response. At data cutoff (May 1st, 2017), 6 (33%) patients remained alive.

**Conclusions**

These preliminary data suggest that silibinin supplementation contributes to the control of brain metastases in lung cancer patients. Further evaluation of the silibinin use in a phase II clinical trial is warranted.

**Legal entity responsible for the study**

Joaquim Bosch-Barrera

**Funding**

None

**Disclosure**

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**362P - Melanoma with V600 BRAF mutations and brain metastases: Experience of targeted therapy in a single center**

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**Background**

The effectiveness of chemotherapy (temozolomide, fotemustine, lomustine) alone and in combination with whole brain irradiation in patients with melanoma with cerebral metastases does not exceed 7-10%, without significant impact on overall survival, which is 2-4 months. Targeted therapy has improved the survival of patients with metastatic melanoma with BRAF V600 mutations. In patients with brain metastases targeted
therapies allow not only to control systemic tumor process, but also to achieve the effect of treatment of cerebral metastases. So, the efficacy (complete and partial regressions of brain metastases) targeted therapy with BRAF inhibitors vemurafenib or dabrafenib in patients with melanoma with BRAF V600 mutations in metastatic brain lesions, according to the literature, varies from 18.0% to 39.2%, with a median survival of patients from 5.3 to 8.2 months. We evaluated the efficacy of targeted therapy (BRAF inhibitors vemurafenib or dabrafenib as monotherapy and also in combinations with MEK inhibitors cobimetinib or trametinib) in patients with melanoma brain metastases.

**Methods**
In Russian N.N. Blokhin Cancer Research Center effect of the various schemes targeted therapy were evaluated in 45 patients with melanoma with BRAF V600 mutations and brain metastases. Patients received the following treatment options: dabrafenib (4 patients), dabrafenib + trametinib (11 patients), vemurafenib (25 patients), vemurafenib + cobimetinib (5 patients). Three patients (6.7%) targeted therapy was combined with whole brain irradiation, in eight patients (17.8%) – in combination with stereotactic radiotherapy/radiosurgery.

**Results**
Complete regression of brain metastases was achieved in 3 patients (6.7%), partial regression in 19 (42.2%), stabilization in 15 (33.3%). Thus, the tumor control in the brain was observed in 37 patients (82.2%). In 43 patients (95.6%) of 45 were also established metastases in other sites (extracranial lesions). Complete regression of metastases in extracranial lesions was achieved in 1 patient (2.3%), partial regression – in 26 (60.4%), stabilization in 13 (30.2%). The median time to disease progression was 5.5 months. The median survival of patients was 8.5 months.

**Conclusions**
The data presented indicate that the targeted therapy with BRAF inhibitors as monotherapy and also in combination with MEK inhibitors in patients with metastatic melanoma with brain metastases provides control over the disease in most patients and has a significant advantage with a group of historical control (chemotherapy ± whole brain irradiation).

**Legal entity responsible for the study**
Russian N.N. Blokhin Cancer Research Center

**Funding**
Russian N.N. Blokhin Cancer Research Center

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

### 363P - Radioprotective effect of xenon in radiation treatment for brain metastases

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**Background**
Surgical treatment, whole brain irradiation (WBI) and stereotactic radiation therapy (RT) are the main treatment strategies for solitary brain metastases. Applying additional boost to the bed of removed metastatic foci seems promising for enhancing local control, but increased radiation exposure affects the central regulation and processes that maintain
homeostasis. The purpose of the study was to evaluate optimization of adjuvant RT with xenon due to its neurotrophic and neuroprotective effects.

Methods
16 patients of the control group received WBI with additional boost once a day (60 Gy in 15 fractions), while 12 patients of the main group received similar RT plus inhalations of a xenon/oxygen mixture twice a week. Clinical and neurological examination was performed and the quality of life was assessed (using QLQ-C15 and BN-20 + 2 questionnaires) for all patients during the treatment. Adaptation reactions were identified and the ratio of their anti-stress/stress types (R as/s) was calculated for integral evaluation of the body condition, individual testing tension (Ut) at the Yin Tang point was studied and EEG parameters were analyzed.

Results
Only patients receiving xenon reported reduced rates of headaches and dizziness, disorders of higher nervous activity, reduced degrees of movement disorders; RT course for these patients was performed in compliance with the accompanying therapy. Assessment of the quality of life by the end of the treatment showed significant improvement in such criteria as physical health and loss of appetite, as well as pain relief, in contrast to the control group. Negative dynamics of integral body parameters, R as/s and Ut was lower than in the control group, and some EEG parameters were normalized after xenon therapy.

Conclusions
Xenon therapy is an effective optimization method for radiation treatment of patients with brain metastases. Its radioprotective and stress-limiting effects allow reduction of adverse effects and toxicity and improvement of the quality of life of patients.

Legal entity responsible for the study
Rostov Scientific Research Institute of Oncology, Russia

Funding
None

Disclosure
All authors have declared no conflicts of interest.

ENDOCRINE AND NEUROENDOCRINE TUMOURS
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442P - Long-term survival of patients with carcinoid syndrome in clinical trials of telotristat ethyl
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Background
Patients with carcinoid syndrome (CS) in the setting of metastatic neuroendocrine tumors (NETs) experience considerable morbidity and mortality. From the time of diagnosis of
metastatic NETs, median survival has been estimated to be approximately 31–75 months. CS is associated with tumoral secretion of serotonin and subsequent debilitating diarrhea, which poses a significant health risk. In previous studies, telotristat ethyl (TE), a tryptophan hydroxylase inhibitor, was effective and well tolerated in treating CS diarrhea. At enrollment, patients in these studies had already survived an average of 6–8 years with metastatic NETs since their initial diagnoses.

Methods
Adverse events reported during treatment with TE were pooled from 2 Phase 2 and 3 Phase 3 clinical trials of TE in patients with CS. The long-term safety of TE was examined, causes of hospitalization and death were reviewed, and an estimate of overall survival was obtained.

Results
A total of 239 patients with CS received treatment with TE in Phase 2 and 3 clinical trials. For these patients, as of the end of 2016, the mean duration of exposure was 1.3 years, and maximum 5.7 years. The leading causes of hospitalization were gastrointestinal disorders and surgical and medical procedures, mostly attributable to the underlying tumor and related treatment. Survival estimates at 1, 2, and 3 years were 93%, 88%, and 77%, respectively. Nearly all deaths were due to progression or complication of the underlying disease, and none were attributable to TE. There was 1 death in Year 4 and no deaths in Years 5 and 6 of patient follow-up in this data set. The median survival with TE was not reached at the end of the 6-year Follow-up period.

Conclusions
Our review of the long-term safety data for TE indicates that patients with CS treated with TE in Phase 2 and 3 studies experienced encouraging survival rates.

Clinical trial identification
NCT02026063, NCT02063659, NCT01677910, NCT01104415, NCT00853047

Legal entity responsible for the study
Lexicon Pharmaceuticals, Inc.

Funding
Lexicon Pharmaceuticals, Inc.

Disclosure

443P - Identifying symptom and quality of life improvements in patients with carcinoid syndrome treated with telotristat ethyl: Qualitative patient exit interviews
Background

Carcinoid syndrome (CS) is a rare condition in patients (pts) with neuroendocrine tumors (NETs), characterized by diarrhea, flushing, and abdominal pain that impact health-related quality of life (HRQoL). We assessed symptoms and HRQoL in pts with inadequately-controlled CS enrolled in TELESTAR (NCT01677910).

Methods

English or German-speaking pts randomized 1:1:1 to 12 wks of double-blinded (DB) treatment with telotristat ethyl (TE) 250mg, 500mg, placebo were invited to a blinded, qualitative, semi-structured exit interview after the DB period to assess symptoms, HRQoL concepts (improved/not changed/worsened), and TE treatment effects. Concepts were freely reported by pts and not solicited. EORTC QLQ-C30 and GINET21 questionnaires assessed HRQoL, daily diaries assessed baseline (BL) bowel movement (BM) frequency. Analyses compared pts with durable response (DRs; predefined as BM frequency reduction of ≥ 30% from BL for ≥50% of DB period) and without durable response.

Results

TELESTAR enrolled 135 pts, 45 per group; 34 pts (9, 16, 9 in TE 250mg, 500mg, placebo, respectively), including 10 DRs consented to interviews. BL age, gender, race, BMs/wk of interviewed pts (IPs) were similar to non-interviewed pts. Most qualitative concepts were captured, to an extent, by the QLQ-C30; most common HRQoL qualitative concepts identified were daily life activities, physical, and psychological, with most TE-treated pts improving in these over the DB period. The most common symptoms (improvement/no change) reported in all IPs were diarrhea consistency (n = 17/n=10), frequency (n = 17/n=9), urgency (n = 11/n=7); flushing (n = 11/n=7), and fatigue (n = 9/n=4). A higher proportion of TE-treated pts and DRs reported symptom and HRQoL concept improvements. Durable response (p < 0.001) and treatment satisfaction (p = 0.0137) correlated with diarrhea QLQ-C30, but no other QLQ-C30/GINET21 scores.

Conclusions

The QLQ-C30 covered most qualitative concepts, but due to the lack of emphasis on key symptoms, may not adequately reflect pt perspectives. Interviews suggested improvements in symptoms and HRQoL with TE treatment and in DRs.

Clinical trial identification

NCT01677910

Legal entity responsible for the study

Lexicon Pharmaceuticals

Funding

Lexicon Pharmaceuticals and Ipsen Pharma SAS

Disclosure


444P - Carcinoid syndrome: Patient outcomes from a European Neuroendocrine Tumour Society (ENETs) centre of excellence

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Background
Carcinoid syndrome (CS), characterised by flushing, diarrhoea, wheeze and fibrotic valvulopathy, arises in patients (pts) with advanced NETs due to serotonin and kallikrein secretion.

Methods
Sequential pts with advanced well-differentiated gastroenteropancreatic NETs (GEP-NETs) treated at The Christie (1998-2017) with ≥1 carcinoid symptom(s) and raised serum/urinary 5-hydroxyindoleacetic acid (5-HIAA) were identified. Ratio of 5-HIAA/upper limit normal (ULN) was calculated. Progression-free (PFS) and overall survival (OS) were estimated (Kaplan-Meier method) and prognostic factors identified (Cox proportional hazards model).

Results
Of 882 pts, 139 (16%) had CS: median (med) age 64 yrs, 55% male, 80% performance status (PS) 0-1, 13% PS 2; 65% had small bowel primary, 10% large bowel, 4% pancreas, 0.7% gastric, 21% unknown primary (consistent with GEP-NET origin). Tumour grade (G) was 1 in 45%; G2 in 29%; symptoms included diarrhoea (91%), flushing (89%), wheeze (22%), and carcinoid heart disease (CHD; 35%). Fifty-seven (41%) had primary resection, and 121 (87%) had liver metastases. In first line, 66% received a somatostatin analogue (SSA), 20% debulking surgery, 14% other. Med baseline 5-HIAA levels were 8.45 x ULN (urinary: 10.56 x ULN, serum: 6.07 x ULN). Med follow-up was 45.7 months (mo). Med PFS and OS were 27.0 (95%CI 17.2-33.9) and 65.4 (95%CI 50.4-76.4) mo. On univariate analysis, small bowel primary (P = 0.045), liver metastases (P = 0.03), Ki-67 (P < 0.01) and 5-HIAA baseline ratio (P < 0.001) were prognostic for PFS; and age (P < 0.01), PS (P < 0.01), primary in situ (P < 0.001), CHD (P = 0.03), Ki-67 (P = 0.03), baseline 5-HIAA ratio (P < 0.001) and use of SSA vs surgery (P = 0.02) were prognostic for OS. On multivariable analysis, high Ki-67 (HR 1.06, 95%CI 1.00-1.12, P = 0.049) and baseline 5-HIAA ratio (HR 1.03, 95%CI 1.01-1.05, P = 0.001) were prognostic for worse PFS. Primary in situ (HR 2.23, 95%CI 1.09-4.54, P = 0.03) and high baseline 5-HIAA ratio (HR 1.02, 95%CI 1.00-1.04, P = 0.04) were prognostic for worse OS. Change in 5-HIAA at 6 mo was not prognostic for PFS (P = 0.42) or OS (P = 0.60).

Conclusions
Baseline 5-HIAA ratio, but not change from baseline to 6 months, was prognostic for PFS and OS. Treatment optimisation is pivotal.

Legal entity responsible for the study
Audit Department - The Christie NHS Foundation Trust, Manchester

Funding
None

Disclosure
All authors have declared no conflicts of interest.

445P - Relationship between symptoms and health-related quality of life benefits in patients with carcinoid syndrome: Post-hoc analyses from TELESTAR
Background
The safety and efficacy of telotristat ethyl (TE) in patients (pts) with metastatic neuroendocrine tumors (NETs) and carcinoid syndrome (CS) not adequately controlled with somatostatin analogs (SSAs) have been demonstrated. TE-treated pts showed significantly greater reductions in bowel movement (BM) frequency and more presented with durable response than placebo (PBO)-treated pts. These post-hoc analyses examined the relationship between improvements in symptoms and health-related quality of life (HRQoL) in pts who were durable responders (DRs; n = 48) and non-durable responders (NDRs; n = 87), irrespective of treatment group, in TELESTAR (NCT01677910).

Methods
Pts were randomized 1:1:1 to TE 250mg, 500mg, and PBO three times daily during the 12-week (wk) double-blind (DB) treatment period; durable response was predefined as a daily BM frequency reduction of ≥ 30% from baseline for ≥50% of the DB period. Clinical symptoms were assessed via daily records, HRQoL by the EORTC QLQ-C30 and QLQ-GINET21 questionnaires. The difference in arithmetic means and associated 95% CIs were used as a descriptive measure of group effects.

Results
135 pts were randomized, 45 in each group. The mean difference [95% CI] in change from baseline between DRs and NDRs at Wk12 was (1.8 [-2.3, -1.2]) for daily BM frequency, (-1.2 [-1.6, -0.7]) for daily flushing, (-38.7 [-70.0, -7.3] mg/24 hrs) for u5-HIAA levels, (-1.2 [-1.8, -0.6]) for abdominal pain severity and (-0.3 [-0.4, -0.2]) for urgency to defecate. DRs showed meaningful and/or significant improvements in QLQ-C30 global health (8.1 [-0.3, 16.5]), summary score (4.9 [0.6, 9.2]), social functioning (5.1 [-4.7, 14.9]), nausea/vomiting (-7.5 [-15.4, 0.4]), pain (-16.0 [-27.0, -5.0]), dyspnea (-5.7 [-15.5, 4.1]), diarrhea (-14.7 [-26.5, -2.9]), and GINET21 gastrointestinal symptoms (-9.3 [-16.3, -2.2]) versus NDRs.

Conclusions
Durable response was associated with reductions in the symptoms and overall clinical burden of CS. DRs showed significant and/or meaningful improvements in global HRQoL, nausea, pain, diarrhea, and gastrointestinal symptoms.

Clinical trial identification
NCT01677910

Legal entity responsible for the study
Lexicon Pharmaceuticals
**Funding**
Lexicon Pharmaceuticals and Ipsen

**Disclosure**
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**446P - Benefit of oral monotherapy with pazopanib in metastatic gastroenteropancreatic neuroendocrine tumours**

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**Background**
Although standard therapy for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can provide symptom relief and delay tumour progression, new strategies are needed for patients with metastatic disease. The aim of this study was to investigate the antitumour activity and safety profile of pazopanib - a selective multi-targeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor.

**Methods**
We enrolled 124 patients with metastatic GEP-NETs. Pazopanib was administered orally at a dose of 800 mg daily with a 28-day cycle. The primary endpoint was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors. The secondary endpoints were overall survival (OS), progression-free survival (PFS) at 6 months and safety profile of pazopanib (general tolerability and toxicity). The third endpoint was to compare the clinicopathological features of tumours and biomarker analysis with survival of the patients.

**Results**
The mean follow-up time was 196±87 days with a range of 67-268 days; 26 patients died within the observation time. 69% of the patients had confirmed pancreatic GEP-NET and 51% had colorectal, gastric and duodenal GEP-NET. 59 (47.6%) patients had G1, 34 (27.4%) G2 and 31 (25%) had G3 GEP-NET. ORR was 24% (19 of 124 patients), stable disease was achieved in 49 patients (39.5%) and PFS at 6 months was 36%. Median OS was 10.2 months (95% CI, 5.4-13.2 months). The most common grade 3-4 adverse events attributed to therapy were neutropenia (11%), proteinuria (14%), diarrhea (7%), and fatigue (12%). Patients with high CgA levels had the highest mortality risk (hazard ratio 3.478, 94% confidence interval 1.313-4.727, p < 0.001) and worse outcomes. Furthermore, extremely high CgA levels (>3000 ng/mL, range 8300-800 ng/mL) were associated with low survival independently from the Ki-67 score in a multivariate Cox regression model.

**Conclusions**
Pazopanib demonstrated a comparable therapeutic efficiency as well as a satisfying safety profile compared to other targeted agents in the treatment of patients with...
metastatic GEP-NETs.

Clinical trial identification
N/A

Legal entity responsible for the study
Faculty of Medicine Osijek

Funding
Faculty of Medicine Osijek

Disclosure
All authors have declared no conflicts of interest.

447P - High hepatic tumor burden and cardiovascular comorbidities linked to carcinoid heart disease

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Background
One of the most common functioning syndromes associated with neuroendocrine tumors (NET) is the carcinoid syndrome (CS). By releasing vasoactive substances, these tumors can cause fibrotic complications, including right-sided valve heart fibrosis, named carcinoid heart disease (CHD). Factors associated with the onset and progression of CHD are poorly understood. We aimed to investigate prognostic factors associated with CHD.

Methods
Retrospective study of consecutive patients (pts) with advanced NET and CS and/or elevated 24h-urinary 5HIAA who performed an echocardiogram to screen for CHD. CHD was defined as echocardiographic evidence of moderate to severe tricuspid or pulmonary regurgitation.

Results
From 2009 to 2017 42 pts were included: Median age was 54.4 (19 – 85) years, 24 were female, 69% had midgut NET. The frequency of CHD was 38% (16 pts) CHD was not associated with age (p = 0.79), sex (p = 0.38), bone metastasis (p = 0.66), flushing (p = 0.14) or diarrhea (p = 0.53); the median urinary level of 5HIAA at diagnosis of CHD was numerically higher, albeit not significant, among CHD pts (p = 0.20). CHD was significantly associated with higher volume (>50% of parenchyma) of liver metastases [OR 13.86 (2.57 – 74.68), p = 0.002]. Time from symptoms to diagnosis of NET was borderline significant (p = 0.08). When CHD was defined as at least mild valve regurgitation, the frequency of CHD was 45% (19 patients) and we observed a significant association between the presence of cardiovascular comorbidities and CHD [OR 6.58 (1.09; 39.78), p = 0.040].

Conclusions
CHD is highly frequent among pts with CS. We found that high liver tumor burden and possibly, longer time of symptoms until diagnosis of NET were associated with CHD. Such findings probably imply that a delayed diagnosis negatively affects CS patients, increasing the risk of CHD. Interestingly, we found that concurrent cardiovascular disease was associated with CHD, as a potential predisposing factor.

Legal entity responsible for the study
448P - Bone metastases in patients with neuroendocrine neoplasms: A survey of natural history and clinical management

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Background
Bone metastases (BM) in neuroendocrine neoplasms (NEN) represent a poorly defined issue.

Methods
This is a nationwide survey among Italian institutions dealing with NEN patients. Characteristics of BM, clinical management, skeletal related events (SREs) and disease outcome were recorded.

Results
We analysed 321 patients with histological diagnosis of NEN and BM collected from 18 Italian Centers. Mean age was 59 y.o. (range 13-86). Primary sites were 47% gastroenteropancreatic (GEP), 36% lung, 4% Paraganglioma/Pheochromocytoma (Par/Pheo), 7% unknown, 5% others. The vast majority (72%) of NEN were already metastatic at diagnosis and the liver represented the second most frequent site of metastasis (in 77% of patients) during follow-up, in addition to BM. Bone was the first metastatic site in 41% of cases. Neoplasms were low/intermediate grade in 80% and high grade in 20%. SREs occurred in 32% of cases, mainly in lung and others. Median time to SRE was 4 months. It strictly correlated with the high grade, irrespective of the primary site. Bisphosphonates were administered in 32% of patients. Median survival from BM diagnosis was 65 months (range 45-78) in the whole population, with Par/Pheo at the best and high grade GEP at the worst limit. SRE, high grade (or in alternative high Ki-67) and prior lung metastases resulted significantly associated with worse overall survival at the multivariable analysis. After adjustment for tumor grade, survival of patients with GEP and lung NENs were similar.

Conclusions
This is one of the largest series of NEN patients with BM reported so far. This survey mirrors the Italian real clinical practice in this setting, as it included most Centers involved in NET patients’ management. It showed that overall, BM from NEN are associated with a relatively long survival. Bisphosphonates were used in a low percentage of cases, probably related to SRE. Tumor grade confirmed its value in separating two survival categories, irrespective of primary site. The results of this analysis generated hypotheses for prospective trials in homogeneous clinical settings.

Legal entity responsible for the study
449P - Financial toxicity in patients with neuroendocrine tumors: Impact of a chronic disease on patients’ economic situation

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Background
The diagnosis of cancer imposes physical, emotional and financial burdens on patients. So far, the socio-economic impact of cancer for patients in Germany is poorly understood. The aim of the project is to provide an overview on patients' financial losses due to a neuroendocrine tumor (NET) diagnosis as well as possible psychosocial effects.

Methods
This prospective quantitative study recruited n = 123 patients with NET from November 2016 to March 2017 at the National Center for Tumor Diseases, University Hospital Heidelberg. They completed a survey on patients’ income, cancer-related out-of-pocket costs, disease burden (Distress Thermometer), quality of life (EORTC-LQ 29/30), health status (EQ-5D) and demographic data.

Results
78.0% (n = 96) of the patients stated to have higher out-of-pocket costs because of their disease, mostly in terms of travel expenses and co-payments for medication. With regard to loss of income, 29.3% (n = 36) of the participants reported a minus, which is beyond 800€ per month in almost half (44.4%) of these cases. 61.5% of the persons affected by income losses cannot compensate these by savings or credits. 33.3% (n = 41) of the responding patients indicated that they have to cut back on their expenses of daily living as a result of their disease. Higher cancer-related out-of-pocket costs per month were associated with lower estimation of patient's quality of life (p = 0.003), lower self-reported health status (p = 0.013) and a more severe perception of disease burden (p = 0.036) whereas a higher monthly income was strongly correlated with better quality of life (p = 0.008)/health status (p = 0.008) and lower disease burden (p = 0.006).

Conclusions
Given the fact that the majority of surveyed patients has to face financial losses due to their cancer diagnosis which is accompanied by the experience of distress as well as worsened quality of life and health status, there is a need for targeted measures that could prevent financial problems and reduce emotional burdens. Further research is required to address this aim.

Clinical trial identification
The trial was approved by the Instituional Research Ethics Committee (approval S-458/2016).

Legal entity responsible for the study
National Center for Tumor Diseases, University Hospital Heidelberg
Background
Advanced wd-NET patients (pts) are commonly treated with SSAs. PEI may be under-estimated in trials due to difficulties in distinguishing carcinoid syndrome-related diarrhoea and PEI.

Methods
In this single-institution, prospective, observational study, sequential pts with advanced wd-NET were commenced on SSAs and followed for a minimum of 12 months (or until disease progression). Toxicity was prospectively assessed monthly. Faecal elastase testing (FE) (for diagnosis of PEI) and quality of life (QoL) questionnaires (QLQ-C30 and QLQ-GI.NET21) were performed 3-monthly.

Results
Of 52 pts recruited (Jan 15-Apr 16), 50 were eligible: median age 65.8 yrs; 58% male; ECOG performance status 0 (42%), 1 (46%) or 2 (12%); primary: small bowel (60%), pancreas (22%), lung (12%) and other (6%). Baseline median Ki-67 was 3.1% (range 0.7-25), serum 5HIAA: 195 nmol/L (95%CI 145-318) and chromogranin A (CgA): 327 ng/mL (95%CI 140-582). Most pts were metastatic (92%), non-functional (66%) and started SSA first-line (88%); depot SSA was octreotide in 60%, lanreotide in 40%.

Forty-one pts (82%) started full-dose SSA (4-weekly octreotide 30mg or lanreotide 120mg); 96% achieved full dose; 3 pts required dose reduction due to toxicities. Grade (G) 1-2 toxicities were flatulence (50%), abdominal pain (32%), diarrhoea (30%), fatigue (20%), PEI (22%), nausea (16%), hyperglycaemia (6%), anorexia (4%) and constipation (2%). G 3-4 toxicities were few (G3 hyperglycaemia (n = 1) and G3 PEI (n = 1); no G4). Twelve pts (24%) developed SSA-related PEI (4 clinical diagnosis, 8 FE-confirmed) at a median of 2.9 mo (95%CI 1.7-8.6) after starting SSA; 11/12 (92%) pts received enzyme replacement. Questionnaires identified fatigue, insomnia and diarrhoea as the most important baseline symptoms; SSA therapy did not negatively-affect QoL. Estimated median progression-free survival (PFS) was 29.9 mo (95%CI 21.4-not reached). High baseline CgA was an independent factor for shorter PFS (HR 1.01 (95%CI 1.001-1.1); p-value 0.001) after adjustment for other factors (baseline 5HIAA, Ki-67).

Conclusions
SSA-induced PEI occurs in 1:4 pts; clinicians should actively identify and treat.

Legal entity responsible for the study
Background

The CLARINET core study established the antitumour activity of lanreotide Autogel 120mg/28 days (LAN) in metastatic enteropancreatic neuroendocrine tumours (NETs). The vast majority of the core study population (96%) had stable disease (SD) at baseline, but the LAN open-label extension (OLE) also included patients with progressive disease (PD; while receiving placebo [PBO] in the core study). Here, we report the final analysis of time to subsequent death/PD for patients with PD switched to LAN.

Methods

In the core study, patients with metastatic well-/moderately differentiated non-functioning enteropancreatic NETs received LAN/PBO for 96 weeks or until death/PD (RECIST 1.0). Eligible patients for the OLE (NCT00842348) had SD at core-study end or PD (with PBO only) during the core study. Adverse events (AEs) were recorded at 4-weekly visits. CT/MRI scans from OLE baseline (week 1) and every 24 weeks subsequently were assessed locally for PD (RECIST 1.0). Primary objective: long-term safety. Secondary objective: long-term efficacy, with assessments including PFS and time to subsequent death/PD (from Kaplan–Meier analyses; months approximated as 4 weeks).

Results

89 patients were treated in both core and OLE studies (42 LAN–LAN [SD, n = 41]; 47 PBO–LAN [SD, n = 15]); 40% of the LAN–LAN vs. 47% of the PBO–LAN group had treatment-related AEs. Overall median LAN PFS, based on the intent-to-treat population (n = 101), was 38.5 months. Seven PD events (no deaths) occurred during the OLE in 15 patients entering with SD from the PBO arm of core study. In total, 32 patients with PD whilst receiving PBO in the core study entered OLE (of 59 potentially eligible); NETs were in pancreas in 17 patients, midgut in 10, hindgut in one, and of other/unknown origin in four. Of these patients, 20 had subsequent PD during the OLE and three died; median time to subsequent death/PD was 19.0 months [95% CI: 10.1; 26.7].

Conclusions
The final analysis of the CLARINET OLE study suggests benefit with LAN in patients who had experienced PD when receiving no NET-specific treatment (PBO), with median time to subsequent death/PD of 19 months.

**Clinical trial identification**
NCT00842348

**Legal entity responsible for the study**
Ipsen Pharma

**Funding**
Ipsen Pharma

**Disclosure**
J.B. Cwikla: Travel expenses paid by Ipsen. E.M. Wolin: Advisory boards for Ipsen and Advanced Accelerator Applications. M. Pavel: Advisory boards and honoraria from Ipsen, Novartis, Pfizer and Lexicon; funding from Ipsen and Novartis for scientific research. A.T. Phan: Consultant for Ipsen and Novartis; Speaker’s bureau for Lilly, Genentech, Celgene, Lexicon, Novartis and Ipsen. M. Raderer: Honoraria from Ipsen, Novartis, Celgene, Roche and EASAI. E. Sedláčková: Consultant role for Ipsen; Speaker’s bureau for Ipsen, Novartis and Merck; funding from Ipsen and Novartis for scientific research; travel expenses paid by Ipsen, Novartis, Roche and Merck. G. Cadiot: Consultant role for Ipsen, Novartis, Advanced Accelerator Applications, and Keocyt; funding from Ipsen and Novartis for scientific research. J. Capdevila: Research, advisory role and speaker for Ipsen, Pfizer and Novartis. G. Rindi: Speaker’s bureau for Ipsen and Novartis. C. Lombard-Bohas: Consultant role for Ipsen, Pfizer and Novartis; funding from Ipsen and Novartis for scientific research. N. Liyanage, X-M. Truong Thanh: Employee of Ipsen P. Ruszniewski: Honoraria from Ipsen and Novartis; consultant role for Ipsen; Speaker’s bureau for Ipsen and Novartis; funding from Ipsen and Novartis for scientific research. M. Caplin: Honoraria from, consulted for, and participated in Speaker’s bureau for Ipsen and Novartis.

**452P - Temozolomide-capecitabine (TemCap) chemotherapy for neuroendocrine neoplasms (NENs): Time to maximum response and optimal treatment duration**

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M. Nasralla (Manchester, United Kingdom) C. Nuttall (Manchester, United Kingdom)

M. Frizziero (Manchester, United Kingdom) Z. Kordatou (Manchester, United Kingdom)

M. G. McNamara (Manchester, United Kingdom) R. A. Hubner (Manchester, United Kingdom)

P. Manoharan (Manchester, United Kingdom) W. Mansoor (Manchester, United Kingdom)

J. W. Valle (Manchester, United Kingdom)

**Background**

TemCap is an option for treatment of NENs; benefit of treatment until progression rather than a fixed 6-month (mo) course remains unclear.

**Methods**

Patients (pts) diagnosed with advanced NEN (pathology-confirmed), treated with TemCap with follow-up and available radiological response data were eligible for this retrospective study. Efficacy was assessed by RECIST v1.1.

**Results**

Of 62 pts identified (Jan’12-Jan’17), 60 were eligible. Median (med) age at starting
TemCap was 63.6 yrs; 50% were male; Performance Status (PS) 0-1 (83.3%), 2 (16.7%); with NEN of lung (33.3%), pancreas (21.7%), small bowel (16.7%), colorectal (3.3%) and other (25.0%) origin. The med Ki-67 was 12% (range 1-29); most (83.3%) were well-differentiated [grade (G)1/typical (18.3%); G2/atypical (65%); G3 (16.7%)], non-functional (75.0%) and metastatic (90.0%). Pts received TemCap as first- (33.3%) or second- (35.0%) line, for a med of 5.58 mo (95%CI 5.33-5.78). After 6 cycles, 38 pts (63.3%) were progression-free (i.e. eligible for maintenance TemCap [mTemCap]); 11 received mTemCap, 27 did not. Rationale for mTemCap was good response (n = 7), good tolerance (n = 3) or pts’ wishes (n = 1). Overall, 29 pts (48.3%) had stable disease and 14 pts (23.3%) achieved a partial response (PR); med reduction in responding pts was -56.7% (95%CI -76.4 to -33.3); 4 additional pts (6.7%) achieved a reduction >20% but <30%. Time to PR was 3.9 mo (95%CI 2.45-15.24); time to maximum response was 10.7 mo (7.2-11.8). By the end of follow-up, 95% and 75% of pts had stopped TemCap and progressed, respectively; estimated med PFS and overall survival (OS) were 10.1 mo (95%CI 6.7-14.2) and 27.3 mo (95%CI 16.35-NR), respectively. Achieving a PR was an independent factor (multivariable Cox regression) impacting on PFS (HR 0.2 (95%CI 0.1-0.6); p = 0.001); landmark analysis (excluding pts with early (3 mo) progression; n = 10) confirmed such findings.

Conclusions
Achieving a PR impacts on PFS in pts treated with TemCap. Although PR is an early event, maximum response is not achieved until later in pts’ treatment/follow-up; mTemCap until progression is appropriate for pts who are progression-free at 6 mo and have good tolerance to treatment.

Legal entity responsible for the study
N/A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

453P - Efficacy of recombinant human endostatin combined with chemotherapy in advanced pancreatic neuroendocrine tumors
Y. Cheng (Beijing, China)

Background
Dacarbazine or temozolomide, an oral analog of dacarbazine, showed activity against advanced pancreatic NETs when administered alone or in combination with other agents. Targeting pathways involved in angiogenesis, such as VEGFR TKI is also active in advanced pNETs. Endostatin is an endogenous angiogenesis inhibitor, rhEndostatin combined with chemotherapy prolonged overall survival compared with chemotherapy alone in advanced non-small cell lung cancer.

Methods
14 patients with histologically confirmed, locally advanced or metastatic pancreatic well-differentiated NETs with radiologic progression within the previous 12 months received the study regimen: Temozolomide was administered orally 150-200 mg/m2/d, d1-7. Dacarbazine and 5-FU were both administered intravenously at a dose of 250mg/m2/d and 500mg/m2/d respectively, d1-5. rhEndostatin was administered
intravenously at a dose of 15mg/d, d1-14, repeated every 21 days. CT/MRI was performed at baseline and every 3 cycles after initiation of treatment. Radiologic response was classified according to RECIST 1.1 criteria.

**Results**

Patients received a median of 6 treatment cycles (range, 2 to 8 cycles). Of the 14 patients, 6 patients received temozolomide and 8 received the DTIC + 5-FU combined with rhEndostatin. 5 patients used temozolomide as maintenance therapy, the median maintenance therapy cycles was 6 (range, 2 to 18 cycles). ORR was 43% (CR: 1 patient, PR: 5 patient), DCR was 86%, mPFS was 12 months, overall survival has not been reached. No grade 3/4 toxicity occurred.

**Conclusions**

rhEndostatin combined with temozolomide or darcarbazine-based chemotherapy was effective in treatment of advanced pNETs and was well tolerated.

**Clinical trial identification**

NCT01845675

**Legal entity responsible for the study**

Peking Union Medical College Hospital, Ethic Committee

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

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454P - Comparison of clinical efficacy of SST analogues therapy (lanreotide autogel vs. octreotide LAR) in treatment of patients with advance, non-resectable pancreatic neuroendocrine tumours (pNETs)

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J. Palucki (Warsaw, Poland)

L. Sawicki (Warsaw, Poland)
K. Roszkowska-Purska (Warsaw, Poland)
M. Kidd (Branford, United States of America)

L. Bodei (Milan, Italy)
I. Modlin (New Haven, United States of America)
J. Cwikla (Olsztyn, Poland)

**Background**

Use of somatostatin analogues can be considered in pancreatic NET G1/G2 as a first-line therapy. This retrospective study aimed to compare the efficacy of octreotide long-acting release (OCT) and lanreotide Autogel (LAN) in patient with advanced G1/G2 pNETs, comparison between LAN and OCT in naïve patients, based on progression free survival (PFS).

**Methods**

Ninety-two patients with histological proven G1 or G2 pNETs were retrospectively analyzed (41 men; 51 women; mean age 53.7 years [range 21-87 years]). The patients were assigned randomly to OCT (n = 42) and LAN (n = 50) groups. Evaluations included comparison of PFS between groups with LAN and OCT administered at 28-day intervals, objective response rate (ORR) calculated based on CT/MRI imaging performed every 6 month. The clinical efficacy was based on PFS and time to subsequent death/PD using Kaplan –Meier, radiological response was classified according to RECIST 1.0 criteria.

**Results**

Median PFS for all patients was 16.0 months (CI 22.8-34.9); in LAN group PFS 22 months (CI 21.9-39.5) vs OCT 15 (CI 18.1-35.1), P = 0.28 (Cox Mantel test). The significant
difference was noted in group of patients with G2 tumors LAN 22 months (CI 19.5-35.0) vs. OCT 7 months (CI 8.2-22.2) P = 0.01. Even higher significant difference was obtained in males group G2: LAN 23.5 (CI 16-44.6) vs. OCT 6.0 months (CI 3.3-14.3). There was no significant difference in female patients: LAN 17.5 mo (CI 15.4-34.8) vs. OCT 13 months (CI 8.2-29.4), but the trend favorable LAN over OCT. Additional analysis in patients with liver metastasis showed similar trend, but no significant difference. There was no difference in PFS between groups with G1 tumors in male or female patients and those without liver involvement.

Conclusions
Lanreotide Autogel is preferable SST therapy in G2 pNET, especially in male patients. Additional it seems to be also more effective in female patients but without statistical significance. The trend of better efficacy in terms of increase PFS seems to be in favor of LAN in patients with liver involvement as well. There was no significant difference in groups of patients with G1 pNEN and those without liver involvement.

Legal entity responsible for the study
Agnieszka Kolasinska-Cwikla

Funding
None

Disclosure
All authors have declared no conflicts of interest.

455P - Metastatic neuroendocrine neoplasia (mNEN) treatments in over 70 years (y) old patients: A retrospective outcome analysis

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Background
NEN incidence increases with age. Elderly population is usually underestimated in clinical trials due to presence of co-morbidities and low performance status (PS) and thus prognosis' informations are lacking. Our study aims to analyze the outcome in a retrospective cohort of elderly metastatic NEN patients (pts) who underwent different treatments.

Methods
From June 2006 to march 2016 we collected data from pts ≥70 y with mNEN. Comorbidities were summarized by the Charlson Comorbidity Index (CCI). Kaplan-Meier method was used to estimate overall survival (OS), Cox's proportional hazard model to assess the impact of known prognostic factors. Adjusted hazard ratios (HR) were calculated with 95% confidence interval (95% CI).

Results
We identified 145 pts ≥70 y with mNEN. Pts characteristics were resumed in the table. Median follow up was 72.3 (53.2-85.1) months. First Line treatment was: somatostatin analog (SSA) in 79 pts, peptide radionuclide therapy (PRRT) in 23, chemotherapy (CHT) in 36 pts. Seven pts didn’t receive first line treatment and 102 pts received more than 1 line treatment. PS ECOG and FDG PET results were identified as independent
prognostic factors for OS assessed by a multivariate Cox regression model, with a higher risk for patients with PS ECOG ≥0 and with positive FDG PET, while age at diagnosis showed a hazard ratio of 1.10 (95%CI:0.99-1.26). Median OS was 5.1y (3.4-6.6). No difference in mOS were seen according to CCI. G1/G2 NEN pts who underwent PRRT as first line had a mOS of 6.5 y (3.3-NE), SSA 5.7 y (4.2-7) and CHT 5.9 y (0.4-NE) respectively. G3NEN pts treated with CHT had a mOS of 1.5 y (1.0-2.5).

Table: 455P

**Pts characteristics N (%)**

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>86 (59.3)</td>
</tr>
<tr>
<td>Female</td>
<td>59 (40.7)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>74 (70-87)</td>
</tr>
<tr>
<td>70-74 years</td>
<td>89 (61.4)</td>
</tr>
<tr>
<td>75-79 years</td>
<td>40 (27.6)</td>
</tr>
<tr>
<td>80+ years</td>
<td>16 (11.0)</td>
</tr>
<tr>
<td>PS ECOG</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>59 (45.7)</td>
</tr>
<tr>
<td>1</td>
<td>60 (46.5)</td>
</tr>
<tr>
<td>≥2</td>
<td>10 (7.8)</td>
</tr>
<tr>
<td>Unknown(UK)</td>
<td>16</td>
</tr>
<tr>
<td>CCI</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57 (41.0)</td>
</tr>
<tr>
<td>1</td>
<td>52 (37.4)</td>
</tr>
<tr>
<td>2</td>
<td>19 (13.7)</td>
</tr>
<tr>
<td>≥3</td>
<td>11 (7.9)</td>
</tr>
<tr>
<td>UK</td>
<td>6</td>
</tr>
<tr>
<td>Syndromic</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (29.4)</td>
</tr>
<tr>
<td>No</td>
<td>101 (70.6)</td>
</tr>
<tr>
<td>UK</td>
<td>2</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>33 (26.2)</td>
</tr>
<tr>
<td>G2</td>
<td>62 (49.2)</td>
</tr>
<tr>
<td>G3</td>
<td>31 (24.6)</td>
</tr>
<tr>
<td>UK</td>
<td>19</td>
</tr>
<tr>
<td>Metastatic sites</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>58 (40.0)</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>29 (20.0)</td>
</tr>
<tr>
<td>Both</td>
<td>58 (40.0)</td>
</tr>
</tbody>
</table>

**Conclusions**

Our results suggest a positive impact of various treatment on OS in mNEN elderly patients.
and the prognostic value of FDG PET and PS ECOG. Prospective clinical trial are needed to confirm our retrospective data.

**Legal entity responsible for the study**
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.) IRCCS

**Funding**
None

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

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**456P - Modified staging classification for gastric neuroendocrine carcinomas on the basis of the American Joint Committee on cancer**

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**C. Zheng** *(Fuzhou, China)*
**P. Li** *(Fuzhou, China)*
**J. Lin** *(Fuzhou, China)*

**Background**
The purpose is to explore the value of the seventh edition of AJCC staging and improved AJCC staging in the evaluation of the prognosis of gastric neuroendocrine carcinoma (GNEC).

**Methods**
We analyzed retrospectively the clinical and pathological data of 427 GNEC patients from SEER database and 129 GNEC patients in single center. AIC and C index were used to evaluate the distinguishing capability of different TNM staging systems.

**Results**
In SEER database, the 5-year survival rate stratified by AJCC staging of GENC (I, IIa, IIb, IIIa, IIIb, IV) were 68%, 61%, 46%, 22%, 21%, and 10% respectively. While in single center, the 5-year survival rate of different stages were 100%, 60%, 27%, 16%, 22%, and 0% respectively. From the survival curve analysis, there are significant crossovers between the IIIB survival curves of SEER database as well as single center and those of IIIA and IIIB. In SEER database, the T staging and the age of disease diagnosis were independent factors affecting the prognosis of IIIB patients. According to the T staging, the IIIB was divided into four subgroups: T1N1, T2N1, T3N1, and T4N1. According to the principle of similar survival rate, the new AJCC staging is composed of different stages: nI(T1N0M0), nIIa (T1N1M0, T2N0M0), nIIb (T2N1M0, T3N0M0), nIIla (T3N1M0, T4N0M0), nIIIb (T3N1M0, T4N0M0) and nIV (T1-4NxM1). The survival curve of the new AJCC staging showed less crossover per stage, obtaining a smaller AIC value (1572 vs. 1583) and a smaller c-index (0.7505 vs. 0.7421). It is discovered that through employing the data of single center as external validation, the new AJCC staging can better distinguish different TNM staging.

**Conclusions**
Dividing IIIB of the seventh edition of AJCC staging into various sub-stages has significant prognostic value and the new AJCC staging can better distinguish the stages of GNEC.

**Legal entity responsible for the study**
Changming Huang

**Funding**
None

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

457P - Predictive factors in GEP-NEN: The integrated role of Ki67, beta-catenin and morphology

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Background
The WHO 2010 classification divides gastro-entero-pancreatic neoplasms (GEP-NENs) into G1, G2 and G3, according to Ki67 and/or mitotic index. Several studies have proposed to further divide G3 diseases in at least two subgroups, defined by Ki67 and/or morphological features. We investigated the morphological or immunohistochemical features associated with poorer prognosis and whether the G3 category could be further divided according to such features.

Methods
We evaluated 314 consecutive GEP-NEN patients. Surgical specimens of primitive tumors were assessed for morphology (m0: well-differentiated; m1: poorly-differentiated), Ki67 and beta-catenin (B01 absent or not-nuclear localization; B2 nuclear localization). Those features were correlated with overall survival (OS) and disease-free survival (DFS) after surgery by means of Cox multivariable models. The model performance was evaluated by means of Harrell’s C index.

Results
Median follow-up was 84 months (95% CI: 74-103). Based on Ki67 only, the WHO 2010 classification allowed to distinguish three classes with different prognosis (5-year OS: ≤2%: 97.0%, 2-20%: 90.9%, >20%: 14.5%). When considering Ki67 as continuous variable, and by including also morphology and beta-catenin in the multivariable OS model, patient-specific estimates were obtained, thereby improving the prognostic classification, particularly for G3 patients, which could be split in further sub-groups (Table). Harrell’s C index was 0.864. Similar results were obtained for DFS.

Conclusions
WHO 2010 classification stratifies the risk of OS and DFS for G1 and G2 diseases. On the other hand, the risk of death for G3 disease varies according to Ki67 values, morphology and beta-catenin. Morphology has the strongest predictive power, segregating two macro groups in which beta-catenin has a lower differential effect while a prognostic gradient by Ki67 (up to Ki67 ≤55) is evident.

Table:

547P Joint distribution of patients according to WHO 2010 classification by the results of the prognostic model

<table>
<thead>
<tr>
<th>WHO 2010 classification</th>
<th>m0,B01 Ki67 ≤2</th>
<th>m0,B2 Ki67 ≥2</th>
<th>m0,B01 Ki67 2-20</th>
<th>m0,B2 Ki67 2-20</th>
<th>m1,B01 Ki67 ≤2</th>
<th>m1,B2 Ki67 ≤2</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (Ki67 ≤2)</td>
<td>89</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G2(2 &lt; =20)</td>
<td>0</td>
<td>95</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

New Prognostic model's macro groups by Ki67 grading
G3(20≤55) 0 0 0 0 17 7 12 9 0
G3 (Ki67 >55) 0 0 0 0 0 0 0 0 83

Clinical trial identification
NO CLINICAL TRIAL

Legal entity responsible for the study
FONDAZIONE IRCCS Istituto Nazionale Tumori, Milano Ethical Committee Approved 48/16

Funding
None

Disclosure
All authors have declared no conflicts of interest.

458P - The preoperative blood lymphocyte-to-monocyte ratio acts as a superior prognostic factor and predicts tumor metastasis in gastric neuroendocrine neoplasms after surgery
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Background
The aim of this study is to investigate the prognostic significance of the preoperative blood lymphocyte-to-monocyte ratio (LMR) in gastric neuroendocrine neoplasms (g-NENs).

Methods
We enrolled 177 patients who had been diagnosed with g-NENs and undergone radical surgery. Receiver operating characteristic curve analysis was used to identify the optimal value for the LMR. Univariate and multivariate survival analyses were used to identify prognostic factors. A nomogram was adopted to predict recurrence free survival (RFS) and overall survival (OS) after surgery.

Results
The LMR was significantly lower in patients with g-NENs than in matched normal volunteers (NVs) (P < 0.05) and was associated with age, tumor site, tumor size, depth of invasion, the lymph node ratio (LNR) and lymphovascular invasion (all P < 0.05). Multivariate analysis demonstrated that the LMR was an independent prognostic factor for RFS and OS. The concordance index (C-index) of the nomograms for RFS (OS), which included the lymph node ratio, histological type and the LMR, was 0.776 (0.760), which was higher than the C-index of the traditional TNM staging system [0.678 (0.667)]. The recurrence rate was 38.9% (69/177), and the median time to recurrence was 10 months. We noted a significant correlation between the LMR and tumor recurrence, especially liver, peritoneal and lymph node metastases (all P < 0.05).

Conclusions
As an independent prognostic factor for survivals in patients with g-NENs, the LMR combined with the lymph node ratio and histological type had a more superior ability to predict clinical outcomes in post-surgery patients than the traditional TNM staging system. Patients with low LMRs require close surveillance to identify tumor recurrence early.
Background
Neuroendocrine tumours (NETs) are uncommon. Little data exist to guide follow-up in resected disease, with no consensus regarding the optimal follow-up frequency or modality. Follow-up imaging regimens are extrapolated from other gastrointestinal tumours. As NETs are heterogeneous, this may result in both over-use and underuse of investigations in patients.

Methods
A population-based retrospective cohort study using linked data from the Institute for Clinical Evaluative Sciences and the Ontario Cancer Registry (capturing more than 99% of incident cases in Ontario) was conducted to evaluate patients diagnosed with gastroenteropancreatic NETs in Ontario, Canada from 1994 to 2012. Recurrence-free survival and the frequency of cross sectional imaging (abdominal computed tomography (aCT), magnetic resonance imaging (aMRI) and ultrasound (aUS)) were the main outcomes.

Results
Nine hundred and thirty-six patients were identified with median follow-up 47 months. The mean age was 59, 51% were female, and distribution of primary cancers was: small intestine 47%, pancreas 20%, large intestine 21%, rectum 6.4%, stomach 6.0%. The median survival time to a composite outcome of recurrence or death was 7.2 years, and 9.5 years if censoring on death. The cumulative incidence of recurrence was 8.4% (95% CI 6.8% to 10.3%) within one year, 33.7% (95% CI 30.4% to 36.9%) within five years, and 48.5% (95% CI 44.4% to 52.4%) within 10 years. The rate of recurrence significantly increased with age (HR = 1.529 for age 50-70 compared to < 50, p = 0.0003) and pancreatic primary (HR = 1.463, p = 0.0006), but not income quintile (p = 0.1071), rurality (p = 0.1931) or gender (p = 0.3787). The rate of use of aCTs, aMRIs and aUS decreased over time, from 1.04 per 100 patient-days in months 1-3 to 0.22 at months 49-60. On average, 1.59 abdominal CTs per patient were performed in the first year, 0.83 in the second year and 0.52 in years 3-5.

Conclusions
Unlike colon cancer, significant numbers of NETs recur between 5-10 years after curative surgical resection. These data support the lengthening of follow-up for resected NETs to a minimum of 10 years. Future research should focus on the impact of imaging on early detection of recurrence and survival outcomes.

Legal entity responsible for the study
Sunnybrook Research Institute

Funding
None
460P - Elevated levels of 5-HIAA and CgA in patients with PanNETs from the CLARINET Study

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Background
While carcinoids frequently synthesize, and secrete serotonin into the circulation, and 5-HIAA is a common biomarker in the carcinoids, measurement of 5-HIAA in non-carcinoid PanNET patients (i.e. no hormone-related symptoms or nonfunctional) is not routinely recommended by international guidelines. The incidence of serotonin-producing PanNETs may be underestimated, with potential impact on clinical outcome when serotonin levels remain elevated. We sought to characterize 5-HIAA and CgA levels in PanNET patients who participated in the large placebo-controlled phase III CLARINET Study.

Methods
Evaluable data available for urinary 5-HIAA and serum CgA for patients with PanNET in CLARINET study were analyzed. Urinary 5-HIAA and Serum CgA were assessed at baseline and every 12 weeks thereafter through Week 96. Changes in urinary 5-HIAA and serum CgA levels were calculated using a non-parametric Wilcoxon 2-sample test. Biochemical response for urinary 5-HIAA or serum CgA was defined as baseline > upper limit of normal (ULN, 41.6 µmol/d 5-HIAA; 98.1 µg/L CgA) and ≥50% decrease from baseline or a decrease to a value ≤ ULN on study.

Results
91/204 patients in CLARINET had PanNETs. Evaluable data for urinary 5-HIAA and serum CgA concentrations were available in 79 and 88 patients, respectively. A substantial number of patients with PanNET had elevated (>ULN) urinary 5-HIAA levels (21/79; 27%) and/or serum CgA (63/88; 72%). Among the 21 PNET patients with baseline 5-HIAA >ULN, biochemical response was achieved in 85% (11/13) lanreotide-treated patients compared with 63% (5/8) in patients on placebo at the last available value (p = 0.33). Among patients with baseline CgA >ULN, biochemical response was achieved in 66% (19/29) of lanreotide vs. 18% (6/34) of placebo-treated patients (p = 0.0002). Limited sample sizes precluded robust analysis for statistically significant differences in the lanreotide vs. the placebo group among patients with elevated biomarkers at baseline and biochemical response.

Conclusions
The percentage of patients with elevated urinary 5-HIAA was unexpected. The concept of PanNET and secretion of serotonin may need to be redefined. The potential of 5-HIAA and CgA as biomarkers of response and follow-up in nonfunctioning PanNET is alluring,
but requires further study. Data from additional prospective studies are needed to impact clinical practice guidelines.

Clinical trial identification
NCT00353496

Legal entity responsible for the study
Ipsen Biopharmaceuticals

Funding

461P - The prognostic value of cytokeratin 7, 19, thyroid transcription factor-1 and CD117 expression in lung neuroendocrine tumors of various grades.

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Background
Neuroendocrine tumors of the lung (NETL) are a wide range of tumors with various malignancy grades and prognosis.

Methods
We performed immunohistochemical assessment of the diagnostic biopsies and surgical specimens from 205 patients with NETL aged 55-61 years and identified 61 (29.8%) typical carcinoids (TC), 44 (21.5%) atypical carcinoids (ATC), 84 (41%) small cell neuroendocrine carcinomas (SCNEC) and 16 (7.8%) large cell neuroendocrine carcinomas (LCNEC). Markers of neuroendocrine differentiation (synaptophysine, chromogranin A and CD56) and cytokeratins (CK) 7 and 19, thyroid transcription factor-1 (TTF-1), CD117 were used.

Results
Most often, the expression of CK7 and CK19 was found in LCNEC (71.4%, 10/14 and 91.7%, 11/12 respectively), less frequently, in ATC and SCNEC (52.8%, 19/36 and 52.4%, 22/42; 43.9%, 29/66 and 68.2%, 45/66 of cases, respectively), whereas in TC it was rare (13.3%, 6/45 and 19.3%, 11/57 respectively). The rates of CK7 and 19 expression were significantly lower in the TC, compared to the SCNEC and LCNEC (h<0.01, v.) The expression of TTF-1 was very rare in the TC (11.6%, 5/43 of cases) and significantly more often in ATC (60.5%, 23/38) and in SCNEC and LCNEC (79.2%, 57/72 and 75%, 9/12 of
cases, respectively). TTF-1 expression was significantly less frequent in typical than in ATC, SCNEC and LCNEC ($h < 0.01, v.$). The expression CD117 was absent in the TC (0%, 0/27), very rare in the ATC (17.4%, 4/23) and significantly more often in SCNEC and LCNEC (95.7%, 43/47 and 42.8%, 3/7 of cases, respectively).

**Conclusions**
Expression of TTF-1, CK7, 19 and CD117 in the NETL is characteristic for a less differentiated cell immunophenotype and allows for identification of the risk group with unfavorable clinical outcome among low-grade TC and ATC.

**Legal entity responsible for the study**
L. Gurevich

**Funding**
Not applicable

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

**462P - A nomogram based on tumor-associated neutrophil-to-lymphocyte ratio to predict survival prognosis for patients with gastric neuroendocrine neoplasms**

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**Background**
This study investigated the predictive value of the tumor-associated neutrophil-to-lymphocyte ratio (TA-NLR) on clinical outcomes for patients with gastric neuroendocrine neoplasms (g-NENs) after radical surgery.

**Methods**
Data from 142 patients who were diagnosed with g-NENs and underwent radical gastrectomy at our department from March 2006 to March 2015 were prospectively collected and retrospectively analyzed. Receiver operating characteristic curve analysis was used to identify the optimal value for TA-NLR. Univariate and multivariate survival analysis were used to identify prognostic factors for g-NENs. A nomogram was adopted to predict RFS and OS after surgery.

**Results**
TA-NLR was not significantly associated with clinical characteristics (all $P > 0.05$). TA-NLR significantly correlated with tumor recurrence, especially with liver and lymph node metastasis (both $P < 0.05$). A multivariate Cox regression analysis identified the TA-NLR as an independent prognostic factor for recurrence-free survival (RFS) and overall survival (OS) (both $P < 0.05$). The concordance index (C-index) of the nomograms, including the TA-NLR, Ki-67 index and lymph node ratio, for RFS (OS) was 0.788(0.759) and was higher than the C-index of the traditional TNM staging system [0.672(0.663)].

**Conclusions**
TA-NLR was an independent prognostic factor for patients with g-NENs regarding RFS and OS. Nomograms with the TA-NLR, Ki-67 index and lymph node ratio had a superior ability to predict clinical outcomes for postoperative g-NENs patients, as well as the traditional TNM staging system.

**Legal entity responsible for the study**
Changming Huang
**Background**
Small intestinal neuroendocrine tumors (siNETs) are notoriously difficult to diagnose, especially in an early stage. The EXPLAIN study aimed to investigate 92 plasma proteins (PP), previously shown to be cancer related, in an attempt to improve the accuracy in diagnosis of siNETs.

**Methods**
This non-interventional exploratory study in the nordic countries analysed 136 patients with siNET from 17 hospitals and 144 age and sex matched controls (all with written consent). Exclusion criteria: NET not confirmed, previously treated for NET, other malignant diseases, chronic inflammatory disease, kidney or liver failure. Blood samples (4 ml) were obtained at first visit. Samples analysis used the Proseek Multiplex Oncology II assay (Olink) to measure relative levels of the 92-cancer related PP. In addition, chromogranin A (CgA) was analyzed centrally (Akademiska Lab. Uppsala). Data was subjected to statistical supervised learning techniques (SSLT): random forest and support vector machine.

**Results**
This is the first interim analysis. Patient characteristics: age 65±10 (mean±SD), 58% male, 48% G1 and 52% G2, 88% N1 and 65% M1, 23% >3 bowel mov/d and 11.5% >3 flushes/d. CgA (mean (SD), nmol/L) in 115 patients free from proton pump inhibitor treatment (PPI): 42.37 (86.62), in 21 NET patients with PPI: 68.41 (74.21), in 132 controls free from PPI: 3.67 (3.57) and in 12 controls treated with PPI: 11.83 (8.97). Several PP (>20) showed significant p<.005 different mean levels compared with controls (t-test with Satterthwaite correction). Ten valuable PP in the model: CgA, LYN, ABL1, DKN1A, TXLNA, MUC-16, EGF, MetAP 2, VIM and MK.

<table>
<thead>
<tr>
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<th>SVM – Radial</th>
<th>SVM – Linear</th>
<th>Random Forest</th>
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<tbody>
<tr>
<td>Accuracy (95% CI)</td>
<td>0.8429 (0.7362, 0.9189)</td>
<td>0.8714 (0.7699, 0.9395)</td>
<td>0.8857(0.7872, 0.9493)</td>
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<tr>
<td>Sensitivity</td>
<td>0.7647</td>
<td>0.7941</td>
<td>0.8824</td>
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<tr>
<td>Specificity</td>
<td>0.9167</td>
<td>0.9444</td>
<td>0.8889</td>
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<tr>
<td>AUC</td>
<td>0.9191</td>
<td>0.9428</td>
<td>0.9404</td>
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Conclusions
Both a high level of sensitivity and specificity (0.9) were obtained using our multi plasma protein strategy combined with SSLT for the diagnosis of siNET. Further development of the machine learning model is ongoing.

Legal entity responsible for the study
Peter Myrenfors Ipsen

Funding
Ipsen

Disclosure
All authors have declared no conflicts of interest.

464P - CXCR4 inhibition by ulocuplumab prevents EMT of pNET cells in vitro
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Background
NETs overexpress CXCR4. We have previously shown that stimulation of CXCR4 by its ligand SDF-1 promotes EMT and increases the distant tumor spread of NET cells. Ulocuplumab (Ulo) is a fully human IgG4 mAb designed to inhibit the binding of SDF-1 to CXCR4. We investigated the effects of Ulo in preventing pNET spreading in vitro.

Methods
Complement-dependent cytotoxicity (CDC), Ab-dependent cell cytotoxicity (ADCC), Ab-dependent cell phagocytosis (ADCP) and direct Ab-induced apoptosis were investigated using three pNET cell lines (BON1, CM, QGP1) treated with Ulo. Transcriptome profiling was performed by RNAseq following incubation with SDF-1 in the presence or absence of Ulo. Flow cytometry was used to characterize the EMT-related phenotype of NET cells, as well as their expression of immune checkpoints in response to EMT-inducing stimuli. Migration and invasion of pNET cells towards liver and bone fragments was evaluated by transwell assays. The effects of Ulo on the intracellular signaling activated by CXCR4 stimulation were investigated by western-blot (WB), while confocal microscopy assessed the nuclear expression of CXCR4 after high-quality nucleocytoplasmic fractionation.

Results
Ulo failed to induce CDC, ADCC and ADCP in pNET cell lines, in absence of significant direct tumor cell killing. Ligand stimulation of CXCR4 promoted an EMT-like transcriptional shift (upregulation of SNAIL, ZEB1, SMAD2), which was abrogated by Ulo. Treatment with SDF-1 induced cadherin switch, but was unable to alter the membrane expression of immune checkpoints including PD-L1, PD-L2 and CD38. Both in vitro migration and invasion of pNET cells towards liver and bone were significantly suppressed by CXCR4 blockade. Stimulation of CXCR4 induced the phosphorylation of Akt, ERK, and NF-kB, resulting in Vimentin overexpression as well as acquirement of mesenchymal patterns including enhanced spindle index. These effects, inhibited by Ulo, were paralleled by a substantial enrichment of CXCR4 on the nuclear membrane.

Conclusions
Ulo suppresses EMT in pNET cell lines by both disabling the intracellular signaling downstream CXCR4 activation and preventing its nuclear localization. The pathophysiology of nuclear CXCR4 needs to be investigated.
465P - Interim baseline characteristics from RIFTOS MKI, a global non-interventional study assessing the use of multikinase inhibitors (MKIs) in the treatment of patients with asymptomatic radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC): A European subgroup analysis

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Background
RIFTOS MKI was designed to compare the time to symptomatic progression from study entry in patients with RAI-R DTC for whom there was a decision to treat or not to treat with an MKI in the real-life setting. Here, we report interim baseline characteristics for a subgroup of patients from Europe.

Methods
RIFTOS MKI is a non-interventional study enrolling patients from USA, Japan, Europe, and rest of the world with asymptomatic RAI-R DTC. The decision to initiate MKIs at study entry was at the discretion of the treating physician. Final analysis will be performed once 700 patients have been enrolled and the last enrolled patient has been followed for 24 months.

Results
Of the 80 patients enrolled from Europe, the median duration of observation was 165 days; 51% were male and the median age was 67 years. Most patients had an ECOG performance status of 0 or 1 (96%) and distant metastasis at initial visit (81%). The most frequent histology was papillary (61%). The median time from initial diagnosis of DTC to study entry was 7.7 years. RAI refractoriness was mainly due to lack of RAI uptake (70%) and the median time from RAI classification to initial visit was 25 months. The average dose per RAI treatment and median cumulative activity of RAI were 4.6 and 13.0 GBq, respectively.

Conclusions
The interim baseline characteristics results presented here are similar to those previously reported in phase III studies. The study is ongoing.

Clinical trial identification
NCT0230344

Legal entity responsible for the study
Bayer
Background

MANEC is a rare entity and evidence on its prognosis and management is limited.

Methods

Demographic/clinicopathological/survival data of consecutive patients (pts) with a diagnosis of MANEC (2010 WHO criteria) from 4 European centres were retrospectively reviewed.

Results

Fifty-three pts were identified (01/06-03/17); median (med) age: 62 yrs (range 34-89), male: 70%, ECOG PS 0-1: 60%, with primary tumours from small/large bowel in 34 (64%), oesophagus/stomach: 13 (24.5%), pancreas/biliary tract: 5 (9.5%), unknown (UNK): 1 (2%). Forty percent had an adult comorbidity evaluation (ACE)-27 score of 0. The neuroendocrine (NE) component (predominant histology in 40%) was poorly-differentiated (PD) in 45 (85%) [Ki-67≥55%: 58%]. Most frequently-expressed immunohistochemical (IHC) markers were synaptophysin (100%), chromogranin A (CgA) (58.5%) and CDX2 (51%). Histology was PD NE in 64% from recurrent/metastatic sites (n = 14 pts). Of 28 (53%) pts with localised disease (LA), 26 (93%) had curative surgery (7 had neoadjuvant chemo-radiotherapy (CT-RT), 6 adjuvant CT, 1 peri-operative CT), 1 (3.5%) had definitive CT-RT and 1 (3.5%) had UNK management; 16 (57%) recurred. Forty-one pts (77%) were treated for advanced (adv) disease: 20 (49%) platinum-based CT, 3 (7%) irinotecan-based CT, 1 (2.4%) gemcitabine, 3 (7%) UNK CT regimen, 1 (2.4%) RT, 1 (2.4%) CT-RT, 11 (27%) best supportive care (BSC), and 1 (2.4%) UNK management. Med follow-up time was 10.4 months (mo) (95% Confidence Interval (CI) 5.15-13.09). Med overall survival (OS) for all pts was 18.6 mo (95% CI 11.4-40). Med recurrence-free survival and OS in pts
with LA was 19.4 mo (95% CI 5.8-30.9) and 21 mo (95% CI 12.1-40). Med progression free survival (PFS) and OS in pts with adv disease was 4.6 mo (95% CI 3.3-6.7) and 13.6 mo (95% CI 8.8-33.1). On univariable analysis, ACE-27 score (0 vs ≥ 1) was prognostic for better PFS and OS (both p < 0.05); IHC negativity for CgA and active treatment (vs BSC) were prognostic for better PFS (both p < 0.05).

Conclusions
PD NE histology in MANECs was predominant in both diagnostic and recurrent/metastatic tumour samples. Active treatments were offered to most pts but more effective therapy is clearly needed.

Legal entity responsible for the study
The Christie NHS Foundation Trust

Funding
The Christie

Disclosure
All authors have declared no conflicts of interest.

467P - Incidence of adrenal gland tumor as a second primary malignancy: SEER based database

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Background
Adrenal gland tumors are sporadic and heterogeneous, with an incidence (excluding childhood neuroblastoma) of 0.05% in the US. Advances in cancer treatment in the last few decades have resulted in increased survival in most paediatric and adult cancer types. The aim here is to report the incidence of adrenal gland tumors as a second primary tumor based on data from the SEER database.

Methods
Data from the Surveillance, Epidemiology, and End Results ‘SEER’ program of the National Cancer Institute, using the SEER*stat software (version 8.3.2) was obtained. All cancer sites using the Multiple Primary Standardized Incidence Ratios ‘MP-SIR’ session were selected. SEER 13 Regs Research Data from 1992 to 2013 was used.

Results
Data from a total of 2,887,468 persons with cancer were reviewed, 117 of whom had suffered second primary adrenal tumors. One of these patients had two events of adrenal cancer as a second primary, resulting in a total of 118 incidences. The overall standardized incidence ratio (SIR) of adrenal gland tumor as a second primary was 1.49. A high percentage of this event was found in elderly patients, especially those of white race. High incidence of the event was detected in specific primary tumor sites: hypopharynx (O/E=44.59), stomach (O/E=4.95), small intestine (O/E=8.86), liver (O/E=8.74), breast (O/E=1.78), kidney and renal pelvis (O/E=3.19), other endocrine including thymus (O/E=38.27), nodal NHL (O/E=3.79), and Chronic Myeloid Leukemia (O/E=11.15).

Conclusions
Little is available in the literature about adrenal gland tumors as a second primary tumor. Its incidence is high in both white race and elderly cancer survivors in the US. The risk of
cancer survivors suffering from a second primary adrenal gland tumor should receive more attention in the US. This would ideally be through follow-up programs at specialized national cancer networks, especially for rare tumors like those of the adrenal gland.

Legal entity responsible for the study
None

Funding
None

Disclosure
All authors have declared no conflicts of interest.

468P - Activity of temozolomide (TMZ) in patients (PTS) with malignant pheochromocytoma or paraganglioma (MPP): A mono-institutional retrospective study

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Background
MPP are very rare neuroendocrine tumors and, currently, there is no standard chemotherapy for their treatment. TMZ showed some benefit in digestive neuroendocrine tumors. We investigate TMZ activity in PTS with MPP.

Methods
Retrospectively, we evaluated TMZ activity in MPP PTS treated at our oncological center, Veneto Institute of Oncology, from January 2015 to March 2017. The inclusion criteria were: pathological diagnosis of MPP, ECOG PS 0-2, no haemopoietic, renal and hepatic abnormalities. TMZ schedule was 150-200mg/m² for 5 consecutive days every 28 days until progression disease or unacceptable toxicity. CT scan and urinary concentrations of metanephrines were performed every 12 wks; evaluation of tumor response was performed according to RECIST 1.1 criteria. Germinal mutational analysis of the genes of susceptibility to pheochromocytoma/paraganglioma (SDHx, MAX, TMEM127, RET, VHL, FH) was performed. Aberrant hypermethylation of MGMT promoter was analyzed on DNA obtained from surgical tissue. Median OS and PFS were estimated by the Kaplan-Meier method. Toxicity was evaluated by CTCAE v.4.

Results
We enrolled 12 consecutive PTS; 7 were males; ECOG PS was 1 and 2 in 9 and 3 PTS. MAX gene was mutated in 1 PT. SDHB gene was mutated in 2 PTS. MGMT promoter was methylated in 1 patient. No other genetic mutations were found. 5 PTS were already treated with a prior chemotherapy (3 sunitinib, 1 capecitabine, 1 dacarbazine) and 4 with a prior MIBG. 9 PTS were evaluable for response: 2 PTS had a partial response, 5 stable disease, 2 progressive disease. Median follow up was 9.2ms (range 1.1-28ms). 2 PTS received TMZ for more than 2 years and other 2 PTS for more than 1 year. Median PFS and OS were not reached (95% CI = 3.4ms-n.a.; 6.2ms-n. a, respectively). Urinary metanephrines levels seem to correlate with response. Hypertension decreased significantly in 5 PTS during TMZ treatment. No grade 3-4 toxicity was recorded.

Conclusions
TMZ is an active and safe treatment for MPP, regardless of previous treatment. A
prospective phase II study is ongoing.

Legal entity responsible for the study
Giuseppe Lombardi

Funding
None

Disclosure
All authors have declared no conflicts of interest.

469P - Neuroendocrine carcinoma of the uterine cervix: A retrospective monocentric study

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A. Ducteil (Montpellier, France) D. Azria (Montpellier, France) C. Bourgier (Montpellier, France)
C. Kerr (Montpellier, France)

Background
Neuroendocrine cervical carcinoma (NECC) is a very aggressive and rare disease. To date, only 2 prospective studies with scarce patient numbers have been reported in the literature. Here we studied a NECC patients (pts) cohort treated with current anticancer treatment modalities.

Methods
All pts with NECC were retrieved from 1996 to 2013 in our institute (n = 14). 3D-conformal radiation therapy combined to concomitant chemotherapy (RT-CT) was performed to all pts. Chemo- regimen (CT) was cisplatin plus etoposide or carboplatin plus etoposide. Mean total dose to clinical target volume (CTV) was 48 Gy.

Results
Pts and treatments characteristics. Mean age was 48.5 years old. Most of pts had a loco regional disease (n = 11): stage IA (n = 1), IB (n = 1), IIA (n = 2) and IIB (n = 7); 3 pts were stage IVB. Pelvic and/or lombo-aortic lymph nodes involvement was observed in 42.8% pts (n = 6). Among them, 3 pts were treated with an extended lombo-aortic radiation field. Among the entire cohort, 2 treatment modalities were distinguished: (i) most of pts were treated with neoadjuvant CT followed by concurrent RT-CT (n = 9). Either pulsed-dose rate (PDR) brachytherapy (n = 4) or colpo-hysterectomy (=3) was performed according to tumor response. Adjuvant CT was performed to 3 pts in this subgroup (mean number of cycle: 3); (ii) colpo-hysterectomy followed by concomitant RT-CT and PDR brachytherapy (n = 1), adjuvant CT delivered to 1 patient (3 cycles). Pts outcome. Median follow up was 10 years (range, 0.3-11.2). Median overall survival (OS) was 1.9 years; (IC95% [0.8 –NC]); 1-, 2- and 5-y OS were 79%, 48% and 40% respectively. Median progression free survival (PFS) was 11.7 months (IC95% [6 - 59]); 1-, 2- and 5- y PFS were 50%, 29% and 21% respectively. At the time of study analysis, 5 pts were still alive without any progression disease and are considered as long patient survivor (follow up at least more than 6 years).

Conclusions
Despite the small number of pts in our study, pts outcome was consistent with the literature. This study showed a large variety of treatment modalities. To date, there is no consensus on how to treat these pts. However, owing to poor pts outcome, aggressive treatment modalities are probably required.
470TiP - AGITG NABNEC: A randomised phase II study of nab-paclitaxel in combination with carboplatin as first line treatment of gastrointestinal neuroendocrine carcinomas

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B. Markman (Melbourne, Australia) S. Yip (Sydney, Australia) E. Gibbs (Sydney, Australia)
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M. MICHAEL (Melbourne, Australia) K. Wilson (Sydney, Australia) J. Simes (Sydney, Australia)
L. Lipton (Melbourne, Australia)

Background
Neuroendocrine carcinomas (NEC WHO grade 3) are aggressive cancers that are rapidly fatal. There have been no randomised trials to date to establish standard therapy for advanced gastrointestinal (GI) NECs. Etoposide and carboplatin are used by extrapolation from small cell lung cancer data. Paclitaxel is also active in NECs but there is no data on the role of nab-paclitaxel. This randomised study aims to establish if carboplatin and nab-paclitaxel combination is an effective and tolerable treatment for advanced GI NECs.

Trial design
NABNEC has commenced as a randomised phase II multicentre trial enrolling adults with advanced and/or metastatic non-resectable GI NECs. Patients are randomised to: Arm A (n = 47) IV nab-paclitaxel 100 mg/m² on Day 1 every week and IV carboplatin AUC = 5 on Day 1 every 3 weeks OR: Arm B (n = 23) IV etoposide 100mg/m² on Days 1-3 every 3 weeks and IV carboplatin AUC = 5 on Day 1 every 3 weeks. Treatment will continue until disease progression or unmanageable toxicity. The primary endpoint is objective response rate (RR) by RECIST 1.1. At 6 months, the RR in the intervention group would need to be at least 50% to justify further investigation. A total sample size of 70 patients with a 2:1 randomisation (intervention to control) will have 80% power with 95% confidence to rule out a 30% objective RR in favour of a more clinically relevant RR of 50% at 6 months. Secondary endpoints include progression free survival, overall survival, safety as measured by NCI-CTCAE V4.03, and quality of life using EORTC QLQC30 and QLQ-GINET21 questionnaires. Translational research endpoints include (1) blood and tissue biomarkers (prognostic and/or predictive) correlated with clinical endpoints including (a) circulating tumour cells, (b) mutation profile by whole exome sequencing, (c) DNA methylation profile and (2) utility of 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging as an early predictor of response and association of SUV max with clinical endpoints. NABNEC has opened to recruitment at 9 study sites and is currently enrolling patients. The randomised NABNEC study will run at 20 sites in Australia and New Zealand. ANZCTR # 12616000958482.

Clinical trial identification
471TiP - A multicentre, randomised, double-blind, parallel-group, placebo-controlled trial of apatinib in local progressive or metastatic radioactive iodine-refractory differentiated thyroid cancer

Y. Lin (Beijing, China) S. Qin (Nanjing, China)

Background
Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) is a big challenge in the management of thyroid cancer. Sorafenib and lenvatinib are the 2 FDA-approved tyrosine kinase inhibitors (TKIs), which might not be affordable for most of the Chinese patients (pts). Apatinib is an oral TKI targeting VEGFR-2, with a patient assistance program available in China. It achieved a quick Tg decline of 21% 2 weeks later and an objective response rate (ORR) of 90%, showing promising efficacy in RAIR-DTC (Lin et al, ATA 2016, Short Call Poster 65; Lin et al, Oncotarget, Epub Feb. 02, 2017). Thus, this study aimed to further evaluate the efficacy and safety of apatinib in treating RAIR-DTC.

Trial design
This study is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, phase III trial in China. Adult pts with locally advanced or metastatic RAIR-DTC are eligible. The inclusion criteria include at least one measurable lesion; disease progression within the past 12 months; and ECOG PS 0–2. Pts are defined as RAIR-DTC if they have target lesion(s) without iodine uptake, received one RAI treatment (≥3.7 GBq [≥100 mCi]) but progressed within the past 12 months, received two RAI treatments or more with a time interval of less than 12 months and progressed at least 12 months later), or received cumulative RAI activity over 22.2 GBq (≥600 mCi). Previous targeted therapy is not allowed. Enrolled patients will be randomly assigned to receive apatinib (500 mg qd) and placebo, respectively. Four weeks is defined as one cycle. Dose increase to 750 mg and dose reduction to 250 mg are allowed. The primary endpoint is progression free survival. The secondary endpoints include disease control rate, ORR, duration of response, changes in serum Tg and TgAb concentration, quality of life, and safety. A multiple Cox proportional hazards model is used to evaluate the hazard ratios after adjusting iodine uptake, metastatic lesion site, gender, and age. 118 pts will be recruited assuming a 106.9% increase in median PFS in the apatinib arm compared with the placebo arm. As of 2nd May 2017, 3 eligible patients have been enrolled.

Clinical trial identification
NCT03048877 (Release date: February 7, 2017)
472TiP - Phase 2 clinical investigation of BPM31510 (ubidecarenone) alone and in combination with gemcitabine in patients with advanced pancreatic cancer

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Background
BPM31510 is an ubidecarenone lipid nanodispersion that switches cancer energy generation from glycolysis to mitochondrial oxidative phosphorylation to elicit anticancer effect. BPM31510 is well tolerated as a monotherapy and at an established MTD of 110mg/kg in combination with Gemcitabine in a Phase I clinical trial. Preclinical in vivo pancreatic models demonstrate that BPM31510 alone and in combination with gemcitabine significantly improves duration of survival; supporting the Phase 2 evaluation of BPM31510 in patients with advanced metastatic adenocarcinoma.

Trial design
Eligible patients (aged ≥ 18 y) relapsed/refractory to standard treatment (ST) and met inclusion/exclusion criteria. Each patient receives 110mg/kg IV BPM31510 in a 144-hour infusion alone or in combination with gemcitabine. Tumor response is evaluated at wk10 and then every 8 wks. Investigator observations and reports by treated patients provide clinical assessments not specifically defined in the protocol. This study initially will enroll ten (10) patients in the BPM31510 (monotherapy arm) and ten (10) patients in the BPM31510 plus gemcitabine (combination therapy arm) with intent to enroll the additional 15 patients into the applicable treatment arm(s) into the expansion stage based on RECIST v1.1 clinical response. The goal is to evaluate the Overall Response Rate (ORR) in patients treated with BPM31510 alone or in combination with gemcitabine along with Overall Survival (OS); Progression-Free Survival (PFS); Time to Progression (TTP); Tumor Response using Adaptive Molecular Responses (multi-omic molecular profiling); Evaluate Change in CA 19-9 levels and patient reported Quality of Life using the validated FACT-HEP patient-reported outcomes instrument.

Clinical trial identification
BPM31510IV-05

Legal entity responsible for the study
BERG, LLC

Funding
BERG, LLC

Disclosure
A. Niewiarowska: Clinical investigator paid by BERG, LLC to conduct studies. R. Sarangarajan: Employee, co-founder and has stock options of BERG, LLC. D. Lucius: Employee and has stock options of BERG, LLC. N. Narain: Employee, co-founder and has...
GENITOURINARY TUMOURS, PROSTATE

K. Fizazi (Villejuif, France) D. Lorente Estelles (Valencia, Spain)

794P - EPI-506 (ralaniten acetate), a novel androgen receptor (AR) N-terminal domain (NTD) inhibitor, in men with metastatic castration-resistant prostate cancer (mCRPC): Phase 1 update on safety, tolerability, pharmacokinetics and efficacy

U. Vaishampayan (Detroit, United States of America) R. B. Montgomery (Seattle, United States of America) M. S. Gordon (Scottsdale, United States of America) D. C. Smith (Ann Arbor, United States of America) K. Barber (Houston, United States of America) A. De Haas-Amatsaleh (Houston, United States of America) N. Thapar (Houston, United States of America) C. Chandhasin (Houston, United States of America) F. Perabo (Houston, United States of America) K. N. Chi (Vancouver, Canada)

Background

EPI-506 (ralaniten acetate) is being studied in a Phase 1/2 study as a first-in-class transcription inhibitor of the AR NTD.

Methods

Open-label, single-arm, Phase 1/2 study evaluating EPI-506 administered orally. The Phase 1 is a modified 3 + 3 design to establish safety, tolerability, pharmacokinetics (PK), maximum-tolerated-dose (MTD) and the recommended phase 2 dose (RP2D) of EPI-506. Anti-tumor activity is evaluated by PSA and imaging. Inclusion criteria include: mCRPC with progression after ≥1 line of hormonal therapy or chemotherapy, failure to treatment with enzalutamide and/or abiraterone.

Results

Twenty-one patients (pts) have been enrolled in the dose escalation phase over 6 dose levels (80 - 2,400 mg). Median age was 72 (range 58-87). Prior treatments included enzalutamide only (N = 9), abiraterone only (N = 3) or both (N = 9). Eight pts also had prior chemotherapy. Twelve pts discontinued due to disease progression and 2 pts due to adverse events (AEs): Grade 4 elevated amylase (probably related; at 640mg) and Grade 4 gastrointestinal bleeding (unrelated). Median exposure was 87 days at cut-off (range 21-418). Most frequently reported treatment emergent AEs were diarrhea (N = 8), nausea (N = 6), and pain in extremities (N = 5). One possibly related Grade 3 AE (AST elevation) was observed at 1280 mg. PK data demonstrate a dose-proportional profile for Cmax and AUC together with a positive food effect above 640 mg. Three of 21 evaluable pts demonstrated PSA declines ranging from 4 – 29%, and one pt with unchanged PSA at doses >1,280 mg. Three pts have had prolonged treatment (median of 286 days; range 219 – not reached), after intrapatient dose escalation. The study is currently enrolling pts with a total dose of 3,600 mg in both a QD and a BID dosing schedule.

Conclusions

EPI-506 is well-tolerated with an acceptable safety profile. PK indicates dose-proportionality. PSA declines and stable disease have been observed at higher dose cohorts in this ongoing study. This study is the first to evaluate targeting the AR NTD, a region critical for transcriptional function of all known AR species.

Clinical trial identification
Background
Castrate-resistant prostate cancer (CRPC) is a deadly disease which warrants new therapies. Clinical evidence supports a beneficial effect of immune stimulation in CRPC patients shown by sipuleucel-T. Dendritic cells (DC) are the immune system’s professional antigen presenting cells. The use of new DC subpopulations could improve their outcome.

Methods
In this phase II trial, HLA-A*02.01 positive chemo-naive CRPC patients were randomly assigned (1:1:1) to myeloid DC (mDC), plasmacytoid DC (pDC) or combined mDC + pDC vaccinations. Patients had disease progression by rising PSA or increase in measurable disease by RECIST 1.1 and PCWG2. Patients received DC vaccination loaded with the tumor-associated antigens MUC1, NY-ESO-1, and MAGE-C2. Radiological responses were assessed on 68Ga-PSMA PET-CT scan (incl. RECIST 1.1), iron oxide-enhanced MRI scan of lymph nodes (nano-MRI) and MRI bones. Primary endpoint is the immunological response post-DC vaccination. Main secondary endpoints are safety and feasibility, radiological PFS and PSA response.

Results
We present the early clinical results of the first 12 patients. Patients were assigned to mDC vaccinations (n=5), pDC vaccinations (n=5) or combined mDC + pDC vaccinations (n=2). All vaccine types were tolerated well (grade 1-2 toxicity in 4/12 patients). Most importantly, 8 of 12 patients (67%) showed radiological stable disease after 6 months using PSMA PET-CT scanning confirmed by (nano-) MRI scans. In patients with at least 9 months follow-up (n=6), 5 still show stable disease. Radiological stable patients showed a trend to an increased PSA doubling time (PSAdt); prevaccination PSAdt was 8.7 months (95% CI: 4.0-13.3) vs. 19.9 months (95% CI: 10.4-29.3) at 6 months.

Clinical responses in the first twelve CRPC patients treated with blood-derived DC
vaccinations.

<table>
<thead>
<tr>
<th>Blood-derived DC treated patient&lt;sup&gt;^&lt;/sup&gt;</th>
<th>Treatment at screening</th>
<th>GS</th>
<th>Disease sites</th>
<th>Side effects</th>
<th>Radiological response&lt;sup&gt;$&lt;/sup&gt; at 6 mo</th>
<th>Baseline PSA (ug/l)</th>
<th>PSA after 3 mo (ug/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LHRH + AA 4+5</td>
<td>Local, bone</td>
<td>None</td>
<td>SD</td>
<td>5.8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>LHRH 4+4</td>
<td>Local</td>
<td>None</td>
<td>SD</td>
<td>4.6</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LHRH + AA 3+4</td>
<td>Local</td>
<td>Hematoma</td>
<td>SD</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LHRH + AA 4+3</td>
<td>LN, bone</td>
<td>UTI</td>
<td>PD</td>
<td>39</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>SO + AA 3+4</td>
<td>LN</td>
<td>Diarrhea</td>
<td>SD</td>
<td>4.8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LHRH + AA 5+5</td>
<td>LN</td>
<td>FLS, fatigue</td>
<td>SD</td>
<td>6.3</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>LHRH + AA 4+5</td>
<td>Local, bone</td>
<td>None</td>
<td>SD</td>
<td>3.6</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>LHRH + AA 5+5</td>
<td>Local, LN, bone</td>
<td>None</td>
<td>PD</td>
<td>8.4</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>LHRH 5+4</td>
<td>LN</td>
<td>None</td>
<td>SD</td>
<td>5.7</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>LHRH + AA 4+5</td>
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<td>None</td>
<td>PD</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>LHRH 3+4</td>
<td>Local, LN, bone</td>
<td>None</td>
<td>PD</td>
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<tr>
<td>12</td>
<td>LHRH + AA 4+4</td>
<td>Bone Local, LN, bone</td>
<td>Dizziness</td>
<td>PD</td>
<td>41</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

AA: oral anti-androgen therapy (bicalutamide in nine patients and abiraterone plus dexamethasone); GS: Gleason score; FLS: flu-like symptoms; LHRH: luteinizing hormone-releasing hormone; progressive disease; PSAdt: prostate-specific antigen doubling time; SD: stable disease; SC: subcapsular orchidectomy; UTI: urinary tract infection; vac: vaccinations.

<sup>^</sup> vaccination with mDC (patients 1-5), pDC (patients 6-10) or combined mDC + pDC (patient 11 and 12).

<sup>#</sup> only vaccine-related Common Terminology Criteria for Adverse Events grade 1-2 side effects.

<sup>$</sup> radiological responses were assessed on advanced imaging with 68Ga-PSMA PET CT scans, nano-MRIs, and MRI bones using RECIST 1.1 and PCWG2 criteria.

* radiological and biochemical progression of disease was already present after 4 months, with vaccination.

**Conclusions**

Innovative DC vaccination is feasible and safe in early CRPC patients. Clinical results of the first 12 vaccinated patients showed radiological stable disease in 67% of patients at 6 months.

**Clinical trial identification**

ClinicalTrials.gov Identifier: NCT02692976. First received: September 30, 2015

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**796P - Phase I expansion cohort of TAS-115, a novel oral MET/VEGFR/FMS inhibitor, for castration-resistant prostate cancer patients (CRPC pts) with bone metastases**

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Background
TAS-115 is a novel small-molecule inhibitor of hepatocyte growth factor receptor (MET) and vascular endothelial growth factor receptor (VEGFR) with antitumor activity in preclinical models. It has also been shown that TAS-115 inhibits Feline McDonough Sarcoma oncogene (FMS) kinase, essential for the differentiation of osteoclasts, and is expected to be effective against bone metastases. In this expansion cohort of phase I trial, the safety and efficacy of TAS-115 were evaluated in CRPC pts with bone metastases.

Methods
Eligible CRPC pts with bone metastases who were refractory to standard treatment including docetaxel, abiraterone and/or enzalutamide were enrolled. Two dose levels of TAS-115 (450 and 650 mg/body/day) were administered orally with a 5-days-on/2-days-off schedule for up to 21 days per cycle in this expansion cohort. Efficacy was evaluated based on the RECIST ver 1.1 and bone scan response, defined as 30% decrease in bone scan index (BSI) calculated by quantitative software of BONENAVI®(FUJIFILM RI Pharma, Japan; EXINI bone®, Exini Diagnostics, Sweden). Toxicities were evaluated based on the CTCAE ver 4.03.

Results
As of Apr 2017, a total of 15 pts received TAS-115 (9 pts with 450 mg, and 6 pts with 650 mg). Bone scan response was reported in 4 of 9 pts (44.4%) who had baseline BSI ≥0.5%, which is equivalent to grade≥1 extent of disease. The best overall response per RECIST was stable disease in 7 of 15 pts (46.7%). These efficacies were observed regardless to dose levels. One patient had a long administration period exceeded to 15 months without disease progression, and another one patient experienced remarkable pain relief induced by bone metastases. TAS-115 had no effect on the PSA and ALP. The major (≥30%) adverse drug reactions (ADRs) were anorexia, fatigue, nausea, thrombocytopenia, rash, AST increased, anemia, vomiting and edema. The rate of grade ≥3 to all ADRs was 18.8%. These AEs were recovering by interruption of TAS-115.

Conclusions
Toxicities of TAS-115 were acceptable and manageable in CRPC pts, and preliminary anti-tumor activity, especially against bone metastases was recognized. A phase II trial for CRPC pts with bone metastases is ongoing.

Clinical trial identification
JapicCTI-132333/163448

Legal entity responsible for the study
Taiho Phermaceutical CO., LTD.

Funding
Taiho Phermaceutical CO., LTD.

Disclosure
Background
Despite toxicity and no clear clinical benefit, non-metastatic recurrent prostate cancer (nmPC) is typically treated with medical castration in North America. SM88 is a non-toxic novel combination therapy based on the Warburg effect, with activity in a variety of cancers including prostate (JCO 2017 e Abstract1). End of phase 1 results demonstrated stable or rising testosterone levels while achieving CTC (circulating tumor cells) benefit and no radiographic progression events (JCO 2017e Abstract2). We now report phase II data.

Methods
Starting in Sept 2016, a prospective Phase Ib/II of SM88 (230mg po bid) enrolled recurrent nmPC with rising PSA (PCWG3 definition) and detectable CTCs, but no radiographically identified lesions.

Results
8 (of 34 planned) subjects have completed at least 1 cycle (median 5, range 1-7). Mean age was 69.7 (62-80); all had prior ADT after curative intent RT (50%) or surgery (50%); no patient is currently on ADT. Mean testosterone level (T) was 581.4 ng/dL and rose or remained stable in the subjects except for one patient who entered the trial castrate (<2.5) from prior RT. Overall 62.5% had some grade 1-2 adverse event (AE) but there were no drug related serious AE. EORTC-QOL-P30 relating to intimacy (Q50-54) improved or remained stable. In subjects with more than 1 cycle (n = 5), CTCs fell to undetectable (n = 1) or decreased by >30% (n = 4); at up to 6 cycles, no PSA progression (PCWG3) and no radiographic progression was reported (n = 8). No subject required other toxic therapy (100% subsequent treatment free survival). Available preliminary neutrophile:lymphocyte ratio (N::L)(n = 6) improved while urinary NTx, bone specific AlkPhos and LDH trends were essentially unchanged. Table:

<table>
<thead>
<tr>
<th>subject #</th>
<th>cycles completed</th>
<th>T ng/dL</th>
<th>CTCs baseline</th>
<th>Max Decrease</th>
<th>N:L Max Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>635.7</td>
<td>26.75</td>
<td>100%</td>
<td>78%</td>
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<tr>
<td>2</td>
<td>6</td>
<td>&lt;2.5</td>
<td>44.75</td>
<td>77%</td>
<td>37%</td>
</tr>
</tbody>
</table>
Conclusions
We propose that hormonal castration is not necessary for nmPC disease control based on a preliminary assessment of both Phase Ib and II data of SM88. CTCs and N:L were improved while maintaining normal T. These early biomarker indicators are consistent with the observed 100% radiographic progression free survival and avoidance of additional toxic therapy. A phase III RCT is planned for confirmation of these results.

Legal entity responsible for the study
Tyme Inc

Funding
Tyme Inc

Disclosure
G. Del Priore, S. Hoffman, G. Sokol: Current or potential ownership of stock or options and/or salary support from Tyme Inc. W-T. Chen, H. Dong: Employee of Vitatex. Tyme Inc has a commercial relationship with Vitatex whereby Vitatex provides blinded results to the CRO supervising the ongoing clinical trial.

798P - Impact of the addition of metformin (Met) to abiraterone (Abi) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) progressing on Abi treatment: A phase II pilot study

M. Mark (Chur, Switzerland) D. Klingbiel (berne, Switzerland) U. Mey (Chur, Switzerland) R. Winterhalder (Luzern, Switzerland) C. Rothermundt (St. Gallen, Switzerland) S. Gillessen (St. Gallen, Switzerland) R. Von moos (Chur, Switzerland) G. Manetsch (Chur, Switzerland) R. Cathomas (Chur, Switzerland)

Background
Abi has become one of the standard 1st line treatments in mCRPC. Cross-talk signalling pathways such as PI3K/Akt/mTOR represent a possible resistance mechanism against Abi. The oral antidiabetic agent Met has been shown to have antiproliferative effects via inhibiting mTOR. We hypothesized that the addition of Met to pts with PSA progression on Abi could influence resistance to Abi and thus delaying start of second line therapy.

Methods
Men with mCRPC experiencing PSA progression on first line Abi were enrolled in this prospective single-arm open-label multicentre Phase II trial. Pts with visceral metastases were excluded. Abi (1000mg qd)/Prednisone (5mg bd) treatment was continued and pts received Met 1000mg bd in addition. Primary endpoint was progression-free survival (PFS) at 12 weeks according to RECIST 1.1 or PCWG2 criteria. Secondary endpoints included PFS, PSA response rate, OS, toxicity and safety. 25 pts were planned to consider the trial uninteresting (H0: PFS at 12 weeks ≤ 15%) or promising (H1: ≥ 35%) using a 5% significance level and a 80% power.

Results
25 pts with a median age of 76 years (IQR 72-82), were included between November 2013-September 2016 in 3 Swiss cancer centres. Median time to development of
castration resistance was 19.5 months (mts) (IQR 11-24), and median duration on Abi before study entry was 12.1 mts (IQR 8-19). PFS rate at 12 weeks was 12% (3 of 25 pts), median PFS was 9 weeks (IQR 7-11) and median OS 20.7 mts (IQR 14-23). One patient had PSA decline of 30% and another one of 26%, all other had PSA progression. 4 pts (16%) had radiographic progression at week 12. 11 pts (44%) had grade 1 and two pts each grade 2 (8%) or grade 3 (8%) gastrointestinal toxicity (nausea, diarrhoea).

Conclusions
The addition of Met to Abi in pts with mCRPC after PSA progression on Abi did not have a substantial impact on PFS or PSA response. Toxicity of Met in combination with Abi was higher than expected.

Clinical trial identification
NCT01677897

Legal entity responsible for the study
Michael Mark

Funding
Janssen

Disclosure
S. Gillessen, R. Cathomas: Advisor for the Janssen on advisory boards. All other authors have declared no conflicts of interest.

799P - Steroid switch: Reversal of resistance to abirateron acetate (AA) and prednisolone (P) combination in metastatic castration-resistant prostate cancer (mCRPC) patients
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Z. Küronya (Budapest, Hungary)K. Nagyíványi (Budapest, Hungary)L. Geczi (Budapest, Hungary)

Background
AA+P has shown to improve overall survival (OS) in large, randomized trial in the treatment of mCRPC both in pre and post-docetaxel setting. AA is a steroidal CYP17A1 inhibitor, which suppresses androgen synthesis. Because of secondary mineralocorticoid excess it is licensed in combination with P.

Methods
Based on previous data reporting responses following steroid switch upon progression during AA+P a prospective study in mCRPC pts was started. (Lorente at al BJC (2014) 111, 2248–2253).

Results
23 mCRPC pts were treated with AA (1000 mg q.d.) and P (5 mg b.i.d). Pts characteristics were as follows: median age 73 (95% CI 69-77) years, median Gleason score 8 (7-9), time-span since diagnosis was median 5.6 (3.6-7.8) yrs and all pts. had previous docetaxel treatment and received concomitant androgen deprivation treatment. Pts were on AA+P therapy for median 11.4 (6.4-19.8) mos. In case of PSA progression steroid switch has been applied to dexamethasone (D) (0.5 mg q.d). The PSA progression-free survival on AA+D combination was 5 (3.7-5) mos. 13 (57%) pts are still on AA+D treatment. The OS for AA was 53 (39-53) mos.

Table:

<table>
<thead>
<tr>
<th>Schedule</th>
<th>PSA progression-free survival</th>
<th>PSA (ng/ml) at</th>
<th>PSA (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
During AA+P therapy >25% decrease in PSA occurred in 65% of pts and further decrease (>25%, compared to the nadir during AA+P treatment) has been seen in 26% pts during AA+D treatment.

Conclusions
D can induce further response during AA therapy by reversing glucocorticoid receptor activation or by superior activity of D administered even as a single agent. Our data supports that steroid switch may induce further PSA regression.

Legal entity responsible for the study
Fruzsina Gyergyay

Funding
None

Disclosure
All authors have declared no conflicts of interest.

800P - Phase II study of prednisone-dexamethasone switch in metastatic castration resistant prostate cancer (mCRPC) patients treated with abiraterone and prednisone (AA+P)

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Background
Abiraterone Acetate (AA) improves overall survival in mCRPC patients. It is administered with prednisone (P) to decrease the adverse events derived from CYP171A supression. In phase I/II of AA without steroids, dexamethasone (D) 0.5mg/day was added after biochemical progression reaching a 25% of PSA decline. In a retrospective post-docetaxel cohort, Lorente et al (BJC, 2014) reported that the switch induced durable biochemical responses in 40% of cases.

Methods
This is a multicentre-prospective phase II study. Its primary aim was to evaluate the antitumour activity of the change of concomitant P 5mg/12h to D 0.5mg/24h daily in mCRPC patients with biochemical and/or limited radiological progression after ≥12 weeks of AA+P treatment. Biochemical response and progression free survival (bPFS) were evaluated by PCWG2 criteria. Radiological response and PFS (rPFS) were evaluated after 12 weeks by RECIST and PCWG2 criteria. Using a single-stage ÆHern Phase II design a minimum of 6 PSA responses >30% in 25 enrolled patients were required to
accept the alternative hypothesis (α:5%, 1-β:80%). PTEN and TMPRSS2-ERG in archival tumour-biopsies, AR aberrations in ctDNA and AR-V7 in exosomal RNA were evaluated. The Kaplan-Meier curves were used to calculate survival outcomes.

**Results**

26 patients were included. Their clinical characteristics are shown in Table 1. No new safety concerns were observed with AA+D. A decline in PSA≥30% and ≥50% were observed in 12 (46%) and 8 (35%) patients, respectively; two radiological responses were observed; bPFS and rPFS after P to D switch were 4.2 months (CI 95% 2.2-6.2) and 11.8 months (CI 95% 6.9-16.8), respectively.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AA+D pre-CT (n = 14)</th>
<th>AA+D post-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Median (range)</td>
<td>72.9 60-85</td>
<td>72.9 66-78</td>
</tr>
<tr>
<td>Baseline PSA Median (range)</td>
<td>26.6 4.5-367</td>
<td>39.9 6.9-1880</td>
</tr>
<tr>
<td>Gleason 6-7 8-10 UK</td>
<td>5 36 8 57 1 7</td>
<td>6 50 6 50</td>
</tr>
<tr>
<td>ECOG 0-1 2</td>
<td>13 80 1 7</td>
<td>12 100</td>
</tr>
<tr>
<td>Metastases Bone Nodes Visceral</td>
<td>12 86 8 57 1 7</td>
<td>12 100 4 33 3 25</td>
</tr>
</tbody>
</table>

**Conclusions**

In selected clinically stable mCRPC patients the P to D switch as adjuvant of AA could be an acceptable and active therapeutic option. Biomarkers correlation with P to D switch benefit will be reported.

**Clinical trial identification**

NCT02928432

**Legal entity responsible for the study**

Spanish National Cancer Research Centre (CNIO)

**Funding**

Spanish National Cancer Research Centre (CNIO)

**Disclosure**

D. Lorente Estelles: Speaker fees and advisory boards: Janssen. All other authors have declared no conflicts of interest.

**801P - Effect of sequence on outcome of prostate cancer patients: retrospective study of a French cohort**

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**Background**

several drugs are approved in prostate cancer (PC), both in localized and metastatic setting. Challenge of daily practice is the sequencing of available agents for optimal disease management. Trying to extract actionable information from the overall history of disease for each patient remains a difficult task but could provide new insights for better sequencing. This retrospective analysis aimed to follow-up patients included in the Rising-PSA phase 3 clinical trial (R-PSA-CP-03) until death or last contact.

**Methods**

we retrospectively analyzed therapies received by pts included in R-PSA at the HEGP hospital (Paris, France). Drugs were coded in 8 categories: LH: LHRH modulators, AA: anti-androgens, AA2: new generation AA, DC: docetaxel, CZ: cabazitaxel, EX: blinded
experimental drugs, P: therapeutic pause, PCB: placebo(experimental). Sequence rank, therapy duration and their interaction was estimated using both a conditional repeated events model (CREM) and a multi-state model (MSM) based on Markov process stratified on disease setting. Covariables included in the models were: age and Gleason score at inclusion time.

**Results**

152 pts included between 01/2003 and 09/2007 were followed > 10 years. Metastatic progression: 70(46%). Death: 31(20%). Median age(y): 64(51-80)), Gleason ≥8: 47(31%). Median (range) number of sequences received: M0=8(1-15) & M1=6(1-19) including pauses. Number of times each therapy was used whatever the sequence (%M0/%M1): LH(48/10), AA(6/6), AA2(0/22), DC(10/10), CZ (0/10), EX(1/6), PCB(0/2), P(35/34). Upon CREM, the overall model fitted perfectly well the time on therapies and their sequence (robust estimation: p < 0.00001). Main effects were mostly related to docetaxel, cabazitaxel and experimental drugs in the metastatic setting. Effect of sequence was significant but no therapy x sequence interaction proved to be significant. Comparable results were obtained upon MSM and will be presented.

**Conclusions**

to our knowledge, this is the first attempt to model the entire course of PC taking into account both therapies and sequence. Given the complexity of our model, these results should be validated with further studies and methods.

**Clinical trial identification**

R-PSA-CP-03

**Legal entity responsible for the study**

ARTIC

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

802P - Patient preference between Cabazitaxel and Docetaxel for first-line chemotherapy in metastatic castrate-resistant prostate cancer (mCRPC): Results from the CABADOC randomized trial

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**Background**

Docetaxel and cabazitaxel are taxane chemotherapy approved in men with mCRPC after they demonstrated improved overall survival in first- and second-line, respectively. Recent data suggested similar efficacy when used in the first-line setting (Sartor O, ASCO 2016). These two taxanes have different safety profiles. Assessing patient preference between docetaxel and cabazitaxel would contribute to further differentiate between these two agents.
Methods
The CABADOC study is a randomized trial with a cross-over design. Patients with mCRPC were randomized in a 1:1 ratio to receive either docetaxel 75mg/m2/q3w x 4 followed by cabazitaxel 25mg/m2/q3w x 4, or the reverse sequence. Randomisation was stratified based on prior abiraterone or enzalutamide. The primary endpoint was patient preference between taxanes, assessed in patients who had received at least one cycle of each taxane and who had not experienced a progression after the first taxane. Prescott’s test was used to analyze the primary endpoint taking into consideration the period effects.

Results
From June 2014 to October 2016, 195 patients were randomized in 17 centers. The median age was 70 years and the median PSA was 49 ng/mL. Patients received 3.8 ± 0.7 and 3.2 ± 1.5 cycles of chemotherapy during the first and the second period, respectively. The eligible population for the primary endpoint comprised 150 patients (45 patients were ineligible for the primary endpoint as per protocol). Among them, 66 preferred cabazitaxel (44% IC_{95%} = [36-52]), 40 preferred docetaxel (27% IC_{95%} = [20-34]), and 44 expressed no preference between taxanes (29% IC_{95%} = [22-37]) (p = 0.009). A greater proportion of patients preferred the first received taxane (44%, IC_{95%} = [36-52]) versus the second taxane (27%, IC_{95%} = [20-34]), or had no preference (29% IC_{95%} = [22-37]). Less fatigue and improved quality of life were the two main reasons provided by patients for their choice. There were 3 toxicity-related deaths (1.5%). Pharmaco-economic analysis, toxicity, and quality of life data will be presented.

Conclusions
A higher proportion of men with mCRPC who are candidates to receive a taxane prefer cabazitaxel over docetaxel.

Clinical trial identification
NCT02044354

Legal entity responsible for the study
Gustave Roussy

Funding
Sanofi

Disclosure
K. Fizazi: Advisory boards/honorarium for Amgen, Astellas, AstraZeneca, Bayer, Clovis, Curevac, Essa, Genentech, Janssen, Orion, Sanofi. G. Gravis: Travels supported by Astellas, Janssen and Sanofi. M. Gross-Goupil: Advisory boards/honorarium for Amgen, Astellas, Janssen, MSD, Sanofi. A. Fléchon: Honorarium from Astellas, Bayer, Janssen, Sanofi Transportation supported by Pfizer, Sanofi, Astellas, Janssen, MSD, AstraZeneca, Roche, Ipsen, Novartis. All other authors have declared no conflicts of interest.

803P - Indirect comparison of abiraterone acetate and docetaxel for treatment of metastatic “hormone-sensitive” prostate cancer

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Background
Androgen deprivation therapy (ADT) with or without chemotherapy (docetaxel [DOC]) is recommended in the clinical guidelines as the mainstay of management for metastatic “hormone-sensitive” prostate cancer (mHSPC). The LATITUDE trial demonstrated the efficacy of abiraterone acetate in combination with prednisone and ADT (ADT+AA+P) vs ADT in newly diagnosed mHSPC pts with high-risk disease (NDx HRD). We performed an indirect comparison to determine the relative efficacy of AA vs DOC in mHSPC.

Methods
We conducted a systematic literature review of randomized controlled trials (RCTs) of treatments for mHSPC. To increase comparability of results across studies, the population of interest from LATITUDE and DOC studies was restricted to men with NDx HRD and/or high volume disease (NDx HVD). Two RCTs (CHAARTED, GETUG-AFU 15), both evaluating ADT vs DOC+ADT, met the inclusion criteria. Fixed effects Bayesian network meta-analyses (NMAs) were performed to estimate the relative treatment effects for ADT+AA+P vs DOC+ADT on overall survival (OS) and radiographic progression-free survival (rPFS). The HVD subgroup of LATITUDE was used in the main analysis. The LATITUDE ITT population (NDx HRD) was included as a sensitivity analysis. As STAMPEDE did not report an NDx HVD/HRD subgroup, its M1 population was included in a sensitivity analysis.

Results
The results for HRD/HVD suggested improvement with ADT+AA+P vs DOC+ADT in OS (HR 0.84) and in rPFS (HR 0.73), with Bayesian probabilities (P) for ADT+AA+P 86.8% (OS) and 99.2% (rPFS) more effective. Main results were consistent with all sensitivity analysis results (Table). Table:

<table>
<thead>
<tr>
<th></th>
<th>ADT+AA+P vs ADT</th>
<th>ADT+DOC vs ADT</th>
<th>ADT+AA+P vs ADT+DOC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LATITUDE</td>
<td>CHAARTED GETUG-AFU</td>
<td>STAMPEDE</td>
</tr>
<tr>
<td></td>
<td>HVD &amp; HVD &amp; HRD</td>
<td>15</td>
<td>M1</td>
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<td>Main analysis</td>
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<td>OS</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>rPFS</td>
<td>X</td>
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<tr>
<td>Sensitivity analysis</td>
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<tr>
<td>OS</td>
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<td>OS</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>rPFS</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

803P
Conclusions
Our analyses suggest that ADT+AA+P has greater reduction in risk of progression and death vs ADT+DOC. In absence of head-to-head trials, indirect comparisons based on Bayesian NMA can provide useful insights to clinicians and reimbursement decision makers on the relative efficacy of treatment options for men with mHSPC.

Clinical trial identification
NCT01715285 (LATITUDE), NCT00309985 (CHAARTED), NCT00104715 (GETUG-AFU 15)

Legal entity responsible for the study
Janssen Global Services, LLC

Funding
Janssen Global Services, LLC

Disclosure

804P - Practice patterns in metastatic castration-resistant prostate cancer (mCRPC): Evidence from the veterans health administration

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S. Narayanan (South San Francisco, United States of America) S. Lin (South San Francisco, United States of America)
S. Carroll (South San Francisco, United States of America) L. Hsu (South San Francisco, United States of America)
J. Graff (Portland, United States of America) R. Dreicer (Charlottesville, United States of America)
S. Gupta (Salt Lake City, United States of America) C. Low (Salt Lake City, United States of America)
B. C. Sauer (Salt Lake City, United States of America)

Background
Practice patterns for metastatic castration-resistant prostate cancer (mCRPC) have evolved over the last decade due to introduction of agents such as abiraterone and enzalutamide. This study examines mCRPC treatment practices over a 10-year period (which includes the time periods before and after the introduction of novel oral anti-androgens) for the first 3 lines of therapy in the largest nationwide integrated health system in the United States, the Veterans Health Administration.

Methods
By linking patient information from the Veterans Affairs (VA) Clinical Cancer Registry to clinical notes, laboratory, procedure and imaging data from the VA Corporate Data Warehouse (CDW), we identified patients who were diagnosed with prostate cancer at the VA and ultimately developed mCRPC, defined as radiological evidence of metastasis and evidence of rising PSA levels concomitant with surgical (bilateral orchietomy) or medical castrate testosterone levels (≤ 50 ng/dL within the last 3 months or ongoing treatment with
androgen deprivation). Therapies used to treat mCRPC were extracted from CDW pharmacy dispensation records (docetaxel, abiraterone, enzalutamide, cabazitaxel, and others).

**Results**

From 2006 to 2015, 120,374 patients were diagnosed with prostate cancer, of whom 3,637 developed mCRPC. Median age at initial prostate diagnosis was 68 years (range, 41-94), average BMI was 26.5 (range, 9-59), average CCI score was 1.5 (range, 0-12) and average PSA was 45.5 ng/mL. Practices for the first 3 lines of treatment from 2006 to 2010 and 2011 to 2016 are summarized in Table 1. Patients diagnosed with mCRPC between 2006 and 2010 were more likely to receive cytotoxic therapy than patients diagnosed between 2011 and 2016 (37% vs 22%). Compared with the cohort diagnosed between 2006 and 2010, the later cohort was more likely to receive treatment (44% vs 62%) and was also more likely to receive > 1 line of therapy (20% vs 37%). For patients diagnosed between 2011 and 2016, the most common therapies were as follows: 1L, abiraterone (29%); 2L, abiraterone (15%) and enzalutamide (14%); and 3L, enzalutamide (8%).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1L, % pts 2L, % pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOC 27%, AA 22%, ENZ 6% AA 13%, ENZ 10%, DOC 4% ENZ 6%, DOC 4%, AA 3%</td>
<td>DOC 37%, AA 4%, ENZ 1% AA 7%, MIT 5%, CAB 3% AA 3%, ENZ 2%, DOC 2%</td>
<td>AA 29%, DOC 22%, ENZ 9% AA 15%, ENZ 14%, DOC 6% ENZ 8%, DOC 5%, AA 3%</td>
</tr>
<tr>
<td>No treatment, % pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1L 43%, 2L 68%, 3L 86%</td>
<td>1L 56%, 2L 80%, 3L 90%</td>
<td>1L 38%, 2L 63%, 3L 81%</td>
</tr>
<tr>
<td>Top 3 most common treatment sequences from 1L to 2L (% of pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOC-AA (11%) AA-ENZ (8%) AA-DOC (4%)</td>
<td>DOC-AA (7%) DOC-MIT (5%) DOC-CAB (3%)</td>
<td>DOC-AA (12%) AA-ENZ (11%) AA-DOC (5%)</td>
</tr>
</tbody>
</table>

AA, abiraterone acetate; CAB, cabazitaxel; DOC, docetaxel; ENZ, enzalutamide; MIT, mitoxantrone * ≤15 patients were treated with radium-223 dichloride or sipuleucel-T

**Conclusions**

Our study is the first to describe adoption of non-chemotherapeutic treatments in a nationwide cohort of patients with mCRPC treated in the largest integrated healthcare system in the United States. Further research will focus on understanding clinical outcomes associated with this shift in practice patterns.

**Clinical trial identification**

N/A

**Legal entity responsible for the study**

Ahmad Halwani, MD

**Funding**

Genentech, Inc.
Disclosure

805P - Efficacy and safety of first-line combined androgen blockade in advanced prostate cancer: A meta-analysis

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F. Liu (Shanghai, China) S. Ren (Shanghai, China) H. Wang (Shanghai, China) X. Lu (Shanghai, China)
X. Gao (Shanghai, China) C. Xu (Shanghai, China)

Background
Combined androgen blockade (CAB) is one of the therapies for advanced prostate cancer. In this analysis, we compared the efficacy and safety of first-line CAB with castration monotherapy in advanced prostate cancer patients.

Methods
The meta-analysis was PRISMA compliant and was registered in PROSPERO (CRD42016054301). We searched PubMed, EMBASE, Cochrane and Scholar for randomized controlled trials (RCTs) published through 12th December 2016 and compared efficacy and safety of first line CAB vs. luteinizing hormone releasing hormone agonists (LHRHa) monotherapy/orchiectomy in advanced prostate cancer. Overall survival (OS) and progression free survival (PFS) were the primary outcomes (fixed/random effects model). Safety was the secondary outcome. Sub-group analyses included: i) Eastern vs. Western patients; ii) non-steroidal anti-androgen (NSAA) vs. steroidal anti-androgen (SAA). Studies with reported HR/presenting median survival and JADAD score >2 were included.

Results
We identified 16 studies (6084 patients; West-12; East-4) for inclusion. CAB treatment significantly improved the OS (14 RCTS; HR 0.90; 95% CI 0.84 to 0.97, P = 0.003) and PFS (13 RCTs; HR 0.89; 95% CI 0.80 to 1.00, P = 0.04) in advanced prostate cancer patients, compared with monotherapy. No significant difference in OS (P = 0.71) and PFS (P = 0.49) was observed between Western vs. Eastern patients. CAB with NSAA significantly improved OS (HR 0.88; 95% CI 0.82 to 0.95, P = 0.0009) and PFS (HR 0.85; 95% CI 0.73 to 0.98, P = 0.007); whereas, CAB with SAA reported similar OS (HR 1.03; 95% CI 0.86 to 1.25, P = 0.74) or PFS (HR 1.01; 95% CI 0.87 to 1.17, P = 0.74) compared with castration monotherapy. Incidence of grade 3 or 4 AEs was not significantly different between CAB and castration monotherapy (P = 0.1083).

Conclusions
First-line CAB therapy significantly improved OS and PFS in advanced prostate cancer patients, with no significant difference in grade 3 or 4 AEs compared with castration monotherapy.

Legal entity responsible for the study
Shanghai Changhui Hospital. 168 Changhui Road, Shanghai 200433, China

Funding
AstraZeneca

Disclosure
All authors have declared no conflicts of interest.

806P - Outcomes of prechemotherapy (pCRx) abiraterone acetate (AA) or enzalutamide (E) for metastatic castration-resistant prostate cancer (mCRPC) after ADT + Docetaxel (D) or ADT alone for metastatic hormone sensitive prostate cancer (mHSPC) in a multi-institution hospital-based registry

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Background
The E3805: CHAARTED trial noted that the addition of D to ADT was associated with a hazard ratio (HR) of 0.56 (95% confidence interval [CI], 0.44 to 0.70; P < 0.001) for time to CRPC and resulted in a prolongation of overall survival (OS). Therefore, we postulated that pCRx AA or E had greater activity after ADT+D compared to after ADT alone.

Methods
A cohort of mCRPC patients (pts) treated with pCRx AA or E for mCRPC between 2014 and 2017 was identified from three hospitals’ IRB approved databases. Patients were grouped by use of D for mHSPC. This time frame was chosen as ADT+D became a valid therapeutic option for mHSPC in 2014 and thus time to pCRx and follow-up were short. The endpoints included OS (time to death from all causes) from ADT start, time to AA/E start from ADT start, and OS from AA/E start. Survival outcomes were analyzed by Kaplan-Meier method.

Results
Of the 102 identified, 50 (49%) had previously received ADT alone, while 52 (51%) had ADT+D. No statistically significant difference in OS from ADT start or from AA/E start was observed between the 2 cohorts (Table 1). Notably, survival in both groups from ADT start was shorter than commonly reported. Yet, deaths in the ADT+D group were 12 vs. 21 in the ADT alone, after a median follow-up of 24.4 and 29.8 months, respectively.

Conclusions
In a cohort of ADT/ADT+D treated mCRPC pts with short times to pCRx AA/E and follow-up, the efficacy of AA/E is similar regardless of previous use of D. It is possible that the pts selected for ADT+D had poorer prognostic factors and yet still did at least as well
with AA/E and deaths were lesser. Larger sample sizes, longer follow-up, and better characterization of patient and tumor factors are needed to assess the efficacy of different sequences.

Table:

<table>
<thead>
<tr>
<th>pCRx</th>
<th>AA/E</th>
<th>N (%)</th>
<th>N Deaths (median follow-up mo)</th>
<th>Median OS from ADT start (95% CI mo)</th>
<th>P-value</th>
<th>Time to AA/E start (95% CI mo)</th>
<th>P-value</th>
<th>Median OS from AA/E start (95% CI mo)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADT</td>
<td>50</td>
<td>21 (29.8) (49%)</td>
<td>33.5 (22.4 – NR)</td>
<td>0.2047</td>
<td>11.0 (8.5 – 13.7)</td>
<td>0.7265</td>
<td>17.3 (13.7 – NR)</td>
<td>0.6514</td>
</tr>
<tr>
<td></td>
<td>ADT+D</td>
<td>52</td>
<td>12 (24.4) (51%)</td>
<td>NR (NR-NR)</td>
<td></td>
<td>12.8 (11.1 – 15.7)</td>
<td></td>
<td>NR (13.1 – NR)</td>
<td></td>
</tr>
</tbody>
</table>

Legal entity responsible for the study
Edoardo Francini

Funding
None

Disclosure

807P - First interim results of the radium-223 (Ra-223) REASSURE observational study: Analysis of patient (Pt) characteristics and safety by use of abiraterone and/or enzalutamide (Abi/Enza)

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M. Schostak (Magdeburg, Germany) J. Sylvester (Lakewood Ranch, United States of America)
S. George (Buffalo, United States of America) M. Tucci (Orbassano, Italy)
C. Mantz (Fort Myers, United States of America) P. Borrega (Cáceres, Spain) P. Ziem (Neubrandenburg, Germany)
R. Concepcion (Nashville, United States of America) K. Miller (Berlin, Germany)
O. Sartor (New Orleans, United States of America) J. Kalinovsky (Bratislava, Slovak Republic)
Y. De Sanctis (Whippany, United States of America) B. Tombal (Brussels, Belgium)

Background
Ra-223 prolongs survival with a favorable safety profile in metastatic castration-resistant
prostate cancer (mCRPC). The pivotal phase 3 ALSYMPCA trial had a relatively short 3-year follow-up and was conducted before availability of 2nd generation hormonal agents. The REASSURE study was designed to assess long-term safety (7 years follow-up) and conducted in an era when pts had access to other effective 1st line agents such as abi/enza.

Methods

REASSURE is a global, prospective, single-arm, observational study that enrolled pts with mCRPC with bone metastases planned to start Ra-223. Treatment decision was made independently before enrollment. We undertook a planned interim descriptive analysis of safety and drug completion based on prior or concomitant abi/enza use.

Results

REASSURE enrolled 1106 pts in N. America and Europe from Sep 2014 to Sep 2016. The interim analysis included 583 pts who received ≥1 Ra-223 dose (Table; median 7 months observation). Prior abi/enza use was reported in 168 (29%) and concomitant in 153 (26%) pts. Treatment-related adverse events (TRAEs) occurred in 37%; prior abi/enza 45%, no prior abi/enza 34%; concomitant abi/enza 29%, no concomitant abi/enza 40%. TRAEs were most often gastrointestinal or hematological, with permanent discontinuation of Ra-223 in 6%; prior abi/enza 8%, no prior abi/enza 5%; concomitant abi/enza 5%, no concomitant abi/enza 7%. Serious TRAEs (mostly hematologic) occurred in 4.5% leading to permanent Ra-223 discontinuation in 1.5%.Table:

807P Baseline characteristics and treatment completion by prior or concomitant* abi/enza

<table>
<thead>
<tr>
<th>Prior – Yes (n = 168)</th>
<th>Prior – No (n = 415)</th>
<th>Concomitant – Yes (n = 153)</th>
<th>Concomitant – No (n = 430)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG 0–1, n (%)</strong></td>
<td>122 (73)</td>
<td>329 (79)</td>
<td>121 (79)</td>
</tr>
<tr>
<td>No. of metastases**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>42 (26)</td>
<td>123 (32)</td>
<td>53 (37)</td>
</tr>
<tr>
<td>6–20</td>
<td>81 (51)</td>
<td>221 (58)</td>
<td>86 (60)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>39 (24)</td>
<td>67 (17)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Superscan</td>
<td>14 (9)</td>
<td>21 (5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>ALP (U/L), median</td>
<td>155</td>
<td>115</td>
<td>114</td>
</tr>
<tr>
<td>&lt;140 U/L, n (%)</td>
<td>58 (35)</td>
<td>153 (37)</td>
<td>54 (35)</td>
</tr>
<tr>
<td>≥140 U/L, n (%)</td>
<td>73 (43)</td>
<td>126 (30)</td>
<td>51 (33)</td>
</tr>
<tr>
<td>PSA (ng/mL), median</td>
<td>136</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>LDH (U/L)***, median</td>
<td>327</td>
<td>260</td>
<td>291</td>
</tr>
<tr>
<td>Prior docetaxel or cabazitaxel, n (%)</td>
<td>96 (57)</td>
<td>100 (24)</td>
<td>46 (30)</td>
</tr>
<tr>
<td>Completed 5 or 6 Ra-223 doses, n (%)</td>
<td>87 (52)</td>
<td>282 (68)</td>
<td>106 (69)</td>
</tr>
</tbody>
</table>

* Prior = abi/enza stopped before starting Ra-223. Concomitant = any overlap with Ra-223.

** Pts undergoing more than one imaging modality may be reported in multiple categories.

***
LDH was available for 209/583 patients.

Conclusions
Ra-223 has a good short-term safety profile when used in the routine clinical practice setting. Prior or concomitant abi/enza does not appear to increase TRAE incidence. Pts who had prior abi/enza had a lower rate of completing full Ra-223 dosing, perhaps reflecting poorer prognosis or more advanced disease as suggested by higher median PSA and LDH levels.

Clinical trial identification
NCT02141438

Legal entity responsible for the study
Bayer Healthcare

Funding
Bayer Healthcare

Disclosure

808P - A phase II study of enzalutamide (Enz) with dutasteride (Dut) or finasteride (Fin) in men ≥ 65 years with hormone-naive systemic prostate cancer (HNSPCa)

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M. Riese (Milwaukee, United States of America) J. Burfeind (Milwaukee, United States of America)
K. Musto (Milwaukee, United States of America) C. Feng (Rochester, United States of America)
E. Messing (Rochester, United States of America) S. Mohile (Rochester, United States of America)
C. Fung (Rochester, United States of America)

Background
Older men are at risk for adverse events (AEs) from androgen deprivation therapy (ADT). In prior studies, peripheral androgen blockade with bicalutamide and Fin was better tolerated but less efficacious than ADT in HNSPCa. The potential synergism of Enz and
Dut/Fin provided the rationale for this Phase II study.

**Methods**
Eligible subjects were ≥ 65 yrs; at risk of AEs from ADT as determined by treating physicians; had metastatic (M1) or non-metastatic (M0) HNSPCa with a PSA doubling time <9 months; and had testosterone >50 ng/dl. Enz (160mg daily) with Dut (0.5mg daily) or Fin (5mg daily) was given until progression per the Prostate Cancer Working Group 2 guidelines or unacceptable AEs. Comprehensive geriatric assessment (CGA) was done at baseline and every 4 months. The primary endpoint is time to PSA progression. The secondary endpoints are time to PSA nadir, AEs, and effects on CGA domains.

**Results**
As of 4/15/17, we completed study enrollment of 40 subjects. Herein, we report outcomes of the first 31 subjects with a median follow-up of 43 weeks. Median age at enrollment was 80 yrs. 29%, 61%, and 10% had ECOG performance status of 0, 1, and 2, respectively. 45% had M0 and 55% had M1 HNSPCa. Gleason’s sum was 6, 7, >8, and unknown in 19%, 49%, 23%, and 9%, respectively. At enrollment; the median PSA was 12.71 ng/ml. CGA showed cognitive impairment in 61%, physical impairment in 54%, depression in 16% and impairment of instrumental activities of daily living in 13%. The median time to 90% PSA decline was 7 weeks. 79% of patients had 80% DHT decline by 9 months. At the time of analysis, all patients had PSA decline of > 90% without radiographic evidence of disease progression. Baseline CGA did not correlate with efficacy (P-values >0.1). Common Grade 1 AEs included gynecomastia (26%), fatigue (35%), hot flashes (22%) and paresthesia (13%). None had Grade 3 or 4 AEs. Three men withdrew from the study due to treatment-related AEs (Grade 2 fatigue and paresthesia). Another three patients withdrew due to unrelated issues.

**Conclusions**
Enz with Dut/Fin appears to be safe and efficacious for older patients with M0 and M1 HNSPCa. Future research will report effects of treatment on CGA domains.

**Clinical trial identification**
NCT02213107

**Legal entity responsible for the study**
University of Rochester

**Funding**
Astellas and Pfizer Inc

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

809P - Cabazitaxel plus prednisone and prophylaxis of neutropenia complications in the treatment of metastatic castration-resistant prostate cancer after failure to docetaxel: A multicenter, non-comparative, open-label, phase IV study

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**Background**
This study aimed to evaluate the effectiveness of granulocyte colony-stimulating factor (G-CSF) and ciprofloxacin in the prophylaxis of hematological complications in mCRPC.
patients treated with cabazitaxel after docetaxel failure and at risk for neutropenia.

**Methods**

Phase IV, non-randomized, open-label, single-arm interventional study, with men aged ≥65 years (or < 65 years and 25% irradiated bone marrow), presenting mCPRC after docetaxel failure, ECOG status ≤1, life expectancy >12 weeks, that provided informed consent. Cabazitaxel 25 mg/m² was given with prednisone on day 1 every 21 days. G-CSF was administered on days 2 to 8 of each cycle or until ANC >2,000/mm³ and ciprofloxacin 1000mg on days 5 to 12. Primary endpoint was the rate of neutropenia grade ≥3 during the first cycle; secondary endpoints were the rate of neutropenia grade ≥3, febrile neutropenia, diarrhea grade ≥3, PSA response and quality of life (FACT-P) during treatment. Statistical significance was set at 0.05 and 95% confidence intervals were determined.

**Results**

46 patients with median age 71.5 years (mean: 71.8 years) and 69.0 months on median since diagnosis (mean: 75.2 months) of prostatic cancer were included. Among the 45 treated patients, exposed to a median of 9.0 cycles (mean: 9.5 cycles) during 210 days, 40.0% (95% CI, 25.7%-54.3%) presented one episode of neutropenia grade ≥3 during the first cycle. During treatment, 42.2% patients presented at least one neutropenia grade ≥3; febrile neutropenia occurred in one patient (2.2%) as well as diarrhea grade ≥3. Twenty-nine patients (64.4%) achieved PSA response and 77.2% improved FACT-P score in at least one visit. Three patients (6.7%) had a serious TEAEs leading to death (none related to treatment), and 13.3% had 7 TEAEs leading to treatment discontinuation (3 related to treatment).

**Conclusions**

Prophylactic G-CSF and ciprofloxacin was effective in the prevention of neutropenia grade ≥3 and other hematological complications during the mCRPC treatment with cabazitaxel 25 mg/m² in patients who were at risk for neutropenia.

**Clinical trial identification**


**Legal entity responsible for the study**

Sanofi

**Funding**

Sanofi

**Disclosure**


810P - Assessment of health-related quality of life (HRQL) in PROSELICA: A Phase 3 trial assessing cabazitaxel 20 mg/m2 (C20) vs 25 mg/m2 (C25) in post-docetaxel
Background

PROSELICA (NCT01308580) assessed effect of C20 vs C25 on overall survival in a non-inferiority study of pts with mCRPC. Primary analyses included assessment of HRQL in the overall population. Post-hoc subgroup analyses investigated changes in HRQL in pts receiving C20 vs C25 according to median treatment cycles received (6).

Methods

Functional Assessment of Cancer Therapy Prostate (FACT-P) was used to assess HRQL. The least square means of change in FACT-P total score (TS) from baseline (BL) was assessed via a mixed-effect model for repeated measurements and differences were compared for C20 vs C25 in pts receiving > 6 or ≤ 6 treatment cycles.

Results

Overall change in FACT-P TS from BL to Cycle 10 was not significantly different for C20 vs C25 (C20 n = 137: 0.02 [95% CI -2.57, 2.61]; C25 n = 141: 1.33 [95% CI -1.26, 3.93]; p = 0.369). For evaluable pts who received > 6 cycles, change in FACT-P TS from BL to Cycle 10 favored C25 but not C20 (C25 n = 140: 3.06 [95% CI 0.25, 5.86], p = 0.033; C20 n = 137: 2.67 [95% CI -0.17, 5.51], p = 0.065). Difference in change was not significant for C20 vs C25 (-0.39 [95% CI: -3.66, 2.88], p = 0.816). For evaluable pts who received ≤ 6 cycles, change in FACT-P TS from BL to Cycle 6 favored pts receiving C25 (C25 n = 49: -4.61 [95% CI: -8.27, -0.95], p = 0.014; C20 n = 39: -6.58 [95% CI: -10.46, -2.69], p < 0.001) but the difference between the treatment arms was not significant (-1.96 [95% CI: -6.8, 2.87], p = 0.426). Increasing cycles, BL ECOG performance score (0–1 vs ≥ 2) and receiving > 6 cycles significantly improved FACT-P TS change from BL (p < 0.001). Difference in treatment dose (C20 vs C25) did not have a significant effect on FACT-P TS change from BL (p = 0.354).

Conclusions

In the overall population, HRQL did not differ significantly from BL to Cycle 10 for C20 vs C25. Additionally, there were no significant differences between the two treatment arms (C20 vs C25) in either subgroup (> 6 or ≤ 6 cycles). A significant change in HRQL from BL to Cycle 10 was observed in patients who received > 6 cycles of C25. Funding: Sanofi.

Clinical trial identification

NCT01308580

Legal entity responsible for the study

Sanofi

Funding

Sanofi

Disclosure

D. Ford: Honoraria from Astellas, Janssen and Sanofi. L. Mourey: Personal fees and non-financial support from Sanofi, Astellas, Janssen, Pfizer and Novartis, personal fees
817P - Prostascore: A simplified tool for predicting outcomes among patients with treatment-naïve advanced prostate cancer

O. Abdel-Rahman (Cairo, Egypt)

**Background**

The objective of this study is to propose and validate a new simplified model “prostascore” to help predict the outcomes of treatment-naïve patients with advanced prostate cancer.

**Methods**

Through SEER*Stat program, surveillance, epidemiology and end results (SEER) database was queried for eligible records spanning the period from 2010 to 2013. Multivariate analysis for the candidate prognostic factors (extent of extra-prostatic disease, PSA level and grade) was conducted through a Cox proportional model. Prostascore was then calculated for each patient. Cancer-specific and overall survival analyses according to prostascore were conducted through Kaplan-Meier analysis/log-rank testing.

**Results**

A total of 8727 patients with treatment-naïve advanced prostate cancer and complete baseline data were identified in the period from 2010-2013. The following factors were associated with better cancer-specific survival (isolated regional nodal disease, lower PSA level and lower grade group) (P < 0.0001). Based on the results of the multivariate analysis, the prostascore was described. A prostascore point was given for each of: PSA level ≥ 60 and grade group 4 or 5. The site/distribution of extra-prostatic disease were given the following points: 0 for isolated regional lymph nodes (N1), 1 for non regional lymph deposits (M1a), 2 for bone deposits (M1b) and 3 for other sites (M1c). A total prostascore was then calculated for each case in the cohort (which may range from 0 to 5). After assignment of a prostascore for each patient, cancer-specific and overall survivals were compared according to the score. Pair wise comparisons between all different scores were conducted. For both cancer-specific and overall survival assessment according to the prostascore model, P values for pair wise comparisons among different score points were significant (P<0.0001). Table-1 shows number of patients and three year cancer-specific survival years according to prostascore.

<table>
<thead>
<tr>
<th>Score N(%)</th>
<th>3-year cancer-specific survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1024 (11.7%) 98%</td>
</tr>
<tr>
<td>1</td>
<td>1639 (18.8%) 97%</td>
</tr>
</tbody>
</table>
Conclusions
Prostascore is an easy and reliable tool for predicting the outcomes of patients with
treatment-naïve advanced prostate cancer. Further validation within the context of other
treatment settings and population-based cohorts is recommended.

Legal entity responsible for the study
Omar Abdel-Rahman

Funding
None

Disclosure
All authors have declared no conflicts of interest.

813P - Real-world use of docetaxel for metastatic castration-resistant prostate
cancer in China: Results from a large observational study

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Background
This study investigated real-world patterns of docetaxel use for metastatic
carcinoma who received ≥1 dose of
cstration-resistant prostate cancer (mCRPC) in China.

Methods
A prospective, multi-centre, observational study of Chinese adults (≥18 years) with
histologically confirmed metastatic prostate adenocarcinoma who received ≥1 dose of
docetaxel following hormonal therapy failure (disease progression and serum testosterone
<50 ng/dL). The primary endpoint was patterns of docetaxel use. Secondary endpoints
included median overall survival (mOS), prostate-specific antigen (PSA) response rate
(RR) and reasons for docetaxel discontinuation. Variables are summarised as mean (SD)
unless specified. All patients provided written informed consent.

Results
From August 2011 to June 2016, 403 patients were enrolled at 32 centres and 315
(78.2%) completed the study. The mean number of docetaxel cycles and dose were 4.4
(2.86) and 66.9 mg/m2 (9.12), and treatment compliance was 94.0% (10.94%). mOS was
similar for docetaxel after 1st- or 2nd-line hormonal therapy (Table), and was longer in
patients without visceral metastases versus those with visceral metastases (23.3 months
vs. 17.4 months, P = 0.019). Planned docetaxel treatment was completed by 30.8% (124)
of patients; the most common reasons for discontinuation were 'other reasons' (23.3%
[94]), cost of medical expenses (22.6% [91]), and tumor progression (14.1% [57]).
Treatment-emergent AEs (TEAEs) occurred in 20.8% (84), and serious TEAEs in 4% (16),
of patients. Table:

813P

<table>
<thead>
<tr>
<th>Pattern of use of docetaxel in</th>
<th>n (%)</th>
<th>Median overall survival, PSA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>898 (10.3%)</td>
<td>91%</td>
</tr>
<tr>
<td>3</td>
<td>2161 (24.8%)</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>2537 (29.1%)</td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td>466 (5.4%)</td>
<td>76%</td>
</tr>
</tbody>
</table>
**Chinese patients with mCRPC**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (Rate, %)</th>
<th>Months (95% CI)</th>
<th>Rate, % (n/n&lt;sup&gt;a&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>403 (100)</td>
<td>22.4 (20.4, 25.8)</td>
<td>70.9 (168/237)</td>
</tr>
<tr>
<td>After failure of 1&lt;sup&gt;st&lt;/sup&gt;-line hormonal therapy</td>
<td>170 (42.2)</td>
<td>22.5 (19.2, 29.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>73.6 (64/87)</td>
</tr>
<tr>
<td>After failure of 2&lt;sup&gt;nd&lt;/sup&gt;-line hormonal therapy</td>
<td>125 (31.0)</td>
<td>23.3 (18.1, 26.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67.1 (55/82)</td>
</tr>
<tr>
<td>After failure of ≥ 3&lt;sup&gt;rd&lt;/sup&gt;-line hormonal therapy</td>
<td>51 (12.7)</td>
<td>22.4 (19.0, 36.5)</td>
<td>65.4 (17/26)</td>
</tr>
<tr>
<td>After failure of estramustine therapy</td>
<td>46 (11.4)</td>
<td>20.2 (16.6, 27.7)</td>
<td>69.7 (23/33)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (2.7)</td>
<td>28.6 (17.5, not evaluable)</td>
<td>100.0 (9/9)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Denominator is the number of patients in each category who had PSA ≥20 ng/ml at baseline;

<sup>b</sup> p = 0.781 for median overall survival with initiation of docetaxel following failure of 1<sup>st</sup>- and 2<sup>nd</sup>-line hormonal therapy. mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate specific antigen.

**Conclusions**

Around three-quarters of Chinese mCRPC patients treated with docetaxel initiate treatment after failure of 1<sup>st</sup>- or 2<sup>nd</sup>-line hormonal therapy and mOS and PSA RR are similar in both settings. Docetaxel was relatively well tolerated.

**Legal entity responsible for the study**
Sanofi-Aventis

**Funding**
Sanofi-Aventis

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

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**811P - Cabazitaxel followed by androgen deprivation therapy (ADT) significantly improves time to progression in patients with newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC): A randomized, open label, phase III, multicenter trial**

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**Background**

Patients with newly diagnosed mHSPC have a poor prognosis with a 3-year overall survival (OS) rate of 50%. Recently, combination of docetaxel (75mg/m2 every 6 weeks for 6 cycles) with ADT has become a new standard for such patients, based on results of 2 large phase 3 trials showing a significant OS benefit. In these trials, docetaxel was
initiated within 3 months after ADT start. Timing of ADT and chemotherapy (CT) is controversial. In breast cancer, endocrine therapy is always started after CT, the rational being that ADT will turn clones of tumor cells in to a stage of dormancy where CT is less effective.

**Methods**

This phase 3 trial randomized newly diagnosed mHSPC patients to receive cabazitaxel (CABA), 25 mg/m² every 3 weeks for 10 cycles, followed by ADT (immediately after last CABA cycle) versus ADT alone. Primary end-point was OS. Secondary end-point was progression free survival. The study planned to include 400 patients but was closed prematurely due to low inclusion rate. A total 31 patients with newly diagnosed mHSPC were included and here we present the results.

**Results**

Median follow up was 31 month. Of the CABA treated patients, 66.8% got six cycles or more and 46.7% completed all 10 courses. Median OS was 32.5 months with CABA followed by ADT and 29.5 months with ADT alone (HR 1.43, 95% CI 0.38-5.38). Median progression free survival was significantly longer in CABA treated patients (29 vs 12 months, HR 3.96 (95% CI 1.49-10.49). Main grade ≥ 3 toxicities were neutropenia (66%).

**Conclusions**

In conclusion, results from this prematurely terminated trial suggest that CABA followed by ADT is effective in newly diagnosed mHSPC and shows a manageable toxicity. These results have to be validated in larger randomized trials.

**Clinical trial identification**

NCT01978873

**Legal entity responsible for the study**

Department of Urology, Orebro University Hospital, Sweden

**Funding**

Sanofi aventis

**Disclosure**

All authors have declared no conflicts of interest.

### 812P - Health-related quality of life (HRQL) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel (CBZ) in a prospective observational study (CAPRISTANA)

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**Background**

Cabazitaxel (CBZ) is a taxane approved for mCRPC treatment post docetaxel based on Phase 3 clinical trial data. Observational studies are in progress to gather information on real-world treatment patterns, safety, efficacy and HRQL effect of CBZ outside of clinical trials.

**Methods**

The prospective, observational study CAPRISTANA evaluated the routine clinical use of CBZ (25 mg/m² every 3 weeks plus prednisone 10 mg/day) in pts with mCRPC previously
treated with docetaxel. HRQL was assessed using Functional Assessment of Cancer Therapy - Prostate (FACT-P) version 4 and EQ-5D-3L (including VAS - visual analogue scale) questionnaires at baseline and every two cycles until CBZ discontinuation.

**Results**

A total of 192 pts were treated in 55 centers across 6 countries (Apr 2012–Jun 2016); 161 and 157 pts were evaluable for FACT-P and EQ-5D, respectively. Pts received 6 (median) cycles of CBZ (range 1–24); 53.6% achieved disease control with CBZ. The main reason for CBZ treatment discontinuation was disease progression (58.3%). No new safety signals were identified. In the overall FACT-P score analysis, HRQL improvement during CBZ treatment was recorded in 31.8%, no change in HRQL in 40.4%, and deterioration was recorded in 27.8% of pts. The highest rate of improvement was observed for the Prostate-Specific Concerns subscale (49.3%) and Pain Control subscale (54.2%). The highest rate of deterioration was recorded for the Functional Well-Being subscale (40.9%). Mean FACT-P score and EQ-5D health utility index and VAS scores did not show statistically significant changes during CBZ treatment.

**Conclusions**

In this real-world study investigating HRQL associated with the use of CBZ in pts with mCRPC, no significant changes were observed in mean on-treatment FACT-P score and EQ-5D scores. However, in contrast to observations in prospective clinical studies, pts had improvement in the Pain Control FACT-P subscale. These results suggest that, in addition to the previously demonstrated effectiveness, CBZ treatment may help pts to achieve better pain control.

**Legal entity responsible for the study**

Sanofi

**Funding**

Sanofi

**Disclosure**

G. Barnes: Employee of Sanofi. M. Ghosn: Advisory boards for Sanofi, Astellas and Janssen. I. Koroleva: Research funding and speakers' bureau for AstraZeneca and Teva, travel reimbursement from MSD and Eisai. A. Ozatilgan: Employee of Sanofi. S. Hitier: Employee of Sanofi. J. Carles: Consulting/advisory role to Johnson&Johnson, Bayer, Astellas, BMS, Pfizer and Sanofi. All other authors have declared no conflicts of interest.

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**814P - Longer time from diagnosis to docetaxel treatment results in a shorter survival in metastatic hormonosensitive prostate cancer (mHSPC) patients treated with chemotherapy+androgen deprivation therapy (ADT)**

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**O. Reig** (Barcelona, Spain) A. Montesa (Malaga, Spain) J. Suarez (Barcelona, Spain)

**R. Hajianfar** (Sant Joan Despí, Spain) M. Ribal (Barcelona, Spain) J. Rubio (Valencia, Spain)

**M. Castells** (Barcelona, Spain) R. Villatoro (Malaga, Spain) S. Sandiego (Valencia, Spain)

**D. Olmos Hidalgo** (Madrid, Spain)

**Background**

Addition of 6 cycles of docetaxel to ADT prolongs survival and is the standard treatment for mHSPC based on results of Chaarted and Stampede trials. Prognostic factors have
not been clearly described for these patients. A retrospective analysis of clinical and pathological prognostic factors was performed in 76 patients from 5 academic institutions.

Methods
Retrospective analysis of all (n = 76) mHSPC from 5 Spanish Oncology Centres was performed. All patients had been treated with docetaxel + ADT as first line. Clinical and pathological variables were analyzed: age, Gleason (6-7 vs 8-10), presence of visceral metastases, number of bone metastases (0,1-4,5-20,>20), PSA value at diagnosis and previous to CT, PSA response previous to CT (>25%, 25-50%, 50-100% or no response), time from diagnosis to first docetaxel treatment (>or< 50days). Progression free (PFS) and overall survival (OS) were the endpoints analyzed by log-rank test.

Results
Median PFS was 17m and median OS has not been reached (80% of patients alive at 20 months). Median follow-up: 16.6m. Median age 64,3y (range: 46-80), median PSA at diagnosis 691ng/mL (range:15235-1), median PSA previous to CT 214ng/mL (range:5060-0), PSA responses to ADT previous to CT was 25% in 35 pts (46%), 25-50% in 14 pts (18.4%), less than 50% in 13 (17.2%), no response in 14 (18.4%), Gleason 6-7: 19 (25%), 8-10: 53 (69.7%), UK 3 (5.3%). Median time from diagnosis to docetaxel 45.3 d (range 0-167). PFS nor OS was related to age, PSA at diagnosis, PSA response prior to docetaxel or Gleason. Time from diagnosis to docetaxel (p = 0.04) (median 21 vs 15m; HR:2.2)) and Gleason (median not reached vs 15m; HR: 3.3) were statistically significant factors for PFS. Presence of visceral metastasis (p = 0.08) (20m vs median not reached;HR: 3.8) and time from diagnosis to docetaxel (p = 0.02) (median not reached vs 24m; HR:4.1) were significative factors for OS.

Conclusions
A time from diagnosis to docetaxel start longer than 50 days is associated with lower PFS and OS in m+HSPC patients treated with ADT + docetaxel. Gleason ≥ 8 score correlates with shorter PFS and the presence of visceral metastases with a lower OS.

Legal entity responsible for the study
Dr. Miguel A. Climent Durán

Funding
None

Disclosure
All authors have declared no conflicts of interest.

815P - Prognostic value of systemic inflammatory biomarkers in patients with mCRPC treated with abiraterone in pre-docetaxel setting

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Background
Systemic inflammatory biomarkers have shown a prognostic impact in several solid tumors. The aim of this study was to examine the prognostic role of baseline neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR) and
lymphocyte-to-monocyte-ratio (LMR) and NLR, PLR and LMR changes at 1, 2 and 3 months in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with Abiraterone Acetate (AA) in pre-docetaxel setting.

Methods
We retrospectively included mCRPC pts treated with AA at two Italian hospitals from November 2012 to April 2017. NLR, PLR and LMR were evaluated at baseline and after 1, 2 and 3 months of treatment. The impact of NLR, PLR and LMR on progression-free survival (PFS) was evaluated by Cox regression analyses both in univariate and multivariate fashion. Other clinico-pathological factors, such as PSA baseline level, Time to CRPC, Gleason Score, Presence of Visceral Metastases and Bone Metastases Burden were included.

Results
Fifty mCRPC pts treated with AA were evaluated. At univariate analysis, elevated baseline NLR and PLR were significantly associated with shorter median PFS (p = 0.01, hazard ratio [HR]=1.224 and p = 0.0001, HR = 1.013 respectively); after 1 month of treatment, NLR and PLR were significantly predictors of worst PFS (p = 0.03, HR = 1.320 and p = 0.02, HR = 1.012 respectively). After 2 and 3 months of treatment, only high PLR was associated with poor prognosis (p = 0.01, HR = 1.012 at month 2; p = 0.009, HR = 1.009 at month 3 respectively). LMR didn’t show any prognostic relevance. At multivariate analysis, only baseline PLR was independently associated with PFS (p = 0.006, HR = 1.013).

Conclusions
High baseline and early-assessed NLR and PLR during treatment with AA are associated with shorter PFS in mCRPC pts. PLR more than NLR may be considered as an early and easy-to-perform prognostic marker in this setting.

Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Funding
None

Disclosure
E. Verzoni: Advisory boards: Jannsen. G. Procopio: Advisory board: Astellas, Bayer, Janssen and Roche. All other authors have declared no conflicts of interest.

816P - 68Ga-PSMA-PET/CT as a changing practice tool in biochemically recurrent prostate cancer
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H. Cottas (RIO DE JANEIRO, Brazil) L. H. Araujo (RIO DE JANEIRO, Brazil) D. Herchenhorn (rio de janeiro, Brazil)
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Background
PSMA-PET/CT have demonstrated interesting results in the detection of loco-regional and distant disease in prostate cancer patients with biochemical relapse. Even with low levels of PSA, PSMA imaging is able to identify metastatic lesions, being a possible tool for tailoring treatment decisions. This study aims to describe the use of PSMA-PET/CT in the daily practice and its clinical impact in the management of prostate cancer patients who have rising PSA after curative treatment.
Methods
We performed a retrospective analysis in 29 localized prostate cancer patients of three private Brazilian cancer institutions who underwent PSMA-PET/CT for rising PSA after treatment with curative intent. The clinical impact of PSMA-PET/CT was evaluated by whether the assistant physician changed or not the treatment strategy based solely on PSMA results. In addition, modifications related to local (salvage radiotherapy [SRT], salvage lymphadenectomy [SL]) and systemic (antiandrogen deprivation therapy [ADT], chemotherapy [chemo]) treatment were described.

Results
In total, 29 patients were enrolled. Twenty-seven (93%) had undergone radical prostatectomy, and 2 (7%) radiotherapy as the local curative treatment. Sixteen cases (55%) had not received any radiotherapy previously. The mean Gleason score, PSA level and PSADT at time of the examination were 8, 4.2 (0.05-41) ng/ml and 4.4 (0.4-27) months, respectively. PSMA-PET/CT detected at least one suspicious lesion for prostate cancer in 21/29 (58%) patients. Overall, 15/29 (51%) patients had their treatment strategy changed due to results in PSMA imaging. In only 3/29 (10%) the modifications were related exclusively to systemic protocols (1 avoided ADT, 1 added ADT and, 1 added chemo). Whereas in the 12/29 (41%) remaining cases, treatment strategy change involved local treatment. Of these 12 with a local treatment change, 7 added (6 SL, 1 SRT) and 5 avoided (5 SRT) local therapies.

Conclusions
Half of the patients with biochemical relapse that underwent PSMA-PET/CT had their treatment protocol changed, most changes related to local treatment. Although the role of PSMA imaging is not clearly defined, PSMA-PET/CT has been used as a practice changing tool in the daily practice.

Legal entity responsible for the study
Instituto COI

Funding
None

Disclosure
All authors have declared no conflicts of interest.

818P - PSA doubling time (PSADT) and proximal PSA predict metastasis-free survival (MFS) in men with biochemically recurrent prostate cancer (BRPC) after radical prostatectomy (RP): Implications for patient counseling and clinical trial design

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Background
We previously reported a relationship between PSADT and MFS in BRPC post RP (Pound 1999; Freedland 2007; Antonarakis 2012). In men with PSADT<12 months, who are at
high risk of lethal prostate cancer (PCa), we sought to identify a PSA cutpoint (proximal PSA; PP) that indicates the imminent emergence of metastasis (M+). In this report we combined Center for Prostate Disease Research and Johns Hopkins (CPDR/JHU) databases to investigate the association of the PP value on MFS in men with BRPC and PSADT <12 mths.

Methods
In the CPDR/JHU RP database (31,296), 513 men with BCR (>0.2ng/ml) with PSADT <12 mths who received no adjuvant/salvage ADT/RT were prospectively followed until radiological evidence of M+ are included in this analysis. All patients were evaluated yearly with ≥1 PSA and scans at regular intervals until M+. Associations with MFS were compared using logrank test and Cox regression. The PP is the most recent value ≥6 months prior to M+/censor.

Results
M+ occurred in 218 of 513 patients with BRPC (median follow up 9 years). Risk of M+ increased for PSADT 6.0-7.5, 4.5-6, 3.0-4.5, and ≤3.0 months, adjusted for pT stage and Gleason score. PP ≥ 10 ng/ml significantly increased risk of M+ in pts with PSADT <12 mths, regardless of PSADT subgroup, hazard ratio=2.736, p<.0001. Table 1 shows median MFS by PP in subgroups with PSADT ≤3 mths, 3.01-6 mths, and 6.01-12 mths.

Table:

<table>
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<th>PSADT</th>
<th>Median metastasis-free survival (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal PSA&lt;10 ng/mL Proximal PSA ≥10 ng/mL P value</td>
</tr>
<tr>
<td>6.01-12 mths</td>
<td>20 (n = 277) 5 (n = 64) &lt;.0001</td>
</tr>
<tr>
<td>3.01-6 mths</td>
<td>7 (n = 106) 3 (n = 47) 0.0009</td>
</tr>
<tr>
<td>&lt; =3 mths</td>
<td>3 (n = 48) 1 (n = 21) 0.058</td>
</tr>
</tbody>
</table>

* Based on logrank analysis

Conclusions
In men with PSADT<12 months, PSADT subgroups ≤7.5 months and PP ≥10ng/ml are independent predictors of MFS, adjusted for pT stage and Gleason score. PP ≥ 10ng/ml further define risk of M+ in BRPC with PSADT<12 months. These data can assist physicians during discussions with patients regarding the risk of developing M1 disease and facilitate clinical trial design in this prevalent group of patients.

Legal entity responsible for the study
N/A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

824P - ARV7 status and CTC count: A combined biomarker for the baseline therapeutic decision in each line of mCRPC treatment

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Background
Metastatic Castration Resistant Prostate Cancer (mCRPC) is an entity for which we have more than one therapeutic option. Chemotherapy and novel hormonal agents (NHAs) are the main choices. Despite clinical, biochemical, radiological and histologic parameters, we have not yet confirmed the ideal sequence of regimens. Since PSA is not enough to guide treatment selection in mCRPC, there is a need for a biomarker that would lead us to the ideal regimen choice in each line of therapy for each patient (pt) in order to transform mCRPC into a chronic disease. ARV7 status and circulating tumor cells (CTCs) have shown some potential as biomarkers the last 2 years. The aim of this study was to combine these two biomarkers as a parameter for selecting the optimal treatment strategy. We aimed to categorize mCRPC pts by combining ARV7 status and CTC count and correlating this with response to therapy and, consequently, regimen choice.

Methods
CellSearch was used for CTC counts. We developed a highly sensitive and specific multiplex RT-qPCR assay in the LightCycler platform for the simultaneous quantification of AR splice variants (AR-FL, AR-V7, AR-567, AR-total) in CTCs. 41 pts and 57 samples were categorized in four groups: 1. CTChigh(h) (CTC count >10) ARV7+ (14 samples) 2. CTClow(l) (CTC count ≤ 10) ARV7+ ARV7- (20 samples) 3. CTCh ARV7- (9 samples). Treatment choice at this point was independent of ARV7 status and CTC testing and was selected upon treating oncologist's decision.

Results
PSA response to chemotherapy or NHAs was studied for each group, as well as duration of treatment and change of pt classification in groups. In each group, pts were categorized according to treatment type (chemotherapy, NHAs) and PSA responses were categorized as PSA decline or not. Group 1 pts did not appear to respond to NHAs but only to chemotherapy and had a worse prognosis compared to all other groups; pts in group 2 appeared to have an excellent and long term response to NHAs, though if chemo was received they also responded equally to both treatment options and had a better prognosis compared to all other groups; pts in group 3 responded better to chemotherapy than NHAs (though not excluding NHAs as a treatment choice); pts in group 4 responded to chemo and not NHAs.

Conclusions
Pts CTCl and ARV7- could safely be treated with NHAs while CTCl and ARV7+ pts could be treated with either chemotherapy or NHAs, with chemotherapy probably being a “safer” choice (less PSA non responses 1/8 vs 3/6). ARV7+ status does not seem to be an exclusion criteria alone for NHAs used in this category. For CTCh pts, chemotherapy is the best choice especially when pts are ARV7+. Since CTC and ARV7 status can change, these could be used as the baseline biomarker for regimen choice.

Legal entity responsible for the study
Evangelos Bournakis

Funding
None

Disclosure
All authors have declared no conflicts of interest.
819P - PSA kinetics impact on CT-PET PSMA uptake in prostate cancer

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Background
CT-PET PSMA has recently been approved to more accurately detect the extent of prostate cancer. Here we examined PSA level and kinetics (PSA doubling time-PSADT) as a predictor of positive up-take in patients evaluated for suspected recurrent disease.

Methods
We retrospectively collected data on 99 patients evaluated by CT-PET PSMA. Mann-Whitney U test and student's T Test (SPSS 20) were applied to test for differences in median in PSA and PSADT level, Pearson test was used for correlation analysis. PSADT was calculated by Memorial Sloan Kettering Cancer Center calculator of 3 recent levels.

Results
Ninety nine patients underwent CT-PET PSMA. Their median age was 71 (52-94) years. Uptake was detected in 84 (84.8%) patients; 51 (51.5%) patients with metastatic disease (lymph nodes, bones, visceral) and 33 (33.3%) patients with only localized disease (prostate, prostatic bed after prostatectomy). Median Gleason 8 (6-10), median PSA 4.66 (0.12-272) ng/ml. CT-PET was positive in 57.1%, 88.9% and 96.8% of patients with PSA levels of ≤ 1, >1-2 and >2 ng/ml, respectively, and 91.7%, 90.5% and 81.8% of patients with PSADT ≤2, >2-6 and > 6 months, respectively. Only median PSA levels were significantly associated with any uptake: 5.90 ± 35.71 vs. 0.35 ± 4.18 ng/ml, p < 0.001. Median PSADT, but not PSA, was statistically associated with metastatic disease compared to only local disease: 6.2 ± 13.64 vs. 20.3 ± 130.52 months, p < 0.001. Similar results outcome were obtained using student's t-test (data not shown). Gleason score predicted for CT-PET PSMA metastatic uptake (median 8 vs. 7, p = 0.02). There was no correlation between Gleason score and PSADT (r = -0.197, p = 0.058).

Conclusions
The decision to perform CT-PET PSMA in prostate cancer patients suspected to have recurrent or metastatic disease should be based on PSA levels. PSADT is a significant marker for positive metastatic CT-PET PSMA uptake.

Legal entity responsible for the study
Avishay Sella

Funding
None

Disclosure
All authors have declared no conflicts of interest.

821P - A polymorphism in the promoter of the FRAS1 gene is associated with metastatic prostate cancer

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K. Penney (Boston, United States of America) T. Gerke (Tampa, United States of America)
M. M. Pomerantz (Boston, United States of America) G. Lee (Boston, United States of America)
D. Nitsch (Hamburg, Germany) C. Huttenhower (Boston, United States of America)
L. Mucci (Boston, United States of America)
Background
Inflammation and one of its mediating transcription factors, NF-kappa B signaling (NFκB) have been implicated in prostate cancer (PrCa) carcinogenesis. We sought to define whether germline gene polymorphisms that interact with NFκB are associated with metastatic disease after prostatectomy (RP) or radiation (XRT) for localized disease.

Methods
Using a bioinformatics approach interrogating publicly available datasets, we defined a genome-wide functional association network specific to lethal PrCa consisting of 351 genes and 8,154,133 high-confidence functional associations related to the NFκB pathway. The dense module searching (DMS) method was used to analyze 419,461 SNPs from a previously conducted genome wide association study (GWAS) case-only study of 196 lethal PrCa cases compared to 368 indolent controls in the Harvard School of Public Health (HSPH) Cohorts. Top hits from DMS were then tested in two independent PrCa cohorts: (i) ECOG/DFCI (n = 254 cases, 256 controls) and (ii) Fred Hutchinson Cancer Research Center (FH, n = 570 cases, 103 controls). In all 3 studies, “controls” were men with PrCa who are alive with no evidence of metastasis at least 8-years after RP or XRT and “cases” were men who developed metastatic disease after RP or XRT (FH, HSPH, ECOG) or with de novo presentation (ECOG).

Results
From the DMS, 40 SNPs with a minor allele frequency > 0.1 were associated with lethal PrCa. Of these, rs1910301 in the promoter region of FRAS1 was nominally associated with lethal disease in all 3 studies with similar size effects: the odds ratio (OR) for the A allele was 1.40 (\(p = 0.02\)) in HSPH, 1.35 in ECOG/Gelb (\(p = 0.04\)), and borderline significant in FH [OR 1.3, \(p = 0.07\)]. Fixed effects meta-analysis of all three cohorts found a significant association: OR = 1.38 95% CI: 1.15-1.66; \(p\)-value 0.005.

Conclusions
A SNP in the promoter region of FRAS1, which forms a gene unit with FREM2 and together regulate epidermal-basement membrane adhesion and cell migration, is associated with metastatic PrCa. FREM2 is an NFκB regulated gene and mutations in FREM2 and FRAS1 are associated with the Fraser syndrome. Further work is needed to determine the effect of rs1910301 on FRAS1 function and cellular adhesion and the metastatic process.

Legal entity responsible for the study
Christopher Sweeney

Funding
US Department of Defense, NIH

Disclosure
C.J. Sweeney: Consultant with compensation and research: Janssen (C, R); Astellas (C, R); Sanofi (C, R); Bayer (C, R), Sotio (R), Pfizer (C). All other authors have declared no conflicts of interest.

820P - Combining functional imaging with circulating biomarker analysis to improve prognostication of metastatic castration-resistant prostate cancer (mCRPC)

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Background

Biomarkers for treatment personalization in mCRPC could improve patient outcomes. Multiple tests on blood have reported associations with worse outcome, including serum lactate dehydrogenase (LDH), chromogranin A (CgA), neutrophil-lymphocyte ratio (NLR) and more recently AR copy number (CN) in plasma DNA (Conteduca, Ann Oncol 2017). Biological data suggest an association between choline uptake and androgen receptor (AR) expression. We here aimed to integrate \(^{18}\text{F}\)-fluorocholine (FCH) uptake on PET/CT with plasma AR CN and other routinely obtained circulating biomarkers and evaluate associations with outcome.

Methods

We determined plasma AR DNA by digital PCR and Taqman from 105 CRPC samples collected before abiraterone (n = 65) or enzalutamide (n = 40). Pre-treatment serum LDH, CgA, NLR were also measured. FCH-PET/CT scan was performed at baseline and SUVmax, total lesion activity (TLA) and metabolic tumor volume (MTV) were calculated. Patients (pts) were dichotomized in high and low according to receiver-operating characteristic (ROC) curves. Main endpoints were the correlation of FCH-PET/CT parameters with circulating biomarkers and their impact on progression-free/overall survival (PFS/OS).

Results

Plasma AR CN gain was observed in 27 pts (25.7%) and correlated significantly with high SUVmax (p < 0.0001), TLA (p < 0.0001), MTV (p = 0.0006) and greater number of lesions on FCH-PET/CT (p < 0.0001). On multivariable analysis, SUVmax, plasma AR, CgA, NLR and LDH were significantly associated with outcome (Table 1).

Table: 820P Multivariable cox proportional hazard analysis of predictors of progression-free survival and overall survival

<table>
<thead>
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<th>PFS</th>
<th>OS</th>
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<tr>
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<td>p</td>
</tr>
<tr>
<td>TLA*</td>
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<tr>
<td>&lt;563979</td>
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<td>1.00</td>
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<tr>
<td>≥563979</td>
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<td>MTV*</td>
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<td>&lt;112</td>
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<tr>
<td>≥112</td>
<td>0.81 (0.33-2.00)</td>
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<tr>
<td>SUVmax*</td>
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<td>1.00</td>
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<tr>
<td>≥50.00</td>
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<td>Previous chemotherapy</td>
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</tr>
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<td>CgA*, ng/mL</td>
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<tr>
<td><strong>≤360</strong></td>
<td><strong>&gt;360</strong></td>
<td><strong>CI</strong></td>
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<td>Median dsDNA concentration, ng/mL</td>
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<td>1.00</td>
<td>1.18 (0.60-2.33)</td>
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<tr>
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<td>2.18 (1.18-4.00)</td>
<td>0.012</td>
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</tbody>
</table>

* cut-off determined by ROC curve

**Abbreviations:** ALP, alkaline phosphatase; AR, androgen receptor; CgA, chromogranin A; CI, confidence interval; dsDNA, double-strandend DNA; ECOG, Eastern Cooperative Oncology Group; FCH PET/CT, 18F-fluorocholine positron emission tomography/computed tomography; HR, hazard ratio; LDH, lactate dehydrogenase; MTV, metabolic tumor volume; NLR, neutrophil-lymphocyte ratio; PS, performance status; PSA, prostate-specific antigen; SUV, standardized uptake value; TLA, total lesion activity.

**Conclusions**

Choline uptake was significantly related to plasma AR CN gain as well as elevated NLR, CgA, and LDH values. This analysis identified independent predictors of survival in mCRPC and more accurate prognostic distinct groups using molecular, laboratory and imaging features. The potential integration of these non-invasive biomarkers could be as a tool for a better treatment selection of CRPC. A larger prospective evaluation is warranted.

**Clinical trial identification**
Legal entity responsible for the study
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) Srl – IRCCS.

Funding
None

Disclosure
V. Conteduca: Speaker honoraria or travel support: Astellas, Janssen-Cilag and Sanofi-Aventis. G. Attard: Honoraria, consulting fees, or travel support: Astellas, Medivation, Janssen, Millennium Pharmaceuticals, Ipsen, Ventana, ESSA Pharmaceuticals, and Sanofi-Aventis; grant support: Janssen, AstraZeneca, Arno. U. De Giorgi: Speaker honoraria or travel support: Astellas, Janssen-Cilag and Sanofi- Aventis. All other authors have declared no conflicts of interest.

822P - Phenotypic circulating tumor cell (CTC) classifier of genomic instability (GI) associates with improved overall survival (OS) for metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving platinum agents in addition to taxanes

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Background
The presence of GI has been associated with DNA Damage Response (DDR) genomics. mCRPC pts with DDR(-) can have treatment (Tx) efficacy with poly ADP ribose polymerase inhibitors (PARPi). Similar Tx benefit for DDR(-) pts has been observed with alkylating agents such as platinum Tx in small cohorts. However, obtaining and sequencing metastatic biopsies is currently not scalable for routine use in the clinic due to accessibility, cost and time to result. We previously developed an imaging-based phenotypic classifier to predict presence of GI from individual CTC morphology and demonstrated that these pts had statistically worse OS when receiving androgen receptor signaling inhibitors (ARSi) or Taxanes. In a separate cohort, the same classifier predicted improved PSA response when pts were treated with a PARPi + ARSi vs. ARSi alone. Here, we examined if GI(+) mCRPC pts can have improved OS when receiving a commonly available and inexpensive platinum chemotherapy.

Methods
89 blood samples were collected from mCRPC pts prior to taxane Tx (n = 62) or a combination of taxane + platinum (T+P) (n = 27), and processed utilizing the Epic Sciences platform. Choice of therapy was at the discretion of attending physician without knowledge of CTC results. The percent of predicted GI cells per pt sample (%pGI) was calculated after single-cell characterization. Pts were followed for OS.

Results
Pts receiving a T+P combination had higher CTC burdens and lower PSA levels but otherwise showed similar pre-Tx characteristics to taxane-only pts. In a multivariate model
containing %pGI, therapy class, and total CTC burden (to help correct for disease burden and severity), a significant interaction between the T+P combination and increasing %pGI, and increased OS (HR: 0.14, CI: 0.026 to 0.72, p = 0.018) was observed.

Conclusions
The results of this study suggest that in a prospective setting with a balanced cohort, pts with high %pGI might have improved OS on taxanes with the addition of platinum agents. Prospective validation of the signature is planned.

Legal entity responsible for the study
MSKCC

Funding
Epic Sciences

Disclosure

823P - Expression of steroid hormone transporter, SLCO1B3, is mediated by a CBP/p300 regulatory mechanism in prostate cancer

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Background
Recent studies support the role of steroid hormone transporters in modulating intratumoral androgen concentrations, thereby promoting castration-resistant prostate cancer (CRPC) progression. The organic anion polypeptide 1B3 (OATP1B3) transporter is expressed de novo in prostate tumors and contributes to the transport of androgen into these cells. Polymorphic variations in the SLCO1B3 gene encoding OATP1B3 are related to clinical outcome in men with prostate cancer receiving androgen deprivation therapy (ADT) or those with CRPC. The current study elucidates the mechanism of de novo SLCO1B3 expression in prostate cancer. We discovered that chetomin, a known inhibitor of HIF-1α- and CBP/p300 binding, was a potent inducer of SLCO1B3 transcripts.

Methods
We investigated the transcriptional regulation of SLCO1B3 expression by CBP/p300 using siRNA-mediated gene silencing or treatment with various CBP/p300 inhibitors (C646, HATi II) to determine the effects on gene transcription, downstream pathways, and transporter-dependent uptake studies.

Results
Treatment with various CBP/p300 inhibitors (CH1 or HAT binding domains) significantly increased the expression of SLCO1B3 and subsequent transporter-mediated androgen uptake in tumor cells. Specific downregulation of p300 or CBP by siRNA reduced SLCO1B3 expression in prostate cancer cells (22Rv1, LNCaP, and PC3), suggesting that CBP/p300 interacts with specific transcription factors essential for driving SLCO1B3 expression. Cells treated with ADT elicited differential effects on transporter expression in
AR-positive vs AR-null cells. Studies are currently underway to identify cofactors involved in forming the CBP/p300 transcriptional complex regulating SLCO1B3 expression.

Conclusions
De novo OATP1B3 expression in prostate cancer is a mechanism of tumoral resistance to ADT resulting in greater androgen uptake. Taken together, the data suggest that ADT resistance and transporter-dependent increased uptake of residual androgens result from CBP/p300-mediated SLCO1B3 expression. OATP1B3 should be considered a viable biological target for therapeutic intervention in prostate cancer.

Legal entity responsible for the study
National Institutes of Health

Funding
National Cancer Institute (NIH)

Disclosure
All authors have declared no conflicts of interest.

825P - Limited value of currently used germline brca mutations predictive tools in prostate cancer

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G. Durán Oregay (Malaga, Spain) C. Muriel (Malaga, Spain) J. Pasqual (Malaga, Spain)
C. Fernández de Souza (Malaga, Spain) M. Domínguez Recio (Malaga, Spain) G. Grau (Malaga, Spain)
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Background
Germline BRCA1 and BRCA2 mutations have been associated to poor prostate cancer (PrCa) outcomes and may have implications for cancer treatment. Identification of these carriers would also serve for the early identification of other family members at increased risk of breast and ovarian cancer. Several tools have been developed to estimate the probability of a gBRCA mutations in the context of a family history of breast and/or ovarian cancer but its performance has not been evaluated in PrCa patients.

Methods
This is single-centre study aimed to: 1) compare the contribution of PrCa to identify families known to harbour a germline BRCA1 or BRCA2 mutation; and 2) estimate the ability of predicting a BRCA mutation in these families based on the cancer history at the time of PrCa diagnosis. A comprehensive reassessment of families attending our Familial Cancer screening program at Málaga Univ. Hospitals between 2012-16 identified 104 families known to harbour a gBRCA mutations. gBRCA mutation risk estimations were calculated with 2 commonly used risk assessment models: BRCAPRO 6.0 and Manchester Score (MS).

Results
Finally, a total of 98 families (42 BRCA1, 56 BRCA2) were included in the study, after exclusion for further analyses of families with PrCa cases in non-carriers (phenocopies). As expected, PrCa was more common in BRCA2 carriers (2 vs 19, p = 0.002). Median age of PrCa diagnosis was 70 yrs (48-83). Male breast cancer was more common in families with PrCa (24% vs 4% p = 0.003), particularly in BRCA2 families (26.3% vs 5.4%, p = 0.023), but no other differences in family history of cancer were observed between
families with or without PrCa cases and therefore their scores using BRACAPRO and MS did not differ. A ≥ 10% probability of finding a BRCA2 mutation was identified in 47% of families using BRCAPRO, decreasing to 21% when the proband was the PrCa patient (p = 0.002). Similar results were observed when the probability was calculated using MS (42% vs 21%, p = 0.011)

Conclusions
The currently available predictive tools underestimate the probability of a BRCA mutation when the proband is a prostate cancer patient and should not be used as unique tools to decide which PrCa patients should undergo genetic testing.

Legal entity responsible for the study
Institutod e Investigación Biomédica en Málaga (IBIMA)

Funding
Asociación para el apoyo de la Investigación O

Disclosure
All authors have declared no conflicts of interest.

826P - Prevalence and baseline clinico-pathological associations of germline deleterious mutations in DNA repair genes (gmDDR) in a metastatic castration resistant prostate cancer (mCRPC) prospective spanish cohort (PROREPAIR-B study)

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D. Lorente Estelles (Valencia, Spain)J. Villaguzmán (Ciudad Real, Spain)G. Grau (Málaga, Spain)
A. Rodríguez-Vida (Barcelona, Spain)K. Ibañez (Madrid, Spain)E. Gonzalez-Billalbeitia (Murcia, Spain)
L. Magraner (Madrid, Spain)J. Garde (Valencia, Spain)S. Hernando Polo (Alcorcon, Spain)
J. Arranz Arija (Madrid, Spain)R. Villatoro (Málaga, Spain)B. Pérez Valderrama (Sevilla, Spain)
P. Lapunzina (Madrid, Spain)E. Castro Marcos (Madrid, Spain)D. Olmos Hidalgo (Madrid, Spain)

Background
DNA repair has been reported as a frequent altered pathway in mCRPC. The prevalence of gmDDR has been recently estimated in a retrospective pooled analysis of 7 UK-US institutions as 11.8% in mCRPC (Pritchard, NEJM 2016). However, geographic differences are expected and its association with the phenotype of mCPRC in other populations remains unknown.

Methods
PROREPAIR-B study is a prospective multicenter observational cohort study. Blood samples and clinical data have been collected prospectively in 38 centers across Spain. Germline DNA was extracted from EDTA blood samples using Flexigene®. Sequencing libraries were generated from 250ng of gDNA using a custom panel of 124 genes related to DNA repair and familial cancer, with the NimbleGen SeqCap XL Target Enrichment (Roche®) technology. Validation of pathogenic mutations by Sanger, MLPA or additional NGS has been performed only for 24 genes included in the BROCA panel. Preliminary statistical analyses have been conducted comparing clinico-pathological characteristics at diagnosis and at mCRPC between carriers and non-carriers.

Results
38 validated gmDDR were detected in 419 patients (9.1%), with 5 additional cases
undergoing further validation studies. BRCA2 was the most frequently mutated gene (n = 14) followed by ATM (n = 8), BRCA1 (n = 4) and CHEK2 (n = 4). Characteristics at prostate cancer diagnosis (dx): 99% caucasian; median age 66y (41-92); Gleason <7 41% vs ≥ 8 59%; localized stage 35% vs stage IV 65%. Characteristics at mCRPC dx: median age 73y (43-94); ECOG 0-1 91% vs 2 9%; presence of visceral 8%, bone 87% and lymph node metastasis 46%; median baseline PSA 26.95ng/ul (<0.02-5198). Bone metastases were significantly more common at mCRPC dx in carriers (95% vs 80%, p = 0.04), as well as ALP>2*UNL (37% vs 19%, p = 0.03) and Albumine < 4g/dl (45% vs 21%, p = 0.02). No significant differences were observed between carriers and non-carriers in age at dx or mCRPC, Gleason, stage at dx, PSA, LDH, Hemoglobin, visceral or nodal metastases at mCRPC dx (p > 0.05).

Conclusions
This is the first study that reports the prevalence of gmDDR in a cohort of mediterranean mCRPC patients.

Clinical trial identification
NCT03075735

Legal entity responsible for the study
Spanish National Cancer Research Centre (CNIO)

Funding
Spanish National Cancer Research Centre (CNIO)

Disclosure
All authors have declared no conflicts of interest.

827P - Comprehensive characterization of BRCA1 and BRCA2 alterations in circulating tumor DNA and tumor tissue in men with prostate cancer: Implications for clinical care

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R. Devere White (Sacramento, United States of America) J. Chung (Cambridge, United States of America)
S. M. Ali (Cambridge, United States of America) M. Dall’Era (Sacramento, United States of America)

Background
Alterations in genes encoding for DNA damage repair (DDR) such as BRCA1 or 2 – as detected by next generation sequencing (NGS) – can predict for sensitivity to PARP inhibitors or platinum-based chemotherapy in advanced prostate cancer (PC). Detection of these alterations either in tumor tissue or in circulating tumor DNA (ctDNA) in men with advanced PC is clinically actionable in certain clinical contexts. Previously, we reported the comprehensive molecular characterization of DNA DDR genes in 936 unique primary & metastatic PC specimens (Dall’era, ASCO GU 2017) where 24.4% had at least 1 mutation in a DNA repair gene. We also reported that DNA DDR alterations were more common in metastatic vs. localized disease. We sought to expand this work by employing NGS in ctDNA as part of clinical care to ascertain the mutational status of BRCA1 and 2 in men with PC.

Methods
The nature and prevalence of BRCA1 and 2 alterations in ctDNA were determined from 207 men with PC through the Foundation ACT NGS assay. Mean depth of coverage was
Similarly, BRCA1/2 alterations in 936 unique PC specimens were assessed as part of the Foundation One NGS assay. Mean depth of coverage was >500X.

**Results**
In ctDNA specimens from 207 patients, 15 (7.2%) harbored known or likely deleterious BRCA1 (n = 4) and/or BRCA2 (n = 12) alterations consisting of 19 short variants and 2 rearrangements. One case had 4 variants in BRCA2 while 3 cases had 3 variants, of which 1 case had both BRCA1 and 2 variants. An additional 17 ctDNA cases (8.2%) harbored BRCA1/2 alterations categorized as variants of unknown significance (VUS). In the 936 tumor specimens, 118 (12%) had known or likely deleterious BRCA1 (n = 11) or BRCA2 (n = 107) alterations consisting of 4 rearrangements, 89 short variants, and 30 copy number variants. VUS were not available for tumor specimens.

**Conclusions**
Potentially actionable BRCA1 and/or BRCA2 alterations are detectable in ctDNA or tumor tissue in up to 15% of men with PC in this large dataset of specimens obtained in the course of clinical care. Employing plasma-based ctDNA NGS provides a clinically convenient means for assessing the status of DNA gene repair alterations comparable to that of tumor tissue.

**Legal entity responsible for the study**
University of California Davis Comprehensive Cancer Center and Foundation Medicine

**Funding**
None

**Disclosure**
R. Hartmaier, S.M. Ali: Employee of Foundation Medicine. All other authors have declared no conflicts of interest.

828P - Durable prostate cancer control in a randomized trial of optimal timing of dose escalated (76 Gy) radiation and 6 months ADT in prostate cancer

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J. Craig (Ottawa, Canada)
R. Macrae (Ottawa, Canada)
G. Perry (Ottawa, Canada)
J. Bowen (Sudbury, Canada)
S. Morgan (Ottawa, Canada)
O. Holmes (Ottawa, Canada)
S. Grimes (Ottawa, Canada)

**Background**
A pooled analysis of trials using conventional dose radiation (XRT) indicates 6 months androgen deprivation therapy (ADT) improves prostate cancer survival in Gleason 7 disease (D'Amico, JCO 2011). The benefit of ADT when used in combination with dose escalated XRT remains controversial. In EORTC 22991 trial 6 months ADT improved disease free survival at all XRT dose levels (Bolla, JCO 2016). We present long-term results of dose escalated XRT (76 Gy) in combination with 6 months ADT in the context of a Phase 3 Trial evaluating the optimal timing of ADT in combination with XRT.

**Methods**
438 pts were entered on the trial. Inclusion criteria were cT1-T3, Gleason < 8, PSA < 30. Low risk pts were excluded. ADT consisted of 6 mo Total Androgen Blockade (TAB) with Goserelin and Biclutamide. Pts were randomized to upfront XRT (day 1 of ADT) or XRT after 4 months ADT. Median follow-up is 12 yrs. 10 yr overall Survival (OS), Cause Specific Survival (CSS) PSA Disease Free Survival (DFS) and Local DFS were estimated using Kaplan-Meier (KM) method.
Results
Clinical characteristics are as follows: mean age 69; 69% cT1-T2A, 31% cT2B-T3; 75% Gleason 7; mean PSA = 10. Protocol compliance: 96% of pts completed 6 mo TAB and 99% completed 6 mo Goserelin. 4% of patients stopped Biclutamide early (3% due to Grade 1-3 reversible liver toxicity). 4% of patients developed late Gr 3 proctitis. 10 yr results: PSA DFS 83%, CSS 98%, OS 76%, and local DFS 95%. The results by treatment arm will be presented in the near future.

Conclusions
The durable DFS, local control and CSS support the benefit of 6 mo ADT in combination with Dose Escalated (76 Gy) XRT. The favourable compliance, tolerance and toxicity data support this treatment approach. Potential survival benefits of ADT in intermediate risk prostate cancer will be evaluated by mature results from EORTC 22991 and RTOG 0815 trials.

Clinical trial identification
OTT 01-01

Legal entity responsible for the study
Ottawa Hospital Research Institute

Funding
None

Disclosure
All authors have declared no conflicts of interest.

829P - Initial results from AQUARiUS, a prospective, observational, multi-centre phase IV study assessing patient-reported outcomes (PROs) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated with abiraterone acetate plus prednisone (AAP) or enzalutamide (ENZ)

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L. Dourthe (Strasbourg, France) D. Beal-Ardisson (Lyon, France) E. Pintus (Slough, United Kingdom)
R. Trepiakas (Naestved, Denmark) M. Lukac (Beerse, Belgium) S. Van Sanden (Beerse, Belgium)
L. Dearden (High Wycombe, United Kingdom)

Background
AQUARIUS is an ongoing study evaluating PROs and medical resource use in 2 cohorts of chemotherapy naïve mCRPC pts newly initiated on AAP or ENZ in the real-world setting.

Methods
The study prospectively collects PROs on quality of life, cognition, fatigue and pain using EORTC QLQ-C30, FACT-Cog, BFI-SF and BPI-SF questionnaires, respectively, for 12 months (mo) in 211 pts. This analysis describes PRO data for pts with 3-mo follow-up (N = 105). Multivariate repeated measures linear and logistic regression models were used to analyse change from baseline scores and risk for clinically meaningful worsening, respectively, adjusting for baseline characteristics.

Results
Baseline characteristics were well balanced between the ENZ (N = 59) and AAP (N = 46) cohorts. PRO items with significant differences (p < 0.05) between the 2 cohorts consistent
Across time points on continuous and/or binary endpoints are reported in the table. Change from baseline comparisons favour AAP over ENZ for mo 1, 2 and 3 for perceived cognitive impairments (e.g., 1.1 vs -5.9 at mo 3) and cognitive functioning (e.g., -0.6 vs -14.9 at mo 3) and for mo 2 and 3 for usual level and interference of fatigue (e.g., -0.7 vs 1.0 and -0.2 vs 0.7 at mo 3). Within the first 3 mo ENZ-treated pts had a significantly higher risk of experiencing clinically meaningful worsening in perceived cognitive impairments vs AAP-treated pts.

### Table:

Mean change in score from baseline for AAP (N = 46) vs ENZ (N = 59)

**Interpretation of the PRO items:** for FACT-Cog and QLQ-C30 higher scores are favourable, for BFI-SF lower scores are favourable.

<table>
<thead>
<tr>
<th>PRO item</th>
<th>Month 1</th>
<th></th>
<th></th>
<th></th>
<th>Month 2</th>
<th></th>
<th></th>
<th></th>
<th>Month 3</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AAP</td>
<td>ENZ</td>
<td>Score</td>
<td>P value</td>
<td>AAP</td>
<td>ENZ</td>
<td>Score</td>
<td>P value</td>
<td>AAP</td>
<td>ENZ</td>
<td>Score</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Mean (n*)</td>
<td>difference (95% CI)</td>
<td></td>
<td>Mean</td>
<td>Mean (n*)</td>
<td>difference (95% CI)</td>
<td></td>
<td>Mean</td>
<td>Mean (n*)</td>
<td>difference (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Perceived cognitive impairments range 0-72 (FACT-Cog)</td>
<td>2.1 (42)</td>
<td>-2.7 (53)</td>
<td>4.77 (1.26, 8.29)</td>
<td>0.008</td>
<td>1.4 (34)</td>
<td>-5.4 (41)</td>
<td>6.65 (2.79, 10.51)</td>
<td>&lt;</td>
<td>1.1 (25)</td>
<td>-5.9 (37)</td>
<td>6.97 (1.16, 12.79)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cognitive functioning range 0-100 (QLQ-C30)</td>
<td>2.4 (41)</td>
<td>-5.7 (53)</td>
<td>6.01 (0.47, 11.55)</td>
<td>0.034</td>
<td>2.6 (32)</td>
<td>-8.3 (42)</td>
<td>9.48 (2.73, 16.24)</td>
<td>0.007</td>
<td>0.6 (26)</td>
<td>-14.9 (38)</td>
<td>11.9 (0.74, 23.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Your usual level of fatigue range 0-10 (BFI-SF)</td>
<td>-0.4 (41)</td>
<td>0.3 (54)</td>
<td>-0.58 (-1.43, 0.27)</td>
<td>0.179</td>
<td>-0.6 (33)</td>
<td>0.7 (42)</td>
<td>-1.20 (-2.14, -0.26)</td>
<td>0.014</td>
<td>-0.7 (26)</td>
<td>1.0 (35)</td>
<td>-1.5 (-2.9, -0.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Fatigue interference range 0-10(BFI-SF)</td>
<td>-0.1 (42)</td>
<td>0.0 (53)</td>
<td>-0.38 (-1.10, 0.35)</td>
<td>0.308</td>
<td>-0.4 (34)</td>
<td>0.2 (42)</td>
<td>-0.99 (-1.82, -0.15)</td>
<td>0.021</td>
<td>-0.2 (26)</td>
<td>0.7 (35)</td>
<td>-1.3 (-2.4, -0.2)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Clinically meaningful worsening (vs improvement or no change) for AAP (N = 46) vs ENZ (N = 59): Defined as the difference from baseline ≥ minimal important difference (0.5 x SD of baseline pts)

<table>
<thead>
<tr>
<th>PRO item</th>
<th>Month 1</th>
<th></th>
<th></th>
<th></th>
<th>Month 2</th>
<th></th>
<th></th>
<th></th>
<th>Month 3</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AAP</td>
<td>ENZ</td>
<td>Odds ratio</td>
<td>P value</td>
<td>AAP</td>
<td>ENZ</td>
<td>Odds ratio</td>
<td>P value</td>
<td>AAP</td>
<td>ENZ</td>
<td>Odds ratio</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>% (n*)</td>
<td>% (n*)</td>
<td>(95% CI)</td>
<td></td>
<td>% (n*)</td>
<td>% (n*)</td>
<td>(95% CI)</td>
<td></td>
<td>% (n*)</td>
<td>% (n*)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Perceived cognitive impairments (FACT-Cog)</td>
<td>7 (42)</td>
<td>34 (53)</td>
<td>0.15 (0.04, 0.56)</td>
<td>0.005</td>
<td>6 (34)</td>
<td>49 (41)</td>
<td>0.07 (0.02, 0.28)</td>
<td>&lt;</td>
<td>8 (25)</td>
<td>38 (37)</td>
<td>0.16 (0.003, 0.76)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Evaluable pts
†
Regression model estimates Note: 7 pts (2 AAP, 5 ENZ) included in this intention-to-treat analysis switched treatment within the first 3 months; results were consistent in the per protocol analysis and censoring analysis.

Conclusions
Initial results suggest favourable outcomes for perceived cognitive impairments and functioning, and fatigue for AAP vs ENZ within the first 3 months after treatment initiation.

Clinical trial identification
NCT02813408

Legal entity responsible for the study
Janssen Pharmaceutica N.V.

Funding
Janssen Pharmaceutica N.V.

Disclosure
A. Thiery-Vuillemin: Grants and non-financial support from JNJ, personal fees from Astellas, grants from JNJ and Sanofi, grants and personal fees from Ipsen, Roche, BMS, and Pfizer. M.H. Poulsen: Sponsor of study from Janssen Pharmaceutica. A. Reid: Honoraria from Janssen, travel and grant support from Janssen and Astellas and awarded a place in Janssen's 'Key Opinion Leaders of the future' programme. G. Ploussard: Advisory board and honoraria from Astellas and Janssen. E. Pintus: Grants from Janssen, non-financial support from Astellas, personal fees from Astellas and non-financial support from Janssen. R. Trepiakas: Personal fees from Janssen-Cilag and Astellas. M. Lukac: Personal fees from Parexel International Czech Republic s.r.o, on behalf of Janssen Pharmaceutica NV, Beerse, Belgium. S. Van Sanden: Employee of Janssen and hold stock in Johnson & Johnson. L. Dearden: Employee of Janssen. All other authors have declared no conflicts of interest.

830P - Assessment of association between clinical characteristics and prostate specific antigen (PSA) progression in men with prostate cancer (PCa) receiving a leuprorelin acetate implant: Results from the non-interventional German cohort LEAN study
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M. Studen (Holzkirchen, Germany)

Background
The impact of GnRH (gonadotropin-releasing hormone) therapy on comorbidities and lifestyle is complex but important to consider in men with PCa. The LEAN study aims to analyse associations between various anamnestic factors and PSA dynamics in men with advanced, hormone-dependent PCa receiving a leuprorelin acetate solid implant (Leuprorelin Sandoz®/Leuprone® HEXAL®).

Methods
Patients were enrolled at 190 German centres from January 2014. Metabolic data, body measures, PSA and testosterone were assessed at baseline and during 1-year follow-up. Cox model analyses assessed associations between anamnestic factors and PSA progression. Data are presented as mean±standard deviations.
Results
A total of 959 patients have been recruited. Median patient age was 75 years (range 50–93; ≥65: 90%) and median body mass index (BMI) was 28 kg/m² (range: 18–49; >30: 22%). Primary diagnosis of PCa was 26±47 months before inclusion, with PSA levels of 32±53 ng/mL [median: 11] and serum testosterone of 3.6±2.16 ng/mL [median: 3.5]. Six of the 12 (median) core biopsies were positive at primary diagnosis, with a Gleason Score of 7.5±1.2 (median: 7). A total of 189 patients (27%) had previous radical prostatectomy 29±50 days (median: 7) before inclusion. Over 50% of patients had concomitant cardiovascular disease and 16% had disorders of glucose or lipid metabolism. At 3, 6, 9 and 12 months after the start of leuprorelin therapy, median PSA values decreased to 0.6, 0.3, 0.2 and 0.2 ng/mL, respectively, and median testosterone levels were 0.2, 0.2, 0.2 and 0.2 ng/mL. PSA progression occurred in 168 patients: in 28% of patients with BMI ≤30 and in 26% with BMI >30, indicating no clear association with BMI (p = 0.7427). Cox model analyses also showed no clear influence on PSA progression of other anamnestic factors.

Conclusions
Patients in the LEAN study represent a real-life population receiving therapy with a GnRH agonist. Results show no clear influence of anamnestic factors on PSA progression.

Clinical trial identification
DRKS00005643

Legal entity responsible for the study
N/A

Funding
This study was funded by Hexal AG/Sandoz International GmbH.

Disclosure

831P - Neuropsychiatric adverse events of enzalutamide and abiraterone acetate plus prednisone treatment: Contrasting a meta-analysis of randomized clinical trials with real world reporting patterns from EUDRA
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Background
Enzalutamide (ENZ) and abiraterone acetate plus prednisone (AAP) are oral antiandrogens indicated in Europe ¹ for the treatment of metastatic castration resistant prostate cancer (mCPRC). A comparative preliminary analysis of cognitive decline and mood changes in mCRPC patients receiving ENZ and AAP has been reported². However, a meta-analysis for these adverse effects (AEs) has not been available in the literature.

Methods
Following on from the methodology presented by Ruiz et al.³ a further meta-analysis was performed to estimate the pooled Relative Risk (RR) of neuropsychiatric AEs for AAP and
ENZ. A complementary analysis of the EUDRA database was performed to explore the consistency of the real world adverse drug reactions (ADR) reporting pattern with the meta-analysis. Calculation of Proportional Reporting Ratios was performed following EUDRA guidelines.

**Results**

The meta-analysis results indicate that patients treated with ENZ had a statistically significant higher risk of restless leg syndrome, anxiety, headache and insomnia vs control (Table). Both ENZ and AAP showed increased significant risk for falls vs control. The Proportional Reporting Ratio (PRR) of suspected ADRs reported in EUDRA is higher with ENZ than with AAP for all the variables analyzed. Table:

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Headache</th>
<th>Seizures</th>
<th>Falls</th>
<th>Dizziness</th>
<th>Hallucinations</th>
<th>Restless leg syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAP COU-AA</td>
<td>2267</td>
<td>1.12</td>
<td>1.0</td>
<td>1.60</td>
<td>0.97</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>301 &amp; 302</td>
<td></td>
<td>(0.89-1.40)</td>
<td>(0.09-10.95)</td>
<td>(1.03-2.49)*</td>
<td>(0.77-1.23)</td>
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<td>(95%CI)</td>
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<td>7498</td>
<td>29 (0.49)</td>
<td>18 (0.22)</td>
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<td>56 (0.45)</td>
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<td>(1.67-3.17)*</td>
<td>(0.86-1.76)</td>
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<td>ENZ PREVAIL</td>
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<td>(1.67-3.17)*</td>
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<tr>
<td>ENZ EUDRA ADRs</td>
<td>24258</td>
<td>197 (2.10)</td>
<td>258 (4.69)</td>
<td>383 (2.04)</td>
<td>414 (2.29)</td>
<td>66 (3.4)</td>
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*p < 0.05

**Conclusions**

The analysis suggests that some neuropsychiatric AEs are more prevalent with ENZ vs placebo than AAP vs prednisone. The reporting trend in EUDRA is consistent with this result.

**Legal entity responsible for the study**

Janssen

**Funding**

Janssen-Cilag

**Disclosure**

M. Sanchez Iznala: Market access manager at Janssen Pharmaceuticals in Spain. R.
832P - Influence of an international consensus conference on practice patterns in advanced prostate cancer (APC)

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J. Hsu (Duarte, United States of America)
B. Tombal (Brussels, Belgium)
M. R. Sydes (London, United Kingdom)
A. Omlin (St. Gallen, Switzerland)
S. Gillessen (St. Gallen, Switzerland)

Background

Development of several agents and combinations in metastatic castrate-naïve (mCN) and castration-resistant (mCR) PC has led to uncertainty in best management approaches. The Advanced Prostate Cancer Consensus Conference (APCCC) 2017 convened to provide expert opinions on open questions.

Methods

57 questions (Qs) selected from a sample of consensus Qs to be voted on at APCCC 2017 were administered as a pre- and post-conference survey to attendees. Matched responses before and after APCCC 2017 were compared to identify changes in attendees’ treatment preferences in APC.

Results

From 2/2017-4/2017, pre- and post-conference surveys from 120 attendees were collected mostly from medical oncologists (41.7%) and urologists (40.8%). Attendees reached a consensus ≥75% vote in the same pre- and post-meeting question in 10/57 Qs (15.7%). A < 75% consensus vote to ≥ 75% vote (or vice-versa) change was seen in 3 key areas: abiraterone or enzalutamide was more favored as first-line option in patients (pts) who progressed on docetaxel ≤6 months in CNPC (60.0% pre- to 75.9% post-meeting), 2 years was the favored duration of osteoclast-targeted therapy in mCRPC (53.3% to 75.0%), and more next-generation imaging (MRI or PET/CT) was favored in mCRPC (12.7% to 24.1%) while CT and bone scan changed from 79.7% to 70.7% of votes.

Consensus ≥75% votes was not reached in the majority of Qs, but notably there were more post-conference votes for: using a lower dose of cabazitaxel 20 mg/m² vs 25 mg/m² (24.2% to 32.8%), carboplatin in refractory mCRPC with DNA repair defects (27.5% to 42.2%), adding ADT to salvage XRT (29.1% to 49.1%), ≤3 metastases as a definition for oligometastatic PC (48.7% to 70.8%), recognition of ADT causing bone loss/fractures (57.4% to 66.4%), vitamin D + calcium in pts on ADT (62.6% to 71.7%), and osteoclast-targeted therapy in pts on ADT with osteopenia/osteoporosis (42.6% to 59.3%).

Conclusions

To the best of our knowledge, we are among the first to compare pre- and post-meeting responses that highlight interesting changes in provider preferences in APC management. Consensus conferences such as APCCC where expert opinions are discussed provide a unique learning experience and delineate key areas of controversy in APC where further study is needed.

Legal entity responsible for the study

The Advanced Prostate Cancer Consensus Conference
Background
To analize the results of adjuvant and salvage radiotherapy after radical prostatectomy and to determine prognostic factors of biochemical relapse free survival (BRFS).

Methods
302 patients were treated at our institution over a 12-year period. Overall survival and biochemical-relapse free survival were calculated using Kaplan-Meier and multivariate Cox regression analysis was used to assess differences between groups.

Results
Mean age at diagnosis was 65 years (42-80). All patients underwent radical prostatectomy combined with pelvic lymphadenectomy in 47.1% of cases. Adjuvant RT was performed in 113 patients and salvage RT in 183 (9 for local recurrence). The distribution of patients by pT stage was pT2a-b(30.3%), pT2c (35%), pT3(29%) and pT4(2.3%). Upgrade in Gleason score between biopsy and prostatectomy was experienced by 46.7% of patients. Positive surgical margins were reported in 56.5% of cases. Neoadjuvant androgen ablation before surgery was given to 36.5%. Mean pre-RT PSA of 0.46ng/ml (0-12.8) and mean dosis to surgical bed was of 70Gy (60-76Gy). Mean follow-up was 58.85 months (1-153 months). Overall survival at 5 and 10 years was 98.1% and 94.3%, respectively and BRFS at 5 and 10 years was 76.5% vs. 61.8%, respectively. The timing of RT (ART vs. SRT) and pre-RT PSA <0.5 ng/ml were significant predictors of longer BRFS.

Conclusions
Postoperative radiation therapy provides excellent long-term overall survival with an acceptable BRFS. Pre-RT PSA <0.5ng/ml and adjuvant RT were predictors of better outcomes.

Legal entity responsible for the study
Hospital Ramón y Cajal

Funding
The Advanced Prostate Cancer Consensus Conference
Disclosure

All authors have declared no conflicts of interest.

834TiP - Randomized phase III trial of ipatasertib vs. placebo, plus abiraterone and prednisone/prednisolone, in men with asymptomatic or mildly symptomatic previously untreated metastatic castrate-resistant prostate cancer (mCRPC)

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Background

In a Phase Ib/II study, the small-molecule AKT inhibitor ipatasertib in combination with abiraterone and prednisone/prednisolone demonstrated an improved radiographic progression-free survival (rPFS) vs abiraterone and prednisone/prednisolone alone, with greater benefit in patients with phosphatase and tensin homolog (PTEN)-loss tumors. This randomized Phase III trial will evaluate the efficacy, safety and pharmacokinetics (PK) of ipatasertib vs placebo (both combined with abiraterone and prednisone/prednisolone) in patients with previously untreated mCRPC.

Trial design

Eligible patients must have untreated asymptomatic or mildly symptomatic mCRPC with progressive disease by Prostate Cancer Clinical Trials Working Group 3 criteria, ongoing androgen deprivation therapy or castrated state and ECOG PS 0 or 1. Treatments with second-generation CYP450 inhibitors or androgen-receptor blockers and untreated or active central nervous system metastases are not allowed; however, prior chemotherapy for hormone-sensitive disease is permitted. Eligible cases will be randomized 1:1 to abiraterone 1000 mg QD + prednisone/prednisolone 5 mg BID plus ipatasertib 400 mg QD or placebo. Crossover between treatment arms is not allowed. Stratification factors are prior taxane-based therapy in the hormone-sensitive setting, progression factor (prostate-specific antigen [PSA] only vs other), presence of liver or lung metastasis, tumor PTEN status by immunohistochemistry (loss vs non-loss) and geographic region. The primary efficacy endpoint is investigator-assessed rPFS (intent-to-treat population and patients with PTEN-loss tumors). Additional endpoints include time to pain progression, time to next cytotoxic chemotherapy, overall survival, additional patient-reported outcomes, time to first opioid use, time to PSA progression, safety and PK. Approximately 850 patients will be enrolled at 200 centers worldwide.

Clinical trial identification

NCT03072238.

Legal entity responsible for the study

F. Hoffmann-La Roche Ltd

Funding

F. Hoffmann-La Roche Ltd

Disclosure

J. de Bono: Scientific advisor: Genentech/Roche Advisory boards:
835TiP - A phase 2 trial of ODM-201 maintenance therapy in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with a AR targeting agent and non-progressive on a second line taxane (SAKK 08/16)

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Background

Treatment with the AR targeting agents abiraterone or enzalutamide followed by a taxane is currently the most used treatment for men with mCRPC. Further treatment after response to chemotherapy is only indicated in case of disease progression, with limited treatment options available. ODM-201 (Darolutamide) is a second-generation oral androgen receptor antagonist which has demonstrated a good safety profile and antitumor activity in mCRPC. This trial evaluates whether the immediate use of darolutamide after successful chemotherapy can prolong radiographic progression-free survival (rPFS) compared with watchful waiting in patients with mCRPC.

Trial design

This is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial (NCT02933801) conducted in approximately 19 sites in Switzerland and Italy. Patients with mCRPC are required to have been previously treated with abiraterone or enzalutamide and have no evidence of disease progression on docetaxel or cabazitaxel. Patients (N = 88) will be randomized 1:1 to receive 600 mg darolutamide BID or placebo BID, both with best supportive care, until disease progression. Patients will be stratified by country, WHO performance status (0, 1 vs 2), presence/absence of visceral metastases, enzalutamide vs abiraterone prior to chemotherapy, and planned start of trial treatment after last taxane dose (<35 days vs ≥ 35 days). The primary endpoint is rPFS at 12 weeks after treatment initiation. The secondary endpoints are rPFS, time to PSA progression, time to symptomatic/clinical progression, event-free survival, overall survival, PSA response (30%, 50%, 90%, and best), duration of PSA response (50%), adverse events,
and fatigue. The rPFS rate at 12 weeks after treatment initiation will be compared between the two treatment arms using a one-sided test statistic using the Kaplan–Meier method. Recruitment is ongoing, with the first patient randomized on 20.04.2017.

Clinical trial identification
NCT02933801

Legal entity responsible for the study
Swiss Group for Clinical Cancer Research (SAKK)

Funding
Bayer HealthCare Pharmaceuticals Inc.

Disclosure
S. Gillessen: Advisory Boards: AAA International, Active Biotech, Astellas, Bayer, Bristol-Myers Squibb, Curevac, Dendreon Corporation, Ferring, Glaxo Smith Kline, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX, Millennium Pharmaceuticals, Novartis, Pfizer, Orion, Roche, Sanofi Aventis R. Cathomas: Advisory Board for Bayer, Janssen, Astellas, Sanofi, Pfizer, Novartis, Roche, Amgen, AstraZeneca, BMS, MSD. All other authors have declared no conflicts of interest.

836TiP - The TRITON clinical trial programme: Evaluation of the PARP inhibitor rucaparib in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) associated with homologous recombination deficiency (HRD)

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J. Arranz Arija (Madrid, Spain) G. Daugaard (Copenhagen, Denmark) K. Fizazi (Villejuif, France)
E. Gez (Tel Aviv, Israel) A. Heidenreich (Köln, Germany) F. Joly Lobbedez (Caen, France)
R. McDermott (Dublin, Ireland) A. S. Merseburger (Lübeck, Germany) J. Piulats Rodriguez (Barcelona, Spain)
B. Sautois (Liege, Belgium) S. Sridhar (Toronto, Canada) C. N. Sternberg (Roma, Italy)
S. Watkins (Boulder, United States of America) A. Simmons (Boulder, United States of America)
S. Shetty (Boulder, United States of America) A. Golsorkhi (Boulder, United States of America)
C. J. Ryan (San Francisco, United States of America) H. Scher (New York, United States of America)

Background
Recent data show that ≈20% of pts with mCRPC have a germline or somatic alteration in either BRCA1, BRCA2 or ATM (homologous recombination [HR] genes) (Robinson et al. Cell. 2015;161:1215-28), suggesting these molecular markers may be used to select pts with mCRPC for targeted treatment with a poly(ADP-ribose) polymerase inhibitor (PARPi). PARPis have demonstrated preliminary evidence of antitumour activity in pts with sporadic mCRPC and an HR gene mutation (Mateo et al. N Engl J Med. 2015;373:1697-708). These results provide a strong rationale for investigating rucaparib in pts with mCRPC associated with HRD.

Trial design
TRITON2 is a phase 2 study evaluating rucaparib 600 mg BID in pts (n≥160) with mCRPC who have a deleterious germline or somatic BRCA1, BRCA2 or ATM mutation (per local and/or central testing). Pts with tumours with an alteration in any of 12 additional prespecified HR genes (eg, RAD51C, RAD51D or PALB2) may enrol in an exploratory cohort. Pts must have progressed on androgen receptor (AR)-targeted therapy and on 1 prior taxane-based chemotherapy for mCRPC. The primary endpoint of TRITON2 is response rate (modified RECIST v1.1/PCWG3 in soft-tissue disease and PSA response
with nonmeasurable disease). TRITON3 is a randomised phase 3 study evaluating rucaparib 600 mg BID vs physician’s choice of treatment (abiraterone, enzalutamide or docetaxel) in pts (n̸≠400) with mCRPC with a deleterious germline or somatic BRCA1, BRCA2 or ATM mutation (per local and/or central testing). Pts must have progressed on AR-targeted therapy for mCRPC; pts who received prior chemotherapy for mCRPC or PARPi treatment are excluded. Pts will be randomised 2:1 to rucaparib or physician’s choice; the latter group may cross over to rucaparib after radiographic progression confirmed by independent radiology review (IRR). The primary endpoint of TRITON3 is IRR-confirmed radiographic progression-free survival (modified RECIST v1.1/PCWG3 criteria). Pretreatment blood samples will be collected from all pts in both trials to enable development of a plasma-based companion diagnostic that predicts rucaparib sensitivity.

**Clinical trial identification**

TRITON2 – EudraCT 2016-003162-13, NCT02952534; TRITON3 – NCT02975934

**Legal entity responsible for the study**

Clovis Oncology, Inc.

**Funding**

Clovis Oncology, Inc.

**Disclosure**


**837TiP - Phase I study of apalutamide (ARN) plus abiraterone acetate (AA), docetaxel (D) in patients (pts) with metastatic castrate-resistant prostate cancer**
Background
Androgen receptor (AR) targeted therapy is the mainstay of treatment for PC, with potent AR signaling inhibitors and CYP17 inhibitors leading to improved survival. Taxanes are the only chemotherapy class to demonstrate a survival benefit in prospective randomized studies. Docetaxel (D), inhibits AR trafficking from the cytoplasm to the nucleus via stabilizing microtubules, suggesting D may complement AR-pathway targeted therapies. Recent randomized studies showing a > 1 year median survival benefit in men treated with the combination of effective direct AR-targeted therapy combined with D, suggesting that “vertical pathway blockade” in which combinations of AR-directed therapies with complementary mechanisms of action are more effective than sequential use (Sweeney NEJM 2015, James Lancet 2016). Two phase 3 trials are testing the combination of AR signaling inhibitors and CYP17 inhibitors. The safety of combining D with AA is pts with mCRPC was demonstrated in the COU-AA-206 (Tagawa Eur Urol 2016). Combinations of therapies targeting different pathways have the potential to improve efficacy.

Trial design
A multicenter phase 1 dose-escalation study will be conducted to determine the maximum tolerated dose (MTD) of ARN (novel AR signaling inhibitor) combined with AA (CYP17 inhibitor) and D (taxane) in chemotherapy-naïve mCRPC pts with ECOG performance status 0-2. Following determination of MTD, a cohort expansion at the recommended Phase 2 dose will occur. Starting doses are 120 mg/day ARN with 1000 mg/day AA, D 75 mg/m² every 3 weeks, and prednisone 5 mg BID. Upon completion of D, pts may continue ARN and AA. The primary endpoint is the safety and tolerability of ARN when dosed with AA and D. Tumor tissue will be collected prospectively to evaluate exploratory biomarkers predictive of response and resistance. In addition, pre- and post-treatment circulating tumor cells will be interrogated for AR localization and AR splice variants. Circulating tumor DNA will also be collected pre- and post-therapy to explore resistance mechanisms.

Clinical trial identification
NCT02913196

Legal entity responsible for the study
Weill Cornell Medical College

Funding
Janssen Scientific Affairs, LLC

Disclosure
838TiP - ARASENS: A phase 3 trial of darolutamide in males with metastatic hormone-sensitive prostate cancer (mHSPC)

B. Tombal (Brussels, Belgium) F. Saad (Montreal, Canada) M. Hussain (Chicago, United States of America) C. N. Sternberg (Rome, Italy) K. Fizazi (Villejuif, France) E. D. Crawford (Boston, United States of America) K. Yamada (Whippany, United States of America) C. Kappeler (Berlin, Germany) I. Kuss (Berlin, Germany) M. R. Smith (Boston, United States of America)

Background
While androgen-deprivation therapy (ADT) demonstrates antitumor activity in mHSPC with prolonged disease control, resistance ultimately occurs and patients die of castration-resistant PC (CRPC). Approximately 10-50% of PC subjects develop CRPC in < 5 yr. Chemohormonal therapy per ESMO guidelines is recommended as first-line treatment of metastatic, castration-naïve disease in men fit enough for chemotherapy. Darolutamide (ODM-201) is a unique investigational oral androgen receptor (AR) antagonist that binds the AR and AR mutants (eg, W742L and F877L) with high affinity and selectivity, thus, inhibiting receptor function and dihydrotestosterone binding with negligible blood-brain barrier penetration. In the phase 1/2 ARADES and ARAFOR trials, darolutamide had antitumor activity and was well tolerated in men with mCRPC (Fizazi et al. Lancet Oncol 2014; Massard et al. Eur Urol 2016). As a result of this encouraging activity in mCRPC, the ARASENS trial is evaluating darolutamide plus standard ADT + docetaxel in men with mHSPC.

Trial design
This international, randomized, double-blind, placebo-controlled, phase 3 trial (NCT02799602) is being conducted in 23 countries. 1300 men with newly diagnosed mHSPC will be randomized 1:1 to either 600 mg (2 × 300 mg) darolutamide BID with food, equivalent to a total daily dose of 1200 mg or placebo, both with ADT + docetaxel (6 cycles after randomization), and stratified by extent of disease and alkaline phosphatase levels. Key inclusion criteria are confirmed PC with documented metastases, started ADT ± first-generation androgen inhibition therapy ≤12 wk before randomization, and Eastern Cooperative Oncology Group performance status 0 or 1. The primary objective is to show superior overall survival with darolutamide vs placebo, both with ADT + docetaxel. Secondary end points include time to CRPC, initiation of subsequent anticancer therapy, symptomatic skeletal event-free survival (SSE-FS), time to first SSE, initiation of opioid use, pain progression, and worsening of physical symptoms, all measured at 12-wk intervals. Safety will be assessed. The trial is open for enrollment, FPFV was in November 2016, and >110 sites in 16 countries are enrolling.

Clinical trial identification
NCT02799602

Legal entity responsible for the study
Bayer

Funding
Funded by Bayer. Darolutamide was discovered at Orion Corporation and is being jointly developed with Bayer.
Disclosure

839TiP - A phase II clinical trial of radium-223 activity in patients (pts) with metastatic castration-resistant prostate cancer (mcrpc) with asymptomatic progression while on abiraterone acetate or enzalutamide besides AR-V7 mutational status (EXCAAPE)

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Background
Radium-223 is indicated for pts with mCRPC with symptomatic bone metastases. Biomarkers for radium-223 treatment and its correlation with AR-V7 splice variant, are both under research. The aim of this study is to assess the activity and safety of radium-223 stratified by AR-V7 status in asymptomatic pts who have progressed while on abiraterone acetate or enzalutamide treatment.

Trial design
This is a single-arm, multicenter, phase IIA clinical trial. Pts will receive radium-223 at a dose of 55 kBq per kilogram, given at 4-weeks intervals for 6 intravenous injections, until progression or unacceptable toxicity. We will screen for AR-V7 splice variant and CTCs number after inclusion, at the end of treatment and at progression. We predict that the number of AR-V7[+] pts will be 25% at inclusion. Major inclusion criteria are: (1) mCRPC according to standard Prostate Cancer Working Group (PCWG2)-2 criteria, (2) asymptomatic according to Brief Pain Inventory short form, (3) ≥24 weeks of prior treatment with abiraterone acetate or enzalutamide, (4) adequate organ function and performance status. The primary endpoint is the radiographic progression-free survival (rPFS) according to the PCWG-2 criteria. A total of 52 pts were predefined for the primary analysis using the one arm log-rank test. In both cohorts, we test the null hypothesis that true median rPFS is ≤ 3 months versus the alternative hypothesis that is ≥ 6.3 months. The one-sided type I error was 0.025 in both AR-V7 subgroups. A sample size of 13 pts is needed in the AR-V7[+] subgroup to attain 80% power. In accordance with the expected ratio between cohorts, we will include 39 pts in AR-V7[-] subgroup. The secondary objectives are to investigate the safety of the treatment, to determine the association
between AR-V7 status and tumor response and to establish the relationship between circulating tumor cells number with radium-223 activity. Trial registration number is NCT03002220. Date of registration was 20/10/2016. First patient included on 20/12/2016.

Clinical trial identification
NCT03002220, Initial Release Date: 20/Oct/2016

Legal entity responsible for the study
Medica Scientia Innovation Research-MEDSIR

Funding
Bayer Hispania S.L.

Disclosure

840TiP - Stereotactic ablative radiotherapy (SABR) for oligoprogressive metastatic castration-resistant prostate cancer (mCRPC) during abiraterone therapy: A phase I study

U. Emmenegger (Toronto, Canada) S. Cheng (Toronto, Canada) K. Zukotynski (Hamilton, Canada)
P. Cheung (Toronto, Canada)

Background
Despite recent therapeutic advances, there is a continuing need for novel prostate cancer treatment strategies. Some men with mCRPC may present at some point with oligometastases, a state between loco-regional and widespread metastatic disease with metastases being limited both in number and location. This oligometastatic state exists de novo, can be induced by effective systemic therapies, or may present under the picture of oligoprogression. The latter is a situation where ≤ 3-5 metastatic tumor sites progress, while all other metastases are controlled by ongoing systemic therapy. The typical practice would be to change systemic therapy at this point. SABR is an emerging treatment option for oligometastatic or oligoprogressive malignancies. Used for this indication SABR may improve survival and delay the need to change systemic therapy. However, some patients may derive limited benefit only because of early and widespread metastatic progression following SABR. While there are no validated biomarkers to predict these two scenarios to date, circulating tumor DNA (ctDNA) is a minimally invasive and highly informative biomarker platform for identifying molecular changes associated with treatment outcome.

Trial design
In the absence of published evidence on the use of SABR for oligoprogressive mCRPC in men undergoing abiraterone therapy, we are conducting a phase I study to determine the incidence of acute and late toxicities (primary endpoint) associated with delivering SABR to all oligoprogressive metastatic sites in 30 men with mCRPC on abiraterone. We also aim to collect preliminary efficacy data of such an approach as secondary endpoints (eg time to biochemical, radiological and/or symptomatic progression following SABR). Using conventional imaging, eligible mCRPC candidates will be identified based on ≤ 5 SABR amenable progressive metastatic lesions (≤ 3 in any one organ system) while all other
metastases remain stable or are responding to abiraterone therapy. Before SABR, we will collect ctDNA to perform gene copy number and mutational analyses of prostate cancer relevant genes as a means to predict sustained responses to SABR.

**Clinical trial identification**

N/A

**Legal entity responsible for the study**

Sunnybrook Research Institute, Toronto, ON, Canada

**Funding**

Janssen Inc., Canada

**Disclosure**

U. Emmenegger: Research support for this study and paid advisory board meetings of the manufacturer of abiraterone. All other authors have declared no conflicts of interest.

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841TiP - A randomized phase II study comparing cabazitaxel/prednisone to cabazitaxel alone for second-line chemotherapy in men with metastatic castrate resistant prostate cancer (mCRPC): CABACARE

C. Buonerba (Napoli, Italy) D. Bosso (Napoli, Italy) S. De Placido (Napoli, Italy) G. Di Lorenzo (Napoli, Italy)

**Background**

In the TROPIC study, cabazitaxel (CAB), administered with prednisone (PDN) 10 mg daily, showed significant advantage in OS and PFS in patients (pts) progressing during or after docetaxel (DOC) treatment. Similar to DOC, CAB has been approved in combination with daily PDN, although the contributing role of PDN to efficacy and safety has been poorly investigated. Corticosteroids have a variety of effects, which may be either favourable, mediated by adrenal androgen and cytokine suppression, or detrimental, because of adverse events associated with long-term use, promiscuous activation of AR, immunosuppression, activation of AR variants highly sensitive to PDN even at low concentrations. Moreover PDN acts as a CYP3A4 inducer, affecting clearance of taxanes. It has been shown that AR point mutations are rare in therapy-naive pts but occur in 15-45% of CRPC pts and can increase AR affinity for a wide range of steroids. Over 100 mutations have been described. In the CHAARTED trial DOC was safely administered without daily PDN showing important clinical benefits in OS, PFS, and time to CRPC.; Safety data for CAB without PDN are lacking. AR-V7 positivity and RB loss/inactivation have been identified as potentially implicated in progression with next-generation targeted agents. We also would like to prospectively assess their role as predictive biomarkers of CAB activity.

**Trial design**

CABACARE is a randomized, phase II, open label, multicenter study comparing CAB at 25 mg/m2 q21 plus daily PDN (10 mg) vs CAB at 25 mg/m2 q21 alone in mCRPC pts progressed during or after DOC treatment. The study is designed to test non-inferiority in terms of PFS, according to PCWG-2, of CAB alone vs CAB plus PDN, assuming that the two arms are equally effective. Each arm will enroll 110 pts. Main secondary objectives are: safety, QoL, pain assessment, overall response rate (ORR), PSA response, time to PSA progression, time to radiological progression; OS; and time to skeletal related events (SRE). The influence of Arv7 and RB status on CAB activity will also be evaluated.

**Clinical trial identification**
Background

The evolution of CRPC is heterogeneous, and despite progress in its management, with several new agents approved for CRPC, we are still so far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed.

Trial design

PROSABI is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with AA. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with AA. Primary end point: to validate the prognostic value for overall survival (OS) of the expression signature (ES) in peripheral blood of 9 genes described by Olmos et al (Lancet Oncol 2012). Secondary end points: a) to study the prognostic role for progression-free survival of the ES; b) to analyse the prognostic role for OS of early changes in the ES; c) to compare the prognostic and predictive utility of the ES with other ES (Ross et al, Lancet Oncol 2012); d) to validate in this patient cohort prognostic nomograms described for CRPC. Exploratory outcomes: a) to establish prognostic value for TMPRSS-ERG and PTEN; b) to determine the prognostic value for serum testosterone levels; c) to analyse the role of serum chromogranine; d) to study the prognostic role of AR splicing variants; e) to explore new somatic and germinal variants in peripheral blood and tissue associated to dissemination, response and resistance to AA. PROSABI is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC patients. 220 patients will be accrued to provide appropriate statistical power to detect at least 91 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 184 patients have been included. Blood samples are collected before,
during (pre-cycle 3) and after progression to AA. Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification
NCT02787837

Legal entity responsible for the study
Spanish National Cancer Research Centre (CNIO)

Funding
Spanish National Cancer Research Centre + grant from Janssen

Disclosure
All authors have declared no conflicts of interest.

843TiP - PRORADIUM: Prospective multicentre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with radium-223

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R. García Domínguez (Salamanca, Spain) J. Puente (Madrid, Spain) J. Piulats Rodríguez (Barcelona, Spain)
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Background
Several new agents have been approved for CRPC, but we are still so far from being able to predict which group of patients might benefit from a particular strategy. Therefore, the identification of new predictive and prognostic biomarkers is urgently needed. In this setting, bone metabolism markers (BMM) assume particular importance regarding to R223.

Trial design
PRORADIUM is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with R223. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with R223. Primary end point: to validate the prognostic value for overall survival (OS) of serum BMM expression described by Primo N Lara et al (JNCI 2014). Secondary end points: a) to analyse the prognostic role for PSA response regarding to BMM expression; b) to correlate radiological response with BMM; c) to investigate the association of skeletal related events with BMM; d) to analyse the prognostic role of alkaline phosphatase before and during R223; e) to analyse the prognostic value of “Bone Scan Index” in response evaluation; f) to analyse the prognostic role for OS of AR-V7 and AR amplification; g) to validate the prognostic role of the expression signature described by Olmos et al (Lancet Oncol 2012) in peripheral blood. Exploratory outcomes: a) to validate prognostic nomograms described for CRPC; b) to explore new somatic and germinal variants in peripheral blood and tissue associated to response and resistance to R223. PRORADIUM is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC patients. 161 patients will be accrued to provide appropriate statistical power to detect at least 85 events (deaths) to analyse the main outcome. Currently, 48 centres are active for
recruitment and 54 patients have been included. Blood samples are collected before, during and after progression to R223. Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification
NCT02925702

Legal entity responsible for the study
Spanish National Cancer Research Centre (CNIO)

Funding
Bayer Hispania, S.L

Disclosure
A. Medina: Honoraria from Bayer Hispania, S.L. All other authors have declared no conflicts of interest.

844TiP - PROSENZA: Prospective multi-centre study of prognostic factors in castration resistant prostate cancer (CRPC) patients treated with enzalutamide (ENZ)

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Background
CRPC is a heterogeneous disease, and despite new agents approved, the optimal sequence of treatment remains unclear, far from personalised medicine that may offer the maximal benefit for the patient. For that reason, our aim is the identification of new biomarkers in CRPC patients treated with conventional therapy.

Trial design
PROSENZA is a prospective multicentre observational study in metastatic CRPC designed to explore biomarkers in patients treated with ENZ. Key inclusion criteria: a) histological confirmation of prostate cancer; b) documented criteria (PCWG2) for CRPC; c) availability of tumour tissue; d) candidate for standard treatment with ENZ. Primary end point: to study the prognostic value for overall survival (OS) of the detection of androgen receptor splicing variant 7 (AR-V7) and/or amplification of AR (AR+) in peripheral blood in this cohort. Secondary end points: a) to analyse the correlation between PSA response and AR-V7 and/or AR+; b) to evaluate the correlation between radiological response and AR-V7 and/or AR+; c) to study changes in AR-V7 frequency and/or AR+ pre and post ENZ; d) to analyse and correlate the prognostic role of AR-V7 and AR+ with other biomarkers as testosterone serum levels, PTENloss or TMPRSS-ERG fusions. Exploratory outcomes: a) to validate in this cohort prognostic nomograms described for CRPC; b) to validate the prognostic role of the expression signature described by Olmos et al (Lancet Oncol 2012) in peripheral blood; c) to explore new somatic and germinal variants in peripheral blood and tissue associated to dissemination, response and
resistance to ENZ. PROSENZA is part of the PROCURE Biomarkers network, a multicentric spanish platform for biomarkers discovery in CRPC. 187 patients will be accrued to provide appropriate statistical power to detect at least 71 events (deaths) to analyse the main outcome. Currently, 48 centres are active for recruitment and 54 patients have been included. Blood samples are collected before, during and after progression to ENZ Prospective data collection will be linked. This study may help to incorporate new biomarkers in clinical practice and improve the selection of therapy in mCRPC.

Clinical trial identification
NCT02922218

Legal entity responsible for the study
Spanish National Cancer Research Centre

Funding
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Disclosure
A. Medina: Honoraria from Astellas. All other authors have declared no conflicts of interest.

GENITOURINARY TUMOURS, NON-PROSTATE
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856P - Avelumab treatment of metastatic urothelial carcinoma (mUC) in the phase 1b JAVELIN solid Tumor study: updated analysis with ≥6 months of follow-up in all patients
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Background
Avelumab, a human anti–PD-L1 monoclonal antibody, has shown promising efficacy and safety in patients (pts) with mUC. We report an updated analysis of avelumab treatment in 2 cohorts of pts from JAVELIN Solid Tumor (NCT01772004).

Methods
Pts with mUC whose disease had progressed after platinum-based therapy or were cisplatin ineligible received avelumab 10 mg/kg Q2W. Tumors were assessed every 6 weeks by independent review (RECIST v1.1). Endpoints included objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety (NCI CTCAE v4.0), and tumor PD-L1 expression. Kaplan-Meier (K-M) method was used to estimate DOR, PFS, and OS.

Results
As of Sep 2016, 249 pts had received avelumab and were followed for ≥6 mos (median 13.6 mos); 43 pts (17.3%) remained on treatment. 13 pts (5.2%) were cisplatin ineligible,
including 7 (2.8%) platinum naïve. Confirmed ORR in all pts (n = 249) was 17.3% (95% CI 12.8–22.5; complete response in 4.4%) and the disease control rate was 44.6%. Response was ongoing in 34/43 pts (79.1%), median DOR was 20.1 mos (95% CI 9.7–20.1) and the K-M estimate of DOR of 6 mos was 92.7% (95% CI 79.1–97.6). In evaluable pts (n = 206), ORR in PD-L1+ and PD-L1– subgroups (≥5% tumor cell cut-off) was 25.6% and 13.7%, respectively. Median PFS was 1.6 mos (95% CI 1.4–2.7), median OS was 8.2 mos (95% CI 6.3–10.8), and the K-M OS rate at 12 mos was 41.9% (95% CI 34.8–48.7). 170/249 pts (68.3%) had a treatment-related adverse event (TRAE) of any grade, most commonly infusion-related reaction (23.3%) and fatigue (17.3%). 26 pts (10.4%) had a grade ≥3 TRAE, most commonly fatigue (1.6%), elevated lipase (1.6%), and pneumonitis (1.2%). 43 pts (17.3%) had an immune-related AE (grade ≥3 in 3.6%). 8 pts (3.2%) discontinued avelumab due to a TRAE. There was 1 treatment-related death (pneumonitis).

Conclusions

Avelumab showed durable clinical activity and had a manageable and tolerable safety profile in pts with mUC irrespective of PD-L1 expression. A phase 3 trial of avelumab as maintenance therapy after first-line platinum-based therapy for advanced UC is ongoing.

Clinical trial identification

NCT: NCT01772004 Protocol number: EMR 100070-001

Legal entity responsible for the study

Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany

Funding

Funding was provided by Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany

Disclosure

### Background

Advanced UC is most often seen in senior pts, in whom age-related complications such as renal dysfunction and poor performance status (PS) preclude 50% from receiving standard first-line cisplatin treatment. In the phase 2 KEYNOTE-052 trial (NCT02335424), first-line pembrolizumab had clinically meaningful antitumor activity (ORR, 24%) and was well tolerated in cisplatin-ineligible pts with UC. Results from the subgroup of pts who were considered senior (≥65 y or ≥ 75 y) and had ECOG PS 2 are presented.

### Methods

Pts were cisplatin ineligible and had advanced UC, measurable disease (per RECIST v1.1), ECOG PS 0-2, and no prior systemic chemotherapy. Pts received pembrolizumab 200 mg Q3W. Radiographic imaging was performed at wk 9, then Q6W for the first year, and Q12W thereafter. The primary end point was ORR (RECIST v1.1, independent radiology review).

### Results

Of 370 pts, 302 (82%) were ≥65 y, 179 (48%) were ≥75 y, 120 (32%) were ≥65 y with ECOG PS 2, and 78 (21%) were ≥75 y with ECOG PS 2. Median follow-up was 5 mo. ORR (95% CI) was similar to that reported in the overall study population regardless of age cutoff (Table). Poor PS did not impact ORR in senior pts (Table). 6-mo PFS rates were consistent across senior groups (Table). 64% (≥65 y), 66% (≥75 y), 58% (≥65 and ECOG PS 2), and 64% (≥75 y and ECOG PS 2) of pts experienced treatment-related AEs. 16% of pts ≥65 and ≥75 y and 17% of pts ≥65 and ≥75 y with ECOG PS 2 experienced grade ≥3 treatment-related AEs. Table:

<table>
<thead>
<tr>
<th>≥65 y</th>
<th>≥75 y</th>
<th>≥65 y and ECOG PS 2</th>
<th>≥75 y and ECOG PS 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 302</td>
<td>n = 179</td>
<td>n = 120</td>
<td>n = 78</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>23 (19-28)</td>
<td>23 (17-30)</td>
<td>24 (17-33)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (2-7)</td>
<td>2 (1-6)</td>
<td>2 (0.2-6)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (15-24)</td>
<td>21 (15-27)</td>
<td>22 (15-31)</td>
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<tr>
<td>6-mo PFS, %</td>
<td>30%</td>
<td>27%</td>
<td>28%</td>
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</table>
Conclusions
Results from subgroup analyses of senior pts with poor PS in KEYNOTE-052 confirm that first-line pembro elicits clinically meaningful responses consistent with the overall study population. Pembro is well tolerated in cisplatin-ineligible pts with UC, including those who are senior with poor PS.

Clinical trial identification
NCT02335424; January 7, 2015

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

Funding
Merck & Co., Inc.

Disclosure

858P - Sacituzumab govitecan (IMMU-132) for patients with pretreated metastatic urothelial cancer (UC): interim results
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Background
Pts with metastatic UC have limited therapy options. Immune checkpoint inhibitors (CPI) are now given to patients with advanced UC, but only about 25% respond. We are studying the safety and efficacy of sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate, in pts with UC refractory to other therapies.

Methods
In this phase I/II study (NCT01631552), pts with metastatic UC who progressed after ≥1 prior systemic therapy were treated with IMMU-132 at 10 mg/kg on days 1 and 8 of 21-day cycles, until progression or unacceptable toxicity. All intention-to-treat (ITT) pts, including those who relapsed/progressed after CPI therapy, are evaluated for safety, ORR by RECIST 1.1 (confirmed PR/CR), PFS, and OS. Response-evaluable (RE) pts received ≥ 2 doses and ≥ 1 post-baseline CT (RECIST 1.1) assessment.

Results
41 pts (39M/2F; median age 68 y, range 50-91) were enrolled (RE = 36); ECOG 0/1: 31%/69%; median of 3 (range 1-6) prior therapies, including 34/41 platinum and 15/41 CPI regimens. Metastatic sites: lymph node 68%, lungs 54%, liver 32%, bone 27%; overall visceral disease, 31/41 (76%). Pts received a median of 12 (range 1-58) doses. ORR in the ITT population was 34% [14/41 (1 CR, 13 PR); ORR was 39% in the RE group, including 5/13 (39%) with liver mets]; 14 SD (39%); 8 PD (20%), and 5 inevaluable. In responders, 13/14 had prior platinum, 8/14 (57%) ≥3 prior therapies, and 4 prior CPI [4/13 in the RE group (31%), where IMMU-132 was ≥4th line of therapy in 11/13 pts]. Median time to response: 1.9 mos. Median duration of response: 12.9 mos (95%CI, 5.1-12.9), with 8/14 continuing therapy. Clinical benefit rate (CR+PR+SD≥6 mos) is 44%; 56% for SD ≥ 4 mos. In the 41 ITT pts, median PFS and OS are 7.2 (95% CI, 5.0-10.7) and 15.5 mos (95% CI, 8.9-17.2), respectively. Grade ≥3 adverse events ≥5% were 28% neutropenia, 9% febrile neutropenia, 9% fatigue, 9% anemia, 6% diarrhea.

Conclusions
With an ITT ORR of 34%, PFS of 7.2 mos, OS of 15.5 mos, and duration of response of 12.9 mos in 41 unselected pts with advanced pretreated UC (median of 3 prior therapies), these interim results show IMMU-132 is a promising agent in pts relapsed/refractory to chemotherapy and immune checkpoint inhibitors.

Clinical trial identification
NCT01631552

Legal entity responsible for the study
Immunomedics, Inc.

Funding
Immunomedics, Inc.

Disclosure
Background
Fibroblast growth factor receptor (FGFR) signaling is deregulated in urothelial carcinomas (UC). Rogaratinib is an oral inhibitor of FGFRs 1-4 with demonstrated antitumor activity in bladder cancer xenograft models. We report the results from a rogaratinib phase I trial expansion cohort in UC patients selected based on FGFR1-3 mRNA tumor overexpression and/or presence of activating mutations in the FGFR3 gene.

Methods
Patients with locally advanced or metastatic UC who have progressed or ineligible for standard therapy were screened for high FGFR1-3 mRNA expression levels by RNA in situ hybridization (RNAscope®) and Nanostring® assays utilizing fresh or archival FFPE tumor specimens. FGFR3-activating mutations were evaluated by a PCR based assay (Qiagen). Patients were treated with rogaratinib 800mg BID on a continuous regimen. Tumor response was assessed by RECIST, v1.1. Adverse events were classified using CTCAE v4.03 criteria.

Results
Biopsies from a total of 109 patients with advanced UC were screened, with 42.3% found to be FGFR positive: of which 87% due to FGFR3 mRNA overexpression, 4% FGFR1, and 9% mixed FGFR isoform mRNA expression. Co-occurrence of FGFR3-activating mutations and high FGFR3 mRNA expression was seen in 8% of patients. Among 20 patients with UC treated with rogaratinib, 16 (75%) had tumor shrinkage in target lesions with 9 (45%) showing tumor shrinkage of more than 20%, and 6 (30%) having a partial response (PR). Disease control rate (CR+PR+SD>12w) was 75%. Three patients with a PR had elevated tumor FGFR3 mRNA levels without corresponding genomic alterations. The most frequent AEs were hyperphosphatemia and diarrhea.

Conclusions
Selection of UC patients for treatment with rogaratinib based on FGFR1-3 mRNA expression levels in archival tissue was feasible and identified patients benefitting from treatment without having aberrations of FGFR-encoding genes. Rogaratinib has a favorable safety profile and showed anti-tumor activity in biomarker-selected UC patients which warrants further clinical development.

Clinical trial identification
NCT01976741
Background
Cisplatin-based regimens are the mainstay of treatment (tx) for mUC. Unfortunately, pts with mUC are often elderly and have comorbid conditions that preclude cisplatin-based tx. This CTEP-sponsored trial seeks to assess the efficacy and tolerability of GE in this population.

Methods
A Simon 2 stage design was employed (7 + 14). To proceed to full accrual first stage required 2 or more confirmed responders- complete (CR) or partial (PR) response. To be a positive trial, 7 responders were required. Tx consisted of Gemcitabine 1gm/m2 and Eribulin 1.4mg/m2, both on Day (D) 1 and D8 of a 21-D cycle and continued until progression (PD) or unacceptable toxicities. Cisplatin ineligibility was defined as creatinine clearance (CrCl) <60 (but ≥30) ml/min, grade 2 neuropathy, or grade 2 hearing loss.

Results
Between 6/2015 and the report cutoff date of 5/2017, 24 eligible pts with a median age of 73 (range: 62-88) were enrolled. Demographics: 20 males, 4 females. ECOG performance status of 0/1/2 was seen in 11/11/2 pts. Sites of disease included: nodes 16, lungs 8, liver 7, bladder 5, bones 2. Median number of cycles was 3.5 (range 1-16). 2+ confirmed PRs in the first 7 pts allowed the trial to proceed to full accrual. Of 19 evaluable pts, 2 had a CR, 10 had a PR, 5 had SD and 1 had PD. The objective response rate (ORR) was 63%. Overall survival (OS) 14.9 months (5.6, 21.9+); and progression free survival (PFS) was 6.9 months (5.3, 16.1+). Duration of response (DOR) was 4.6 months (range: 0.5, 15.0). Among the first 21 pts 7 had a PR and 2 had a CR and 5 were inevaluable for response, with an ORR of 43%. All 24 pts were evaluable for toxicities; the most common any grade toxicities included fatigue 83%, neutropenia 75%, anemia 63%, alopecia 50%, elevated AST 46%, constipation and nausea 42% each and thrombocytopenia 36%.
Conclusions
GE exceeded the threshold for efficacy in this trial. The endpoints of ORR, OS and PFS compare favorably to the commonly used regimens in this setting such as gemcitabine-carboplatin with a confirmed ORR of 36.1% and OS of 9.3 months. These data support further development of this combination in pre-and post immunotherapy settings.

Clinical trial identification
NCI-9653

Legal entity responsible for the study
NCI

Funding
None

Disclosure
All authors have declared no conflicts of interest

861P - Expression of long non-coding RNA MFI2-AS1 is a strong predictor of recurrence in sporadic localized clear-cell renal cell carcinoma

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Background
Improved patient stratification is a challenge in adjuvant clear-cell renal cell carcinoma (ccRCC) trials. Long non-coding RNAs (lncRNAs) are genome-wide regulators with potent prognostic value. We aimed to predict risk of ccRCC recurrence based on lncRNA expression from two independent cohorts.

Methods
Identification of prognostic lncRNAs was performed in a training set of 351 samples of localized ccRCC from the Cancer Genome Atlas, using Cox regression based on disease-free (DFS) and overall survival. Functional annotation of differentially expressed genes according to lncRNA expression was performed. The validation cohort included 167 localized ccRCC patients. Gene expression was studied by qRT-PCR. Kaplan-Meier estimators and Cox regression models were used for survival and multivariate analyses. Primary endpoint was DFS.

Results
MFI2-AS1 was best candidate lncRNA in the developmental study. Its expression was associated with immune response genes expression. In the validation cohort, MFI2-AS1 expression was associated with shorter DFS (Hazard Ratio (HR) for relapse 3.5, \( p = 0.0001 \)), independently from Leibovich recurrence classification and grade. Combined with Leibovich classification, MFI2-AS1 status improved prediction of recurrence, with a C-index of 0.70 compared to 0.67 for MFI2-AS1 alone and 0.66 for Leibovich classification alone. In patients with aggressive tumors (Leibovich ≥ 5), MFI2-AS1 expression was associated with a dramatically increased risk or relapse (HR 12.16, \( p < 0.0001 \)) compared to patients with undetectable MFI2-AS1 who had ultimately favorable outcomes. MFI2-AS1 expression was also correlated with high tumor burden.
Conclusions
MFI2-AS1 is a potent predictor of recurrence in localized ccRCC. Combined with historical classifications, it provides a highly accurate patient stratification that may be useful in adjuvant settings.

Legal entity responsible for the study
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Funding
Fondation Avec

Disclosure
N. Tannir: Honoraria and consulting: Bristol-Myers Squib, Exelixis, Nektar, Novartis, Pfizer, Argos, Calithera. Research funding: Bristol-Myers Squib, Exelixis, Epizyme, Novartis, Miranti. All other authors have declared no conflicts of interest.

862P - Treatment and outcome after Immune checkpoint inhibitors (ICI) in metastatic Urothelial Carcinoma (mUC): A European perspective
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Background
PD-1/PD-L1 inhibitors are changing the current landscape of mUC. Outcomes after discontinuation of ICI are unclear in this population.

Methods
Data from 8 European institutions was retrospectively collected. Target population was patients progressing on ICI. Univariate and multivariate analysis for overall survival (OS, calculated from the last date of ICI until death from any cause) as well as potential predictive factors of response to post-progression therapy (ppT) were performed. Tests were two-sided.

Results
From March 2013 to April 2017, 291 patients were identified. 227 (78%) experienced progression (PD) on ICI. Median post-progression OS of ICI was 5 months (95% CI 3.7-6.3), being 8.6 (95%CI 7.5-9.7) if receiving ppT vs 1.8 (95%CI 1.5-2.1) if best supportive care alone (p < 0.001, HR 0.23, 95%CI 0.16-0.32). OS increased according to number of lines received after PD (p < 0.001, HR 0.29, 95%CI 0.21-0.39). In the multivariate analysis, shorter duration of ICI, visceral metastases and female sex correlated with worse OS. Prior response to ICI was associated with improved OS in the univariate analysis only. Use of cisplatin-based chemotherapy, location of primary tumor, histology and age did not modify OS. Of patients progressing on ICI, 95 (42%) received subsequent treatment: 84% had 1 systemic line, 14% 2, and 2% 3 lines. RR to 1st ppT was 49% vs 21% for 2nd line or beyond. Median OS was 7.8 months when 1 line of therapy was received after ICI (95%CI 6.6-8.9) vs 18 (95%CI 8.5-27.4) when 2 or more.
Prior exposure to CT (OR 0.19, p = 0.003) and shorter duration of ICI (OR 0.24, p = 0.012) were correlated with worse RR in the multivariate study. Prior exposure to chemotherapy (CT) did not impact in the OS of these patients. RR to 1st line CT was 56% when used before exposure to ICI vs 66% when used after (p 0.3). Details on patient characteristics, univariate and multivariate analysis will be presented.

Conclusions

Many patients do not receive subsequent chemotherapy, including CT-naive patients. Patients who receive post-ICI therapy have good outcomes. ICI does not appear to confer resistance to CT. Retrospective analysis is prone to bias.

Legal entity responsible for the study

Alfonso Gómez de Liaño Lista

Funding

None

Disclosure

Y. Loriot: AstraZeneca, Roche, MSD, Pfizer, Astellas, Janssen, Clovis, Bristol-Myers Squib. T. Powles: Roche/Genentech, AstraZeneca, MSD. M. Van der Heijden: Roche/Genentech, AstraZeneca, Astellas, Bristol-Myers Squib, MSD. All other authors have declared no conflicts of interest.

863P - Phase 2 study of pembrolizumab alone or combined with acalabrutinib in platinum-refractory metastatic urothelial carcinoma (mUC)

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D. J. George (Durham, United States of America)

Background

PD-1/PD-L1 inhibitors have shown clinical benefit in mUC; however, the ORR is 15-25%, highlighting the need for more effective therapies. Gunderson, et al 2015 showed activation of Bruton tyrosine kinase (BTK) in myeloid cells of the pancreatic tumor microenvironment. As myeloid suppression impairs T-cell anti-tumor function, BTK inhibition may augment checkpoint inhibitor T-cell activation. This study assessed safety and efficacy of the PD-1 inhibitor pembrolizumab (P) alone or with the BTK inhibitor acalabrutinib (PA) in mUC.

Methods

Patients (pts) with mUC who progressed with ≥1 line of platinum chemotherapy were randomized 1:1 to P (200 mg Q3W IV) or PA (200 mg Q3W+100 mg BID PO). Pts who progressed (irRECIST) with monotherapy were permitted to cross over to combination therapy. Primary objectives were safety and ORR (local review, RECIST 1.1). Secondary endpoints included PFS and OS. Tumor PD-L1 expression was evaluated by Q²Solutions.
Results
Between Jun 2015 and Jan 2016, 75 pts were treated with P (n = 35) or PA (n = 40); cross over, n = 10. Median age, 66 y; men, 76%; ECOG PS 0-1, 97%; median prior therapies, 2 (range, 1-4). In P/PA median (mos) time on study treatment, 2.96/1.94; median follow-up, 11.2/6.1. Grade 3-4 treatment-emergent AEs (%) in ≥15% of P or PA was anemia (20) in P and fatigue (23), increased alanine aminotransferase (23), urinary tract infection (18), and anemia (15) in PA. There were 3 fatal AEs in PA: hemoptysis and sepsis (unrelated); pneumonia (P-related). ORR was 26% (CR, 9%) with P and 20% (CR, 10%) with PA. Median PFS was similar between treatment arms; median OS was 11.4 and 6.3 mos in P vs PA (Table). Most pts (49/60) had PD-L1+ tumors; expression was not associated with improved ORR (Table).

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab n = 35</th>
<th>Pembrolizumab + acalabrutinib n = 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety, n (%) (excluding events after cross over)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade 3-4 AE</td>
<td>17 (49)</td>
<td>29 (73)</td>
</tr>
<tr>
<td>Any treatment-related grade 3-4 AE</td>
<td>6 (17)</td>
<td>21 (53)</td>
</tr>
<tr>
<td>Any grade 3-4 SAE</td>
<td>12 (34)</td>
<td>20 (50)</td>
</tr>
<tr>
<td>Any treatment-related 3-4 SAE</td>
<td>0 (0)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>AE leading to study drug discontinuation</td>
<td>7 (20)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Grade 5 AE</td>
<td>0 (0)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Treatment-emergent AEs, n (%) (any grade, ≥30% of all pts)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (46)</td>
<td>33 (83)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13 (37)</td>
<td>17 (43)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (20)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (20)</td>
<td>14 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (29)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI) [n/N]</td>
<td>26 (13, 43) [9/35]</td>
<td>20 (9, 36) [8/40]</td>
</tr>
<tr>
<td>Overall population</td>
<td>23 (8, 45) [5/22]</td>
<td>22 (9, 42) [6/27]</td>
</tr>
<tr>
<td>PD-L1+ population</td>
<td>1.6 (1.4, 4.2)</td>
<td>2.2 (1.4, 3.5)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>11.4 (5.7, NE)</td>
<td>6.3 (3.6, 12.3)</td>
</tr>
<tr>
<td>12 mo OS, % (95% CI)</td>
<td>44.1 (27.2, 59.8)</td>
<td>38.5 (23.5, 53.3)</td>
</tr>
</tbody>
</table>

AE, adverse event; CI, confidence interval; mo, month; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; SAE, serious adverse event; OS, overall survival.

Conclusions
Most pts tolerated the study treatment, although more PA-treated pts had grade 3-4 AEs. Acalabrutinib plus pembrolizumab did not improve ORR over pembrolizumab alone in pts
with mUC, regardless of PD-L1 status.

**Clinical trial identification**
NCT02351739

**Legal entity responsible for the study**
Acerta Pharma

**Funding**
Acerta Pharma

**Disclosure**

**864P - Long non-coding RNAs are differentially expressed between bladder cancer subtypes**

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**Background**
The recent identification of molecular bladder cancer subtypes by whole transcriptome
studies showed similarities to molecular breast cancer phenotypes. We here validate these subtypes with a sensitive 36 gene nCounter screening and analyse relevant lncRNA for their differential expression.

**Methods**

RNA has been extracted from chemotherapy-naïve muscle-invasive bladder cancer (MIBC) after radical cystectomy (follow-up: 12 years, n = 48). A multiple marker gene panel has been quantified with the nCounter technology. In silico validation of the classifier geneset on 170 MIBCs has been performed. All squamous carcinoma were excluded. LncRNAs were analyzed in a clustering-independent assessment. Multivariate analyses were performed by a Cox proportional hazards model.

**Results**

36 consensus genes were generated by Venn diagrams based on the Mannheim, Lund, Chungbuk and MDA cohorts. This minimal set of genes generated 3 stable clusters: basal, luminal and infiltrated. The subtype specific assessment of 14 IncRNAs relevant in bladder cancer showed a highly subtype specific expression for 9 IncRNAs. The infiltrated subtype, characterized by an activated p53 downstream signature, showed an overexpression of SRA1 and MEG3 (p ≤ 0.003) - the latter is known for promoting the expression of TP53. The IncRNAs H19, GAS5, TUG1 and CBR3-AS1 showed a significant upregulation in the luminal subtype (p < 0.05) whereas SNHG16 showed an exclusive suppression. MALAT1 was suppressed in the basal subtype. A distinct cutoff of the lncRNA H19 allowed a risk stratification into high- and low-risk patients. The luminal subtype and H19 were the only independent risk factors in multivariate analysis adjusted for TNM and were predictive for a 3- to 4-fold higher risk of death (p < 0.03).

**Conclusions**

In this study, MIBC subtypes have been validated by a sensitive quantification method. Molecular subtypes and H19 prove to be independent risk factors superior to TNM. This study demonstrates for the first time a differential expression of IncRNA between MIBC subtypes. The potential impact of IncRNA on phenotype determination has to be investigated in vivo.

**Legal entity responsible for the study**

BRIDGE Consortium

**Funding**

None

**Disclosure**

R. Sébastien: Novartis Research Fund. All other authors have declared no conflicts of interest.

865P - Adjuvant chemotherapy after radical nephroureterectomy does not improve survival in patients with upper tract urothelial carcinoma: A joint study of the EAU-Young Academic Urologists and the Upper Tract Urothelial Carcinoma Collaboration

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Background
In patients (pts) with upper tract urothelial carcinoma (UTUC) the benefit of adjuvant chemotherapy (ACT) after radical nephroureterectomy (RNU) is debated. We aimed to analyze the benefit of ACT vs observation (Obs) in an international study.

Methods
Data from 15 centers was collected, totalling 1,544 pts, treated between 2000 and 2015. Criteria for pt selection were: UTUC diagnosis, pT2-4N0/x and/or pN+ stage undergoing RNU. The standardized differences (SD) approach was used to compare subgroup characteristics. Overall survival (OS) was the primary endpoint. The adopted propensity scores (PS) techniques included 1:1 PS matching and inverse probability of treatment weighting (IPTW). Additionally, the IPTW analysis was performed with the inclusion of the covariates, i.e. with doubly robust estimation (DREP). 6-month landmark analysis (LA) was also performed.

Results
A total of 312 pts received ACT and 1,232 observations. Despite differences between the two groups, SD was generally <10% after matching. In the DREP-adjusted comparison, ACT was significantly associated with shorter OS (HR: 1.25, 95%CI: 1.02-1.54, p = 0.032), while no difference was observed in the matched analysis (HR: 1.14, 95%CI: 0.91-1.43, p = 0.268, table). These findings were confirmed in subgroup analyses (pT2N0/x; pT3-4N0/x; pTanyN+), and after LA. Relapse-free survival outcomes were overlapping to OS in the matched analyses (ACT, HR: 1.59 (95%CI: 1.25-2.02, p < 0.001). The limitations of the retrospective studies should be acknowledged.

865P Results of the Cox analyses for the OS endpoint

<table>
<thead>
<tr>
<th>Unadjusted comparison (N = 1,544):</th>
<th>HR</th>
<th>Lower 0.95</th>
<th>Upper 0.95</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.44</td>
<td>1.21</td>
<td>1.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Matched analysis (N = 570):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.14</td>
<td>0.90</td>
<td>1.43</td>
<td>0.268</td>
</tr>
<tr>
<td>Propensity score-adjusted comparison (ATE approach, N = 1,544):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.31</td>
<td>1.08</td>
<td>1.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Doubly-robust procedure (ATE approach, N = 1,544):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group: ACT vs. No ACT</td>
<td>1.26</td>
<td>1.02</td>
<td>1.54</td>
<td>0.032</td>
</tr>
<tr>
<td>Age: 75 vs. 61</td>
<td>1.33</td>
<td>1.18</td>
<td>1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECOG-PS: 1 vs. 0</td>
<td>2 vs. 0</td>
<td>1.37</td>
<td>1.61</td>
<td>1.18</td>
</tr>
<tr>
<td>Pathologic stage: pT3-4N0 vs. pT2N0 pTanyN+</td>
<td>1.30</td>
<td>2.97</td>
<td>0.99</td>
<td>2.26</td>
</tr>
<tr>
<td>vs. pT2N0 pT2Nx vs. pT2N0 pT3-4Nx vs. pT2N0</td>
<td>0.92</td>
<td>1.72</td>
<td>0.69</td>
<td>1.36</td>
</tr>
</tbody>
</table>

Abbreviations: ACT: adjuvant chemotherapy; ATE: average treatment effect; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; OS: overall survival.
Conclusions
ACT does not improve OS compared to Obs in pT2-4 and/or pN+ UTUC. These findings contribute to the uncertainties regarding ACT in UTUC and further support the need for dedicated prospective trials in UTUC, new more potent therapies, and enhanced pt selection criteria.

Legal entity responsible for the study
Andrea Necchi

Funding
None

Disclosure
All authors have declared no conflicts of interest.

867P - Correlation of circulating tumor DNA (ctDNA) assessment with tissue-based comprehensive genomic profiling (CGP) in metastatic urothelial cancer (mUC)

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P. J. Stephens (Cambridge, United States of America)V. A. Miller (Cambridge, United States of America)
B. Forcier (Cambridge, United States of America)J. Chung (Cambridge, United States of America)
S. K. Pal (Duarte, United States of America)

Background
Tissue-based CGP reveals a multitude of actionable targets in patients (pts) with mUC (Ross et al Cancer 2015). Assessment of ctDNA from blood offers the benefit of avoiding risks of biopsy/surgery and allows for serial assessment.

Methods
In pts with mUC, 50-100 ng of ctDNA was extracted from plasma during routine clinical care. Using adapted sequencing libraries, hybrid capture and sample multiplexed sequencing was performed with an Illumina HiSeq 2500 platform to a median coverage depth of 6353X. This CLIA-certified test of 62 genes detected genomic alterations (GAs) at low allele frequencies (0.1% for substitutions, 1% for indels/rearrangements and 20% for copy number amplification). In several pts CGP data was available from separate tissue-based CLIA-certified tests for which methods have been previously reported (Frampton et al Nat Biotechnol 2013). In addition to examining intra-patient differences, we compared the cumulative frequency of GAs in ctDNA to a large pool of tissue-based CGP in pts with mUC (n = 2024).

Results
27 pts (18:9 M:F) with mUC had ctDNA assessment; median age 68 (range, 52-86). There was evidence for ctDNA in the blood for 25/27 pts (93%), and at least 1 GA was observed in 20/27 (74%) cases. The most frequently altered genes were TP53 (63%), TERT-promoter (33%), PIK3CA (15%), FGFR3 (11%), NF1 (11%) and ERBB2 (7%). With the caveat of a limited sample size, the cumulative frequency of selected clinically relevant GAs was distinct in ctDNA and tissue. The frequency of FGFR3 alteration was lower in ctDNA as compared to tissue (11% vs 23%), as was the frequency of ERBB2 alteration (14% vs 7%). A pt with FGFR3 GA in baseline tumor tissue showed disappearance of FGFR3 GA and evolution of a TP53 alteration in ctDNA following treatment with an
FGFR3 inhibitor. In a pt with ERBB2 and TP53 GAs in baseline tumor tissue, ctDNA collected at the time of resistance to cisplatin-based therapy showed persistence of ERBB2 and TP53 GAs and a new NF1 GA.

Conclusions
Using hybrid capture-based genomic profiling of ctDNA, ctDNA was detected in the vast majority of pts with mUC. Utility was demonstrated through detection of potential resistance mutations in pts receiving chemotherapy and targeted agents.

Legal entity responsible for the study
Siraj Ali

Funding
None

Disclosure

866P - Impact of cisplatin-based therapy on long-term survival in advanced urinary tract cancer (aUTC). A retrospective international study of invasive/advanced cancer of the urothelium (RISC)

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Y. Wong (Philadelphia, United States of America) S. K. Pal (Duarte, United States of America)
U. De Giorgi (Meldola, Italy) S. Ladoire (Dijon, France) N. Agarwal (Salt Lake City, United States of America)
E. Y. Yu (Seattle, United States of America) G. Niegisch (Düsseldorf, Germany) C. N. Sternberg (Roma, Italy)
A. Srinivas (Stanford, United States of America) U. Vaishampayan (Detroit, United States of America)
A. Necchi (Milan, Italy) J. E. Rosenberg (New York, United States of America) T. Powles (London, United Kingdom)
J. Bellmunt (Boston, United States of America) M. D. Galsky (New York, United States of America)

Background
Cisplatin-based chemotherapy is the treatment of choice in aUTC. Nevertheless, about 50% of patients are unfit for this treatment. Long-term survival of patients with aUTC has not been adequately studied outside the context of clinical trials. In addition, the impact of cisplatin utilization on long-term survival has not been adequately addressed. We used a multinational database to study long-term survival and the impact of treatment type in unselected aUTC patients as well as to provide benchmarks for future trials.

Methods
Selection criteria: Diagnosis of aUTC, non small-cell histologies, administration of 1st-line chemotherapy, survival data available. Major end point: Overall survival (OS). Fitness-for-cisplatin (FFC) was defined according to Galsky et al (2011). Landmark and conditional survival analysis was used to study the change of prognosis with time from initiation of 1st-line chemotherapy.

Results
1361 patients (median fup: 31 months) were analysed. Survival analyses are shown in the
Cisplatin therapy and FFC were associated with improved long-term survival. FFC patients have a 28% probability of 5-year survival, which is increased to 74% for the 34% of patients who survive 3-years after initiation of cisplatin-based chemotherapy.

**Conclusions**

Published criteria for FFC accurately predict for long-term survival of aUTC patients, following cisplatin-based chemotherapy, while patients not treated with cisplatin have inferior outcome. Probability of long-term survival was increased with time after initiation of 1<sup>st</sup>-line (cisplatin or no-cisplatin) therapy.

**Legal entity responsible for the study**

RISC investigators

**Funding**

None

**Disclosure**

Y-N. Wong: The author was at Fox Chase Cancer Center at the time the study was conducted but is now a Janssen Scientific Affairs employee. All other authors have declared no conflicts of interest.

868P - Comparison of circulating tumor DNA (ctDNA) profile in metastatic urothelial carcinoma (mUC) derived from the upper tract (UT) and lower tract (LT)

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G. Sonpavde (Birmingham, United States of America) L. A. Kiedrowski (Redwood City, United States of America)  
R. J. Nagy (Redwood City, United States of America) K. Banks (Redwood City, United States of America)  
R. Lanman (Redwood City, United States of America) P. Grivas (Cleveland, United States of America)

**Background**

We have previously reported ctDNA profile in 246 patients (pts) with mUC derived from the LT (mLTUC) (Grivas et al ASCO GU 2017). mUC derived from the UT (mUTUC) is a
clinically distinct entity with a more aggressive disease course. The ctDNA profile of mUTUC has not been previously characterized.

**Methods**

Data was obtained from pts with mUTUC who received ctDNA profiling as a part of routine clinical care using a CLIA-certified, CAP-accredited platform evaluating up to 70 genes. Genomic alterations (GAs) were pooled for the entire cohort. Comparison to the previously reported mLTUC was performed using the chi-square test.

**Results**

Between Oct 2014 and Apr 2017, ctDNA results from 75 pts (M:F 30:45) with mUTUC were assessed. Median age of the cohort was 69 (range, 40-90). A median of 6.2 months had elapsed from the time of diagnosis with mUC and ctDNA assessment. Genomic alterations (GAs) were detected in 71 pts (95%), with an average/median of 4.5/3 GAs per pt (range, 0-35). Treatment related data was available in 30 pts (40%). The frequency of GAs in mUTUC vs mLTUC was as follows: TP53 (51% vs 52%), PIK3CA (20% vs 18%), ARID1A (16% vs 17%), EGFR (8% vs 13%), ERBB2 (8% vs 7%), FGFR3 (7% vs 11%), BRCA2 (6% vs 7%) and NF1 (6% vs 8%) (P=NS for all comparisons). Alteration types were diverse; for instance, FGFR3 alterations included fusion (FGFR3-TACC3 [n = 5]) and mutation (S249C [n = 3] and Y373C [n = 2]). Correlation of ctDNA profile with treatment and clinical outcome will be presented at the meeting.

**Conclusions**

Despite representing a clinically distinct entity, mUTUC demonstrated a ctDNA profile similar to that of mLTUC. These data may inform the design of clinical trials of targeted therapy (e.g., FGFR3 and ERBB2 inhibitors) in mUC, suggesting that inclusion of both mUTUC and mLTUC may be warranted.

**Legal entity responsible for the study**

Neeraj Agarwal

**Funding**

None

**Disclosure**

L.A. Kiedrowski: LAK is an employee of Guardant Health. R.J. Nagy: RJN is an employee of Guardant Health. K. Banks: KB is an employee of Guardant Health. R. Lanman: RL is an employee of Guardant Health. All other authors have declared no conflicts of interest.

869P - Modeling of Tumor Kinetics and Overall Survival to Identify Predictive Factors for Efficacy of Durvalumab in Patients with Urothelial Carcinoma (UC)

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R. Narwal (Mountain View, United States of America) C. Jin (Mountain View, United States of America)
A. Gupta (Gaithersburg, United States of America) Y. Ben (Gaithersburg, United States of America)
P. Mukhopadhyay (Gaithersburg, United States of America) B. Higgs (Gaithersburg, United States of America)
L. Roskos (Gaithersburg, United States of America)

**Background**

Durvalumab is a human mAb that binds to PD-L1 and blocks its interaction with PD-1 and CD80. The objectives of this analysis were to describe the longitudinal tumor size profiles, identify factors predicting tumor growth and regression, and associate tumor kinetics with overall survival (OS).
Methods
Longitudinal tumor size and OS data obtained from UC patients (Study 1108; NCT# CD-ON-MEDI4736-1108) who received durvalumab were analyzed using a nonlinear mixed effect model that describe tumor growth, tumor killing, and delay in immune response leading to tumor killing. An OS model was developed by linking model-predicted tumor size over time to survival hazard in a constant hazard model. Potential predictive factors of tumor growth and regression, as well as survival were evaluated in a multivariate covariate analysis in the tumor kinetic and OS model, respectively.

Results
Tumor kinetic and OS models adequately described the longitudinal tumor size and survival data from UC patients. The most influential factor associated with more rapid tumor growth was high baseline neutrophil-to-lymphocyte ratio (NLR), while lymph node disease was associated with decreased growth rate. Tumor (TC) or immune cell PD-L1 expression (IC), baseline tumor size and liver metastasis were identified as predictive factors for tumor killing. Simulations showed increased response rates with higher TC and/or IC (by 6/9%, and 18/24%, with 25% and 50% cutoff for TC/IC, respectively). After accounting for tumor response, the risk of death decreased with higher TC/IC and lower baseline hemoglobin and albumin levels, while liver metastasis, lymph node disease, and prior carboplatin treatment were associated with higher risk.

Conclusions
Tumor kinetic modeling identified factors that predict tumor growth and shrinkage following durvalumab therapy in UC patients, and permits investigation of predictive biomarker strategies considering confounding factors. Joint modeling that associates predicted tumor kinetics with OS allows model-based extrapolation of missing data and evaluation of other factors influencing OS after accounting for change in tumor size over time.

Clinical trial identification
NCT01693562 (September 14, 2012)

Legal entity responsible for the study
MedImmune

Funding
MedImmune

Disclosure

870P - Expression of Galectin-1 Determines Tumor Recurrence and Cancer-specific Survival in Patients with pT3 Upper Urinary Tract Urothelial Carcinoma

Y. Su (Kaohsiung, Taiwan) H. Luo (Kaohsiung, Taiwan) C. Huang (Kaohsiung, Taiwan) M. Hsieh (Kaohsiung, Taiwan)

Background
Upper urinary tract urothelial carcinoma (UTUC) is an aggressive and lethal disease. For
patients with locally advanced UTUC, recurrence of tumor is frequent, and lacks of predictive biologic markers limited the choice of postoperative treatment. Galectin-1 (GAL1) is a β-galactoside-binding protein, participating in many parts of tumorigenesis, including cell proliferation, invasiveness, metastasis, and angiogenesis. However, the role of GAL1 in UTUC has not been fully investigated. The aim of this study was to examine the prognostic impact of GAL1 in patients with UTUC.

Methods
The study enrolled 86 UTUC patients who underwent radical nephroureterectomy and bladder cuff excision with final pathologically diagnosed as pT3N0 stage between January 2005 and December 2012. Perioperative characteristics and pathologic features were recorded. Immunohistochemical staining of tumor specimens using anti-GAL1 antibody were performed. UTUC cell line (BFTC-909) was used for in vitro study of tumor invasiveness and migration. Kaplan-Meier analyses and Cox proportional regression models were used for univariate and multivariate survival analyses.

Results
Using 10% expression of GAL1 protein as a cutoff point, the study population could be classified as GAL1-high (GAL1 > 10%, n = 35) or GAL1-low (GAL1 ≤ 10%; n = 51) group. Basic clinicopathologic characteristics were comparable between two groups. In univariate analysis, high GAL1 expression was significantly associated with a worse recurrence-free survival (RFS; p = 0.028) and cancer-specific survival (CSS; p = 0.025). Multivariate analysis showed GAL1-high is an independent factor for RFS (HR 2.43; 95% CI 1.17-5.05, p = 0.018) and CSS (HR 4.04; 95% CI 1.25-13.03, p = 0.019). In vitro study, we found that knockdown of GAL1 reduced UTUC cancer cell migration and invasion significantly.

Conclusions
Galectin-1 expression is a reliable prognostic factor for locally advanced UTUC. GAL1 inhibition may serve as a potential therapeutic target for patients with UTUC.

Legal entity responsible for the study
Yu-Li Su

Funding
None

Disclosure
All authors have declared no conflicts of interest.

871P - Identification of genomic features underlying response of muscle-invasive bladder cancer (MIBC) to neoadjuvant sorafenib, gemcitabine, and cisplatin (SGC) in an open-label, single-arm, phase 2 study

D. Raggi (Milan, Italy) A. Paoli (Milano, Italy) M. Dugo (Milano, Italy) P. Giannatempo (Milan, Italy) L. De Cecco (Milano, Italy) M. Colecchia (Milano, Italy) M. Daidone (Milano, Italy) A. Necchi (Milano, Italy) M. Sensi (Milano, Italy)

Background
Genomic analyses demonstrated that MIBC can be grouped into molecular subtypes that portend different outcomes with neoadjuvant chemotherapy (NACT). SGC was active in MIBC, showing a response rate (downstaging to pT < 2) of 54.3% in 46 patients (pts) in a
We analyzed 25 pts, 18 responders (R) and 7 non-responders (NR). GEP and CNV profiles were generated using Affymetrix Clariom™ D and OncoScan™ assays. Samples were assigned to claudin-low (CL), basal (B) or luminal (L) subtypes according to the BASE47 and BCL40 signatures. Genes differentially expressed or amplified/deleted between NR and R were functionally analyzed using Ingenuity Pathway Analysis (IPA) and Gene Set Enrichment Analysis.

Results
Transcriptional subtypes were robustly assigned to 24/25 pts: 13 were classified as L, 10 CL and 1 B. A significant association between subtypes and therapeutic response was observed (p = 0.002), with all L samples falling in the R group while CL were split between R and NR (5 vs 5). To avoid confounding related to the subtype we restricted the comparison of R and NR to CL samples. Through the use of IPA we identified activation of an IRF7-driven transcriptional program (p = 3.88E-12) in NR samples. In the NR group we found a positive enrichment of gene sets related to mRNA processing, cell cycle and oxidative phosphorylation and a negative enrichment of defensins. In addition, 19 genes were both significantly overexpressed and amplified in NR whereas copy number gains on chromosome 17, 18 and 20 characterized R samples. Limitations include the unassessable role of S contribution to GC.

Conclusions
Altogether, the results indicate that L tumors are responsive to SGC. Comparisons between R and NR within the CL group outlined potential genomic predictors of response. Once validated, pt selection criteria for NACT may be substantially improved. Comparison with profiling of response to NA pembrolizumab will be shown (NCT02736266).

Clinical trial identification
N/A

Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale dei Tumori

Funding
Affymetrix

Disclosure
All authors have declared no conflicts of interest.

872P - Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib (c) vs everolimus (e) in advanced renal cell carcinoma (rcc)

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Background
C inhibits tyrosine kinases that promote oncogenesis and resistance to antiangiogenic therapy in RCC, including MET, AXL, and VEGF receptors. In the phase 3 METEOR trial (NCT01865747), C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs E in patients (pts) with advanced RCC after prior VEGFR-targeted therapy (Choueiri, Lancet Oncol 2016). The current study evaluated outcomes based on plasma biomarker levels.

Methods
Plasma samples collected at baseline and during treatment from 621 of 658 randomized pts were analyzed for HGF, MET, Gas6, AXL, VEGF, VEGFR2, CA9, and IL-8 by ELISA (Assay Gate, Ijamsville, MD). PFS and OS were analyzed based on low vs high (< median vs ≥ median) biomarker levels at baseline.

Results
Analyses of PFS and OS based on baseline biomarker levels showed improvement with C vs E (hazard ratio <1) for all analyses of both low and high levels. PFS improvement for C vs E was most pronounced for low baseline levels of AXL and VEGF, while OS improvement for C vs E was most pronounced for low baseline levels of HGF, Gas6, AXL, and VEGF (Table). For a subset of biomarkers, medians for PFS and OS were longer for low baseline levels vs high for both treatment arms. Differences in OS medians for low vs high levels were largest for HGF (not reached [NR] vs 15.4 mo for C; 19.4 mo vs 13.0 mo for E), Gas6 (NR vs 17.2 mo for C; 18.4 mo vs 13.9 mo for E), VEGF (NR vs 16.1 mo for C; 18.4 mo vs 14.9 mo for E), and IL-8 (NR vs 17.2 mo for C; 19.4 mo vs 13.0 mo for E).

Table:

<table>
<thead>
<tr>
<th>Plasma Biomarker C vs E, Hazard Ratio (95% CI) for OS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Biomarker</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>HGF</td>
</tr>
<tr>
<td>MET</td>
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<td>Gas6</td>
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<tr>
<td>AXL</td>
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<tr>
<td>VEGF</td>
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<tr>
<td>VEGFR2</td>
</tr>
<tr>
<td>IL-8</td>
</tr>
</tbody>
</table>

Conclusions
PFS and OS improved with C irrespective of baseline plasma biomarker levels in previously treated pts with advanced RCC vs E. However, low baseline levels of a subset of biomarkers were associated with better clinical outcomes with C.

Clinical trial identification
NCT01865747

Legal entity responsible for the study
Exelixis, Inc.

Funding
Exelixis, Inc.
Disclosure

873P - RX-3117, an oral hypomethylating agent to treat advanced solid tumors (st): Interim results from an ongoing phase 2a study in advanced urothelial cancer
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J. Poore (Rockville, United States of America) C. Peterson (Rockville, United States of America)
E. Benaim (Rockville, United States of America)

Background
RX-3117 is an oral small-molecule hypomethylating agent, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder and colorectal cancers. Data from the stage 1 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with advanced urothelial cancer are described below.

Methods
This Phase 2a study with a 2-stage design (NCT02030067) evaluates the efficacy of RX-3117 in eligible subjects (aged ≥ 18 years) with advanced urothelial cancer previously treated with an unlimited number of prior therapies. Primary objectives include safety and efficacy of the recommended Phase 2 dose (RP2D) and schedule identified in the Phase 1 portion of the study. Subjects received 700 mg of oral RX-3117 daily for 3 weeks with 1 week of rest in each 4-week cycle. The response criteria of complete response or partial response in 1 or more subjects or stable disease for 4 cycles in 2 or more subjects in Stage 1 in order to proceed to Stage 2.

Results
As of May 2017, 10 subjects with advanced urothelial cancer were treated with RX-3117 (4 females, 6 males). Of those 10 subjects, 70% received ≥ 3 prior therapies, had
performance score of 0-1 and multiple disease sites (lung, liver, lymph nodes and pelvis). Two subjects met the protocol defined response criteria of stable disease for 4 cycles of RX-3117 treatment; one subject received treatment for 168 days and another subject continues receiving therapy (147 days at abstract submission). In addition, 1 subject showed tumor shrinkage as measured by RECIST (-15%); another subject still on treatment showed a 19% tumor reduction after 2 cycles of RX-3117. Related adverse events were G2 anemia, G1 anorexia, G1 epistaxis, G1 fatigue, G1 nausea, G1 diarrhea, G1/G2 vomiting, G2 mucositis, G3 leukopenia, G1/G3 neutropenia, and G3 thrombocytopenia. One subject had a treatment delay and dose reduction.

Conclusions
Single agent RX-3117 appears to be safe and well tolerated and shows evidence of preliminary tumor activity. The predefined efficacy criteria was met in Stage 1, and Stage 2 is ongoing. Results from Stage 1 of the phase 2a will be presented.

Clinical trial identification
NCT02030067

Legal entity responsible for the study
Rexahn Pharmaceuticals, Inc

Funding
Rexahn Pharmaceuticals, Inc

Disclosure
J. Poore, C. Peterson, E. Benaim: Employee of Rexahn Pharmaceuticals, Inc. All other authors have declared no conflicts of interest.

874P - Immune correlates for the efficacy of PEGylated Human IL-10 (AM0010) with nivolumab in renal cell cancer

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N. Daver (Houston, United States of America)
A. Hung (Redwood City, United States of America)
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Background
At therapeutic concentrations AM0010 stimulates the cytotoxicity, survival and proliferation of CD8 T cells. IL-10 receptors and PD-1 are expressed on activated and exhausted CD8 T cells, providing a rationale for combining AM0010 and an anti-PD-1. AM0010 alone had partial tumor responses (PR) in 4 of 16 pts with poor to intermediate risk RCC. In dose escalation, 4 of 8 RCC patients receiving AM0010 plus pembrolizumab in 3rd line, had a PR. The mPFS was 16.7 months.

Methods
29 pts with metastatic RCC were enrolled on AM0010 (10 or 20 ug/kg daily SC) and nivolumab (3mg/kg, q2wk IV). Two had favorable, 20 had intermediate and 4 had poor IMDC risk (3 data not available). Pts. had a median of 1 prior therapy (range 1-3), and at least one VEGFR-TKI. Tumor responses were assessed following irRC. Immune related
cytokines in the serum, activation of blood derived T cells and clonal identity of peripheral T cell were measured.

Results
AMO010 plus nivolumab or pembrolizumab was well tolerated. TrAEs were reversible and transient. 14 patients on 20ug/kg AM0010 daily SC and nivolumab had at least 1 G3/4 TrAE, including anemia (10), thrombocytopenia (5), hypertriglyceridemia (5). Two pts had a reversible cytokine release syndrome with splenomegaly and increased immune mediated red blood cell phagocytosis most likely precipitated by T-cell activation, as both pts had objective tumor responses. Patients treated with 10ug/kg AM0010 and anti-PD-1 did not have hematologic G3/4 TrAEs. As of May 1 2017, PRs were observed in 9 of 26 evaluable pts (35%). An additional 12 pts have stable disease (46%), 7 of those have a tumor reduction > 30% (in progress). The mPFS and mOS has not been reached, the mFU is 7.7 months (range 0.5-13.7). AM0010 + anti-PD1 increased Th1 cytokines in the serum, proliferation of PD1+ Lag3+ CD8 T cells and oligoclonal expansion of novel T cell clones in the blood. The expansion of invigorated T cells and the clonal expansion correlated with tumor responses.

Conclusions
AM0010 in combination with anti-PD-1 is well-tolerated in RCC pts, the recommended phase 2 dose is 10ug/kg. The efficacy and the observed CD8 T cell activation is promising and encourages the continued study of AM0010 in combination with nivolumab.

Clinical trial identification
NCT02009449

Legal entity responsible for the study
ARMO BioSciences

Funding
ARMO BioSciences

Disclosure
A. Hung: Stock employment. P. Van Vlasselaer: Employment stock ledership. M. Oft: Employment. All other authors have declared no conflicts of interest.

875P - Outcomes of patients with metastatic urothelial carcinoma (mUC) with exclusive bone metastases: Focus on a special patient population

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S. Ladoire (Dijon, France)J. Baniel (Petach Tikva, Israel)S. Crabb (Southampton, United Kingdom)
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T. Powles (London, United Kingdom)A. Bamias (Athens, Greece)L. C. Harshman (Boston, United States of America)
J. Bellmunt (Boston, MA, United States of America)M. D. Galsky (New York, United States of America)

Background
Patients (pts) with aUC with exclusive bone metastatic spread represent a rare subgroup of pts with unique clinical features. These pts deserve special consideration, as they are
usually excluded from clinical trials due to the lack of measurable disease according to RECIST criteria. We focused on their access to treatment and outcomes in a retrospective study.

**Methods**

Cases were extracted from the pool of 1,911 pts with a diagnosis of mUC from the RISC database (db). Data from 23 centers was collected. Results of 1\textsuperscript{st}-line, platinum-based chemotherapy in bone-only pts were compared with those from the remaining pts in the RISC db. Summary statistics were used to describe pt characteristics and outcomes. Kaplan-Meier method was used to estimate time to event outcomes such as progression-free survival (PFS) and overall survival (OS). Both OS and PFS are measured from the date of diagnosis of metastatic disease. Univariable and multivariable Cox analyses were performed. All tests were two-sided and statistical significance was defined as a p-value ≤0.05.

**Results**

A total of 128 evaluable pts (6.7%), treated between 02/1997 and 04/2013, were identified. ECOG-PS was ≥1 in 85.9% vs. 66.3% of the remaining pts from RISC db. 73 (57%) received 1\textsuperscript{st}-line chemotherapy, that was platinum-based in all pts, and 28 of them (38.4%) 2\textsuperscript{nd}-line CT (vs. 75.8% and 42.5%, respectively, from the RISC db). On multivariable analyses, only the chemotherapy administration was significantly associated with improved OS among bone-only mUC pts (p < 0.001). Among platinum-treated pts (total evaluable N = 972), significantly-different PFS and OS estimates were observed according to the bone metastases status (no bone metastases vs. bone metastases only vs. bone + other, p < 0.001). 2-year PFS was: 37.4%, 28.8%, 25.9%. 2-year OS was: 35.5%, 15.8%, 23.0%, among the above subgroups, respectively.

**Conclusions**

Pts with bone only metastases are less likely to receive systemic therapy than pts with metastases to other sites, likely due to lower PS. The prognostic impact of having exclusive bone metastases or additional sites seems to be equally poor. Clinical trials with new agents should focus on this population.

**Legal entity responsible for the study**

Andrea Necchi

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

876P - Efficacy of cabozantinib (C) after PD-1/PD-L1 checkpoint inhibitors in metastatic renal cell carcinoma (mRCC): The Gustave Roussy experience

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**Background**

Optimal treatment sequence in mRCC remains unclear, although PD-1/PD-L1 inhibitors are becoming standard of care in second or third-line. There is little evidence about the efficacy of antiangiogenic therapies after immune checkpoint inhibitors (ICI), especially of
C, which was recently approved for mRCC. We report our initial experience of C efficacy after prior ICI.

**Methods**
We conducted a retrospective analysis of mRCC patients (pts) enrolled on clinical trials at Gustave Roussy with ICI with a special focus on C as subsequent therapy. Clinical outcome during C treatment, including Time to Treatment Failure (TTF), Objective Response Rate (ORR), Overall Survival (OS) and safety are reported.

**Results**
After a median follow-up of 60 months (mo), among 127 pts treated with ICI (n: 107; nivolumab), 44 (35%) were still on-treatment and 5 pts had stable disease after treatment interruption. Among the 78 pts who progressed after ICI, 22 pts (28%) never received further treatment. 56 pts (72%) received further therapies: 18 (32%) C, 25 (44%) Axitinib (A) and 13 (24%) other (O). C was given as third-line or beyond in 27% and 73% of pts, respectively. Before starting C, pts were only intermediate or poor prognosis by IMDC criteria. Considering all evaluable pts, ORR was 33%, median TTF was 7.99 mo and median OS was 12.33 mo. Focusing on C, ORR was 42% and no pts presented progressive disease as best response versus 37% for A with 2% progressive disease. Currently, median TTF and OS on C are not yet estimable (0.92-not reached); update on clinical outcome will be presented. Moreover, C demonstrated acceptable safety profile and the rate of treatment discontinuation because of adverse events was 11%.

**Conclusions**
In mRCC pts previously treated by ICI, treatment with C seems to be very active, irrespective of number of prior treatments or IMDC risk group. Prior PD-1/PD-L1 exposure did not influence safety of subsequent C therapy. Interestingly, activity of A also appears excellent, raising the hypothesis of enhanced efficacy of TKI after ICI.

**Clinical trial identification**
Not applicable

**Legal entity responsible for the study**
Not applicable

**Funding**
None

**Disclosure**
B. Escudier: Honorarium received from: Bristol-Myers Squib, Novartis, Pfizer, Ipsen, Roche, Bayer, Calithera, Acceleron, EUSA, Eisai. All other authors have declared no conflicts of interest.

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**877P - Second-line treatment patterns and outcomes of metastatic bladder cancer patients in clinical practice**

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**J. Black-Shinn (The Woodlands, United States of America)**

**M. Boyd (The Woodlands, United States of America)**

**N. Robert (The Woodlands, United States of America)**

**A. Kamat (Houston, United States of America)**

**Background**
There is no universally accepted standard therapy for second-line (2L) treatment of metastatic bladder cancer (mBC). We sought to evaluate treatment patterns and outcomes of patients (pts) receiving 2L treatment for mBC.
Methods
We identified pts receiving initial mBC treatment during an index period from January 2010-June 2014 by review of electronic health records (EHR) of McKesson Specialty Health/US Oncology, with follow-up through July 2016. Patients who subsequently received 2L therapy were included in this analysis. The Kaplan-Meier method was utilized to evaluate outcomes from 2L treatment initiation.

Results
Of 1155 pts receiving 1L treatment during the index period, 391 (33.9%) pts received 2L treatment and were eligible for analysis. The median age was 70 years (range 36-89) and 81.1% were men. Median time to initiation of 2L therapy following mBC diagnosis was 7.8 months(mos). 2L therapy was used in 33.6% of pts who received 1L cisplatin(cis)-based therapies and 34.0% of those who received other 1L therapies. 51.4% of 2L pts received combo-therapy; the common (>5% of total 2L utilization) regimens were carboplatin(carbo)/gemcitabine(gem) (14.8%), carbo/paclitaxel(pac) (12.0%), and cis/gem (7.7%). 48.6% of 2L pts received monotherapy; the common regimens were pac (17.4%), docetaxel (10.5%), pemetrexed (8.2%), and gem (6.6%). For the composite outcome of third-line therapy initiation or death, the median time-to-event for all 2L regimens was 5.2 mos (95% confidence interval [CI], 4.5 to 6.0). Median overall survival (OS) for all 2L regimens was 9.4 mos (95% CI, 8.2 to 11.1). Time-to-event outcomes were significantly different across the various regimens (p = 0.0005).

Conclusions
This real-world data provides important insights into patterns of care and outcomes for 2L mBC pts. These results concur with other observational studies in this time frame, suggesting that only one third of 1L mBC pts progress to 2L treatment. Taxane and platinum-based regimens predominated in the 2L, although patterns of treatment were consistent with prior research showing that no clear standard of care exists for these pts. Monotherapy and combination regimens are utilized in equal proportions, both producing poor outcomes for mBC pts.

Legal entity responsible for the study
Kyle Flannery et al. had final responsibility for conduct and reporting of this study.

Funding
Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA

Disclosure

878P - Comparing ITC results from lenvatinib plus everolimus for second-line treatment of advanced/metastatic renal cell carcinoma: Crossover versus no crossover
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G. Meier (Woodcliff Lake, United States of America) H. McElroy (Singapore, Singapore)
Background
An indirect treatment comparison (ITC) involving lenvatinib plus everolimus (LEN+EVE) was conducted using networked data from HOPE 205, CHECKMATE-025, METEOR, AXIS, RECORD-1 and TARGET. The ITC incorporated adjustments for crossover to investigational treatment. Results showed superiority of LEN+EVE over EVE alone; and inferiority versus pazopanib (PAZ) or sunitinib (SUN) alone in overall survival (OS) for second-line treatment of advanced/metastatic renal cell carcinoma. No statistically significant differences in OS were found between LEN+EVE versus nivolumab (NIV), cabozantinib (CAB), axitinib (AXI), or placebo.

Methods
A subsequent analysis was conducted using intention to treat (ITT) to evaluate the impact of crossover correction on OS estimates and additionally to uncover any potential bias due to its absence. Three ITC scenarios were analyzed: A) all comparators plus placebo versus EVE; B) all comparators versus placebo; and C) LEN+EVE versus all comparators.

Results
Scenario “A” showed consistent variance in survival benefit for ITT versus crossover by an average of 20%. Hazard ratios for AXI versus EVE shifted from below null (0.98) to above null (1.27); and mortality risk (placebo vs. EVE) moved 51% further from null (1.15 vs. 1.67). ITT estimates for Scenarios “B” and “C” showed on average 9% and 14% differences in OS benefits, respectively, versus crossover. In Scenario “C”, estimates for LEN+EVE versus PAZ or LEN+EVE versus SUN showed superiority with ITT data (0.82 or 0.75) but were inferior (1.2 or 1.09) with crossover.

Conclusions
Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness profile and also on the cost-effectiveness results, and may lead to inconsistent resource allocation decisions.

Clinical trial identification
NA
Legal entity responsible for the study
Eisai Inc
Funding
Eisai Inc
Disclosure
G. Meier, M. Guo: Employees of Eisai Inc. H. McElroy: Employee of Covance Market Access Services, which was paid by Eisai for literature review and statistical services. All other authors have declared no conflicts of interest.

879P - Urine-derived lymphocytes (UDLs) as a non-invasive surrogate marker of tumour infiltrating lymphocytes (TILs) in patients with muscle invasive bladder cancer (MIBC)

Background
The therapeutic targeting of PD-1 and PD-L1 has led to durable responses in metastatic bladder cancer, yet the majority of patients (pts) fail to respond. Here, we characterised the immune phenotype and TCR repertoire in tumour and UDLs in patients with MIBC for the identification of potential T cell biomarkers of response and resistance to checkpoint blockade.

Methods
Matched bladder tumour, normal urothelium (NU), urine and peripheral blood mononuclear cells (PBMC) were collected from 30 pts undergoing cystectomy. Multi-parametric flow cytometry and immunohistochemistry were used to determine the abundance of CD8⁺, CD4⁺ FoxP3⁺ (CD4eff) and CD4⁺ FoxP3⁺ (Treg) T cell subsets and co-inhibitory (PD-1, CTLA-4, TIM-3) and co-stimulatory (ICOS, 4-1BB) immune checkpoint molecules. T cell receptor (TCR) repertoire was determined using quantitative high throughput sequencing of α and β TCR chains followed by Decombinator bioinformatics analysis.

Results
UDLs were identified in 19/24 (80%) of MIBC pts with tumour in situ compared to 3/6 (50%) pts with pathological downstaging (pT0) following neo-adjuvant therapy. Urine, tumour and PBMC specimens were found to have a similar CD8/Treg ratio that was significantly higher in NU. Co-stimulatory and co-inhibitory checkpoint molecules were similarly distributed across CD8⁺, CD4eff and Treg within tumour, urine and NU compartments, however significantly different to PBMC, irrespective of prior treatment. Preliminary analysis revealed a higher degree of similarity between the TCR repertoires of urine and matched tumour as compared with urine and NU or urine and PBMC samples.

Conclusions
These data suggest that UDLs are an accessible source of T cells from pts with MIBC that accurately map the immune landscape of TILs. UDL analysis represents a liquid biopsy to inform clinically relevant immunological parameters, including the CD8/Treg ratio, target checkpoint expression and TCR repertoire, irrespective of prior treatment. Further translational studies are ongoing to evaluate whether UDL analysis may serve as a non-invasive, dynamic biomarker to predict immunotherapy outcome in MIBC.

Clinical trial identification
University College London (UCL)/University College London Hospital (UCLH) BioBank for Health and Human Disease (NC06.11)

Legal entity responsible for the study
UCL/UCLH

Funding
UCL/UCLH

Disclosure
C. Swanton: Grants/research supports: Pfizer Honoraria or consultation fees: Roche Ventana, Celgene, Pfizer, Novartis; Stock shareholder: Grail, Epic Biosciences, Apogen
Background

Although many drugs are available in RCC, we still lack predictive biomarkers of disease recurrence or progression for personalized treatment. NEORAD clinical trial (NCT01715935) was designed to evaluate biomarkers modulation by everolimus (Ev) prior to nephrectomy on several tissue and circulating cells.

Methods

French open-label, exploratory, single-arm, multicenter trial, part of PREDICT consortium. Population: locally-advanced (LA), metastatic (M) RCC. Endpoints: primary: objective clinical benefit (CR, PR, SD upon RECIST 1.1) after 6 weeks neoadjuvant Ev (10 mg daily) prior nephrectomy; secondary: PFS, OS, toxicity. Multi-region sequencing (biopsy and surgery specimens) explored mutational status of genes of interest. After nephrectomy, Ev was reintroduced in M pts until PD or end of 12m follow-up. Treatment was continued until PD or unacceptable toxicity.

Results

25 pts accrued (44 screened) between 05/2012 and 07/2015: LA = 14, M = 11 underwent biopsy at screening for tissue sampling then further nephrectomy. Population (LA/M): clear-cell=13/10, papillary=1/1, median age(y): 60/63, sarcomatoid component: 3 M pts, ECOG-PS: 0=10/4, 1=4/7, extra-renal metastatic sites: bone, lung, nodes, adrenal. Change in renal tumor size between baseline and D42: 0%. In M, Ev was resumed for 8 pts after nephrectomy with 2 PR and 6 SD. PFS (mo): M = 3.1 [1.41; 12.2]. Median follow-up (mo): 17.4 [3.3; 43.2]. PFS at 12 months: LA = 78%, M = 18% Toxicity of Ev was as expected and no adverse event in terms of surgical procedure was observed. Pts with following gene mutations exhibited a poor PFS: SEDT2: HR = 2.54 (0.63 – 10.28), BAP1: HR = 3.19 (0.78 – 13.12), TSC2: HR = 2.37 (0.49 – 11.53); further correlations will be presented at ESMO meeting.

Conclusions

NEORAD was the 1st neoadjuvant study of Ev in RCC. Despite limited number of pts, we generated a large amount of longitudinal data including exome sequencing, circulating biomarkers, angiogenesis and immunity factors. All these data could help decipher mechanisms of resistance, evaluate predictive signatures or add further knowledge to mechanisms involved in mTOR pathways.

Clinical trial identification
Background

The effects on survival of adjuvant therapy with a VEGF-TKI after nephrectomy for RCC are uncertain. Survival rates, times and benefits were predicted by medical oncologists at baseline for each patient they recruited to SORCE.

Methods

Medical oncologists at 20 sites in ANZ and 12 in the UK answered the following questions at baseline for each patient they recruited: the predicted overall survival rate at 5 years (SR) and predicted overall survival time (ST) without adjuvant sorafenib; and, the predicted absolute improvements in SR and ST with 1 year of adjuvant sorafenib. We used Spearman’s rank correlation ($r_s$) to assess associations, and Wilcoxon signed rank tests to assess differences between the paired SR–ST values. We assumed exponential survival distributions to calculate: (i) % alive at 5-yrs corresponding to ST estimates, and (ii) hazard ratios (HRs) corresponding to predicted benefits on overall survival. We hypothesized that these HRs should be less extreme (numerically larger) than the target HR of 0.75 for disease free survival used to design the trial.

Results

The table shows paired estimates of ST and SR from 61 medical oncologists for 176 of the 1711 SORCE patients. Predictions of survival without sorafenib were similar whether based on ST or SR. The predicted benefits of sorafenib based on SR were moderately correlated with those based on ST, but significantly larger. The proportion of HRs > 0.75 was 51% based on SRs vs 66% based on STs. Table:
<table>
<thead>
<tr>
<th>Survival without sorafenib</th>
<th>Improvement with sorafenib</th>
<th>Hazard Ratio</th>
<th>Difference</th>
<th>( r_s )</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Years</td>
<td>Calculated % alive at 5-yr [a]</td>
<td>Estimated % alive at 5-yr [b]</td>
<td>[a]-[b]</td>
<td>[a] vs [b]</td>
</tr>
<tr>
<td>7</td>
<td>(5 to 12)</td>
<td>(50 to 70)</td>
<td>0 (-7 to 9)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>(50 to 75)</td>
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<td>p = 0.6</td>
<td>p &lt; 0.001</td>
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<tr>
<td>1</td>
<td>(1 to 5)</td>
<td>(5 to 15)</td>
<td>-2 (-6 to 1)</td>
<td>0.53</td>
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<tr>
<td></td>
<td>(3 to 10)</td>
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<td>p &lt; 0.0001</td>
<td>p &lt; 0.001</td>
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<tr>
<td></td>
<td>(0.67 to 0.91)</td>
<td>(0.62 to 0.82)</td>
<td>0.09 (-0.01 to 0.21)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

1 Medians (IQRs)

Conclusions
The predicted benefits of adjuvant sorafenib based on SRs were often larger than hypothesized, and larger than predictions based on ST, which were more consistent with the target HR. These data suggest that predictions of benefit in this setting may be more conservative and plausible when based on ST rather than SR.

Clinical trial identification
NCT00492258

Legal entity responsible for the study
NHMRC Clinical Trials Centre, University of Sydney

Funding
Cancer Australia, NHMRC, Bayer, CRUK

Disclosure

882P - Potential impact of avelumab+axitinib (A+Ax) on tumor size (TS) compared with historical data of sunitinib (S) as evaluated by a modeling and simulation (MS) approach

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M. Amantea (San Diego, United States of America) C. Bello (New York, United States of America)
D. Pavlov (San Diego, United States of America) M. Geraldes (New York, United States of America)
M. Martignoni (Milan, Italy) A. Di Pietro (Milan, Italy) G. Andrews (San Diego, United States of America)

Background
Combining an immune checkpoint inhibitor (A) with a targeted VEGF antiangiogenic agent (Ax) may leverage complementary mechanisms of action for treatment of metastatic renal cell carcinoma (mRCC). JAVELIN Renal 100 is a phase (Ph) 1b trial evaluating the clinical activity and safety of A+Ax in treatment-naïve patients (pts) with mRCC. An early evaluation of the effect of A+Ax on TS, i.e. sum of diameters for target lesions, compared to historical S, the standard of care, can inform on decisions for future drug development for A+Ax. Claret et al. have shown that a greater early TS reduction at week 8 of treatment (TR8) is correlated with a longer progression free survival time in trials of 1st line treatment of mRCC. The objective of this analysis is to apply MS methodology to data from JAVELIN Renal 100 to evaluate the potential effect of A+Ax on TS as compared to historical S data.

**Methods**

A tumor dynamic model was applied to the longitudinal TS data obtained from the Ph1b study of A+Ax and from the historical Ph3 trial of S. The model includes 3 parameters representing the rate of tumor growth (KL), the rate of drug effect in reducing tumor size (KD), and the rate of the loss of drug effect (DM). The TR8 for each patient can be derived from the model. A larger KD, smaller DM, and TR8 suggested a greater effect. The parameters and TR8 from the two treatments are estimated and compared using ANOVA.

**Results**

The summaries of the model parameters, TR8, and p-value of ANOVA analysis are presented in the Table below:

<table>
<thead>
<tr>
<th></th>
<th>Avelumab + axitinib (N = 53)</th>
<th>Sunitinib alone (N = 349)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TR8</strong></td>
<td>0.757 ± 0.162</td>
<td>0.808 ± 0.132</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>KL (1/week)</strong></td>
<td>0.011 ± 0.014</td>
<td>0.009 ± 0.012</td>
<td>0.398</td>
</tr>
<tr>
<td><strong>KD (1/week)</strong></td>
<td>0.065 ± 0.027</td>
<td>0.054 ± 0.034</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>DM (1/week)</strong></td>
<td>0.081 ± 0.024</td>
<td>0.095 ± 0.049</td>
<td>0.040</td>
</tr>
</tbody>
</table>

A+Ax resulted in a greater effect on TR8, a faster tumor size reduction and a more sustained effect than S.

**Conclusions**


**Clinical trial identification**

NCT02493751 B9991002

**Legal entity responsible for the study**

Merck KGaA, Darmstadt, Germany; Pfizer Inc, New York, NY, USA.

**Funding**
Background

Patients (pts) with metastatic renal cell carcinoma (mRCC) may present with primary metastases (synchronous disease) or develop metastases during follow-up (metachronous disease). The impact of timing of metastatic disease outbreak on outcomes from targeted therapy (TKI) is unclear.

Methods

We used the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) to assess overall survival (OS) and time to treatment failure (TTF) on first line TKI, and performed Cox regression analyses comparing synchronous (metastases ≤ 3 mo of initial diagnosis of cancer) vs metachronous disease (metastasis diagnosed post initial diagnosis, evaluated by intervals >3-12 mo, >1-2 yrs, >2-7 yrs, and >7yrs).

Results

In 7386 pts with mRCC treated with first line TKI, 3906 pts (53%) had synchronous and 3480 pts (47%) had metachronous metastases. Synchronous vs metachronous disease by intervals >3-12 mo, >1-2 yrs, >2-7 yrs, >7yrs correlated with lower age at TKI initiation (mean 61 yrs vs 61, 62, 63, 66 yrs, respectively, p < 0.0001), higher rate of non-clear cell histology (14% vs 12%, 10%, 10%, 7%, respectively, p < 0.0001), and higher rate of IMDC risk features (mean 2.3 vs 1.6, 0.9, 0.9, 0.8, p < 0.0001). Compared with synchronous disease, the longer time to metastases was significantly associated with improved OS and TTF from TKI therapy initiation in multivariable Cox regression, adjusted for nephrectomy status, histology (cc vs ncc), IMDC risk factors (Hgb, Corrected calcium, Neutrophil, platelets, Karnofsky performance status), number of metastasis (1 vs > 1), age at TKI initiation and year of TKI initiation (2003-2007, 2008-2012, 2013-2016). Table:

<table>
<thead>
<tr>
<th>OS</th>
<th>TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>time to metastases</td>
<td>Total</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
</tr>
<tr>
<td>0-3mo</td>
<td>3906(53%)</td>
</tr>
<tr>
<td>&gt;312mo</td>
<td>1055(14%)</td>
</tr>
<tr>
<td>&gt;12yrs</td>
<td>638(9%)</td>
</tr>
<tr>
<td>&gt;27yrs</td>
<td>1155(16%)</td>
</tr>
<tr>
<td>&gt;7yrs</td>
<td>632(9%)</td>
</tr>
<tr>
<td>Total</td>
<td>7386(100%)</td>
</tr>
</tbody>
</table>

Conclusions
Timing of metastases post initial RCC diagnosis impacts outcome with targeted therapy in mRCC. This may need to be taken into consideration in clinical trial designs.

Legal entity responsible for the study
The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

Funding
The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

Disclosure
F. Donskov: Research funding (to institution) from Novartis, GSK and Pfizer. C. Porta: Consulting or advisory role: Novartis, Bristol-Myers Squib, Pfizer, Jannsen, Eisai, Pelefon, Ipsen, Speaker bureau: Novartis, Bristol-Myers Squib, Pfizer, Ipsen; Eisai Research funding: Pfizer. J.L. Lee: Honoraria from Pfizer and Astellas; consulting fees from Astellas; research funding from Pfizer, Bayer, Janssen, Novartis, and Exelixis. T. Yuasa: Honoraria from Astellas, Novartis, and Pfizer. I.D. Davis: Supported by an Australian National Health and Medical Research Council Practitioner Fellowship (APP1102604) and research funding from Astellas and Exelixis. C. Pezaro: Honoraria from Janssen, Pfizer, Sanofi, Novartis, and Astellas; consulting fees from Novartis; and travel and accommodation funding from Pfizer and Sanofi. R. Kanesvaran: Honoraria from Pfizer, Novartis, Bayer, Astellas, Janssen, Mundipharma, and Sanofi; research funding from Sanofi; and travel and accommodation expenses from Pfizer and Astellas. N. Agarwal: Consulting fees from Pfizer, Exelixis, Cerulean, Argos, and Medivation. C.M. Canil: Advisory Boards for Janssen, Pfizer, Astellas and Amgen; speaking fees from Jansseen and Astellas and travel grants from Novartis and Janssen. T.K. Choueiri: Consulting or advisory role for Bayer, Bristol-Myers Squib (institutional), GSK, Merck, Novartis, and Pfizer; and institutional research funding from AstraZeneca, Bristol-Myers Squib, Exelixis, GSK, Merck, Novartis, Peloton Therapeutics, Pfizer, Roche/Genentech, and TRACON Pharma. D.Y.C. Heng: Advisory boards Pfizer, Novartis, Bristol-Myers Squib, Exilexis. All other authors have declared no conflicts of interest.

884P - SPAZO2 (SOGUG): Comparative effectiveness of pazopanib in metastatic renal carcinoma (mRC): Ineligible (I) vs eligible (E) patients for clinical trials

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J. Maroto Rey (Barcelona, Spain)M. Miranda Pallares (Reus, Spain)M. Climent Duran (Valencia, Spain)
G. Crespo Herrero (Burgos, Spain)J. Meana Garcia (Alicante, Spain)A. Rodriguez-Vida (Barcelona, Spain)
Background
Ineligibility for clinical trials (CT) may be an unfavorable prognostic factor in mRC. There is no information about the effectiveness of pazopanib in patients (pt) ineligible for CT. We aimed to assess the effect of ineligibility in outcomes in mRC, and the effectiveness of pazopanib in this setting.

Methods
SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1st-line pazopanib and subsequent therapies in mRC in several settings. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected, and externally monitored. Ineligibility criteria: ECOG >1, pure nonclear-cell, brain metastases, Hgb <=9 g/dl, renal failure, severe ischemic disease, age >80 y, stroke, chronic liver disease, or recent neoplasia.

Results
A total of 217 pt (40.9%) fulfilled criteria for ineligibility. There were significant differences (I vs E) in age >75 (39% vs 15%), nephrectomy (61% vs 78%), IMDC (favorable: 8.8% vs 17.9%, intermediate: 50.2% vs 68.4%, poor: 41% vs 13.7%), metastases (lymph nodes: 51% vs 41%, lung: 65% vs 72%, liver: 21% vs 15%, bone: 31% vs 22%, skin/soft-tissue: 30% vs 16%, and CNS (13% vs 0%) but no in sex (68% vs 67% males). Discontinuation due to toxicity or comorbidities was 19% vs 17%. There were also differences (p < 0.05) in 2nd-lines (53% vs 61%), response, PFS and OS (Table). Median follow-up was 39 mo. Median PFS and OS were 9.8 and 19.6 mo respectively. After adjusting by IMDC and age (Cox regression), ineligibility was significantly associated with a higher risk of progression (HR: 1.4 95%IC: 1.1 - 1.7) and death (HR: 1.5 95%IC: 1.2 - 1.9). Only anemia and asthenia (all grades) were significantly higher in the I group.

<table>
<thead>
<tr>
<th>Overall</th>
<th>IMDC prognostic subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 530</td>
<td>Favourable (14.2%)</td>
</tr>
<tr>
<td>N = 217</td>
<td>I</td>
</tr>
<tr>
<td>CR</td>
<td>4.4%</td>
</tr>
<tr>
<td>PR</td>
<td>28.5%</td>
</tr>
<tr>
<td>SD</td>
<td>37.3%</td>
</tr>
<tr>
<td>Median</td>
<td>9.8</td>
</tr>
<tr>
<td>PFS*</td>
<td>(9-11)</td>
</tr>
<tr>
<td>Median OS+</td>
<td>19.6</td>
</tr>
</tbody>
</table>

* Months (IC95%); I: ineligible; E: eligible.
Conclusions
In our series, “real world eligible pt” had similar outcome to the obtained in clinical trials. On the contrary, “real world ineligible pt” for clinical trials had significantly lower response rate, and shorter PFS and OS than eligible pt. Pazopanib was safe and effective in both subpopulations of patients.

Clinical trial identification
NCT03091465

Legal entity responsible for the study
SOGUG

Funding
Novartis

Disclosure
J. Arranz Arija: Grant for research from Novartis. Participation in advisory boards for Novartis and Pfizer. B. Pérez Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J.P. Maroto Rey: Advisory Board for Novartis, Pfizer, Ibsen and Bristol. M.A. Climent Duran: Pfizer and Novartis talks, advisory role for Pfizer. All other authors have declared no conflicts of interest.

886P - SPAZO2 (SOGUG): Comparative effectiveness of everolimus (Ev) vs axitinib (Ax) as second-line after first-line pazopanib (1stPz) in metastatic renal carcinoma (mRC)
J. Arranz Arija (Madrid, Spain)B. Pérez-Valderrama (Sevilla, Spain)A. Rodriguez Sanchez (Leon, Spain)J. Puertas Alvarez (Valladolid, Spain)A. Pinto Marin (Madrid, Spain)C. Maximiano Alonso (Majadahonda, Spain)J. Villa Guzman (Ciudad Real, Spain)E. Fernandez Parra (Sevilla, Spain)E. Gallardo Diaz (Sabadell, Spain)J. Gonzalez-Larriba (Madrid, Spain)J. Tafalla Garcia (Madrid, Spain)J. Lambea (Zaragoza, Spain)M. Constenla Figueiras (Pontevedra, Spain)M. Mendez Vidal (Cordoba, Spain)J. Virizuela Echaburu (Sevilla, Spain)F. Vazquez Mazon (Elche, Spain)O. Etxaniz Ulazia (Badalona, Spain)M. Abad Villar (Bilbao, Spain)J. Cassinello (Guadalajara, Spain)J. Jurado Garcia (Granada, Spain)

Background
Pivotal studies of axitinib and everolimus in 2nd-line mRC did not include pt treated with 1stPz. In addition, E vs A have not been directly compared in clinical trials in this setting. We aimed to compare the effectiveness of E vs A in real life, as second-line after pazopanib in mRC.

Methods
SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1stPz and subsequent therapies in mRC in several settings in every day practice. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected by investigators, but monitored and entered in a database by an external CRO.

Results
Out of 285 pt receiving 2nd-line targeted therapies after 1stPz, 189 received either Ax (88, 46.6%) or Ev (101, 53.4%). There were no significant differences (Ax vs Ev), in age (63 y vs 66 y), sex (68% vs 64% males), nephrectomy (76% vs 67%), metastases in lymph nodes (58% vs 52%), liver (21% vs 28%), bone (45% vs 41%), CNS (6%), adrenal (4% vs
5%), pleura/peritoneum (4% vs 6%), or pancreas (4% vs 6%), but there were in age >75 (14% vs 25%), nonclear cell component (1 vs 16%), and lung (85 vs 72%) and skin/soft-tissue (20 vs 28%) metastases. According to the IMDC for 2\textsuperscript{nd}-line targeted therapies, 17% vs 9% of pt were in the favorable risk group, 65% vs 69% in the intermediate risk, and 18% vs 22% in the poor risk. All-grades hypertension (32.6% vs 3.6%) and hypothyroidism (16% vs 6%) were significantly higher with Ax, whereas anemia (21.4% vs 55%), and mucositis (12.3% vs 39%) were more frequent with Ev. Subsequent therapies were given in 56% in Ax vs 46% in Eve. After median follow-up of 28 mo, 74.6 of pt have died. Outcomes and 95%CI are summarized in the table.

### Table:

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>PFS Median (6 months)</th>
<th>OS Median (1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axitinib</strong></td>
<td>13.1%</td>
<td>5.3 (3-7)</td>
<td>11.6 (7-16)</td>
</tr>
<tr>
<td><strong>Everolimus</strong></td>
<td>9.3%</td>
<td>4.6 (3-6)</td>
<td>9.5 (7-12)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>11.2%</td>
<td>5.0 (4-6)</td>
<td>10.7 (8-13)</td>
</tr>
</tbody>
</table>

*Adjusted by IMDC, metastases, age, histology and subsequent therapies.

### Conclusions

In this real world study in pt with mRC, we could not find statistically significant differences in effectiveness between axitinib and everolimus as 2\textsuperscript{nd}-line after 1\textsuperscript{st} line pazopanib. These results validate the use of both drugs in terms of clinical benefit, PFS and OS.

### Clinical trial identification

NCT03091465

### Legal entity responsible for the study

SOGUG

### Funding

Novartis

### Disclosure

J. Arranz Arija: AdBo from Novartis and Pfizer. B. Pérez-Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J. Puertas Alvarez: Participation in advisory board meetings from Pfizer, Astellas, Novartis, Sanofi, GlaxoSmithKline, AstraZeneca, Pharmamar, Hospira, Janssen, Eisai, Roche, Lilly, and Bayer. All other authors have declared no conflicts of interest.

### 885P - Sunitinib versus pazopanib for patients with metastatic renal cell carcinoma: Two Turkish hospital experience, a retrospective comparative case series study

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**E. Aydin** (Istanbul, Turkey)

**I. Cil** (Istanbul, Turkey)

**A. Zirtiloglu** (Istanbul, Turkey)

**D. Tural** (Istanbul, Turkey)

**S. Karabulut** (Istanbul, Turkey)

### Background

Pazopanib (PAZ) and Sunitinib (SUN), are two oral multikinase angiogenesis inhibitors which are prescribed frequently. However, the outcomes in real world of Turkish population have not extensively been studied.
**Methods**
Patients assessed retrospectively at two Turkish hospitals between 2006 and 2016.

**Results**
Median age of patients was 60 (28-87) years and 70% of patients were male. ECOG performance score was 0 and 1 in 73% of patients. Twelve patients (15%) had non-clear cell carcinoma histology. Pathological characteristics, MSKCC risk groups, median follow up, response rates and survival are shown in Table. In the SUN group, the patients had more grade 3-4 adverse events (Table).

<table>
<thead>
<tr>
<th>Sunitinib (n = 41)</th>
<th>Pazopanib (n = 38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSKCC risk group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable 31% Intermediate 56% Poor 12.5%</td>
<td>Favorable 31% Intermediate 47% Poor 21%</td>
<td>p = 0.66</td>
</tr>
<tr>
<td><strong>T3-T4 stage</strong></td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Node positivity (%)</strong></td>
<td>20%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Local recurrence (%)</strong></td>
<td>20%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Median follow-up</strong></td>
<td>18 months</td>
<td>13 months</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>34%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>DCR</strong></td>
<td>78%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>73% (n = 30)</td>
<td>50% (n = 19)</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>8 months</td>
<td>8 months</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>22 months</td>
<td>21 months</td>
</tr>
<tr>
<td><strong>Fatigue, all grades</strong></td>
<td>45%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Skin changes, all grades</strong></td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Anemia, all grades</strong></td>
<td>35%</td>
<td>42%</td>
</tr>
<tr>
<td><strong>Grade 3-4 adverse events</strong></td>
<td>59%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Dose reduction</strong></td>
<td>50%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Treatment cessation</strong></td>
<td>37%</td>
<td>26%</td>
</tr>
</tbody>
</table>

**Conclusions**
In our study, there was no difference in terms of survival between two agents. However, patients treated with SUN had more grade 3-4 adverse effects which prompted dose reduction and cessation.

**Legal entity responsible for the study**
Individuals, Meltem Ekenel and Senem Karabulut

**Funding**
None

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

887P - Negative prognostic factors and resulting clinical outcome in patients (pts) with metastatic renal cell carcinoma (mRCC) included in the Italian nivolumab expanded access program (EAP)

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Background
In recent years, prognostic classifications have been considered an area of growing interest in mRCC. However, independently from the classification used (Memorial Sloan Kettering versus Heng's) the presence of brain, liver and bone metastases (mets) or sarcomatoid features (G4) resulted in a poorer outcome for pts with mRCC treated with targeted therapies (antiangiogenic agents or mTOR Inhibitors). Regarding this topic, the large Italian EAP represent an important opportunity to analyze the impact of nivolumab in pts treated in a daily clinical practice setting.

Methods
Nivolumab was available upon physician request for pts aged ≥18 years who relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Nivolumab 3 mg/kg was administered intravenously every 2 weeks for a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results
Of 389 Italian pts with mRCC enrolled in the EAP, 32 pts (8%) had brain mets, 128 (33%) had liver and 193 (50%) had bone mets. Baseline characteristic are described in the Table. These pts achieved a disease control rate (DCR) of 53%, 45% and 47% respectively. Six and 12 months overall survival rates in the 3 groups of mets were 87.0%, 66.8%, 75.6% and 62.0%, 78.0% and 58.9%, respectively. Histological grading, a matter of high interest, was assigned according to Fuhrman's classification: 51 pts had G4 tumor. The objective response rates in these pts and in the overall population were 23% and 22%, respectively, with a 6 and 12 months OS rate of 61% and 53.6% for the G4 group. The safety profile of the subgroups described above was in line with the general population.

Conclusions
These results suggest that also pts with poor prognostic factors may derive relevant benefits with nivolumab, with safety results consistent with previously reported data.

Table:

<table>
<thead>
<tr>
<th>Age, median (range)</th>
<th>Brain Mets 65 (43-77)</th>
<th>Liver Mets 65 (43-81)</th>
<th>Bone Mets 65 (40-84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male %</td>
<td>72</td>
<td>70</td>
<td>79</td>
</tr>
<tr>
<td>ECOG PS %:</td>
<td>0 1 2 NA</td>
<td>41 50 6 3</td>
<td>42 50 7 1</td>
</tr>
<tr>
<td>Number of prior Therapies</td>
<td>1 2 3 &gt; =4 NA</td>
<td>13 44 37 6</td>
<td>13 37 24 24</td>
</tr>
</tbody>
</table>
Clinical trial identification
Expanded Access Program

Legal entity responsible for the study
Italian RCC EAP Group

Funding
None

Disclosure
S. Bracarda: Advisory Board Member for Pfizer, Novartis, Bristol-Myers Squib, Exelixis, Ipsen, Roche, Genentech, Eusa Pharma. PI for clinical studies with Bristol-Myers Squib, Pfizer, Roche, Exelixis. L. Galli: Advisory Board for Pfizer, Novartis. U. De Giorgi: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen, Astellas, Janssen, Sanofi. G. Procopio, C. Porta: Advisory Board for Bristol-Myers Squib, Pfizer, Novartis, Ipsen. E. Cortesi: Advisory Board for Bristol-Myers Squib, Pfizer, Ipsen. All other authors have declared no conflicts of interest.

888P - Change in neutrophil-to-lymphocyte ratio (NLR) in response to immunotherapy for metastatic renal cell carcinoma (mRCC)

A. A. Lalani (Boston, United States of America) W. Xie (Boston, United States of America) D. J. Martini (Boston, United States of America) C. K. Norton (Boston, United States of America) J. A. Steinharter (Boston, United States of America) D. Bossé (Boston, United States of America) J. Bellmunt (Boston, United States of America) E. M. Van Allen (Boston, United States of America) B. A. McGregor (Boston, United States of America) L. C. Harshman (Boston, United States of America) T. K. Choueiri (Boston, United States of America)

Background
Elevated NLR is associated with worse outcomes in several malignancies, including mRCC. However, its role in the current immunotherapy era is unknown. We investigated the utility of NLR at baseline and during therapy in mRCC patients treated with PD-1/PD-L1 immunotherapy (IO).

Methods
116 patients from Dana-Farber Cancer Institute (Boston, MA) receiving IO-based therapies were included. NLR was examined at baseline and 6 (±2) weeks later. Landmark analysis at 6 weeks was conducted to explore the prognostic value of relative NLR change on overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) using Cox or logistic regression models, adjusted for line of therapy, number of IMDC risk factors, histology and baseline NLR.

Results
Median follow up was 16.3 months (range: 1.4-64.2). Median duration on therapy was 7 months (<1-58.6). IMDC risk groups were: 21% favorable, 56% intermediate, 22% poor-risk. 43% were on first-line IO and 57% on 2nd line or more. Median NLR was 3.7 (1.3-16.1) at baseline and 3.9 (1.1-49.6) at week 6. Higher NLR at baseline and at 6-weeks showed a trend to reduced ORR and worse PFS and OS, and NLR at 6-weeks was a stronger prognostic than baseline values (Table). Compared with no change from
baseline, increase in NLR by ≥25% at 6-weeks was associated with reduced ORR and significantly worse PFS and OS in multivariate analysis, whereas a decrease in NLR by ≥25% was associated with improved outcomes.

**Conclusions**

Early decline and NLR at 6-weeks are associated with significantly improved outcomes in mRCC patients treated with IO, whereas an increase is associated with worse outcomes. The prognostic value of the readily-available NLR warrants larger, prospective validation.

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>ORR(CR+PR)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Adjusted-OR p-value</td>
<td>Adjusted-HR p-value</td>
</tr>
<tr>
<td>Continuous</td>
<td>116</td>
<td>0.58 (0.23-1.42)</td>
<td>1.36 (0.78-2.37)</td>
</tr>
<tr>
<td>Ln(NLR)</td>
<td></td>
<td>0.232</td>
<td>0.269</td>
</tr>
<tr>
<td>Baseline**</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Continuous</td>
<td>113</td>
<td>0.28 (0.11-0.69)</td>
<td>2.39 (1.38-4.15)</td>
</tr>
<tr>
<td>Ln(NLR)</td>
<td></td>
<td>0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>6-weeks**</td>
<td></td>
<td></td>
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<tr>
<td>NLR-change</td>
<td>0.357</td>
<td>0.003</td>
<td>0.008</td>
</tr>
<tr>
<td>6-weeks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Decrease ≥25%</td>
<td>22</td>
<td>1.63 (0.47-5.60)</td>
<td>0.67 (0.31-1.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change</td>
<td>55</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Increase ≥25%</td>
<td>36</td>
<td>0.61 (0.22-1.66)</td>
<td>2.30 (1.30-4.07)</td>
</tr>
</tbody>
</table>

**Natural log-transformed**

**Clinical trial identification**

N/A

**Legal entity responsible for the study**

Dana-Farber/Harvard Cancer Center

**Funding**

None

**Disclosure**

J. Bellmunt: Research support from Novartis and Sanofi; consulting support from OncoGenex, AstraZeneca, Merck, Bristol Myers-Squibb, Genentech, Inovio, Champions Oncology, Seattle Genetics and Pierre Fabre. E.M. Van Allen: Stock and Other Ownership Interests: Syapse; Consulting or Advisory Role: Novartis, Roche, Syapse, Takeda, Third Rock Ventures; Research Funding: Bristol-Myers Squibb T.K. Choueiri: Consulting: Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, Pfizer; Research Funding: AstraZeneca, Bristol-Myers Squibb, Exelixis, GlaxoSmithKline, Merck, Novartis, Peloton Therapeutics, Pfizer, Roche/Genentech, TRACON Pharma. All other authors have declared no conflicts of interest.

**889P - Broad immunomodulating effect of first-line pazopanib in metastatic renal**
Background
The impact of tyrosine kinase inhibitors (TKIs) on tumor immunity of patients (pts) with metastatic renal cell carcinoma (mRCC) is largely unknown. We investigated the activity of pazopanib in counteracting tumor-induced immunosuppression and boosting adaptive immune response.

Methods
Sixteen mRCC pts receiving first-line pazopanib were prospectively analyzed at baseline, 3 and 6 months for blood Immune profiling by multicolor cytofluorimetry. Gene expression analysis was performed by Illumina HT12v4 BeadChip Arrays. Data were evaluated by t-test, enrichment analysis and deconvolution algorithms.

Results
Pazopanib administration (800 mg per os/daily) was associated with a significant decrease of cell subsets involved in immunosuppression, including CD14+ monocytes, monocytic CD14+ HLA-DRneg myeloid derived suppressor cells (MDSC) and CD14+PDL-1+ cells. Similarly, low density CD15+ granulocytic MDSC and CD4+CD25+Foxp3+ regulatory T cells were reduced by treatment. Concomitantly, a boost of antitumor effectors, such as activated T lymphocytes (identified as CD3+PD-1+ T cells) and cytotoxic CD3+CD16+CD56dim NK cells, was observed. Changes were more evident at 3 months and in pts achieving clinical benefit (69%), defined as the sum of partial response and stable disease at first restaging. Interestingly, a statistically significant increase of lymphocyte/monocyte ratio, as determined by routine blood test was also detected. Gene expression analysis confirmed the immunoregulatory effects of pazopanib. By comparing with those collected after 3 months after treatment start and pre-treatment samples, pathway-enrichment analysis revealed a coherent modulation of NK Granzyme A, IL8 signaling and other immune-related pathways. Similarly, using deconvolution algorithms, we observed an enrichment of NK and CD8+ T cell transcripts.

Conclusions
Pazopanib reshapes tumor immunity by reducing immunosuppressive cells (MDSC and Treg) and triggering T cells and NK effectors. These data provide a strong rationale for using Pazopanib both before an immunotherapy and in combination strategies based on the synergism between TKIs and immunotherapy.

Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Funding
None

Disclosure
E. Verzoni: Reports receiving fees for serving on advisory boards from Pfizer and Novartis. All other authors have declared no conflicts of interest.

890P - Prospective comparison of RECIST and alternative response assessment
Background
Combined size and enhancement criteria show potential to predict earlier disease response or progression in metastatic renal cancer (mRCC). We assessed categorisation differences using RECIST 1.1, Choi and modified Choi (mChoi) criteria with normalised rather than absolute enhancement values in phase II of the STAR trial (comparing conventional continuation versus drug free intervals of tyrosine kinase inhibitor treatment in mRCC).

Methods
44 patients underwent contrast-enhanced computed tomography (CE-CT) at baseline, 12 and 24 weeks post therapy. Automated software was used by 2 independent readers to evaluate 104 target lesions. Target lesion sum of longest diameter, normalised enhancement values (relative to aortic attenuation) and subsequent percentage change at 12 and 24-week CT were measured. Response categorisation into stable disease (SD), partial response (PR) or progressive disease (PD) was undertaken by RECIST 1.1, Choi and mChoi response criteria, and discrepant cases scored. Reader agreement was assessed by Cohen's kappa test.

Results
By RECIST 1.1, patients were 68%(n=30)/41% (18)SD, 27%(12)/45%(20) PR, 2%(1)/9%(4) PD and 2%(1)/2%(1) CR at 12 and 24 weeks respectively. At 12 weeks 27 patients had discrepant categorisation: PR by both Choi/mChoi criteria but SD by RECIST in 17 and PR by CHOI, SD by mCHOI in 10. With absolute versus normalised enhancement values, 3 further patients would have remained as SD by mChoi at 12 weeks. At 24 weeks 14 remained discrepant: both Choi/mChoi PR but SD by RECIST in 10, PR by Choi but SD in mCHOI/RECIST in 4 patients. 11 previously discrepant patients by RECIST versus Choi/mChoi became concordant (8 PR, 3 PD) at 24 weeks. The concordance was excellent for RECIST (k 0.9, k 0.8) and mChoi (k 0.9 k 0.79), and good/excellent reader for Choi criteria (k 0.76 k1.0) at 12 and 24 weeks respectively.

Conclusions
Early response, confirmed at 24 weeks, was more frequent for Choi/mChoi than RECIST. Substantial/excellent agreement was noted in response categorisation with normalised versus absolute enhancement indicating this is a potentially robust approach.

Clinical trial identification
This project was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 09/91/21) The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

Legal entity responsible for the study
891P - Outcomes of patients with metastatic renal cell carcinoma (mRCC) who were treated with second-line (2L) vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKI) after first-line (1L) immune checkpoint inhibitor (ICI) therapy

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Background
ICI therapy is an established strategy in mRCC after progressive disease on VEGFR-TKI. Little data exists in the reverse sequence on response rate, progression-free survival (PFS), safety, and tolerability of TKI after 1L ICI therapy.

Methods
This is a retrospective analysis of patients with mRCC treated from 2015 to present with 1L ICI, followed by 2L TKI. Response assessment was provided by a blinded radiologist using RECIST 1.1. Descriptive statistics, Fisher’s test and Wilcoxon rank sum test were used.

Results
We report on 27 clear-cell mRCC patients with follow-up of at least 8 weeks on TKI post 1L ICI. Median age at diagnosis was 58 years. 78% of patients had lung, 37% bone, 37% lymph node, and 7% liver metastasis. As 1L therapy, 7 patients received nivolumab, 17 received nivolumab + ipilimumab, and 3 received nivolumab + bevacizumab. All 27 patients had resolution of Grade 3/4 toxicities from ICI and progressive disease at the time of TKI initiation. Median time from discontinuation of ICI to initiation of TKI was 4.1 weeks (range 0-23.3 weeks). 11 patients (41%) had PR (8 of whom had ≥40% tumor reduction), and 16 (59%) had SD as best response to TKI. Median PFS was 10.0 months (95% CI 6.8, not applicable). 9 patients discontinued 2L TKI after a median of 26.3 weeks (range 4.6-44 weeks), 8 patients because of PD and 1 because of toxicity. 2 patients developed Grade 3 transaminitis and 3 patients Grade 3 hand-foot skin reaction. Age, sex, IMDC risk score, nephrectomy status, and TKI agent did not predict PR or SD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n (%)</th>
<th>PR (n)</th>
<th>SD (n)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>19 (70)</td>
<td>7</td>
<td>12</td>
<td>0.68</td>
</tr>
<tr>
<td>Female</td>
<td>8 (30)</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Localized at presentation 9 (33) 7 2 0.01
Metastatic at Presentation 18 (67) 4 14
IMDC good risk 4 (15) 3 1 0.47
IMDC intermediate risk 19 (70) 7 12
IMDC poor risk 4 (15) 1 3
Nephrectomy 21 (78) 10 11 0.35
Primary in-situ 6 (22) 1 5
Pazopanib 8 (30) 4 4 0.37
Axitinib 12 (44) 3 9
Cabozantinib 7 (26) 4 3

Conclusions
In this small retrospective study, we observed a high response rate (41%), median PFS 10 months, and manageable toxicity in patients with mRCC treated with TKI after ICI. No patients had outright PD on 2L TKI after ICI.

Clinical trial identification
Not applicable (retrospective study)

Legal entity responsible for the study
MD Anderson Cancer Center Dept of Genitourinary Medical Oncology

Funding
None

Disclosure

892P - Treatment beyond progression in patients with advanced RCC participating in the expanded access programme (EAP)

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S. Pignata (Naples, Italy) A. Berruti (Brescia, Italy) G. Tortora (Verona, Italy) D. Tassinari (Rimini, Italy)
S. Panni (Cremona, Italy) A. Pazzola (Sassari, Italy) G. Surico (Lecce, Italy) M. Maio (Siena, Italy)
L. Latini (Macerata, Italy) G. Schinzari (Rome, Italy) V. Adamo (Messina, Italy) E. Ricevuto (L'Aquila, Italy)
F. Cognetti (Rome, Italy) U. De giorgi (Meldola (FC), Italy) G. Carteni (Napoli, Italy) U. Basso (Padova, Italy)

Background
Response patterns of immunotherapies differ from those seen with other approved cancer therapies. Therefore, immunotherapy clinical trials generally allow patients (pts) to continue treatment beyond investigator-assessed radiographic progressive disease (PD) as long as there is ongoing clinical benefit, but to date no data have been reported
regarding treatment beyond PD in routine clinical practice. Here, we report the analysis about the subgroup of pts treated beyond initial PD in the Italian cohort of nivolumab EAP.

Methods
Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIIB/stage IV RCC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events. Patients could continue treatment beyond PD as long as they met the following criteria: investigator-assessed clinical benefit, absence of rapid PD, tolerance of drug, stable performance status and no delay of an imminent intervention to prevent serious complications.

Results
Of 389 nivolumab-treated pts, 231 pts (59%) had PD. Of those, 100 pts (43%) were treated beyond PD. Before being treated beyond PD, the disease control rates (DCR) was 23%, with 5 partial responses (PR) and 18 stable diseases (SD). Post PD, 28 of all pts treated beyond PD achieved a non-conventional benefit, meaning a subsequent tumor reduction or stabilization in tumor lesions. With a median follow-up of 9.2 months (0.1-17.0), 1 year overall survival was 73.5% in pts treated beyond PD and 43.5% for pts who progressed but were not treated beyond PD. The safety profile was consistent to what already observed in the general population.

Conclusions
As already observed in previous studies, these preliminary EAP data seem to confirm that a proportion of pts who continued treatment beyond PD demonstrated sustained reductions or stabilization of tumor burden, with an acceptable safety profile. Further investigation is warranted in order to better define pts who can benefit from treatment beyond PD.

Clinical trial identification
not applicable

Legal entity responsible for the study
Prof. Enrico Cortesi

Funding
Bristol-Myers Squibb

Disclosure
All authors have declared no conflicts of interest.

893P - Improved long-term clinical outcomes and safety profile of sunitinib dosing schedule with 4/2 switched to 2/1 in patients with metastatic renal cell carcinoma

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P. Zhao (Chengdu, China) J. Liu (Chengdu, China) Y. Yang (Chengdu, China) Q. Tang (Chengdu, China)
J. Chen (Chengdu, China) P. Shen (Chengdu, China) H. Zeng (Chengdu, China)

Background
Adverse events (AEs) have been a key issue for sunitinib administration with a standard dosing schedule. We aimed to identify the survival benefit and safety of alternative dosage schedules for sunitinib in patients with metastatic renal cell carcinoma (mRCC).
Methods
Clinicopathologic and survival data of patients treated with sunitinib as first-line therapy were retrospectively reviewed. Patients were classified into three groups: a standard dosing schedule (4/2 schedule), alternative dosing schedule (2/1 schedule), and switched dosing schedule (4/2-2/1 schedule). Treatment-related AEs were recorded and evaluated. Progression-free survival (PFS), overall survival (OS), and potential risk factors were also analyzed.

Results
A total of 99 patients were included. Seventy-five (75.8%) patients were initially administrated with a 4/2 schedule of sunitinib, while 24 were started with the 2/1 schedule. During treatment, 45 (60.0%) patients with an initial 4/2 schedule switched to a 2/1 schedule (4/2-2/1 schedule) due to severe AEs or poor tolerance. The median follow-up time was 37 months. Compared to that with a 4/2 schedule, patients with a 2/1 schedule had a much lower incidence of grade 3/4 AEs (69.6% vs. 40.6%, p = 0.001). Overall, the 4/2-2/1 schedule was associated with the best survival benefits. Among the 4/2, 2/1, and 4/2-2/1 schedule groups, the median PFS was 12.5, 11.0, and 25.0 months, respectively (p = 0.003), and the median OS was 21.0, 28.0, and 52.0 months, respectively (p = 0.030). Multivariate analysis identified the 4/2-2/1 schedule as an independent factor predicting favorable PFS. Although without statistical significance, 4/2-2/1 schedule could decrease 55% risk of death. Furthermore, patients with unfavorable IMDC risk seemed to have more opportunity to achieve better survival from the 4/2-2/1 dosing schedule.

Conclusions
Among the three dosing schedules in the treatment of mRCC, patients with a 4/2-2/1 schedule could minimize treatment-related toxicities; more importantly, patients with 4/2-2/1 schedule could achieve a superior survival benefit. However, prospective clinical trials are required to identify the optimal sunitinib schedule.

Legal entity responsible for the study
Sichuan University

Funding
This work was supported by Natural Science Foundation of China (NSFC 81402110 from Pengfei Shen and NSFC 81672547 from Hao Zeng) and Science and Technology Support Program of Sichuan Province (2015SZ0230-3, Hao Zeng).

Disclosure
All authors have declared no conflicts of interest.

894P - A retrospective study of the management of metastatic renal cell carcinoma brain tumors


Background
The purpose of this retrospective monocentric review was to evaluate the different techniques of stereotactic radiosurgery in the management of brain tumors from renal cell carcinoma (RCC).
Methods
From 2005 to 2015, 120 patients, with a total of 398 brain metastasis of RCC, were treated at least by stereotactic radiosurgery. Median age was 58 years (31–82). Median Karnofski performance status was 90 (50-100). One hundred ten tumors (92%) were clear cell carcinoma. Ninety-nine patients (82.5%) have undergone nephrectomy. The median time between the diagnosis of RCC and the first brain metastasis was 24 months (0-252).

Results
The median number of tumors per patient was 2 (1-46). The median diameter of the tumors was 13 mm (1-60). For the 120 patients, 222 procedures of treatment were recorded and 187 stereotactic irradiations were reviewed. Sixty-one patients (226 metastasis) were treated by Gamma Knife Surgery (GKS) and received a median dose on the 50% prescription isodose of 18 Gy (14-22). The minimal and maximal median dose was respectively 18.4 Gy (12.5-40.1) and 36 Gy (23.3-51.2). Sixty-three patients (136 metastasis) were treated by linear accelerator (photon 10 MV). The minimal (isodose 70%) and maximal (isocentre) median dose were respectively 16 Gy (9.8-25.8) and 20.3 Gy (15.3-33.74). The median disease-free survival time is 5.5 months (0-252). The median survival time between the first brain metastasis diagnosis and death is 13.5 months (0.5-147). The tumor growth control rates at 3, 6, 12 months are respectively 86%, 62%, 36%. Following the 187 stereotactic irradiations, 95 (51%) cerebral disease progressions are recorded, after a median time of 5 months (1-81); 81 progressions (85%) are due to new lesions and 25 (26%) due to local failures. Analyses of prognostic factors related to survival are still in progress.

Conclusions
Stereotactic radiosurgery is associated with a high local control of brain metastasis from RCC without whole brain radiotherapy. The two described modalities present different characteristics whose advantages will be further discussed with the assessment of prognostic and predictive factors of local control.

Legal entity responsible for the study
Assistance Publique des Hôpitaux de Paris (APHP)

Funding
None

Disclosure
All authors have declared no conflicts of interest.

895P - SPAZO2 (SOGUG): Validation of the international metastatic database consortium (IMDC) prognostic classification for targeted therapies as 2nd-line after 1st-line pazopanib (1stPz) in metastatic renal cell carcinoma (mRC)

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M. Lazaro (Vigo, Spain)J. Munoz-Langa (Valencia, Spain)E. Martinez Ortega (Jaen, Spain)
A. Hernández Jorge (Donostia, Spain)M. Campayo Guillaume (Terrassa, Spain)
M. Sereno Moyano (Madrid, Spain)R. Luque Caro (Granada, Spain)Á. Rodríguez Sánchez (Leon, Spain)
Background

Only 2% of pt included in the IMDC prognostic model for 2nd-line targeted agents in mRC had received 1stPz (Ko, Lancet Oncol 2015). We aimed to validate the IMDC model for this population of patients receiving 1stPz.

Methods

SPAZO2 (NCT03091465) was a retrospective real-world study to analyze the effectiveness of 1stPz and subsequent therapies in mRC in several settings in every day practice. Data from 530 pt treated with frontline pazopanib outside CT in 50 centers in Spain were collected by investigators, but monitored and entered in a database by an external CRO.

Results

A total of 285 pt received antiVEGF or mTOR inhibitor as 2nd line (37.6% everolimus, 2.5% temsirolimus, 36% axitinib, 9.9% sunitinib, 8.3% sorafenib, 2.9% cabozantinib, 2.1% pazopanib, 0.4% beva-Inf, 0.4% savolitinib), 242 after true progression and 43 due to other causes after 1stPz. Unlike in IMDC, no pt had received 1st-line immunotherapy. Mean age was 66 y, 67.7% were male, 74.4% nephrectomized, and 12.3% pure nonclear-cell. Metastatic sites were: lung 74%, lymph nodes 55%, bone 36%, soft tissue/skin 27%, liver 24.8%, CNS 7%, adrenal gland 5%, pleura/peritoneum 6%, pancreas 5%, kidney 3% and other organs 2%. Classification of pt into the IMDC risk groups were: favorable (FR, 14.4%), intermediate (IR: 64.2%), or poor (PR: 21.4%). Median follow-up since 2nd-line was 29 mo; 67% of pt has progressed, 64% had received or subsequent lines, and 73% had died. Response, PFS and OS were showed in the table. Differences in PFS and OS were statistically significant among groups (FR vs IR and FR vs PR). The C-Index was 0.635 (95%CI: 0.627 – 0.642). We also provide an estimation of outcomes according to if pt received 2ndline after “true progression” or due to any cause.

Table:

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>FR</th>
<th>IR</th>
<th>PR</th>
<th>Overall</th>
<th>FR</th>
<th>IR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>14.6%</td>
<td>22.5%</td>
<td>15.8%</td>
<td>5.5%</td>
<td>Not reposted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (1)*</td>
<td>5.1 (4-6)</td>
<td>11.5 (5-18)</td>
<td>5 (4-6)</td>
<td>3 (2-4)</td>
<td>3.9</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (2)*</td>
<td>4.7 (4-5)</td>
<td>9.7 (4-15)</td>
<td>4.8 (4-6)</td>
<td>3 (2-4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS (1)*</td>
<td>11.3 (9-13)</td>
<td>24.4 (18-30)</td>
<td>12.7 (10-15)</td>
<td>6.5 (5-8)</td>
<td>12.5 (11-14)</td>
<td>35.3 (28-48)</td>
<td>16.6 (15-18)</td>
<td>5.4 (5-7)</td>
</tr>
<tr>
<td>Median OS (2)*</td>
<td>11.1 (9-13)</td>
<td>19.8 (12-27)</td>
<td></td>
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</tr>
</tbody>
</table>

Months; 1: 2nd-line due to any cause (N = 285); 2: 2nd-line due to progression to Pz (N = 242).

Conclusions

Our results validate the use of the IMDC prognostic classification as a discrimination tool, for predicting prognosis in pt receiving 2nd-line targeted therapies after pazopanib in
mRC. Pt who received 2nd-line after true progression had a poorer prognostic than the predicted by the IMDC.

Clinical trial identification
NCT03091465

Legal entity responsible for the study
SOGUG

Funding
Novartis

Disclosure
B. Pérez-Valderrama: Consulting/Advisory role for Astellas Pharma, Novartis, Pfizer, Pierre Fabre, Bayer, Sanofi, Bristol-Myers Squib and Roche. J. Arranz Arija: AdBo from Novartis and Pfizer. G. de Velasco: Consulting and Advisory board for Pfizer, Novartis, Bayer, Roche. M.A. Gonzalez Del Alba Baamonde: Advisory boards for Novartis, Pfizer, Bristol-Myers Squib, Ipsen. All other authors have declared no conflicts of interest.

896P - A Phase (Ph) 1 dose finding study of X4P-001 (an oral CXCR4 inhibitor) and axitinib in patients with advanced renal cell carcinoma (RCC)

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Background
X4P-001 is an oral, selective, allosteric inhibitor of the chemokine receptor CXCR4, and has been shown to down-regulate hypoxia inducible factor-2α (HIF-2α) and myeloid-derived suppressor cell (MDSC) trafficking in the tumor microenvironment. In multiple RCC xenograft models, the addition of X4P-001 to tyrosine kinase inhibitors (TKIs), including axitinib, increases the efficacy and delays the onset of TKI resistance.

Methods
This is an ongoing phase 1/2 open-label study of X4P-001 in combination with axitinib in patients (pts) with histologically confirmed clear cell RCC who have received ≥1 prior systemic therapy. The Ph1 portion of the study evaluates safety, tolerability, PK, PD and anti-tumor activity of the combination using a 3+3 dose escalation schema (escalating doses of X4P-001+ axitinib at 5 mg BID).

Results
As of 27 April, 2017, sixteen (16) pts were enrolled in the Ph1 portion of the study. The median age was 64 years (range 50-76) and pts had received a median of 2 prior lines of therapy (range 1-5). The doses tested were 200 mg BID, 400 and 600 mg QD of X4P-001 + axitinib. Two doses limiting toxicities (DLTs) were observed at the X4P-001 600 mg QD dose level: one pt had multiple grade (G) 2 adverse events (AEs), including anorexia, cognitive disturbance, fatigue, nausea, vomiting, and somnolence; another pt had G3 dyspnea and fatigue. The MTD/RP2D was determined to be 400 mg QD of X4P-001 + axitinib. Treatment-related AEs (≥ 10%) of any grade were fatigue, diarrhea, hypertension, nausea, headache, anorexia, vomiting, dysphonia, proteinuria, dry eye, dry mouth,
arthralgia, chest pain, cognitive disorder, dysgeusia, stomatitis, weight loss, and elevated creatinine. Treatment-related G3/4 AEs (≥ 10%) were fatigue and hypertension. In addition, one pt had SAE due to G2 diarrhea and G2 creatinine elevation. Of the 9 clinically evaluable pts, 3 had confirmed partial response, 5 had stable disease, and 1 had progressive disease. Median duration on treatment was 6.0 months (range 4.6-12.1).

Conclusions
The combination treatment of X4P-001 and axitinib is well tolerated with preliminary evidence of clinical activity. The Ph2 portion of the study is ongoing.

Clinical trial identification
NCT02667886 First received: January 20, 2016

Legal entity responsible for the study
X4 Pharmaceuticals

Funding
X4 Pharmaceuticals

Disclosure
D.F. McDermott: Paid consultant to Bristol-Myers Squib, Pfizer, Merck, Novartis, Eisai, Exelixis, Array BioPharm, Genentech BioOncology and receives research support from Prometheus S. Blanchette, L. Gan: Employee of X4 Pharmaceuticals. M.B. Atkins: Compensated consultant for Bristol-Myers Squibb, Merck, Roche, Pfizer, Novartis, Peleton, AstraZeneca, Nektar, Acceleron, Eisai and Exelixis and serve on Advisory Boards for X4 Pharma, Merck, Novartis, Roche, Pfizer, Galactone, Agenus and AVEO. All other authors have declared no conflicts of interest.

897P - Efficacy and safety data in elderly patients (pts) with metastatic renal cell carcinoma (mRCC) included in the nivolumab expanded access program (EAP) in Italy

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Background
The risk of developing renal cell carcinoma (RCC) increases with age, and given the constant gain in life expectancy of the general population, RCC is frequently observed in the elderly. More than 80% of cancer pts aged ≥ 70 years have at least one comorbidity requiring treatment, leaving them exposed to drug interactions. Due to high frequency of comorbidities, these pts are often under-represented in clinical trials. The purpose of this analysis is to evaluate the feasibility of treatment with nivolumab in the elderly (≥ 70 years) and very elderly (≥ 75 years) in the EAP in Italy, given a more realistic picture of real world setting.

Methods
Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after at least one prior systemic treatment in the advanced or metastatic setting. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received ≥ 1 dose of nivolumab and were
monitored for adverse events (AEs) using Common Terminology Criteria for Adverse Events.

Results
Of 389 Italian pts with mRCC enrolled in the EAP in Italy 125 pts (32%) had ≥70 years and 70 (18%) had ≥75 years. With a median follow-up of 9.8 months (0.1-16.2) in the elderly population (≥70 years), the disease control rate (DCR) was 58% including 1 patient in complete response (CR), 32 pts in partial response (PR) and 40 patients in stable disease (SD). Regarding the very elderly population (≥75 years), with a median follow-up of 9.8 months (0.1 -14.9), the DCR was 60% including 1 patient with CR, 19 pts with PR and 22 with SD. As of May 2017, 6 and 12 months overall survival (OS) rate were 87.2% and 77.8% respectively in the elderly population. Regarding the very elderly, the 6 and 12 months OS rate was 83.6% and 77.7%, respectively. The safety profile was consistent to what already observed in the general population.

Conclusions
These results suggest that elderly population can benefit from nivolumab treatment with safety results consistent to what previously reported, supporting the use of nivolumab in this subpopulation.

Clinical trial identification
CA209-99M

Legal entity responsible for the study
Sergio Bracarda coordinator Italian RCC EAP Group

Funding
None

Disclosure
All authors have declared no conflicts of interest.

898P - Immune expression profile and sunitinib benefit in metastatic clear cell renal cell carcinoma (ccRCC)

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L. Paré (Barcelona, Spain) P. Galvan (Barcelona, Spain) C. Mallofre (Barcelona, Spain) A. Prat (Barcelona, Spain)
B. Mellado Gonzalez (Barcelona, Spain)

Background
The identification of predictive biomarkers may be useful to select antiangiogenic or immunotherapy treatment in renal cell carcinoma. We here investigated the immune expression profile in sunitinib (SU) or anti-PD1/PD-L1 treated ccRCC patients.

Methods
Forty-two metastatic ccRCC patients treated with SU and 10 patients treated with anti-PD1/PD-L1 antibodies were included in this retrospective biomarker study. 730 immune-related genes (nCounter® PanCancer Immune Profiling Panel, Nanostring) were tested in FFPE tumor specimens. Different immune gene signatures were correlated with clinical outcome. A differential expression analysis between refractory (progression-free survival (PFS) < 3 months) and sensitive (PFS > 3 months) patients to SU and anti-PD1/PD-L1 therapies was performed.

Results
Patients who achieved a partial or complete (P/CR) response with SU had a higher score
of B cell, CD8 T cell, T cell, Th1 cell, Th2 cell, Treg cell and Stromal signatures. Moreover, these signatures were predictive of P/CR to sunitinib (p-value for odds ratio < 0.05). T cell signatures (CD8 T cell, T cell, Th1 cell, Th2 cell and Treg cell) were correlated with a better PFS, while activated dendritic cell (aDC) and stromal signatures were correlated with a better OS (Table). In the cohort of anti-PD-1/PD-L1 treated patients, no differences in the immune signatures were found between responders and no-responders to these drugs. However, differential expression analysis revealed a single gene, TIM-3, that was associated with resistance to anti-PD1/PD-L1 therapies and benefit to SU in ccRCC patients.

**Table:**

<table>
<thead>
<tr>
<th>Signatures</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>CD8Tcell</td>
<td>0.57 (0.37 – 0.89)</td>
<td>0.01235</td>
</tr>
<tr>
<td>Th1cell</td>
<td>0.62 (0.41 – 0.95)</td>
<td>0.02841</td>
</tr>
<tr>
<td>Tcell</td>
<td>0.68 (0.48 – 0.98)</td>
<td>0.03951</td>
</tr>
<tr>
<td>Tregcell</td>
<td>0.67 (0.45 – 0.98)</td>
<td>0.04126</td>
</tr>
<tr>
<td>Th2cell</td>
<td>0.48 (0.24 – 0.97)</td>
<td>0.04155</td>
</tr>
<tr>
<td>Stromal</td>
<td>0.72 (0.50 – 1.03)</td>
<td>0.06923</td>
</tr>
<tr>
<td>Bcell</td>
<td>0.69 (0.47 – 1.03)</td>
<td>0.07271</td>
</tr>
<tr>
<td>aDC</td>
<td>0.78 (0.46 – 1.34)</td>
<td>0.37136</td>
</tr>
<tr>
<td>iDC</td>
<td>0.91 (0.52 – 1.58)</td>
<td>0.74005</td>
</tr>
</tbody>
</table>

**Conclusions**

T cell signatures may be associated with benefit to SU in ccRCC. The value of TIM-3 as a potential biomarker in ccRCC merits further exploration.

**Legal entity responsible for the study**

Hospital Clínic de Barcelona

**Funding**

Fundació Clínic per a la Recerca Biomèdica

**Disclosure**

All authors have declared no conflicts of interest.

**899P - Interim results from PAZOREAL: A non-interventional study to assess effectiveness and safety of pazopanib and everolimus in the changing mRCC treatment landscape**

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**Background**

The treatment (tx) of metastatic renal cell carcinoma (mRCC) has markedly changed over
the last decade with the introduction of targeted therapies including vascular endothelial growth factor receptor (VEGFR) and mammalian target of rapamycin (mTOR) inhibitors. Current tx recommendations include the VEGFR inhibitor pazopanib (PAZ) as first-line option and the mTOR inhibitor everolimus (EVE) after VEGF-targeted therapy. The approval of programmed cell death 1 (PD-1) checkpoint inhibitor nivolumab (NIVO) in 2016 provides an additional second-line option.

Methods
PAZOREAL is a prospective, non-interventional study to evaluate the effectiveness, tolerability, safety and quality of life on the routine tx of 450 adult patients (pts) with histologically confirmed mRCC treated with first-line PAZ, second-line EVE or NIVO, or third-line EVE after NIVO. The main objective is time on drug (TD) in the respective tx lines and overall, other objectives include overall survival, dosing parameters, safety and quality of life.

Results
Between December 2015 and March 2017, 305 pts have been enrolled; 302 in the first-line PAZ cohort and 3 in third-line EVE after NIVO. The latter cohort was opened for documentation after approval of NIVO. 266 first-line pts had a documented first intake of PAZ and were eligible for analysis; 201 (75.6%) had a clear-cell histology. Median TD on PAZ was 6.5 months. For 98 pts (36.8%) discontinuation of PAZ tx was reported. The main reasons were progressive disease (N = 36), followed by toxicity (N = 18) and (serious) adverse event (N = 13). Details on subsequent tx with NIVO or EVE were documented for 24 and 4 pts, respectively, while 8 pts started other therapies in second line. During PAZ tx, the most frequently reported treatment-emergent adverse events (TEAE) of grade 1/2 were diarrhea (N = 57), nausea (N = 36), and fatigue (N = 24), of grade 3/4 were hypertension (N = 11), diarrhea and anemia (each N = 4). Fatal TEAEs were reported in 28 pts with progression being the most common term.

Conclusions
PAZ is an effective and safe first-line therapy for pts with mRCC in a real life setting. Second line therapy has rapidly shifted towards NIVO.

Clinical trial identification
BfArM AWB No. 6687

Legal entity responsible for the study
Novartis Pharma GmbH

Funding
Novartis Pharma GmbH

Disclosure
J. Bedke: Reports consultancies, honoraria or study participation from Bayer, Bristol-Myers Squib, Novartis, Pfizer and Roche. M. Welslau: Reports grants from Novartis, during the conduct of the study. M. Schostak: Reports grants and other from Novartis, during the conduct of the study; and honorarium from Novartis for scientific talks. C. Hering-Schubert: Reports grants from Roche, Novartis, Amgen, Bristol-Myers Squib Boehringer and Cellgene, outside the submitted work T. Wolf: Nothing to disclose. J. Schleicher: Reports grants and personal fees from Bristol-Myers Squib, Novartis; grants from Essai, Celegene; personal fees from Jansen, Pfizer, outside the submitted work. V. Grünwald: Advisory role at Pfizer, Novartis, Bristol-Myer Squibb, Ipsen, Eisai, Roche and has received honoraria from Pfizer, Novartis, Bristol-Myer Squibb, Ipsen, Eisai and Roche.
Background
Higher SUN exposure is associated with better outcomes but SUN PK on day 28 does not correlate with toxicity (# 363, ASCO-GU 2012).

Methods
Toxicity-driven dose/schedule individualization was tested in a prospective phase II study where all pts start on 50 mg/day (d). Pts with minimum toxicity on d 28 are dose escalated to 62.5 mg and then 75 mg. Samples for SU011248 and SU012662 were drawn on day 14 on the first course (100 pts) and again after the optimal dose/schedule had been established (58 pts). 11 patients had 2-3 more samples drawn during continued Rx on the optimal dose.

Results
117 pts were enrolled. Of 108 pts evaluable for response, dose was escalated in 20 pts to 62.5 mg (12 pts) and then to 75 mg (8 pts). In 49 pts eligible for dose reduction by standard criteria, a 50 mg dose was maintained but for 7 - 24 d. Dose was reduced to 37.5 mg in 22 pts and to 25 mg in 10 pts with individualized days on Rx. For 100 pts sampled on the first course the mean concentration (standard error) was 93.8 (3.0) and 29.8 (1.4) ng/mL for SU011248 and SU012662 respectively. For 58 pts, sampled again when optimal dose was established, the mean change from the 1st course for SU011248 and SU012662 was significantly different between dose levels (P < 0.001, Table). The same was true even after dose optimization (p = 0.01). The mean PK values declined over time in 27 pts that remained on 50 mg and a continued decline was seen in 6/11pts with continued sampling. There was no significant difference in PFS and OS between dose levels for all 117 pts.

Conclusions
While dose individualization corrects for some of the differences in PK values on the 1st Rx course, differences remain even after dose optimization emphasizing the importance of pharmacodynamics for toxicity and outcome. An ongoing dose optimization may be important to correct for the decline in PK over time.

Table:

900P
### Dose level (n pts) SU011248 (standard error) During 1st course ng/mL mean change at optimal dose

<table>
<thead>
<tr>
<th>Dose level (n)</th>
<th>SU011248 Mean (SE)</th>
<th>SU012662 Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (n = 27)</td>
<td>90.7 (5.2)</td>
<td>27.6 (2.6)</td>
</tr>
<tr>
<td>&lt; 50 mg (n = 13)</td>
<td>95.4 (10.1)</td>
<td>33.6 (4.6)</td>
</tr>
<tr>
<td>&gt;50 mg (n = 18)</td>
<td>77.1 (5.7)</td>
<td>24.1 (2.6)</td>
</tr>
</tbody>
</table>

### After optimization SU011248 (SE) at optimal dose SU012662 (SE) at optimal dose

<table>
<thead>
<tr>
<th>Dose level (n)</th>
<th>SU011248 Mean (SE)</th>
<th>SU012662 Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg (n = 27)</td>
<td>78.9 (4.7)</td>
<td>27.5 (2.3)</td>
</tr>
<tr>
<td>&lt; 50 mg (n = 13)</td>
<td>72.8 (8.0)</td>
<td>21.7 (2.8)</td>
</tr>
<tr>
<td>&gt;50 mg (n = 18)</td>
<td>106.7 (11.9)</td>
<td>36.5 (3.6)</td>
</tr>
</tbody>
</table>

### Clinical trial identification
NCT01499121

### Legal entity responsible for the study
Dr. Georg A Bjarnason and the Sunnybrook Research Institute

### Funding
Pfizer Canada

### Disclosure

### 901P - Safety and efficacy of Cabozantinib for metastatic renal cell carcinoma (mRCC): real world data from an Italian Expanded Access Program (EAP)
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### Background
Final results from the randomised phase III METEOR trial confirmed a survival benefit of cabozantinib over everolimus in patients (pts) with advanced clear-cell renal cell carcinoma who progressed after at least one previous antiangiogenic inhibitor. The EAP provided the opportunity to treat pts in real world clinical practice.

### Methods
Data were collected from 91 pts treated with cabozantinib across 23 Italian hospitals. Cabozantinib was available, upon physician request, from September to December 2016. Pts were aged 18 years and older, with mRCC and measurable disease, with Performance Status (ECOG) 0 to 2, who had relapsed after one or more prior systemic treatment. 73 pts had clear-cell RCC, while the other 18 had non-clear-cell histologies (type II papillary and chromophobe). The most frequent sites of disease were: lung 53 (58%), lymph nodes 41 (45%), bone 28 (31%), liver 15 (16%) and brain 5 (5%); 42 (46%) pts had two or more sites of disease. Cabozantinib was administered orally at 60 mg once a day in 28 days-cycles. Dose reductions to 40 or 20 mg were allowed if toxicity was encountered. Pts were monitored for adverse events (AEs) using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. The aim of this analysis was to evaluate the safety and activity of cabozantinib in a large unselected population.

Results
Cabozantinib was administered as second line therapy in 28 (30%) pts, as III line in 18 (19%) pts and as further lines in the remaining 45 (51%) pts. At the time of our analysis, grade 3 and 4 AEs were observed in 21% of pts. Among 91 pts, only 5 (5%) discontinued treatment due to AEs. The best overall response was partial in 28 cases (31%), whereas 23 (25%) pts had stable disease and 23 (25%) had progressive disease; 17 pts (18%) have not reached the first response assessment. With a median follow-up of 4 months, the median progression-free survival observed was 3.5 months irrespective of the line of treatment.

Conclusions
Our data suggest that cabozantinib is safe and active in a large unselected population treated according to everyday clinical practice.

Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale dei Tumori of Milan

Funding
None

Disclosure
G. Procopio: Reports receiving fees for serving on advisory boards from Bayer, Bristol-Myers Squibb, Ipsen, Novartis, Pfizer. E. Verzoni: Reports receiving fees for serving on advisory boards from Pfizer and Novartis. All other authors have declared no conflicts of interest.

902P - Prognostic factors for overall survival of patients with advanced renal cell carcinoma – data from the German prospective RCC-Registry

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Background
The identification of prognostic factors is a central question in oncology. They help to predict the course of disease and ideally support the oncologist in treatment decision making in clinical practice. We analysed prognostic factors identified by MSKCC and additional factors for the overall survival (OS) of patients (pts) treated with currently approved agents.

Methods


The prospective German renal cell carcinoma (RCC) Registry includes pts with advanced or metastatic renal cell carcinoma at start of systemic first-line therapy. > 300 oncologists are recruiting pts since 2007. Pts and tumour characteristics, data on all systemic therapies and outcome are collected. The prognostic factors for OS were assessed using a multivariate cox regression model.

Results
Median OS of the 1039 pts (median age 70 years) was 18.6 months (95% CI 16.0 - 20.5 months, 55% events). Median OS in months for low, intermediate and high risk pts according to MSKCC 1999 was 27.3 (23.7-33.8, 48% events), 16.0 (12.7-18.8, 58% events) and 5.3 (3.7-7.2, 74% events). The following factors were significantly associated with shorter OS (p < 0.05: *; p < 0.01: **; p < 0.001: ***): higher age*, non-clear cell histology**, grading G3/4 at diagnosis*, Karnofsky Performance Status <80%***, haemoglobin < lower limit of normal (LLN)***, LDH >1.5x upper limit of normal (ULN)***. Factors significantly associated with longer OS were time from primary diagnosis to metastasis***, BMI 25-30 versus (vs) <25***, BMI>30 vs <25***, lung metastasis only at start of treatment*, non-visceral metastasis only at start of treatment* and hypertension*. Factors not significantly associated with OS were sex, tumour stage at diagnosis (IV vs ULN, tumour localisation (right/left), congestive heart failure, renal disease, diabetes and total nephrectomy.

Conclusions
3 out of 5 MSKCC factors were significantly associated with OS in our cohort. Still, a clear separation of OS between pts with low, intermediate and high risk according to MSKCC could be confirmed. In addition, we identified novel factors also associated with OS.

Clinical trial identification
ClinicalTrial.gov registry: study number: NCT00610012

Legal entity responsible for the study
iOMEDICO AG

Funding
Bayer Vital GmbH, GlaxoSmithKline GmbH & Co. KG, Novatis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG

Disclosure
P.J. Goebell: Received honoraria for paticipation in expert rounds and honoraria/support as a speaker from Astellas, AstraZeneca, Bayer, Bristol-Myers Squib, Eisai, Ipsen, Janssen, Novartis, Pfizer, Sanofi. M. Staehler: Consultant, Honoria and Research Funding: Pfizer, GlaxoSmithKline, Novartis, Bayer, AVEO, Ipsen, Exelixis, EISAI Consultant and Honoria: EUSAPharm, Astellas, Pelloton Consultant and Research funding: Roche Research funding: Immatics, Wilex. N. Marschner: Employed by iOMEDICO which performs the tumorregistry RCC as an CRO Member of advisory boards regarding RCC treatment and Travel grants: Roche, Novartis, Pfizer, Bayer, GSK Corporate sponsored research: Novartis, Pfizer Roche. All other authors have declared no conflicts of interest.

903P - The efficacy and safety of sorafenib in patients with renal insufficiency of advanced renal cell carcinoma: Real- world data of sorafenib in Japan

K. Tatsugami (Fukuoka, Japan)M. Oya (Tokyo, Japan)K. Kabu (Tokyo, Japan)H. Akaza (Tokyo, Japan)
Background
Multiple treatment options are available for patients with advanced renal cell carcinoma (aRCC). However, the safety/efficacy data of these agents in patients with renal insufficiency are limited. To assess the safety/efficacy of sorafenib in aRCC patients with renal insufficiency, we analyzed the real-world data of a nationwide prospective post-marketing surveillance applying propensity score-matched cohorts.

Methods
A total of 3,255 patients with aRCC were enrolled, and 1,226 patients of whom were selected by propensity score matching for estimated glomerular filtration rate (eGFR) <45 (n = 613) and ≥45 (n = 613). Progression free survival (PFS), tumor response, adverse events (AEs), and doses of sorafenib were compared between the two groups.

Results
The median PFS in eGFR<45 and ≥45 was 7.4 months (6.4, 8.8) vs. 8.3 months (6.6, 9.0), respectively. Complete response rates were 1.8% and 3.0%, partial response rates were 24.3% and 26.4%, stable disease rates were 59.8% and 57.7% in eGFR <45 and ≥45, respectively. The mean starting dose was lower in eGFR <45 group (687 mg vs. 726 mg, p < 0.0001), but the median duration of treatment (6.1 vs. 6.6 months) and median daily dose (484 vs. 481 mg) were similar in both groups. The discontinuation rates due to AEs were similar in both groups. Any grade AEs observed ≥20% were hand-foot skin reaction (HFSR) (57.8%), hypertension (37.9%), rash (27.0%), and increases in lipase/amylase (26.9%), and diarrhea (23.1%). The common serious AEs were rash (7.6%), hepatic dysfunction (7.3%), bleeding (6.9%), HFSR (4.9%) and cytopenia (4.6%). The incidence of these common AEs was similar between the groups, except for cytopenia and renal failure which were higher in eGFR <45 group. In the both groups, the eGFR value did not change from the baseline over a year, and it also did not deteriorate even at the time of discontinuation.

Conclusions
Sorafenib has little impact on the renal function in almost all patients with renal insufficiency and provide the fine therapeutic effects for these aRCC patients.

Legal entity responsible for the study
Bayer Yakuhin Ltd.

Funding
Bayer Yakuhin Ltd.

Disclosure

904P - Inflammatory indexes strongly predict clinical outcome in patients (pts) with metastatic renal cell cancer (mRCC) treated with nivolumab: results from the Italian expanded access program (EAP)

U. De Giorgi (Meldola, Italy) G. Procopio (Milan, Italy) A. Guida (Modena, Italy) A. Bearz (Pordenone, Italy) S. Buti (Parma, Italy) U. Basso (Padova, Italy) M. Mitterer (Merano, Italy) C. Ortega (Candiolo, Italy) P. Bidoli (Monza (MI), Italy) F. Ferrau (Taormina, Italy) L. Crinò (Perugia, Italy) A. Frassoldati (Ferrara, Italy) P. Marchetti (Roma, Italy) E. Mini (Florence, Italy) A. Scoppola (Roma, Italy) C. Verusio (Saronno, Italy) G. Fornarini (Genova, Italy) G. Carteni (Napoli, Italy) C. Caserta (Terni, Italy) C. N. Sternberg (Roma, Italy)
Background
Biomarkers for outcome after immune-checkpoint blockade in mRCC are needed. We aimed to verify the prognostic impact of inflammatory indexes based on baseline values of neutrophils (N), lymphocytes (L) and/or platelets (P) in pts with mRCC included in the Italian nivolumab EAP.

Methods
Pts who had received ≥ 1 dose of nivolumab 3 mg/kg every 2 weeks in the Italian EAP after at least one prior systemic therapy for mRCC were enrolled in this study. The pre-treatment systemic immune-inflammation index (SII) defined as P×N/L, neutrophil-to-lymphocyte ratio (NLR) defined as N/L and platelet-to-lymphocyte ratio (PLR) defined as P/L were evaluated to identify a potential correlation with overall survival (OS). X-tile 3.6.1 software was used to identify cut-off values. OS was estimated by the Kaplan-Meier method and compared with the log-rank test. The impact of SII, NLR, and PLR on OS was evaluated by Cox regression analyses and on best overall response rate (ORR) by binary logistic regression.

Results
A total of 346 mRCC pts treated with nivolumab were included. SII ≥ 1375, NLR ≥ 3 and PLR ≥ 232 were considered as elevated levels (high risk groups). One-year OS in low and high SII group was 77% and 36%, respectively (p < 0.0001); 1-year OS in low and high NLR was 76% and 58%, respectively (p < 0.0001); 1-year OS in low and high PLR was 76% and 45%, respectively (p < 0.0001). Likewise, best ORR was higher in pts with low SII (p = 0.008), low NLR (p = 0.06) and low PLR (p = 0.004). In multivariate analysis adjusted for age, gender, risk score (MSKCC), ECOG performance status, presence of liver, brain and/or bone mets, SII, NLR and PLR, the model identified SII as the strongest factor associated with OS (p < 0.0001).

Conclusions
SII, NLR, and PLR are robust inflammatory prognostic factors for predicting outcome in mRCC pts treated with nivolumab. SII is a more powerful predictive system than the other inflammatory indexes for these pts.

Clinical trial identification
expanded access program

Legal entity responsible for the study
Italian RCC EAP Group

Funding
None

Disclosure
U. De Giorgi: advisory board Bristol-Myers Squib. All other authors have declared no conflicts of interest.

905P - CORE-URO-01 study: comparison of safety and efficacy of pazopanib in first-line metastatic renal cell carcinoma (mRCC) with or without renal failure

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Background
Pazopanib has been approved for first-line treatment of patients (pts) with mRCC based on the prospective randomized trial that enrolled only pts with adequate renal function. There are no data on the efficacy and toxicity of pazopanib in pts with renal insufficiency (RI). The aim of this study is to investigate the effect of kidney function on treatment outcomes in pts treated with pazopanib for mRCC.

Methods
We retrospectively analyzed the data of the mRCC pts treated with pazopanib with respect to renal function in fourteen Italian institutions from January 2010 to June 2016. Baseline glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula at the time of therapy initiation. Pts with MDRD<60 mL/min/1.73 m2 (group A) were compared with pts with MDRD≥60 mL/min/1.73 m2 (group B) in terms of response rates, progression free survival (PFS), overall survival (OS) and toxicities.

Results
Two hundred and twenty-nine pts with mRCC were included in this study: 128 pts in group A and 101 pts in group B. 68% of pts were male, median age was 67 years (34-88) and median CrCl was 49.7 ml/min in group A. In group B, 64% of pts were male, median age was 64 years (38-85) and median CrCl was 74 ml/min. Pts with MDRD<60 were more likely to have had a previous nephrectomy (87% vs 79%). Median PFS was 14 months (95% confidence interval [CI] 9.4-18.5) and 17 months (95% CI 11.4-22.8), OS was 30.5 months (95% CI 8-53) and 41.4 months (95% CI 21-62) for MDRD<60 group and MDRD≥60 respectively, with no statistical difference (p = 0.6). The disease control rate was 84% in group A, and 73% in group B (p = 0.1). About toxicity profile, no difference between the 2 groups was reported in terms of incidence of grade 1-2 (73% vs 79%) and grade 3-4 (24% vs 33% respectively, p = 0.2). Dose reductions are statistically more frequent in pts in group A (66% vs 36%, p = 0.04), despite the same percentage of pts in both groups started at dose of 800 mg/day.

Conclusions
Although in this study it is necessary to reduce the dose of pazopanib more frequent in pts with RI, kidney function at therapy initiation does not adversely affect the efficacy and safety of pazopanib.

Legal entity responsible for the study
Cristina Masini

Funding
None

Disclosure
All authors have declared no conflicts of interest.

906P - Impact of haptoglobin polymorphism on survival of renal cell carcinoma patients
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Background
Renal cell carcinoma (RCC) accounts for 2.4% of all malignancies worldwide with 338,000 estimated new cases globally in 2012. With 144,000 deaths annually, RCC is the 16th cancer-related death worldwide. In the last decade, the use of targeted therapy for patients with metastatic RCC has increased exponentially, especially since the breakthroughs with cabozantinib and nivolumab. Apart from the Heng criteria in 1st-line therapy, no robust biochemical markers exist for the prognosis of RCC patients. Here we assessed the prognostic value of haptoglobin (Hp) polymorphisms on survival of RCC patients.

Methods
At interim analysis, 53 metastatic RCC patients were enrolled and Hp phenotypes were determined prospectively. Survival data was retrieved from the electronic patient files. Kaplan-Meier survival analyses were performed for disease-free survival (DFS), progression-free survival (PFS) after 1st- and 2nd-line therapy, and overall survival (OS).

Results
Fifty-eight percent of patients were male. Hp distribution was 19%, 49% and 32% for Hp 1-1, 2-1 and 2-2 phenotypes, respectively. Median follow-up since development of metastatic disease was 4.7 years (95% CI 3.3 – 6.5). Lowest DFS was found in patients with Hp 2-2 phenotypes. This was significant when Hp 2-2 phenotypes were compared with Hp 1-1/2-1 phenotypes (hazard ratio [HR] = 1.93 [95%CI 1.12 – 5.75], P = 0.0255). No significant difference between Hp phenotypes was noticed for PFS after 1st-line therapy. After 2nd-line therapy, longest PFS was observed in patients with Hp 2-1 and 2-2 phenotypes which was better compared with Hp 1-1 phenotypes. Lastly, OS was found to be longer in patients with Hp 2-1 and 2-2 phenotypes, although no significance was observed versus patients with Hp 1-1 phenotypes. Median durations of survival and HRs versus Hp 1-1 phenotypes are given in Table.

Conclusions
Interim analysis shows that Hp phenotype has prognostic potential, especially in DFS and
Background

Pazopanib is characterized by a large interpatient variability in systemic drug exposure. As pazopanib trough levels (>20.5 mg/L) are correlated with clinical outcome (Suttle et al, BJC 2014) in metastatic renal cell carcinoma (mRCC) patients, it is vital to identify factors that influence pazopanib pharmacokinetics (PK). The objective of the current analysis was to evaluate if single nucleotide polymorphisms (SNPs) in the metabolic pathway of pazopanib (i.e. CYP3A4, ABCB1 and ABCG2) affect systemic pazopanib concentrations.

Methods

We analyzed 97 patients who participated in 3 pazopanib PK studies. Starting point of the current analysis was a population PK model for pazopanib (Yu et al, Clin Pharmacokinet 2017). Four SNPs located on 3 genes, that were associated with decrease of function were analyzed using real time PCR: CYP3A4 15389 C>T (*22), ABCB1 3435 C>T, and the ABCG2 SNPs 421 C>A, and 34G>A. The influence of these SNPs on pazopanib bioavailability and clearance (CL) was explored with NONMEM. Statistical significance was determined with the likelihood ratio test using the objective function value (OFV). Trough concentrations (C_{trough}) at 6 weeks after start with doses of 400 to 800 mg once daily (OD), were simulated. A threshold C_{trough} of 20.5 mg/L was used as reference.

Results

From 3 patients, insufficient DNA was isolated to run a PCR analysis. All SNPs were in Hardy-Weinberg equilibrium. Eleven patients (12%) had a variant allele at CYP3A4*22, all of whom were heterozygous. Incorporation of CYP3A4*22 in the NONMEM model resulted in a 35% lower CL for the variant carriers (0.18 L/h vs 0.27 L/h; ΔOFV = -7.8; P < 0.01). Simulated median C_{trough} of patients with CYP3A4*22 with 400 mg OD, 600 mg OD or 800 mg OD were 16 mg/L, 25 mg/L and 33 mg/L, respectively. Simulated C_{trough} for the population excluding the CYP3A4*22 heterozygotes after 800 mg OD was 21 mg/L. No effect of the ABCB1 or ABCG2 SNPs on systemic concentrations were found.

Conclusions

Our analysis shows that CYP3A4*22 carriers have a clinically relevant lower pazopanib
Prospective analysis should point out whether CYP3A4*22 carriers are at risk for more toxicity and require a lower pazopanib starting dose.

**Legal entity responsible for the study**
Erasmus MC, Rotterdam, The Netherlands

**Funding**
None

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

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**908P - Association between biopsychosocial distress (BPSD) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC)**

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P. G. Bergerot (Duarte, United States of America) R. Obenchain (Duarte, United States of America)
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M. C. Maia (Duarte, United States of America) E. Philip (Notre Dame, United States of America)
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**Background**
Depressive symptoms have been associated with poorer OS in pts with mRCC (Prinsloo et al J Behav Med 2015). In other malignancies, BPSD has also been linked to poorer OS, but in mRCC, this association is unclear.

**Methods**
From a single institution, clinicopathologic information from pts with mRCC diagnosed between 2001 and 2016 were collected. Corresponding data from an electronic survey tool was obtained, comprised of 22 core items spanning physical, practical, functional and emotional domains. Each item was self-assessed by the pt on a 5-point Likert scale. The cumulative score was used to characterize BPSD as either as low BPSD (not a problem/mild) vs high BPSD (moderate/severe/very severe). Associations between BPSD level and clinicopathologic criteria (e.g., Heng risk) were interrogated, and OS was compared between patients characterized as low BPSD vs high BPSD.

**Results**
A total of 102 pts (28.4% F/71.6% M) were assessed with a median age of 63 (range, 24-80). 73.4 and 26.6% pts were characterized as having good/intermediate and poor risk by Heng criteria, respectively. 79.3% pts and 20.7% pts were characterized as having low and high BPSD, respectively. No association was found between BPSD and age or gender. However, married patients have a longer survival (48.65 mos vs 34.52 mos, P=.07). Pts with poor risk mRCC were noted to have a higher BPSD as compared to pts with mild BPSD (75% vs 25%, P=.22). Median OS in the overall cohort was 44.2 months (mos). Although not statistically significant, a trend towards prolonged OS in pts with low BPSD vs high BPSD was observed (45.81 mos vs 35.95 mos, P = .81).

**Conclusions**
Our study suggests a potential link between Heng risk and BPSD, and further shows a compelling trend towards poorer OS in pts with higher BPSD. These results warrant confirmation in larger series. Targeted interventions to address elements related to BPSD have the potential to improve patient outcomes and should be developed.
Background
Because renal cell carcinoma (RCC) is diagnosed 75-80% with clear cell histology, there is little data on treatment and outcome of patients (pts) with non-clear RCC. They are reported to have a poorer prognosis and are often excluded from clinical trials. Here, we present data on papillary RCC, the most common non-clear cell subtype (10-15% of RCC).

Methods
The prospective German RCC-Registry includes pts with advanced or metastatic RCC at start of systemic first-line therapy. Data on patient and tumour characteristics, all systemic therapies and outcome are collected. More than 300 medical and uro oncologists are recruiting pts since 2007.

Results
Median age for pts with papillary RCC (n = 92) at start of first-line therapy was 66 years. According to MSKCC risk category, pts were classified into 30% low, 55% intermediate and 2% high risk (12% unknown). From 2007 to May 2016 (data cut) treatment changed. First-line, the use of sunitinib declined and the use of temsirolimus and pazopanib increased. Since 2011 (n = 46), first-line treatments included 33% (n = 15) temsirolimus, 30% (n = 14) sunitinib and 22% (n = 10) pazopanib. The most frequently used second-line treatments since 2011 (n = 28) are sunitinib (36%, n = 10), everolimus and pazopanib (18%, n = 5 each), temsirolimus (11%, n = 3) followed by axitinib and sorafenib (7%, n = 2, each). The most frequently used first -> second-line strategies (first-line since 2011, n = 23) are mTor inhibitors (temsirolimus) -> TKI (35%, n = 8) and TKI -> TKI (26%, n = 6) (TKI: sunitinib, axitinib, pazopanib or sorafenib). Updated data (data cut May 2017) including nivolumab will be presented. Median progression-free survival (PFS) for the first-line was 6.1 months (95% CI 4.0 - 9.9) for pts with papillary RCC versus (vs) 8.6 (7.7 - 9.7) for pts with clear cell RCC (ccRCC, n = 772). For the second-line, median PFS was 3.7 (2.3 – 4.9) vs 4.8 (4.2 – 5.8) (papillary vs ccRCC). Median overall survival (OS) was 12.7 (8.5 – 23.8) vs 20.8 (19.1 – 23.8) (papillary vs ccRCC).

Conclusions
We show first- and second-line treatment of pts with advanced papillary RCC. Our data indicate that prognosis for pts with papillary RCC might be inferior to that of pts with clear cell RCC.

Clinical trial identification
910P - Exome sequencing of tumor samples from S1107 “Randomized phase II evaluation of tivantinib and tivantinib in combination with erlotinib in patients with papillary renal cell carcinoma (pRCC)”

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Background
pRCC is associated with activation of MET pathway, overexpression of EGFR and inferior responses to VEGF inhibition than clear cell RCC. In S1107 we randomized patients (pts) with advanced pRCC and 0-1 prior systemic therapy to MET inhibitor tivantinib at 360 mg BID (Arm 1) or tivantinib 360 mg BID plus EGFR inhibitor erlotinib at 150 mg daily (Arm 2). 66% of pts had no prior systemic therapy; 6% had type 1 pRCC, 42% had type 2, and 52% had no subtype assigned. The study was closed at interim analysis after 55 pts were enrolled and 0% RR was noted. Median PFS was 2.0 and 3.3 months, and OS was 10.3 and 11.3 months in Arms 1 and 2 respectively. These results were inferior to previously reported clinical trials with pRCC. To better understand these outcomes we performed whole exome sequencing of tumor samples collected from pts participating in this study.

Methods
Exome of 16 pts were successfully sequenced using Agilent SureSelect probes. The mean coverage of target regions ranged from 45x to 91x. Only reads aligned to unique genomic location were retained. The single point mutations and small indels were identified using GATK HaplotypeCaller. Copy number analysis was performed using Bioconductor package “DNACopy” and customized R scripts.

Results
Most of the mutations were unique to individual pts indicating high diversity of variants in this patient cohort. Only 1 MET mutation was ascertained affecting tyrosine kinase domain (K1198I). Other mutations associated primarily with type 2 pRCC included CDKN2A, PBRM1, SETD2, KDM6A, FAT1, NF2, CUL. No EGFR and FH mutations were detected. The most affected pathways included WNT, cadherin and mitotic G2-G2/M phase. Somatic copy number variation was challenging to obtain since no matching normal tissues were collected, but MET amplification was suspected in minority of cases.

Conclusions
S1107 patient cohort had a high proportion of pts with molecular subtypes not driven by MET abnormalities and would not be expected to respond well to MET inhibition. Although MET remains a reasonable therapeutic target in pRCC, careful selection of pts exhibiting MET alterations is required to better benefit from therapy with MET inhibitors.

Clinical trial identification
NCT01688973

Legal entity responsible for the study
Southwest Oncology Group

Funding
(NIH/NCI NCTN CA180888;CA180819;CA180820).

Disclosure
P. Twardowski: Consulting/ Speakers Bureau: Sanofi Aventis, Medivation, Astellas, Dendreon, Roche, Janssen, Bayer, Pfizer. E. Plimack: Consulting/ Scientific Advisory: AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Exelexis, Genentech, Horizon Pharma, Inovio, Novartis, Pfizer, Roche Grant/Trials: Acceleron, Agensys, AstraZeneca, Bristol-Myers Squibb, Merck, Peloton, Pfizer. All other authors have declared no conflicts of interest.

911P - Patients (pts) with metastatic non-clear cell renal cell carcinoma (mnccRCC) treated with Nivolumab (Nivo) based immunotherapy as advanced treatment (ATL) line: analysis of a national early access program (EAP)

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Background
Immunotherapy with the anti-PD1 Nivo is a standard ATL for clear cell mRCC. Data on its activity in the rare variant of mnccRCC is limited (case reports). We aimed to report the activity of Nivo in mnccRCC pts treated per a national EAP.

Methods
Records from consecutive mnccRCC pts treated with Nivo ATL per a national EAP in 6 centers were retrospectively reviewed. We report the clinical benefit, progression free survival (PFS), overall survival (OS), and toxicity.

Results
Between 7/2015 – 12/2016, 16 mnccRCC pts (median age 64, male 68%; papillary type 38%, n = 6; chromophobe 44%, n = 7; undifferentiated 12%, n = 2; pure sarcomatoid 6%, n = 1). 62% (n = 10) were treated with second line Nivo, and 38% (n = 6) as third and fourth
line. Heng risk was good/intermediated/poor in 6% (n = 1)/75% (n = 12)/19% (n = 3).
Clinical benefit (stable disease+ partial response) was 37% (4 partial response and 2 stable disease). Median PFS was 3.5 months (mos). After a median follow up time of 8 mos, 100% of the pts with a clinical benefit are still with a benefit and on treatment (range 5-18m). Most pts (69%, n = 11) are alive, with median OS not reached. Toxicity was mild grade 1-2 in the majority of pts (56%, n = 9).

Conclusions
Nivo as ATL may be active in mnccRCC pts, and associated with durable responses and predictable mild toxicity. Future and larger studies are needed to assess the activity of immunotherapy in this uncommon type of mRCC.

Legal entity responsible for the study
the author
Funding
None
Disclosure
All authors have declared no conflicts of interest.

912P - Cabozantinib for the treatment of patients with metastatic variant histology renal cell carcinoma (vhRCC): a retrospective study

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Z. Lim (Houston, United States of America) A. Shah (Houston, United States of America)
E. Jonasch (Houston, United States of America) N. Tannir (Houston, United States of America)

Background
Cabozantinib (C) prolongs overall survival (OS) and progression-free survival (PFS) in patients with metastatic clear-cell renal cell carcinoma (ccRCC) that progressed on first-line VEGFR-TKI. No standard of care systemic therapy exists for the management of patients with metastatic vhRCC.

Methods
This is a retrospective, IRB approved study of patients with vhRCC who received cabozantinib at MD Anderson Cancer Center from January 2014-January 2017. Information collected from the medical records included the baseline characteristics, toxicity, dose reductions, and OS. A blinded radiologist assessed the radiographic response using RECIST v1.1. Descriptive statistics, the Kaplan Meier method and the log rank test were applied using Microsoft Excel and GraphPad Prism version 6 software.

Results
Table:
912P

<table>
<thead>
<tr>
<th>N = 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age, median (range)</td>
</tr>
<tr>
<td>Prior Nephrectomy</td>
</tr>
<tr>
<td>Histology</td>
</tr>
</tbody>
</table>
Mucinous tubular/spindle cell

Prognostic Risk Group MSKCC IMDC
Good/Intermediate/Poor 2/20/8 2/23/5

Number of Prior Therapies 0 1 >1
Median (range) Previous VEGFR Tyrosine Kinase Inhibitor
3 7 20 2 (0-5) 26

Median PFS was 8.6 months (mos) (95% CI: 6.1-14.7), and median OS was 22.7 mos (95% CI: 10.8-NR), median follow up 10.6 months (95% CI: 7.1-14.1). There were no significant differences detected between patients with papillary versus non-papillary histologies with respect to PFS or OS. At last follow up, 13 patients remain on treatment with median time on therapy for all patients of 15.0 months. Of the 28 patients with measurable disease, there were 4 confirmed PRs (2 P, 1 Chr, 1 unclassified) for a 14% ORR. For the entire cohort, 20 of 30 (66.7%) with stable disease, and 6 of 30 with progressive disease (20%), for a disease control rate of 24 of 30 (80%). Of 21 patients who started C at 60 mg/d, 12 (57%) required dose reduction due to toxicity. Multiple patients required treatment breaks but none discontinued therapy due to toxicity.

Conclusions
In this retrospective study, C produced a clinically meaningful benefit in patients with metastatic vhRCC, the majority of whom had PD on prior VEGFR-TKIs. Prospective trials of C in vhRCC are warranted and planned.

Legal entity responsible for the study
Matthew T Campbell

Funding
None

Disclosure
M.T. Campbell: Serve on advisory boards for Eisai and AstraZeneca. M.A. Bilen: Advisory board for Exelixis. N. Tannir: Served as a consultant and has served on advisory board for Exelixis. All other authors have declared no conflicts of interest.

913P - Avelumab in patients with metastatic adrenocortical carcinoma (mACC):
Results from the JAVELIN solid tumor trial

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S. Bauer (Essen, Germany) M. Wermke (Dresden, Germany) H. Grote (Darmstadt, Germany)
A. Von Heydebreck (Darmstadt, Germany) K. Chin (Billerica, United States of America)
J. Gulley (Bethesda, MD, United States of America)

Background
Avelumab is a human anti-PD-L1 IgG1 antibody that has shown promising clinical activity in multiple tumor types, and is approved in the US for the treatment of metastatic Merkel cell carcinoma. Here, we report an updated analysis of avelumab in patients (pts) with mACC, representing the largest prospective monotherapy study performed to date in this rare cancer with limited therapeutic options.

Methods
In a phase 1b cohort (NCT01772004), pts with mACC and prior platinum-based therapy received avelumab at 10 mg/kg IV Q2W until progression, unacceptable toxicity, or
withdrawal. Prior and ongoing treatment with mitotane was permitted. Tumors were assessed every 6 wks (RECIST v1.1). Endpoints included safety (NCI-CTCAE v4.0), best overall response, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

**Results**

As of Dec 31, 2016, 50 pts from 6 countries received avelumab for a median of 3.4 mos (0.5–24.8). Median follow-up was 16.5 mos (11.7-27.6); 5 pts (10.0%) remained on treatment. Median age was 50 y (range 21–71) and median time since diagnosis of metastatic disease was 14.5 mos. 24 pts (48.0%) had received ≥2 prior lines of treatment for advanced disease (median 1, range 0–6). 41 pts (82.0%) had a treatment-related adverse event (TRADE) of any grade; the most common (>15%) were nausea (20.0%) and fatigue (18.0%). 8 pts (16.0%) had a grade ≥3 TRAE, of which only increased ALT (4.0%) occurred in > 1 pt. 12 pts (24.0%) had an immune-related AE of any grade. Confirmed ORR was 6.0% (3 partial responses; 95% CI 1.3–16.5); response was ongoing in 1 pt at data cutoff. 21 pts (42.0%) had stable disease as best response (disease control rate 48.0%). Median PFS was 2.6 mos (95% CI 1.4–4.0). Median OS was 10.6 mos (95% CI 7.4–not estimable) and the 12-mo OS rate was 47.0% (95% CI 31.8–60.9). Responses occurred in 2 pts with PD-L1+ tumors and 1 PD-L1 − (≥5% tumor cell cutoff). In PD-L1 + (n = 12) vs PD-L1 − (n = 30) subgroups, median PFS was 5.5 vs 1.7 mos (HR 0.66; 95% CI 0.3–1.4) and median OS was 14.4 vs 11.5 mos (HR 0.82; 95% CI 0.3–2.2), respectively.

**Conclusions**

Avelumab had a manageable safety profile and demonstrated clinical activity in pts with platinum-treated mACC.

**Clinical trial identification**

NCT: NCT01772004 Protocol: EMR 100070-001

**Legal entity responsible for the study**

Pfizer Inc., New York, NY, USA; Merck KGaA, Darmstadt, Germany.

**Funding**

Funding was provided by Pfizer Inc., New York, NY, USA and Merck KGaA, Darmstadt, Germany.

**Disclosure**

C. Le Tourneau: Provided a consulting role for MSD, Bristol-Myers Squib, Novartis and AstraZeneca and received honoraria from Merck Serono and AstraZeneca. C. Zarwan: Provided an advisory role for Revere Pharmaceuticals and consulting for Perceptive Informatics. C. Hoimes: Provided an advisory role for Seattle Genetics and Eisai, and participated in speaker’s bureau’s for Bristol-Myers Squib and Genentech. D.J. Wong: Received research funding from Armo Biosciences, BioMed Valley Discoveries, Roche-Genentech, Merck, EMD Serono, Bristol-Meyers Squibb, KURA Oncology, AstraZeneca. Provided an advisory role for Bristol-Meyers Squibb. S. Bauer: Research support: Novartis, Blueprint Medicines, Ariad; Consultant: GSK, Novartis, Pfizer, Bayer, Fresenius, Lilly, Blueprint Medicines, Deciphera; Honoraria (CME): Pharmamar, GSK, Pfizer, Bayer; Travel support: Pharmamar, Bayer. M. Wermke: Received research funding from Novartis, Pfizer, Roche, Novartis, Roche, Boehringer Ingelheim and Celgene. Provided an advisory role for Roche, Novartis, Bristol-Myers Squib, AstraZeneca and received honoraria from Roche, Novartis, Boehringer Ingelheim. H.J. Grote: Employee of
914P - Do patients (pts) with advanced nonseminomatous germ cell tumors (aNSGCT) and unfavorable time to normalization (TTN) of tumor markers benefit with prolongation of 1-st line chemotherapy (ChT)?

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Background
Three-four cycles of BEP are commonly recognized as a standard 1-st line ChT in aNSGCT. However, there were no trials studying optimal cycles numbers in this setting, especially in case of unfavorable TTN of tumor markers. We performed retrospective single center analysis to evaluate if pts with unfavorable TTN of tumor markers may benefit with prolongation of induction ChT.

Methods
Inclusion criteria were as follows: (1) ChT-naïve aNSGCT pts treated with etoposide- and cisplatin-based chemotherapy; (2) AFP and hCG levels available at days 0 and 18-22 of cycle 1 to calculate TTN (Fizazi K., JCO 2004). Pts who received less than “standard” number of cycles (3xBEP or 4xEP for IGCCCG good risk, 4xBEP for intermediate and poor risk) for any reason were excluded from the analysis. Cox` regression multivariate analysis was also performed. TTN was calculated by K.Fizazi’s methodic (JCO 2004).

Results
From 1987 to 2011 952 pts with aNSGCT received 1-st line ChT. 584 pts matched the inclusion criteria. Unfavorable TTN had 24 (11%), 61 (41%) and 122 (84%) of pts with good, intermediate and poor IGCCCG risk, respectively. More than standard number of cycles received 199 pts. Prolongation of ChT did not result in significant improvement of OS in any IGCCCG prognostic groups irrespectively of TTN (Table).

<table>
<thead>
<tr>
<th>IGCCCG risk group</th>
<th>TTN/# of cycles</th>
<th>N pts</th>
<th>5-y OS, %</th>
<th>p (HR, 95%CI)</th>
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<tr>
<td>Good</td>
<td>favorable/standard</td>
<td>176</td>
<td>92%</td>
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<td></td>
<td>favorable/&gt;standard</td>
<td>42</td>
<td>98%</td>
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<td></td>
<td>unfavorable/standard</td>
<td>15</td>
<td>93%</td>
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<td></td>
<td>unfavorable/&gt;standard</td>
<td>9</td>
<td>78%</td>
<td>(HR 1,48, 0,24-10.48)</td>
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<tr>
<td>Intermediate</td>
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<td>127</td>
<td>88%</td>
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<td>20</td>
<td>80%</td>
<td>(HR 2,1, 0,73-9,38)</td>
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<td></td>
<td>unfavorable/standard</td>
<td>32</td>
<td>81%</td>
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<td>86%</td>
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<td>unfavorable/standard</td>
<td>23</td>
<td>65%</td>
<td>0,55</td>
</tr>
</tbody>
</table>
Background
NLR is a robust prognostic factor in many solid tumors. Limited data exist about its role in patients with metastatic germ cell tumors (GCTs).

Methods
We utilized a single institution database of patients diagnosed with metastatic GCTs between January 1990 and December 2013 who were treated with chemotherapy at Princess Margaret Cancer Centre. The peripheral blood count prior to first line chemotherapy was used to calculate the derived NLR (absolute neutrophil count divided by the total white blood cell count minus the absolute neutrophil count). Predictive accuracy was assessed as the association between NLR and overall survival and was evaluated using a Cox proportional hazard model adjusted for the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification. Discriminatory accuracy was evaluated by determining the area under the receiver operating characteristic curve (AUROC) for survival at 5 years. The optimal cut-off for NLR selection was chosen based on a highest AUROC.

Results
In total, 475 patients were identified of which NLR data were available from 354 (75%) patients. Among these, 63% were good risk, 23% intermediate risk and 15% poor risk. The 5-year survival for good, intermediate and poor risk groups was 96.3%, 92.4% and 62.9%, while 10-year survival was 94.8%, 92.4% and 62.9%, respectively. Over the whole cohort, a NLR cut-off of 2.5 provided the best discriminatory accuracy with an AUROC of 0.70 (95% CI 0.59-0.75, p < 0.001). In a univariable analysis, NLR >2.5 was associated with a hazard ratio (HR) of 3.91 (95% CI 2.01-7.60, p < 0.001) which persisted after adjustment for IGCCCG risk group (HR 2.33, 95% CI 1.14-4.76, p = 0.02). Among patients with IGCCCG high risk, 5-year survival was 87.5% if NLR ≤ 2.5, whilst if NLR > 2.5, 5-year survival was only 51.3%.

Conclusions
A high NLR is associated with an adverse survival in patients with metastatic GCTs.
undergoing first line chemotherapy and provides moderate discriminatory accuracy in this setting. The utility of NLR appears particularly marked in patients with IGCCCG high risk disease.

**Legal entity responsible for the study**
Senior authors, Dr. Jeremy Lewin and Dr. Eitan Amir

**Funding**
None

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

**916P - Biological assessment of viable germ cell tumor (VT) in patients (pts) with seminoma (S) and non-seminoma (S) using miR371**

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**Background**
The pathological constitution of residual nodes after chemotherapy or of the borderline enlarged retroperitoneal (RP) lymph nodes in clinical stage I (CSI) germ cell tumor (GCT) pts on surveillance is challenging, especially in tumor markers (TM) negative pts. Currently, accurate assessment requires pathological confirmation with RPLND or clinical follow-up to establish a pattern of growth. A plasma-based approach to identify patients with VT would be uniquely valuable.

**Methods**
Formalin-fixed paraffin embedded (FFPE) and plasma from GCTs patients were used for miRNAs extraction. Non-cancer FFPE testicular tissue and plasma from healthy volunteers were used as negative controls. miR371 expression was detected by RT-PCR and relative expression calculated by the 2-ΔΔCt method. miR-93-5p was used as positive internal control. Results were analyzed for associations with clinicopathologic features using Fisher’s exact test.

**Results**
miR371 was over-expressed in all the primary testicular (n = 4) and mediastinal (n = 3) samples while it was undetectable in the atrophic testis (n = 1) and mediastinal or gonadal teratoma (n = 2), confirming the applicability of the technique to the FFPE samples. 21 metastatic samples were analyzed: 2 lung, 1 brain, 17 lymph nodes and 1 IVC tumor thrombus. The samples were collected prior to (n = 2) or after (n = 12) chemotherapy, while 7 pts were treated only with surgery. miR371 was undetectable in any samples (0/9) with no VT on pathological examination and over-expressed in 11/12 (91.6%) of those with viable GCT (OR 145.7; p < 0.0001). 90% of pts with positive miR-371 had negative TM (100% of S and 75% of NS) while no pts with negative miR-371 had positive TM. Plasma miR-371 also showed high correlation with VT (Table).

**Table:**

<table>
<thead>
<tr>
<th>Pts</th>
<th>Initial stage</th>
<th>Stage at the suspicious relapse</th>
<th>Histology</th>
<th>miR71 Evidence of VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>IIA</td>
<td>S</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(RPLND)</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>IIA</td>
<td>S</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(negative PET scan)</td>
</tr>
</tbody>
</table>
Conclusions
Elevated plasma levels of miR-371 correlate with the presence of active germ cell malignancy. These encouraging findings suggest that plasma miR371 levels may lead to biological rather than radiographic assessment of the presence of active GCT in patients with S and NS.

Legal entity responsible for the study
Lucia Nappi

Funding
None

Disclosure
All authors have declared no conflicts of interest.

917P - A single centre retrospective review of testosterone deficiency in germ cell cancer patients

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Background
Testosterone deficiency syndrome (TDS) is frequently described in men treated for germ cell cancer with rates quoted between 11 and 38% (Huddart et al 2005). Observational studies show that TDS reduces quality of life and carries cardiovascular, metabolic and bone health risks. At our institute we observed that men with symptoms of TDS and 'low normal' testosterone (T) (8.6 – 12 nmol/L) were not reliably recognised.

Methods
We collected retrospective data from all germ cell cancer referrals to the Bristol Cancer Institute from 2011 – 2016. We documented age, treatment, at least one random T level within a year of diagnosis (grouped into < 8, 8 – 12 and > 12 nmol/L), details of symptoms and treatment of TDS.

Results
Data was collected on 462 patients (36 excluded with non germ cell diagnoses and 26 excluded due to T never being measured). Median age was 36 years (range 17 – 89) with 85% of patients aged under 50. 58% of men had seminoma, 32% non-seminoma and 10% combined germ cell cancer. 41% of all patients had a T level < 12 nmol/L at first measurement (32% of 20 – 29 year olds, 42% of 30 – 49 and 58% of 50 – 59 year olds) and 16% had T < 8 nmol/L. T therapy was prescribed in 19% of patients. Men receiving adjuvant carboplatin had the highest rate of T therapy (23%) compared with patients on surveillance (18%) and BEP or EP chemotherapy (14%).

Conclusions
In this retrospective series 41% of patients had at least one total T value <12 nmol/L. 19% received replacement. A TDS diagnosis should not be based on a single measurement but regardless of age, once T falls to < 15 nmol/L, severity of TDS sequelae correlate with

3 I IIA S – – (regressing CT scan)
4 I IIA NS + + (progressing CT scan)
further decline (Morgentaler et al 2016). There is a range of what is regarded as normal T and it declines naturally with age. Recognition and management of late effects is important in men with curable cancer and diagnosis must be individualised; addressing symptoms alongside biochemical parameters. This is reflected by germ cell cancer social media websites where men frequently describe serum T in the defined normal range with symptoms of TDS. Further prospective multi-centre studies could better define the prevalence of TDS in these patients and be used to inform a standard diagnostic approach.

Legal entity responsible for the study
Jeremy Braybrooke

Funding
None

Disclosure
All authors have declared no conflicts of interest.

918TiP - Pembrolizumab and nanoparticle albumin bound paclitaxel (nab-paclitaxel) for metastatic urothelial carcinoma (UC) after chemotherapy failure: the open-label, single-arm, phase 2 PEANUT study

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Background
Pembrolizumab (pembro) is a new standard of care in chemotherapy (CT) pre-treated UC patients (pts) and nab-paclitaxel (nPtx) has shown one of the highest activities among CT options in UC. Their combination may overcome resistance to immunotherapy (IT) and result in longer delay in the time to disease progression (PD). We will explore dynamic biomarkers of response to CT+IT.

Trial design
In an open-label, single-arm, single-center, phase 2 trial, pts receive pembro 200 mg intravenously (IV) on D1 and nPtx at the dose of 125 mg/m² IV on D1 and D8. Cycles are repeated every 3 weeks until PD or onset of unacceptable toxicity. Key inclusion criteria are: predominant UC, failure of ≤2 platinum-based CT for metastatic disease (2nd- to 3rd line only). Neoadjuvant/adjuvant CT is counted if relapse occurred ≤6 months of the last CT cycle. Response is evaluated by RECIST criteria v.1.1 every 2 cycles. PD-L1 expression will be assessed at the study conclusion on both immune cells (IC) and tumor cells at a centralized laboratory (Qualtek, Goleta, CA, USA). The primary endpoint of the study is the progression-free survival (PFS). The target is to detect an improvement in the median PFS from ≤3.0 months (H0) to ≥ 5.0 months (H1). To achieve 90% power with a one-sided non-parametric test at the 10% significance level, we estimated that 64 pts must be accrued over 18 months, with follow-up duration of 12 months. PFS will be also analyzed according to the PD-L1 expression. Should the above investigation suggest that the treatment benefit is stronger in PD-L1+ pts, there is the option to expand this cohort up to a maximum of 50 pts. As such, we estimate 85.1% power to detect the target improvement in PFS. The decision of cohort expansion will rely on predictive power (PP) calculation: a PP ≥ 30% will be regarded as promising. Translational analyses will include multiparametric flow cytometry of blood samples, gene expression (RNA-seq, Illumina
HiSeq) and mutation profiling of tumor samples (Ion Torrent Personal Genome Machine). These profiles will be matched with response to treatment and PFS/overall survival (EudraCT number 2017-000579-10).

**Clinical trial identification**
EudraCT number 2017-000579-10

**Legal entity responsible for the study**
Fondazione IRCCS Istituto Nazionale dei Tumori

**Funding**
Merck

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

919TiP - Pembrolizumab ± chemotherapy versus chemotherapy in advanced urothelial cancer: Phase 3 KEYNOTE-361 trial

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**Background**
Inhibitors of programmed death 1 (PD-1) and its ligand PD-L1 are effective for treatment of recurrent, advanced urothelial cancer. Data from KEYNOTE-052 showed first-line pembrolizumab (anti–PD-1) had antitumor activity with an acceptable safety profile in cisplatin-ineligible patients (pts) with advanced urothelial cancer. This suggests pembrolizumab may be effective as first-line treatment, a setting in which only 50% of pts can receive the current standard-of-care, cisplatin-based chemotherapy. A randomized, open-label, phase 3 study in pts with advanced urothelial carcinoma is assessing first-line pembrolizumab ± chemotherapy versus chemotherapy (KEYNOTE-361; NCT02853305).

**Trial design**
Approximately 990 pts with histologically or cytologically confirmed unresectable/metastatic urothelial carcinoma will be randomly assigned 1:1:1 to pembrolizumab 200 mg every 3 weeks (Q3W), pembrolizumab + chemotherapy (investigator’s choice of cisplatin [70 mg/m² Q3W] plus gemcitabine [1000 mg/m² on days 1 and 8 Q3W] OR carboplatin [AUC 5 Q3W] plus gemcitabine if cisplatin ineligible), or chemotherapy alone. Pts must have measurable disease per investigator review (RECIST v1.1), an ECOG PS 0–2, received no prior systemic chemotherapy for advanced urothelial cancer, and provided a tumor biopsy. Treatment allocation will be stratified by chemotherapy (cisplatin or carboplatin) and PD-L1 expression (+ or −). Patients will be treated for 35 cycles of pembrolizumab (pembrolizumab arms only), or until progressive disease or unacceptable adverse events. The primary end points are progression-free survival (RECIST v1.1 per blinded independent central review) and overall survival, assessed in all patients and PD-L1+ patients. Secondary end points are objective response rate and safety. Efficacy will be compared for pembrolizumab versus...
chemotherapy and pembrolizumab + chemotherapy versus chemotherapy. Patient accrual is ongoing; 1 interim efficacy analysis is planned.

Clinical trial identification
NCT02853305; July 29, 2016

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

Funding
Merck & Co., Inc.

Disclosure
T. Powles: Received research funding from Merck, AstraZeneca and Roche; honoraria and travel expense reimbursement from Pfizer, Merck, AstraZeneca, Roche, and Novartis. J.E. Gschwend: Served as advisor for and received honoraria and reimbursements for travel expenses from Bayer, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, and Roche. Y. Loriot: Served as advisory board member for Astellas, Janssen, Roche, MSD, AstraZeneca; received research funding and honoraria from Sanofi and received reimbursement for travel expenses from Roche, MSD, Janssen, and AstraZeneca. J. Bellmunt: Received honoraria from Merck, Genentech, Pfizer, and AstraZeneca. C. Vulsteke: Served as consultant/advisor to Novartis, Leo Pharma, and Roche and received reimbursement for travel expenses from Novartis, Pfizer, and Roche. M. Abdelsalam: Have been an advisory board member for Pfizer, Merck, Novartis, served on speakers' bureaus for Pfizer and Roche, received honoraria from Pfizer, Merck, Roche, Novartis, AstraZeneca, and been reimbursed for travel expenses by Amgen, Roche, AstraZeneca. M. Fleming: Served as advisory board member and as speakers' bureau member for Genentech. M. Markus: Served as consultant/advisor for Biotheranostics. D. Feng: Employed by and own stock in Merck & Co., Inc. C. Poehelein: Employed by Merck & Co., Inc. A. Alva: Received honoraria from and served as consultant/advisor to Eisai and have received research funding from BIND Biosciences, Bristol-Myers Squibb, Genentech, Novartis, and Oncogenex. All other authors have declared no conflicts of interest.

920TiP - Afatinib in patients with advanced or metastatic urothelial carcinoma (UC) with genetic alterations in ErbB receptors 1–3 who failed on platinum-based chemotherapy: The Phase II LUX-Bladder 1 trial

A. Font (Barcelona, Spain) F. X. Real (Madrid, Spain) J. Puente (Madrid, Spain) F. Vazquez Mazon (Elche, Spain) N. Sala (Girona, Spain) J. A. Virızuela (Seville, Spain) A. Rodríguez-Vida (Barcelona, Spain) E. Grande Pulido (Madrid, Spain) D. Castellano (Madrid, Spain) M. A. Climent (Valencia, Spain) E. Gallardo (Barcelona, Spain) A. González del Alba (Palma de Mallorca, Spain) P. L. Fernandez (Barcelona, Spain) P. Jares (Barcelona, Spain) I. Aldecoa (Barcelona, Spain) N. Gibson (Biberach, Germany) J. Serra (Barcelona, Spain) E. Imedio (Bracknell, United Kingdom) E. Ehrnrooth (Copenhagen, Denmark) B. Mellado (Barcelona, Spain)

Background
First-line treatment of patients (pts) with advanced or metastatic UC consists of platinum-based chemotherapy (CT), and currently, there is no well-established therapy following CT failure. Recently, checkpoint inhibitors have shown clinical benefit in this setting, and are likely to become a future standard of care. However, to date, no other targeted therapies have shown significant clinical activity. Given that 20% of UCs harbour ERBB receptor alterations or abnormalities, the blockade of the ERBB pathway may be an effective therapeutic strategy. Indeed, afatinib, an irreversible ERBB family blocker,
demonstrated activity in a Phase II trial in a subgroup of pts with UC harbouring ERBB2/ERBB3 aberrations. These data provide rationale for the current Phase II trial assessing afatinib in pts with UC, molecularly selected for ERBB receptor alterations (LUX-Bladder 1; NCT02780687).

**Trial design**

The Phase II, single-arm LUX-Bladder 1 trial evaluates the efficacy and safety of afatinib in pts with UC and ERBB2/ERBB3 mutations or ERBB2 amplification (Cohort A), or EGFR amplification (Cohort B). Eligible pts are ≥18 years of age, with histologically confirmed advanced/metastatic UC of the urinary tract not amenable to surgery and progression during or after platinum-based CT (previous immunotherapy allowed), ECOG PS 0–1, with archival tissue samples available for pre-screening biomarker analysis. Pts will receive oral afatinib 40 mg/day until disease progression or discontinuation for other reasons. Cohort A will enrol in two stages, with Stage (S) 2 enrolment depending on afatinib anti-tumour activity in S1. The primary endpoint and key secondary endpoint in Cohort A are PFS rate at 6 months and ORR; other secondary endpoints include PFS, OS, disease control rate, duration of response and tumour shrinkage. These endpoints will also be explored in Cohort B. Safety and biomarkers will be assessed in both cohorts. The trial commenced in June 2016. Recruitment is ongoing in Spain and planned in two additional European countries; planned enrolment: Cohort A, 70 pts (S1, n=25; S2, n=45); Cohort B, 10 pts.

**Clinical trial identification**

NCT02780687; 1200.261

**Legal entity responsible for the study**

Boehringer Ingelheim

**Funding**

Boehringer Ingelheim

**Disclosure**


921TiP - A Phase III, randomized, double-blind, multicenter study of adjuvant nivolumab vs placebo in patients (pts) with high-risk invasive urothelial carcinoma
Background
Standard of care for muscle-invasive bladder cancer (predominant form of UC) is cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy + pelvic node dissection or cystectomy + pelvic node dissection alone if cisplatin-ineligible. Some pts undergo surgical resection followed by adjuvant cisplatin-based chemotherapy. Many pts are not candidates for adjuvant chemotherapy or are not treated due to lack of proven survival benefit. UC of the ureter or renal pelvis is typically managed with nephroureterectomy. Despite surgery ± chemotherapy, pts with invasive UC are at high risk of recurrence and death. Based on the efficacy and safety of the programmed death-1 (PD-1) inhibitor nivolumab for metastatic or unresectable UC progressing despite chemotherapy (CheckMate 032 and 275), we are conducting an international phase III study of adjuvant nivolumab vs placebo in pts with invasive UC (originating in bladder, ureter, or renal pelvis) following resection (NCT02632409).

Trial design
Pts must have had radical surgical resection ± cisplatin-based neoadjuvant chemotherapy within the past 120 days and be disease-free (by imaging) ≤4 weeks before randomization. Pts who did not receive cisplatin-based neoadjuvant chemotherapy must be ineligible for or refuse adjuvant cisplatin. Tumor tissue must be provided for biomarker analysis. Pts are ineligible if they had partial cystectomy or partial nephrectomy, or secondary treatment after surgical removal of UC (eg, cisplatin-based adjuvant chemotherapy), prior malignancy within 3 years except those treated with curative intent and in remission, or any condition requiring systemic treatment with immunosuppressants (eg, corticosteroids) within 2 weeks of treatment. Recruitment began in February 2016; target enrollment is 640 pts. Co-primary endpoints: Disease-free survival (defined as the time between date of randomization and date of first recurrence or death) in pts with tumors expressing ≥1% PD-ligand 1 and in all randomized pts. Secondary endpoints: Non-urothelial tract recurrence-free survival, disease-specific survival, overall survival.

Clinical trial identification
NCT02632409

Legal entity responsible for the study
Bristol-Myers Squibb

Funding
Bristol-Myers Squibb

Disclosure
D. Bajorin: Reports grants from Bristol-Myers Squibb, during the conduct of the study; other from Bristol-Myers Squibb, outside the submitted work. M.D. Galsky: Consultant for Astellas, AstraZeneca, Genentech, Merck, Novartis and hold stock options for Dual Therapeutics. Y. Tomita: Received honoraria from Novartis and Pfizer, have been a consultant for Novartis and Ono, and have received research funding for Astellas,
Background
Effective adjuvant therapies for patients (pts) with RCC at risk of recurrence after nephrectomy are lacking. Programmed death ligand 1 (PD-L1) and 2 (PD-L2) expression predicts poor prognosis in RCC. Programmed death 1 (PD-1) inhibitors have demonstrated activity in metastatic RCC, and PD-1 may represent a novel therapeutic target in the adjuvant setting. Pembrolizumab is a PD-1 inhibitor that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This randomized, double-blind, placebo-controlled phase 3 trial will evaluate the efficacy and tolerability of pembrolizumab as adjuvant therapy in pts with RCC who have T2 grade 4, T3, T4, N (+), or stage M1 with no evidence of disease (M1 NED) following nephrectomy and/or metastasectomy (NCT03142334).

Trial design
Key inclusion criteria are: age ≥18 years; histologically confirmed RCC with a clear cell component; intermediate-high or high risk of recurrence, or M1 NED; no prior systemic therapy for advanced RCC; disease-free following complete or partial nephrectomy (and metastasectomy in M1 NED pts) with negative surgical margins; and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Approximately 950 pts will be randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg every 3 weeks by intravenous infusion, or placebo, continued for up to 17 cycles (1 year) or until disease recurrence or treatment discontinuation. Randomization will be stratified by metastasis stage (M0 vs M1 NED); within the M0 group, randomization will be further stratified by ECOG performance status (0 vs 1) and region (US vs rest of world). The primary end point is investigator-assessed disease-free survival (DFS). Radiographic imaging will be performed every 12 weeks. Secondary objectives include overall survival (OS), safety, disease recurrence-specific survival, DFS and OS according to PD-L1 expression status, pharmacokinetics, antidrug antibodies, and patient-reported outcomes. Molecular biomarkers that may be associated with response, safety, pharmacodynamic activity, or mechanism of action will be evaluated as exploratory objectives.

Clinical trial identification
NCT03142334; May 3, 2017

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

Funding
Merck & Co., Inc.

Disclosure
T.K. Choueiri: Ad Board and/or funding: AstraZeneca Bayer Bristol-Myers Squib Cerulean
Background
Nine targeted agents have been approved for metastatic clear cell renal cell carcinoma (mccRCC) in the last 10 years, including VEGFR-tyrosine kinase inhibitors (TKI), mTOR inhibitors and checkpoint inhibitor (CI). Combination of CI nivolumab and ipilimumab is currently compared to sunitinib in a randomised phase III trial in first-line setting. While treatment opportunities of mccRCC are moving rapidly biomarker to select patients to receive TKI or CI are still lacking. Based on transcriptomic analysis, we have defined four distinct molecular groups (ccrcc1 to 4) in patients with mccRCC treated with sunitinib. These groups were mainly characterized by distinct responses to sunitinib as well as distinct immune cell compositions and inhibitory receptor expressions.

Trial design
The proof of concept study BIONIKK is a French multicentric randomised phase II designed to assess the use of molecular groups to select treatment in first-line mccRCC. Molecular group is determined on frozen tumor sample within 2 weeks. Treatment is then allocated between TKI and nivolumab plus ipilimumab for ccrcc2 and 3 and between nivolumab alone and nivolumab plus ipilimumab for ccrcc1 and 4. Main objective is to assess efficacy of each treatment arm according to molecular group. Primary endpoint is overall response rate using RECIST 1.1. Main secondary endpoints include PFS, OS and their relationship to exploratory biomarkers. These latter include protein and gene expression analyses of tumor microenvironment (TME) from formalin-fixed and paraffin-embedded tumor samples. In addition, phenotype and functional status of peripheral blood lymphocytes will be analysed with flow cytometry before and during treatment. A Bayesian model was used to avoid independent analyses of the effect of drugs using hierarchical borrowing. Bionikk is not designed to be conclusive on the superiority of any treatment but will generate important hypotheses on putative biomarkers to select patients to receive TKI, CI alone or in combination. From this point of view, Bionikk is the first biomarker-driven trial in first line metastatic ccRCC.

Clinical trial identification
NCT02960906 First received: August 18, 2016

Legal entity responsible for the study
Association Pour La Recherche des Thérapeutiques Innovantes en Cancérologie

Funding
924TiP - Savolitinib versus sunitinib in patients with MET-driven, unresectable and locally advanced or metastatic papillary renal cell carcinoma: SAVOIR, a randomised, phase III trial

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Background

Papillary renal cell carcinoma (PRCC) is the most common of the non-clear cell renal cell carcinomas (RCCs), accounting for 10–15% of RCCs. However, there are no therapies approved specifically for patients with PRCC, who currently receive treatments approved for clear cell RCC, such as sunitinib. PRCC is often MET-driven (defined as MET kinase domain mutations, MET amplification, chromosome 7 gain and/or HGF amplification). Savolitinib (AZD6094, HMPL-504, volitinib) is a highly selective MET tyrosine kinase inhibitor which demonstrated anti-tumour activity for patients with MET-driven PRCC in a phase II trial.

Trial design

SAVOIR (NCT03091192) is a global, phase III, open-label, randomised, controlled trial evaluating the efficacy and safety of savolitinib, compared with sunitinib, in patients with MET-driven, unresectable, locally advanced or metastatic PRCC. Approximately 180 patients will be randomised at 50–75 sites across 5–10 countries. Eligible patients (aged ≥18 with MET-driven PRCC confirmed by a novel, sponsor designated, validated, targeted next-generation sequencing assay; a Karnofsky performance status ≥80; and measurable disease at baseline) will be randomised in a 1:1 ratio to receive either continuous savolitinib 600 mg (400 mg if < 50 kg) orally, once daily (QD), or sunitinib 50 mg orally QD (4 weeks on/2 weeks off). The primary objective is to determine the efficacy of savolitinib compared with sunitinib in terms of progression free survival (PFS). Tumour assessments (RECIST 1.1, confirmed by blinded independent central review [BICR]) will be performed at screening and the end of every 6-week cycle until 12 months, and every 12 weeks thereafter until disease progression. Secondary endpoints include overall survival, objective response rate, duration of response, best percentage change in tumour size, disease control rate at 6 and 12 months, safety and tolerability, and biomarkers. The impact of savolitinib compared with sunitinib on disease symptoms and quality of life, along with the pharmacokinetics of savolitinib will also be assessed.

Clinical trial identification

Clinical trial registration number: NCT03091192

Legal entity responsible for the study

AstraZeneca

Funding
AstraZeneca

Disclosure

925TiP - A phase 2 study of investigational TORC1/2 inhibitor TAK-228 and TAK-228 plus investigational PI3Kα-selective inhibitor TAK-117 vs everolimus in adults with advanced or metastatic clear-cell renal cell carcinoma (ccRCC) that has progressed on VEGF-targeted therapy

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Background
VEGF-targeted therapies are the cornerstone of first and subsequent lines of therapy in ccRCC; however, resistance develops almost invariably. Another proven therapeutic intervention in ccRCC is treatment with the allosteric mTOR inhibitor everolimus, which only partially inhibits TORC1 and thus results in increased phosphorylation of Akt and paradoxical hyperactive signalling. TAK-228, a highly selective ATP-competitive TORC1 and TORC2 inhibitor, has shown promising antitumor activity and acceptable safety in ccRCC. In a pooled analysis of 2 prior studies of 41 patients (pts) with ccRCC, TAK-228 treatment resulted in 1 CR, 5 PR and 21 pts with SD; 13 pts who achieved ≥SD had prior treatment with a rapalog. The median duration of overall response was 250 d (range, 55–1614). The most common AEs were fatigue, nausea and hyperglycemia. Also, combination of TAK-228 with TAK-117, a selective inhibitor of PI3Kα, has shown more complete and prolonged inhibition of TORC1 and TORC2. This phase 2, open-label, randomized study will evaluate the efficacy and safety of TAK-228 and TAK-228+TAK-117 vs everolimus in pts with advanced or metastatic ccRCC that have progressed on or after VEGF-targeted therapy (NCT02724020).

Trial design
189 pts will be randomized 1:1:1 to TAK-228 30 mg once-weekly on d1, 8, 15, 22 with a light meal; TAK-228 4 mg once-daily (QD) + TAK-117 200 mg QD on d1–3, 8–10, 15–17, 22–24 on an empty stomach; or everolimus 10 mg QD, in 28-d cycles. Pts will be stratified by number of prior therapy lines and IMDC risk category. Pts with histologically confirmed advanced/metastatic ccRCC, ≥1 prior line of VEGF-targeted therapy with PD, KPS ≥70%, and adequate organ function, but no CNS metastasis or prior therapy with agents that target PI3K, AKT, or mTOR are eligible. Pts in the everolimus arm who progress may crossover. An interim futility analysis will be conducted after 30 pts in each arm have received 2 treatment cycles. Primary endpoint is PFS. Secondary endpoints are OS, TTP, ORR, CBR, safety, and QoL. As of January 24, 2017, 54 pts have been screened.
926TiP - Phase Ib/II trial of interleukin-2 (IL-2) and nivolumab in metastatic clear cell renal cell cancer (RCC)

S. Yentz (Ann Arbor, United States of America) A. Alva (Ann Arbor, United States of America)

Background

High dose Interleukin-2 (HD IL2) immunotherapy is standard therapy in suitable patients (pts) with metastatic clear cell RCC who have good performance status. HD IL-2 is unique among RCC therapies in eliciting durable complete responses (DCR) with a median duration of such responses of 12 years. However, the complete response (CR) proportion for HD IL-2 monotherapy is only 7-9%. There is an urgent need to evaluate HD IL2 combination therapies that could increase the response proportion. IL-2 promotes early steps in the lymphocyte activation cascade, increases trafficking of cytotoxic T lymphocytes to the tumor and induces Th1 differentiation of CD4 T helper cells. Nivolumab, an immune checkpoint inhibitor, blocks the interaction between PD-1 on activated T cells and its ligands that are expressed on immune cells and tumor cells. We hypothesize that the combination of HD IL2 and a PD-1 inhibitor would elicit a potent synergistic anti-cancer immune response reflected in improved response proportion and survival with acceptable toxicity in pts with metastatic clear cell RCC.

Trial design
This multi-site Ib/II trial will determine safety and efficacy of HD IL-2 in combination with nivolumab for RCC. Pts with metastatic clear cell RCC, 0-2 prior systemic therapies and candidates for HD IL2 and for nivolumab are eligible. Pts will be treated with HD IL-2 (600,000 IU/kg/dose every 8 hours for up to 14 doses) on Days 1-5 and again on Days 15-19, with nivolumab (240 mg IV every 14 days) starting on Day 8 +/- 3 wks. Pts will continue on nivolumab every 2 wks for up to 48 wks barring intolerable toxicities or consent withdrawal or progressive disease. Nivolumab may potentially be continued beyond first progression. The primary objective/endpoint of the phase 1b portion of the trial is safety of the combination/immune mediated grade 3/4 events of interest. The primary endpoint of the phase II portion of the trial is the overall response proportion (ORR) as assessed by RECIST 1.1. Secondary endpoints are safety/toxicity, overall survival and PFS at 2 years. Planned accrual is 23 evaluable subjects over 2 years. Whole blood and serum will be analyzed for circulating immune cell repertoire and baseline tumor tissue will be sequenced.

Clinical trial identification
NCT02989714

Legal entity responsible for the study
Ajjai Alva

Funding
Prometheus, University of Michigan

Disclosure
A. Alva: Advisory role for Eisai, AstraZeneca and Roche. Received research funding: Genentech, Novartis, Bristol-Myers Squib, BIND Bioscience, Acerta Pharma, Merck, Prometheus Laboratories, Covance, Mirati Therapeutics, United Biosources Corporation, ARIAD, Pfizer & Bayer. All other authors have declared no conflicts of interest.

927TiP - Cabozantinib in patients with advanced penile squamous cell carcinoma (PSCC): the open-label, single-arm, single-center, phase 2, CaboPen trial
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D. Raggi (Milan, Italy) G. Calareso (Milano, Italy) N. Nicolai (Milano, Italy) M. Catanzaro (Milano, Italy)
T. Torelli (Milano, Italy) F. Perrone (Milano, Italy) R. Salvioni (Milano, Italy)

Background
Chemotherapy (ChT) exerts moderate activity in advanced and metastatic PSCC, and efficacy outcomes are poor. Neoadjuvant treatment is a reliable setting to address activity of new drug approach (Necchi A et al. ASCO-GU 2017). The vascular endothelial growth factor (VEGF) receptor is overexpressed in approximately 50% of PSCC. Cabozantinib (Cabo) is a multiple receptor tyrosine kinase inhibitor (TKI) primarily targeting MET and VEGFR2.

Trial design
In an open-label, single-arm, single-center, phase 2 trial, patients (pts) with clinical stage N2-3 (TNM 2009, locally-advanced [LA]) or M1 PSCC will receive Cabo, orally, at a dose of 60 mg/day continuously until surgery, evidence of disease progression or onset of unacceptable toxicity. Prior ChT administration is not allowed. Response will be evaluated by RECIST criteria v.1.1, matched with 18FDG-PET/CT assessment, every 2 months. At each time of disease restaging, responding pts with LA PSCC who will be considered eligible to radical lymphadenectomy will undergo surgery. After surgery, pts will be
managed according to standard guidelines. The primary endpoint (EP) is the objective response-rate (ORR=CR+PR according to RECIST v1.1). Secondary EP are safety, progression-free survival (PFS) and overall survival (OS), and pathologic response. The study is planned according to Simon's Optimal two-stage design, with H1=20% and H0=5%, and type I and type II error rates set at the 10% level. In stage 1, 12 evaluable pts will be accrued. If 1 pt at least will be responding, enrolment will be extended to the 2nd stage for further 25 pts. If, out of the total of 37 pts, 4 at least will be responding, treatment will be declared worthy for further investigations. Stopping rules based on the Bayesian posterior probability (PP) to demonstrate that the ORR exceeded 20% are set. Translational analyses on pre- and post-Cabo tumor samples and matched blood samples will include in-situ hybridization for HPV and next generation sequencing (Ion Torrent Personal Genome Machine). These profiles will be associated with response to treatment and PFS/OS (EudraCT number 2017-001963-19).

Clinical trial identification
EudraCT number 2017-001963-19
Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale dei Tumori
Funding
Ipsen
Disclosure
All authors have declared no conflicts of interest.

HEAD AND NECK CANCER, EXCLUDING THYROID

J. Machiels (Brussels, Belgium) M. Merlano (Cuneo, Italy)

1055P - Nivolumab vs investigator’s choice (IC) in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): treatment effect on clinical outcomes by best overall response in checkmate 141

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G. Blumenschein Jr (Houston, United States of America) K. J. Harrington (London, United Kingdom)
J. Guigay (Nice, France) S. Kasper (Essen, Germany) N. F. Saba (Atlanta, United States of America)
R. Haddad (Boston, United States of America) N. Kiyota (Kobe, Japan) M. Monga (Princeton, United States of America)
M. Lynch (Princeton, United States of America) L. Li (Princeton, United States of America)
M. L. Gillison (Houston, United States of America) J. Fayette (Lyon, France)

Background
In CheckMate 141, nivolumab monotherapy significantly prolonged overall survival (OS) vs IC (median [95% CI]: 7.5 [5.5, 9.1] mo vs 5.1 [4.0, 6.0] mo) and doubled response rate (13.3% vs 5.8%) in patients (pts) with R/M SCCHN. Here, we describe clinical outcomes by best overall response for the nivolumab and IC arms.

Methods
CheckMate 141 (NCT02105636) was a randomized, open-label, phase 3 trial in which pts (N = 361) with R/M SCCHN who progressed on or within 6 mo of platinum-based therapy were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks (n = 240) or IC of methotrexate, docetaxel, or cetuximab (n = 121). We analyzed the primary endpoint of OS and additional endpoint of safety by best overall response (complete or partial response [CR/PR], stable
disease [SD], or progressive disease [PD]), assessed by investigators per RECIST 1.1 every 6 weeks beginning at week 9.

**Results**

The minimum follow-up was 11.4 mo. Baseline demographics were similar across response groups and treatment arms. Median duration of therapy for nivolumab-treated pts with CR/PR, SD, and PD was 12.5 mo, 4.2 mo, and 1.6 mo, respectively. Estimates of median OS, 12-mo, and 18-mo survival rates favored nivolumab vs IC in the CR/PR and SD response groups (Table). The incidence of grade 3–4 treatment-related adverse events was lower for nivolumab vs IC within each of the response groups (CR/PR, SD, and PD).

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>CR/PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab IC</td>
<td>IC</td>
<td>Nivolumab IC</td>
</tr>
<tr>
<td></td>
<td>(n = 32)</td>
<td>(n = 7)</td>
<td>(n = 55)</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>NR (NR, NR)</td>
<td>13.6 (8.9, NR)</td>
<td>10.4 (8.7, 15.2)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.08 (0.01, 0.47)</td>
<td>0.53 (0.33, 0.85)</td>
<td>0.74 (0.51, 1.09)</td>
</tr>
<tr>
<td>12-mo OS rate, % (95% CI)</td>
<td>96.8 (79.2, 99.5)</td>
<td>57.1 (17.2, 83.7)</td>
<td>46.1 (32.4, 58.7)</td>
</tr>
<tr>
<td>18-mo OS rate, % (95% CI)</td>
<td>86.1 (67.0, 94.6)</td>
<td>38.1 (6.1, 71.6)</td>
<td>32.6 (20.0, 45.8)</td>
</tr>
</tbody>
</table>

NR = not reached

**Conclusions**

Pts with CR/PR and SD had improved median OS and survival rates with nivolumab relative to single-agent standard therapy. Nivolumab’s safety profile was favorable vs IC, including for pts with CR/PR whose median duration of therapy was greater than a year.

**Clinical trial identification**

NCT02105636

**Legal entity responsible for the study**

Bristol-Myers Squibb

**Funding**

Bristol-Myers Squibb

**Disclosure**

L. Licitra: Reports consultant/advisory support from Eisai, Bristol-Myers Squibb, MSD, Merck-Serono, Boehringer-Ingelheim, Novartis, AstraZeneca, Bayer Roche and honoraria/consultation fees from Eisai, Bristol-Myers Squibb, MSD, Merck Serono, Debiopharm, Sobi, AstraZeneca. R.L. Ferris: Reports other from Amgen, other from AstraZeneca/MedImmune, other from Bristol-Myers Squibb, other from EMD Serono, other from Lilly, other from Merck, other from Pfizer, other from VentiRx Pharmaceuticals, during the conduct of the study. G. Blumenschein Jr: Reports grants from Merck,
1056P - Estimated costs of treatment-related adverse events (TRAEs) for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) in the checkmate 141 trial

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Background
Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor antibody, is approved in the United States and the European Union for treatment of SCCHN progressing on or after platinum-based chemotherapy. In the phase 3 CheckMate 141 trial, nivolumab significantly improved overall survival vs investigator’s choice (IC) of standard, single-agent systemic therapy (methotrexate, docetaxel, or cetuximab) in patients with R/M SCCHN. This study assessed the estimated costs of managing grade 3–4 TRAEs requiring treatment in CheckMate 141.

Methods
The frequency, grade, and attribution of TRAEs for which treatment was received were extracted from CheckMate 141 patient-level safety data. Grade 3–4 TRAE treatment costs were estimated based on principle diagnosis codes of the International Classification of Disease, 9th Revision in the Healthcare Cost and Utilization Project National Inpatient Sample data (2012–2014), adjusted to reflect 2013-equivalent US costs.

Results
Among the 347 patients in the safety population, 236 received nivolumab and 111 received IC. A total of 88 grade 3–4 TRAEs requiring treatment were observed: 28 among
patients receiving nivolumab and 60 among patients receiving IC. The cost of managing TRAEs per treated patient was 4.5 times higher in the IC arm ($4913) than in the nivolumab arm ($1072). Patients receiving docetaxel and methotrexate had the highest incidence of TRAEs and estimated TRAE management costs (Table).

<table>
<thead>
<tr>
<th>Nivolumab IC (n = 236)</th>
<th>IC combined (n = 111)</th>
<th>Cetuximab (n = 13)</th>
<th>Docetaxel (n = 52)</th>
<th>Methotrexate (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of grade 3–4 TRAEs requiring treatment (%)</td>
<td>28/88 (31.8)</td>
<td>60/88 (68.2)</td>
<td>2/60 (3.3)</td>
<td>36/60 (60.0)</td>
</tr>
<tr>
<td>Total estimated cost of managing grade 3–4 TRAEs, $</td>
<td>253,067</td>
<td>545,374</td>
<td>17,855</td>
<td>333,307</td>
</tr>
<tr>
<td>Cost of managing grade 3–4 TRAEs, mean per treated patient, $</td>
<td>1072</td>
<td>4913</td>
<td>1373</td>
<td>6410</td>
</tr>
</tbody>
</table>

Conclusions
Patients with platinum-refractory R/M SCCHN treated with nivolumab had fewer grade 3–4 TRAEs, lower estimated total costs of managing TRAEs, and reduced TRAE costs per treated patient compared with standard, single-agent systemic therapy.

Clinical trial identification
NCT02105636

Legal entity responsible for the study
Bristol-Myers Squibb

Funding
Bristol-Myers Squibb

Disclosure
S. Bobiak: Former Bristol-Myers Squibb employee (at the time the submitted work was started); Spouse is current employee of Bristol-Myers Squibb. J.W. Shaw, M. Contente, B. Korytowsky: Bristol-Myers Squibb employee and shareholder. D.D. Stenehjem: Consulting fees from Bristol-Myers Squibb; Unrestricted research grant (unrelated to work regarding the content of this abstract) from Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1057P - Phase I trial of cetuximab, intensity modulated radiotherapy (IMRT), and ipilimumab in previously untreated, locally advanced head and neck squamous cell carcinoma (PULA HNSCC)

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Background
Concurrent IMRT with cetuximab (C), an EGFR-specific antibody for PULA HNSCC is suboptimal for intermediate-risk (IR) or high risk (HR) HNSCC. CTLA-4+ Tregs dampen cellular immunity and correlate negatively with clinical outcomes. Thus, we conducted a phase I study adding ipilimumab (ipi), an anti-CTLA-4Ab to standard C-IMRT in patients (pts) with intermediate or high risk PULA HNSCC.

Methods
Key eligibility: stage III–IVb PULA HNSCC [pharynx, larynx]; high-risk [HPV–] or intermediate risk [HPV+ and either: ≥ 10 pack-year tobacco and ≥ N2 disease; or T4 or N3 disease]. A phase I [3 + 3] dose escalation design was used to establish a recommended phase II dose (RP2D). Dose limiting toxicity (DLT) was defined as any grade 4 adverse event (AE) except in-field radiation dermatitis or any immune-related (ir) AE requiring ≥ 2 weeks of systemic steroids.

Results
From July 2013–May 2016, 18 pts enrolled: 5 larynx, 3 hypopharynx, 3 HPV– oropharynx, 7 HPV+ oropharynx; 14 smokers; 2 stage III, 13 stage IVa, 3 stage IVb. Two of 6 pts in cohort 1 experienced grade 3 dermatologic DLT’s: perforating folliculitis and autoimmune dermatitis. Cohort 1 expanded to N = 12 without DLT’s. irAE included: grade 1, 2, and 3 dermatitis [2, 1, and 3 cases], grade 4 colitis [1], and grade 1 hyperthyroidism [1]. Four pts recurred, 3 of whom died. Five patients remain disease-free for >2 years. Median follow up for disease-free patients was 14 months [range 5 &– 37 months]. The probability of 2-year overall survival was 71% [95% CI: 49% &– 100%]. The two-year probability of progression-free survival was 77% [95% CI: 59% &– 100%]. Immune biomarkers demonstrated modulation of suppressive regulatory T cell (Treg) subsets.

Conclusions
Ipi plus C-IMRT is tolerable and yields acceptable survival without cytotoxic chemotherapy for IR and HR patients. The RP2D for ipi plus C-IMRT is 1mg/kg weeks 5, 8, 11, and 14. Treg biomarkers are modulated by this type of immunotherapy.

Clinical trial identification
Clinical trial information: NCT01935921

Legal entity responsible for the study
University of Pittsburgh Cancer Institute

Funding
NIH 5P50CA097190-12 Head and Neck SPORE

Disclosure

1058P - Does hyper-progression exist among head and neck cancer patients treated with immunotherapy?
A. Ortega Franco (Barcelona, Spain) M. Plana (Barcelona, Spain) I. Braña (Barcelona, Spain)
Background

Immunotherapy (IM) improves survival (OS) in recurrent/metastatic squamous cell carcinoma of the head and neck (HNSCC) patients after platinum progression. Hyper-progression (HP) is a pattern of accelerated tumor growth with ECOG deterioration (ECOGdt) that has been described in patients (p) with solid tumors within the first weeks of IM.

Methods

HP is defined by twofold increase in tumor growth rate (TGR) (1). Our aim was to detect HP in a cohort of HNSCC p treated with IM in clinical trials in 2 cancer centers (ICO, VHIO). 1 S Champiat. Clin Cancer Res, 2016.

Results

From 08/2014 to Dec/2016, 69p were included in IM trials. Among them, 46p were evaluable for TGR. Baseline characteristics and IM are listed in Table. After a median follow-up of 9.4 months (m) (1-27), 36p have progressed and 24 have died. Median overall survival (mOS): 14m (8-20), percentile 75% 5m (3-7). TGR decreased in 33 p. TGR increased in 13p, presenting two-fold TGR in 2p, with 2 IM discontinuation within 2 months and 1 ECOGdt, with no differences in mOS compare to the rest (p = 0.8). We also identify 9p with progression within 2m and rapid ECOGdt, which were defined as early progressors (EP). A comparative analysis between EP and no EP was performed (Table). Within EP p, there is a lower proportion of objective response (OR), PDL-1 positivity and cisplatin sensitive (CS) tumors (p > 0.1). EP p had significantly higher proportion of tumor complications (p = 0.013) and worse mOS: 3m (0.8-5.9) vs 15m (3.9-26), HR 3.9 (1.2-10) p 0.008.

<table>
<thead>
<tr>
<th></th>
<th>All cohort n = 46</th>
<th>Progression n = 36</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>No EP n = 27</td>
<td>EP n = 9</td>
</tr>
<tr>
<td>Age</td>
<td>58</td>
<td>56</td>
<td>58</td>
</tr>
<tr>
<td>Male</td>
<td>39 (85)</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Smokers</td>
<td>42 (91)</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>PDL-1 n = 33 Positive</td>
<td>21 (45) 22 (48)</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Locoregional disease (LRD) Metastatic without LRD</td>
<td>33 (71) 13 (29)</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Previsos systemic therapy 0 1 2 ≥3</td>
<td>3 (7) 11 (24) 30</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>(65) 2 (4)</td>
<td>1 1</td>
<td>0.7 0.4</td>
<td></td>
</tr>
<tr>
<td>OR (n = 44)</td>
<td>11 (25)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>TGR increase</td>
<td>13 (28)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>CS (n = 40)</td>
<td>23 (58)</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>AntiPD-1 AntiPDL-1 AntiPDL-1 + CTLA-4</td>
<td>9 (20) 11 (24) 16</td>
<td>5 8 7 4 2 1 5</td>
<td>0.6 0.5</td>
</tr>
</tbody>
</table>
Immunomodulator (IMD) AntiPDL-1 + IMD (35) 4 (9) 2 (3) 4 1 2 0 1 0 0.1 0.5
AntiPD-1 + CT (9) 0.4 1
Tumor complications 8 (17) 3 5 0.013

Conclusions
In our cohort, we did not detect HP as previously defined. However, there is a proportion of p that has poor survival due natural HNSCC history, these p lack of benefit from IM monotherapy and other strategies should be explored.

Legal entity responsible for the study
Catalan Institute of Oncology

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1059P - PD-L1 Detection and Assay Performance in Squamous Cell Carcinoma of the Head and Neck Using PD-L1 IHC 28-8 pharmDx

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J. William (Aliso Viejo, United States of America)
C. Felten (Carpinteria, United States of America)
D. Hanks (Carpinteria, United States of America)
A. Northrup (Carpinteria, United States of America)
D. Jaiswal (Carpinteria, United States of America)
M. Jansson (Carpinteria, United States of America)
T. Phillips (Carpinteria, United States of America)
A. Segal (Carpinteria, United States of America)
I. Satnick (Carpinteria, United States of America)
H. McDonald (Carpinteria, United States of America)
H. Little (Carpinteria, United States of America)
C. Pierce (Carpinteria, United States of America)
B. Wynne (Carpinteria, United States of America)
J. Carnahan (Carpinteria, United States of America)
S. Y. Reddy (Carpinteria, United States of America)
H. Inzunza (San Diego, United States of America)
E. Oroudjev (Carpinteria, United States of America)

Background
Detecting PD-L1 protein expression by immunohistochemistry has shown to be effective in identifying patients who may benefit from treatment with PD-1 targeted immune checkpoint inhibitors. The PD-L1 IHC 28-8 pharmDx assay has been applied in formalin-fixed, paraffin-embedded (FFPE) squamous cell carcinoma of the head and neck (SCCHN) tissues for measuring PD-L1 expression and its associated treatment effect with nivolumab. Assay performance results of PD-L1 IHC 28-8 pharmDx in SCCHN, including validation in external reproducibility, are described.

Methods
Antigen retrieval was conducted on Dako PT Link and automated staining was performed with Autostainer Link 48 platform using the PD-L1 IHC 28-8 pharmDx protocol, per instructions for use. The PD-L1 staining was assessed by tumor proportion score to report the percentage of PD-L1 expression in invasive SCCHN. Assay performance was validated at the ≥ 1% expression level on commercially procured FFPE SCCHN specimens.

Results
PD-L1 expression was measured on 236 unique specimens originating from squamous cell carcinoma of the tongue, tonsil, nasopharynx, oropharynx, hypopharynx, and larynx. The assay demonstrated acceptable sensitivity and reported a large range of PD-L1
expression from 0 to 95% positive tumor cells and 0 to 3+ staining intensity. Acceptable correlation was observed between primary and metastatic specimens and between “sister” blocks from the same patient. Validation of assay precision and robustness (to target retrieval solution pH, target retrieval solution temperature, target retrieval time, and cut section thickness) demonstrated agreement estimates above 97.5% with the lower bound of two-sided 95 percent confidence intervals at 95% or higher. When tested in external sites, intra- and inter-site reproducibility, and intra- and inter-observer agreements were estimated above 94% with the lower bound of two-sided 95 percent confidence intervals at 88% or higher. Stability of PD-L1 staining in aged cut sections demonstrated interim stability at 4 months with ongoing evaluation.

Conclusions
PD-L1 IHC 28-8 pharmDx has shown to be reproducible and robust in detecting PD-L1 expression in FFPE human SCCHN specimens using the Autostainer Link 48.

Legal entity responsible for the study
Agilent Technologies, Inc.

Funding
Agilent Technologies, Inc. and Bristol Myers Squibb

Disclosure

1060P - Programmed death ligand-1 overexpression is a poor prognostic factor for Human papillomavirus-positive tonsillar squamous cell carcinoma
M. Kwon (anyang, Korea, Republic of) M. Hong (seoul, Korea, Republic of) S. Kang (Seoul, Korea, Republic of)

Background
Programmed death-ligand 1 (PD-L1) plays a key role for immune evasion, contributing to carcinogenesis and tumor progression. Tonsillar squamous cell carcinomas (TSCCs) are
the most common human papillomavirus (HPV)-associated oropharyngeal cancers and they frequently present with locally advanced diseases and cervical metastases, which are associated with poor prognoses. Recent studies have reported the close association between PD-L1 and HPV in head and neck SCCs. However, its clinical and prognostic significances in TSCCs remain controversial.

Methods
Immunohistochemical analysis of PD-L1 was performed in 79 formalin-fixed paraffin-embedded blocks of surgically resected specimens. Peptide nucleic acid-based HPV chip test was used for detection of HPV.

Results
PD-L1 expression was observed in 19 cases (24.1%), and clinicopathological features such as invasion to base of tongue, lymphatic invasion, infiltrative tumor border, younger age (<60 years), left side location, and lymph node metastasis represent significant risk factors associated with PD-L1 overexpression in TSCCs. HPV tended to be associated with PD-L1 overexpression, which showed borderline statistical significance (P = 0.066). PD-L1 expression was a strong indicator for poor overall survival but not for disease-free survival. Notably, PD-L1 overexpression had significant effects on worse overall and disease-free survivals in HPV-positive TSCCs. Multivariate analysis revealed that PD-L1 overexpression was an independent prognostic factor for overall survival (P = 0.049, hazard ratio 2.750).

Conclusions
PD-L1 overexpression may predict a poor prognosis and a high risk of recurrence in TSCC patients, especially in HPV-positive tonsil cancers, implying PD-L1 could be potent candidates for a new prognostic and predictive biomarker in tonsil cancers.

Clinical trial identification
none of clinical trial

Legal entity responsible for the study
none

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1061P - The prognostic role of PD-L1 expression in tumor and immune cells in oral cavity squamous cell carcinoma

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morphological characteristics and expression of PD-L1 in tumor and immune cells (clone BCDdx1020) by immunohistochemistry (55 samples were acceptable).

Results
The expression level in tumor cells varied from 0% to 70%: in 24 (43.64%) samples expression of PD-L1% were negative (0%), in 9 (16.36%) - from 1 to 4% (low rate), in 17 (30.91%) - from 5 to 49% (moderate rate) and in 5 (9.1%) - more than 50% (high). In immune cells expression of PD-L1 varied from 0% to 15%: in 7 (12.73%) samples - negative (0%), in 30 (54.55%) - from 1 to 4% (low), in 13 (23.64%) - from 5 to 9% (moderate) and in 5(9.10%) - >10% (high). In 5 samples with high level PD-L1 expression in tumor expression PD-L1 in immune cells was negative. Median OS of patients with PD-L1-negative' tumor was 17 mo (95% CI 8-185), with low rate (1-4%) of PD-L1 expression - 9 mo (95% CI 2-36), with moderate rate (5-49%) - 13 mo (95% CI 7,5-19) and median OS in patients with high rate (>50%) not reached for this time and mean of OS is 55 mo (σ = 14,722) (95% CI 26-84). Median OS of patients with negative PD-L1-status in immune cells was 12 mo (95% CI 4-185), with low rate (1-4%) PD-L1 in immune cells - 13 mo (95% CI 7,5-34,5), with moderate rate (5-9%) - 15 mo (95%CI 9-15) and with hight rate (>10%) - 17 mo (95%CI 3-36) with strong trend of increasing OS with rise of PD-L1 expression in immune cells.

Conclusions
PD-L1 expression in tumor and immune cells are favourable prognostic factors for oral cavity squamous cell carcinoma.

Legal entity responsible for the study
Svetlana Kutukova

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1062P - Immune profile analysis of head and neck squamous cell carcinoma before and after neoadjuvant treatment with the IRX-2 regimen

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A. Nguyen (Ann Arbor, United States of America)J. E. Egan (New York, United States of America)
M. J. Kaplan (Stanford, United States of America)

Background
IRX-2 is an injectable cancer immunotherapy composed of cytokines purified from stimulated peripheral blood mononuclear cells. In a phase 2a trial (n = 27), neoadjuvant IRX-2 significantly increased lymphocyte infiltration (LI) into resected head and neck tumors. Increased LI was associated with changes in fibrosis and necrosis in resected tumors, 65% event-free survival (EFS) at 2 years, and 65% overall survival (OS) at 5 years, better than rates for historical matched controls. Patients with LI greater than the median had improved OS compared to those below the median. This substudy was undertaken to define the mechanisms responsible for the increase in LI with neoadjuvant IRX-2.

Methods
Matched pre- and post-treatment tumor specimens from 7 phase 2a study patients were interrogated with two immune-profiling technologies, multiplex immunohistochemistry (IHC, PerkinElmer, Waltham, MA) and transcriptome analysis (NanoString Technologies, Seattle, WA).

**Results**

Multiplex IHC provided detailed visualization and quantitation of various immune cells in the tumor microenvironment (TME), supporting previous phase 2a pathology findings. Transcriptome analysis provided a global snapshot of the TME, quantitative information on immune cell subsets, and insights into possible mechanisms for changes in LI. Consistent with IRX-2 activation of multiple immune cells in the TME, mRNA expression of B cell, CD4+ T cell, CD8+ T cell, and dendritic cell functional genes was increased on average by 87%, 106%, 6%, and 130%, respectively, following treatment with IRX-2. Increases in chemokine gene expression were observed, suggesting that IRX-2-induced production of chemokines may in part drive tumor LI. Strong evidence of functional immune activation uncovered by transcriptome analysis included an increase in interferon g pathway gene expression and induction of regulatory checkpoint pathways.

**Conclusions**

Neoadjuvant IRX-2 promotes tumor LI and prolongs EFS and OS in patients with head and neck squamous cell carcinoma. Immune profile analyses provided insights into the pathways potentially responsible for IRX-2-induced increases in LI and overall immune activation.

**Legal entity responsible for the study**

IRX Therapeutics, Inc.

**Funding**

IRX Therapeutics, Inc

**Disclosure**


**1063P - Phenotyping of the immune infiltrate in oropharyngeal squamous cell carcinoma: Focus on materials and methods**

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**Background**

Stromal CD8+ lymphocytic infiltration constitutes an independent prognostic marker for better overall survival in patients with oropharyngeal squamous cell carcinoma (OSCC). However, scoring of (novel) biomarkers is often complicated by the lack of standardised methodology which hampers their use in daily clinical practice. We therefore performed a comparative analysis to evaluate the importance of choice of materials and methods in CD8 assessment in patients with OSCC. Other immune cell markers, that is, CD3 and FoxP3 were taken into account as well.

**Methods**

Immunohistochemical analysis of CD3, CD8 and FoxP3 was performed on whole-tissue
sections from 101 treatment-naive patients with OSCC. A comparison of different immune cell markers was made for biopsy material versus resection material when available. Also, different scoring strategies, that is, quantitative versus semi-quantitative analysis were compared with each other.

**Results**

Comparison of biopsy material versus resection material proved a good agreement for expression of the CD3$^+$ T cells ($\kappa = 0.712, \rho = 0.853$), CD8$^+$ T cells ($\kappa = 0.659, \rho = 0.764$) and FoxP3$^+$ T cells ($\kappa = 0.783, \rho = 0.802$). The comparison of quantitative versus semi-quantitative assessment demonstrated strong correlations for the CD3$^+$ T cells ($\rho_{\text{biopt}} = 0.617, \rho_{\text{resection}} = 0.634$), CD8$^+$ T cells ($\rho_{\text{biopt}} = 0.656, \rho_{\text{resection}} = 0.675$) and FoxP3$^+$ T cells ($\rho_{\text{biopt}} = 0.537, \rho_{\text{resection}} = 0.720$).

**Conclusions**

Immunohistochemical analysis of CD3, CD8 and FoxP3 can be performed adequately on biopsy as this appears to be representative for the whole tumour. In addition, this can be done adequately in a semi-quantitative manner without the use of more expensive and time consuming machinery.

**Clinical trial identification**

not applicable

**Legal entity responsible for the study**

Prof. Sylvie Rottey

**Funding**

agency for Innovation by Science and Technology (IWT)

**Disclosure**

All authors have declared no conflicts of interest.

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**1064P - High-dose versus low-dose cisplatin with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck (SCC): An analysis of veteran’s health registry data**

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**Background**

Radiotherapy (RT) with concurrent high-dose cisplatin (HDC) improves outcomes for patients (pts) with SCC. Weekly low-dose cisplatin (LDC) is a widely used alternative approach. The comparative effectiveness and safety of these approaches is unknown. We compared the outcomes of pts treated with HDC and LDC within the Veteran’s Administration Corporate Data Warehouse (CDW).

**Methods**

We identified stage III-IVb SCC patients treated non-surgically with RT and HDC or LDC from 2002 to 2014 in the CDW. Pts were grouped by the dose of their first cycle (HDC vs LDC; intent-to-treat). Variables including cancer site, stage, smoking/alcohol use, and
comorbidities were used to generate propensity scores (PS) for the use of HDC. We compared overall survival (OS) by treatment group using Cox regression models, adjusting for PS. We also determined the risk of toxicities using PS-adjusted logistic regression models.

**Results**

A total of 2,820 pts were included in the analysis: 69.7% received HDC (mean initial dose 96 mg/m²). The mean initial dose of LDC was 30 mg/m². HDC pts were younger (p < 0.001), with lower creatinine (p = 0.002), and lower incidence of baseline neuropathy (p = 0.02). In an unadjusted analysis, HDC was associated with improved OS (Table). After PS adjustment, this difference was no longer statistically significant (p = 0.06). On primary site sub-analysis, HDC provided a benefit only for oropharyngeal primaries (OP). Adjusting for PS, HDC was associated with more renal failure (OR 2.2, 95% CI 1.6-3), neutropenia (OR 2, 95% CI 1.1-3.5), dehydration/electrolyte disturbance (OR 1.3, 95% CI 1.04-1.6), and hearing loss (OR 1.6, 95% CI 1.3-2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Unadjusted HR for OS</th>
<th>95% CI</th>
<th>PS Adjusted HR for OS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 2,820)</td>
<td>0.85</td>
<td>0.77-0.94</td>
<td>0.89</td>
<td>0.80-1.01</td>
</tr>
<tr>
<td>Oral Cavity (n = 182)</td>
<td>0.77</td>
<td>0.56-1.1</td>
<td>0.72</td>
<td>0.50-1.10</td>
</tr>
<tr>
<td>Hypopharynx/Larynx (n = 1,026)</td>
<td>1.00</td>
<td>0.86-1.20</td>
<td>1.1</td>
<td>0.90-1.30</td>
</tr>
<tr>
<td>Oropharynx (n = 1590)</td>
<td>0.78</td>
<td>0.70-0.90</td>
<td>0.81</td>
<td>0.69-0.96</td>
</tr>
</tbody>
</table>

**Conclusions**

While HDC does not improve OS over LDC for the overall cohort of patients with SCC receiving RT with definitive intent, it is associated with a survival benefit for patients with OP. HDC is associated with more adverse events.

**Clinical trial identification**

n/a

**Legal entity responsible for the study**

Keith Sigel

**Funding**

None

**Disclosure**

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1065P - 3-weekly or weekly cisplatin concurrently with radiotherapy for patients
Background
Concurrent chemoradiotherapy with cisplatin is standard for patients (pts) with loco-regionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). The standard regimen includes 3-weekly cisplatin, but weekly regimens are often used to lower toxicity. Reaching a cumulative dose of > 200 mg/m² cisplatin was shown being associated with improved outcome. We herein investigated cumulative dose reached and toxicity between the both widely used 3-weekly and weekly cisplatin regimens with concurrent radiotherapy.

Methods
Multicentre, retrospective analysis of all patients with LA-SCCHN treated at 3 centers in Switzerland between 06/2008 and 12/2015. We used descriptive statistics and logistic regression (uni- and multivariable) to investigate the association between the chosen cisplatin regimen (weekly versus 3-weekly) and the chance to reach the cumulative cisplatin dose of > 200 mg/m². Landmark approach (8 weeks after start of treatment) was applied for investigating the prognostic impact of the cumulative cisplatin dose on survival using Cox regression techniques.

Results
We included 314 eligible pts (3-weekly schedule, N = 127; weekly schedule, N = 187). Median cumulative cisplatin dose was 200 mg/m² (IQR 150-300) for pts treated with a 3-weekly schedule and 160 mg/m² (120-240) for the weekly schedule, consequently more pts treated with a 3-weekly schedule reached a cumulative dose >200 mg/m² (75.6% vs. 47.1%, p < 0.001). This association was also observed in multivariable analysis adjusted for age and sex (OR 3.46, 95% confidence interval [CI], 2.1 - 5.7). The 3-weekly regimen led to a higher rate of renal toxicity (33.1% vs. 20.9%, p = 0.022), but not ototoxicity (15% vs. 12.8%). In the landmark analysis, we could not confirm that a cisplatin dose >200 mg/m² is associated with better survival (HR 1.3, 95% CI 0.8 -1.9).

Conclusions
Significantly more patients receive a cumulative of dose of > 200 mg/m², when treated with a 3-weekly schedule compared to weekly dosing. This comes at the cost of more renal toxicity. Due to the non-randomized nature of this analysis, no conclusions on the efficacy of the respective schedules should be drawn.

Clinical trial identification
Not applicable.

Legal entity responsible for the study
University Hospital Basel

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1066P - Hyperfractionated twice daily re-irradiation (bid re-RT) and chemotherapy (CT) for locoregionally recurrent head and neck squamous cell carcinoma (LR HNSCC): A systematic review (SR)

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Background
Re-RT +/- CT is a salvage option for patients (pts) with LR HNSCC in a previously radiated field, although efficacy and toxicity, and the optimal treatment regimen remains undefined due to a lack of randomized trials. Hyperfractionated bid re-RT, by reducing the dose per fraction may improve radiation (RT) therapeutic ratio and is increasingly used in LR HNSCC. The aim of this SR is to assess the treatment outcomes of bid re-RT + CT in LR HNSCC.

Methods
We conducted a SR of MEDLINE, EMBASE and the Cochrane library up to Nov 2016 for clinical trials of bid re-RT + CT in pts with LR HNSCC. Paired reviewers selected studies for inclusion and extracted data. Individual patient level overall survival (OS) data were extracted where possible from published Kaplan-Meier (KM) curves to construct an aggregate KM curve.

Results
We identified 10 clinical trials (all were phase 1 or 2) with 404 pts. Median (of reported medians) prior RT dose was 64Gy, and median time from prior RT was 30.9m. Seventy-three and 156 pts respectively had CT and surgery as part of 1st line treatment. Median re-RT dose was 60Gy administered as continuous or split courses. The re-RT fields consisted of gross tumor volume plus a minimum margin (range 1-2cm). All CT regimens were combinations either with cisplatin (n = 6) or 5-FU (n = 4), given concurrently with (n = 9) or prior to (n = 1) re-RT. Twenty-eight (7%) pts had debulking surgery prior to re-RT. In pts who were analyzable for toxicities, acute events (>=grade 3) were reported in 252 of 377 (67%) pts and late events (>90d post re-RT) in 87 of 333 (26%) pts. Treatment-related deaths occurred in 26 (6%) pts, mostly due to infection or vascular events. Of the 5 trials with extractable KM curves, estimated median OS was 10.2m (95% CI 8.7-12.6m); 1- and 3-y OS rates were 46.8% and 11.2% respectively. No differences were observed in median OS and toxicity rates based on CT type (Wilcoxon test).

Conclusions
This is the 1st aggregate analysis of bid re-RT and CT in LR HNSCC. Long-term OS was observed in a subset of pts, however treatment-related morbidity was apparent. The optimal re-RT and CT regimen is still undefined and further study is required.

Clinical trial identification
Not applicable

Legal entity responsible for the study
None

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1067P - Raltitrexed versus 5-fluorouracil with cisplatin and concurrent radiotherapy (CCRT) for locally advanced head and neck squamous cell carcinoma (LA-HNSCC): A randomized controlled multi-centered trial

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Background
CCRT has been considered to be the standard of treatment for LA-HNSCC. However, patients receiving CCRT experience a substantial number of treatment-related adverse events, primarily causing oropharyngeal mucositis (OM) and leading to interruption or discontinuation of treatment. Raltitrexed is a specific thymidylate synthase inhibitor with a convenient administration, acceptable toxicity and radiosensitizing property, as the published phase I/II trials have shown. This study aimed to compare the clinical efficacy and toxicity of cisplatin with raltitrexed (RP) or 5-fluorouracil (FP) for LA-HNSCC.

Methods
Eligible patients with LA-HNSCC were randomly assigned in a 1:1 ratio to receive CCRT with either RP or FP. The RP group consisted of 2.5mg/m² intravenous raltitrexed on day 1 and 25 mg/m² intravenous cisplatin on days 1-3. The FP group consisted of continuous intravenous infusions of 600 mg/m² 5-fluorouracil on days 1-5 and 25 mg/m² intravenous cisplatin on days 1-3. Chemotherapy was administrated concurrently with radiotherapy and was repeated every 3 weeks with completion of at least 2 cycles. Primary endpoint was PFS. Secondary endpoints were complete response rates (CRR), OS and safety.

Results
A total of 108 patients with LA-HNSCC enrolled in this study, with 52 patients assigned to the RP group and 56 patients to the FP group. There was no significant difference in CRR between the two arms (42.9% vs 26.8%, respectively, p = 0.074), with the RP group showing a trend of increased CRR. Data of locoregional control, patterns of failure, and survival required further follow-up. The most frequent acute toxicities were bone marrow suppression, gastrointestinal side effects and OM in both arms. The incidence rate of severe OM was significantly lower (P<0.05) in the RP group than in the FP group. The incidence of other adverse effects seen in the two arms were similar (P>0.05).

Conclusions
The efficacy of the RP regimen was similar to that of the FP regimen. The RP regimen had a tolerable safety profile, with a lower incidence of severe OM and, consequently, an improved quality of life. In conclusion, RP is an effective, well-tolerated regimen for LA-HNSCC.

Clinical trial identification
NCT02485548 Release date: June 26, 2015

Legal entity responsible for the study
Xia He

Funding
1068P - The observational ENCORE study: Cetuximab + platinum-based therapy (PBT) for first-line (1L) treatment of patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN)

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**M. Ghiani (Cagliari, Italy)**
**M. C. Cau (Cagliari, Italy)**
**R. Depenni (Modena, Italy)**
**G. Ronzino (Lecce, Italy)**
**L. Livi (Florence, Italy)**
**V. Montesarchio (Napoli, Italy)**
**M. Bretagne (Paris, France)**
**M. Saint-Ghislain (Paris, France)**
**J. Schulten (Darmstadt, Germany)**
**D. Messinger (Mannheim, Germany)**
**A. Sbrana (Pisa, Italy)**
**M. G. Ghi (Venice, Italy)**

**Background**

The randomized, phase 3 EXTREME study established cetuximab + platinum + 5-flurouracil (5-FU) followed by cetuximab maintenance until progressive disease (PD) as the first regimen to yield survival benefits in the 1L management of patients with R/M SCCHN. In EXTREME, the addition of cetuximab increased the overall response rate from 20% to 36%, and extended progression-free survival from 3.3 to 5.6 months and overall survival from 7.4 to 10.1 months. ENCORE is a multinational, non-interventional, prospective, open-label study, seeking to determine how treatment decisions are made, planned and executed by oncologists treating patients with 1L therapy for R/M SCCHN in the real world.

**Methods**

ENCORE prospectively enrolled 219 patients with R/M SCCHN from Algeria, France, Italy, Portugal and Russia. The recommended treatment for these patients is cetuximab + PBT for up to 6 cycles followed by cetuximab maintenance until PD. Patient characteristics, drugs and schedule were recorded; as the study is still ongoing, safety and efficacy will not be reported here.

**Results**

ENCORE patients and the EXTREME patients who received cetuximab + platinum + 5-FU had similar performance status (PS: 13.7 and 12% with PS ≥2, respectively), but dissimilar median age (64 and 56 years, respectively). In ENCORE, 94.1% of patients had a planned treatment of cetuximab + PBT with cetuximab maintenance until PD. The remaining 13 (5.9%) had a fixed treatment duration of 4 to 24 weeks. 37.9% of treatment plans used cisplatin, 61.6% included carboplatin and 3.2% used a taxane. Also, only 53.4% of plans included 5-FU. When developing the treatment plan, 72.1% of all patients were discussed within the context of a multidisciplinary team (MDT). Most plans had the goal of palliative care, and 80% were formulated without a p16 or human papillomavirus status test. Updated data will be presented at congress.

**Conclusions**

The ENCORE study shows that a real-world R/M SCCHN patient population treated with the EXTREME regimen has diverse characteristics and is treated per current recommendations (e.g. in an MDT setting, with cetuximab until PD).

**Clinical trial identification**
EMR 62202-566

**Legal entity responsible for the study**
1069P - Primary surgery versus chemoradiotherapy for advanced oropharyngeal and hypopharyngeal cancer: A propensity-score matched study using a nationwide database

C. Cheng (Taipei, Taiwan)

Background
Traditionally, advanced head and neck cancer has been managed through surgery with or without postoperative radiotherapy. Studies since the 1980s have been advocating organ preservation therapies by using various combinations of chemotherapy and radiotherapy. For treatment of advanced oropharyngeal and hypopharyngeal cancer, there has been a controversy in choosing between primary surgery and chemoradiotherapy. We aimed at conducting a propensity-score matched study from a national database to investigate the survival after primary surgery with or without postoperative radiotherapy versus chemoradiotherapy in patients with advanced oropharyngeal and hypopharyngeal cancer.

Methods
We identified patients with stage III & IVa oropharyngeal and hypopharyngeal cancers between 2004 and 2009 from Taiwan National Health Insurance Claims Database. The study cohort was followed until 2012. We matched patients who received primary surgery to those who received chemoradiotherapy by propensity score calculated by logistic regression. Age at diagnosis, Charlson comorbidity index score, year of cancer diagnosis, clinical stage, receiving chemoradiotherapy, and receiving radiation therapy were well matched in these two groups. Overall survival and disease-free survival were compared using the Kaplan–Meier method.

Results
We identified 1,603 oropharyngeal and 1,512 hypopharyngeal cancer patients. After propensity score matching, 614 patients with oropharyngeal cancer and 638 patients with hypopharyngeal cancer were included in the analysis. For advanced hypopharyngeal cancer (stage III and IVa), the overall survival and disease-free survival in patients receiving primary surgery with or without radiotherapy were statistically better than the matched sample who received chemoradiotherapy. For oropharyngeal cancer, the survival benefit only existed in stage IVa patients who received primary surgery with or without radiotherapy.

Conclusions
The study showed that primary surgery with or without radiotherapy might have survival benefit in patients advanced oropharyngeal or hypopharyngeal cancer as compared to chemoradiotherapy.
Background
CRT including three cycles of cisplatin is considered the standard of care for LA-HNSCC. Around one third of the patients cannot complete cisplatin due to toxicity. Carbo-5FU can be used as an alternative. The aim of this study was to compare tolerability and efficacy between CRT with carbo-5FU and cisplatin.

Methods
This is a retrospective analysis of patients with LA-HNSCC treated with concomitant CRT in two Dutch cancer centers between 2007-2016. All patients received intensity modulated radiotherapy. One center routinely administered carboplatin 300-350 mg/m² at day 1, 22 and 43 followed by 5FU 600mg/m²/day for 96 hours. The other center used cisplatin 100 mg/m² at day 1, 22 and 43. Primary endpoint was chemotherapy completion rate. Secondary endpoints included: reason for discontinuation, number of unplanned admissions, overall survival (OS) and disease free survival (DFS). Associations between clinicopathological parameters and OS were determined with multivariate Cox regression analyses.

Results
In the carbo-5FU cohort (n = 190), 61.6% of the patients completed chemotherapy versus 76.7% (p = 0.001) of the patients in the cisplatin cohort (n = 223). Discontinuation caused by chemotherapy specific toxicity occurred twice as often in the carbo-5FU cohort (odds ratio 2.2, 95%CI, 1.38-3.5). Patients in the cisplatin cohort were more likely to have an unplanned admission (OR 2.96, 95%CI, 2.21-4.27). The risk of death was higher in the carbo-5FU cohort (HR 1.50, 95%CI, 1.06-2.12, p = 0.02) with a three-year OS of 64.6% compared to 76.6% in the cisplatin cohort. Similar results were observed for DFS (HR 1.39, 95%CI, 0.99-1.93, p = 0.06). T-classification, N-classification, smoking and p16 status were independently associated with OS, but chemotherapy regimen was not (HR 1.04, 95%CI, 0.72-1.51, p = 0.84).

Conclusions
Patients treated with carbo-5FU less frequently completed chemotherapy because of chemotherapy specific toxicity. Better OS was observed in the cisplatin cohort, but
chemotherapy regimen was not independently associated with OS.

Legal entity responsible for the study
S.F.Oosting

Funding
None

Disclosure
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1071P - Postoperative radiotherapy with weekly cisplatin in locally advanced head and neck cancer

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Background
The aim of this study is to analyze the results of over 10 years experience with postoperative radiochemotherapy in patients diagnosed of locally advanced squamous cell carcinoma of head and neck based in cisplatin 40mg/m2/week.

Methods
From March 2004 to August 2015, 104 patients were treated in our department. All patients received chemoradiation therapy with adjuvant intent based in the same scheme: radiotherapy 50 Gy to clinical target volume (CTV) and 66-70 Gy to areas with close margin or extracapsular lymph node involvement and weekly cisplatin at 40mg/m2 concomitant to radiotherapy.

Results
The median age was 59 years (range 36-76), 85 patients were male (81.7%) and 19 were female (18.3%). The pathological stage was: 2.9 stage II, 8.7% stage III and 88.4% stage IV. Locations: 38.5% larynx, 38.5% oral cavity, 17.3% oropharynx, and 5.8% hypopharynx. 76.2% of patients received at least 5 cycles of chemotherapy. G3 toxicity was observed in 33% of patients being mucositis and epitelitis the most frecuents. G4 toxicity was not detected in any patient. Median follow-up was 81 months (range 18-137). Two-year and five-year overall survival (OS) were 90% and 76% respectively and disease-free survival (DFS) were 69.07% and 52.57% respectively. In multivariate analysis two or more positive nodes and longer time between surgery and onset of radiotherapy were significant predictors of poorer OS and extracapsular extension, positive margin and longer time between surgery and onset of radiotherapy were significant predictors of poorer DFS.

Conclusions
In our serie, postoperative radiochemotherapy based in weekly cisplatin at 40mg/m2 in patients diagnosed of locally advanced squamous cell carcinoma of head and neck offers a good toxicity profile and results comparable to those published in the literature with 3-weekly cisplatin scheme. The number of positive nodes, longer time between surgery and onset of radiotherapy, extracapsular extension and positive margin were desfavorable prognostic factor related with SLE and OS in the multivariate analysis.
Background
There is increasing evidence showing that concurrent chemoradiotherapy (CCRT) may be inadequate for patients with locoregionally advanced nasopharyngeal carcinoma. Until now, no randomized controlled clinical trial has proved the effectiveness of cetuximab plus CCRT.

Methods
There were 681 consecutive stage III-IVB NPC were included in this retrospective study. 75 underwent CCRT with cetuximab and 606 received CCRT. The nasopharyngeal and neck tumor of all patients were treated by intensity modulation radiated therapy (IMRT).

Results
After matching at a 1:2 ratio, 150 patients were treated with CCRT and 75 with CCRT plus C were selected. The 3-year PFS rates (83.7% vs 72.0%, P = 0.036) and 3-year LRFS rates (98.6% vs 90.2%, P = 0.034) were higher for patients in the CCRT plus C arm than with CCRT alone. Furthermore, a marginal trend of increasing risk of 3-year DMFS rates (83.9% vs 78.4%, P = 0.301) and 3-year OS rates (91.2% vs 85.8%, P = 0.123) was found. The results indicated that CCRT plus C treatment was a significant and independent protective predictor for 3-year PFS (P = 0.015) and LRFS rates (P = 0.047). When focusing on stage T4 and/or N3 in the subgroup, the CCRT plus C arm achieved significantly prolonged 3-year PFS (79.9% vs 62.6%, P = 0.022) and a marginally increased OS (88.0% vs 77.9%, P = 0.086) compared with that of CCRT alone. Additionally, the 3-year LRFS (97.0% vs 90.9%, P = 0.246) and DMFS (79.9% vs 67.8%, P = 0.161) were enhanced in patients with CCRT plus C compared to CCRT alone. When concentrating on stage III patients, there were no considerable statistically significant differences found in 3-year PFS, OS, LRFS, and DMFS rates between patients with and without cetuximab. No significant difference was observed in the late toxicities between the two treatments.

Conclusions
This propensity-matched study reveals that patients with T4 and/or N3 stage could benefit from the combination of cetuximab with the current chemoradiotherapy in locoregionally advanced NPC, although with more acute moderate to severe toxicities. However, this strategy remains to be validated in a prospective randomized controlled study.

Clinical trial identification
This retrospective study has no clinical trial identification.

Legal entity responsible for the study
Hospital Ramón y Cajal
Background
The aim of this study was to evaluate the safety and efficacy of nimotuzumab, a humanized monoclonal antibody against epidermal growth factor receptor, in combination with chemoradiation for head and neck squamous cell cancer (HNC).

Methods
The hospital data of 42 patients with HNC who were treated with nimotuzumab from January 2012 to December 2016 were evaluated. Three patients who had undergone prior surgery were excluded and 39 patients diagnosed with locally advanced (stage III- IVb) unresectable HNC who were treated with concurrent chemoradiotherapy with weekly nimotuzumab were considered for final analysis. Tumour response was calculated as per RECIST criteria 1.1. Subgroup analysis was performed to assess association of tumour response with independent variables such as age, gender, histopathological grades and TNM stages using chi square or Fischer exact test. Overall survival (OS) and progression free survival (PFS) was calculated from date of diagnosis using Kaplan-Meier method. All patients were assessed for toxicity and adverse events (AE) were reported as per common terminology criteria for AE v 4.0. Statistical analysis was done using SPSS software (v19.0).

Results
At 24 weeks after completion of treatment, objective response rate (complete response [CR] + partial response [PR]) was 97.44% with 26 (66.67%) patients showing CR, 12 (30.77%) patients with PR and one patient (2.56%) had stable disease. Subgroup analysis did not show significant association of tumour response, although men, patients older than 65 years, laryngeal cancer, tumour grade III, TNM stage III showed more complete responses. OS at one year and two years was 100% and 72.9%, while PFS at one year and two years was 87% and 54.40%, respectively. Incidence of grade I, II, III and IV toxicity was 30%, 18.18%, 41.82%, 10%, respectively. No grade V toxicity was observed. Common AE observed were neutropenia (20.91%), mucositis (33.64%), vomiting (18.18%), diarrhea (2.73%), skin reaction (24.55%). Nimotuzumab was observed to be safe with no additional adverse events (hypersensitivity, allergic reaction and skin changes) were reported during the study period.

Conclusions
Nimotuzumab is an efficacious and safe option when added to concurrent chemoradiotherapy in patients with locally advanced Head and Neck cancer.

**Clinical trial identification**

125/12

**Legal entity responsible for the study**

Dr. Shyamji Rawat

**Funding**

None

**Disclosure**

D. Pawar: Works in a Pharmaceutical company. S. Chaudhari: works for Pharmaceutical company. All other authors have declared no conflicts of interest.

**1074P - A phase II study of combination chemotherapy with cetuximab/S-1/low dose cisplatin as neoadjuvant manner for oral squamous cell carcinoma patients**

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**Background**

In oral cancer therapy, functional preservation, as well as survival, is a very important matter to consider. One of the methods for organ preservation is an effective preoperative (neoadjuvant) chemotherapy. We previously reported the good antitumor effect and good tolerance of low dose cisplatin/S-1 at ESMO 2004 and 2006. Cetuximab enhances the antitumor effect of cisplatin/5-Fluorouracil. We investigated the feasibility of combining cetuximab/low dose cisplatin/S-1 chemotherapy as a neoadjuvant regimen for patients with oral squamous cell carcinoma.

**Methods**

Consecutive patients (n = 14) with newly diagnosed stage II-IV oral squamous cell carcinoma were enrolled in this study from July 2014 to June 2016. Patients were administered S-1 80mg/m²/day (day 1-14), cisplatin 5 mg/m²/day (day 1-5,8-12) and cetuximab 400mg/m²/day on day 1 and 250mg m²/day on day 8. This was followed by definitive surgery. Clinical response was assessed by clinical findings and/or CT according to RECIST and histopathological effects were evaluated with surgical specimens.

**Results**

The rate of clinical response, including complete response (CR) and partial response (PR), was 85.7%: CR 21.8%, PR 64.3%, SD (stable disease) 14.3%. The rate of histological response was 71.4%: CR 21.4%, PR 50%, no change 28.6%. Toxicities above grade 3 were neutropenia (7.1%), hypokalaemia (7.1%), leukocytopenia (7.1%), thrombocytopenia (7.1%), anorexia (21.4%), diarrhea (7.1%) and nausea (7.1%). Most toxicities disappeared within 8 weeks after chemotherapy. No serious adverse effects were observed in the majority of patients. Conservative surgery was applied to 12 patients, except 2 patients with SD and 5 of 9 patients who needed reconstruction were able to avoid reconstructive surgery.

**Conclusions**

Combination chemotherapy with cetuximab/low dose cisplatin/S-1 represents an effective antitumor therapy with mild to moderate toxicities. It is suggested that this regimen is
superior to low dose cisplatin/S-1 and can promote function preserving surgery.

Clinical trial identification
UMIN000014632

Legal entity responsible for the study
Individual person

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1075P - Role of induction chemotherapy in locally advanced T4b oral cavity cancers: A single Institute experience

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Background
The standard of care for oral squamous cell carcinoma (OSCC) at present, consist of surgical resection followed by adjuvant radiotherapy and chemotherapy as indicated. However, indications of induction chemotherapy (IC) in oral cancers are not clearly defined. This retrospective analysis aimed to investigate the efficacy, toxicity and impact of induction chemotherapy in locally advanced T4b oral cavity squamous cell cancers.

Methods
Patients diagnosed with locally advanced T4b OSCC from January 2013 and March 2017 at our centre, who received 2-3 cycles of IC and then assessed for resectability, were reviewed retrospectively. Patients' profile, response and toxicity of IC, resectability status and overall survival (OS) were evaluated. Statistical analyses were done by SPSS version 17.0.

Results
Total 134 patients received IC, and out of them 98 (73.1%) were males. Median age at diagnosis was 44 years (range 31-60 years). 107 (79.8%) of our patients received doublet chemotherapy (with paclitaxel + cisplatin), and the rest of the patients received triplet regimen (with paclitaxel/docetaxel + cisplatin + 5-FU). Majority of the patients had buccal mucosa cancers (n = 92), followed by gingivo-buccal sulcus (n = 26) and oral tongue (n = 16) primaries. After IC, partial response was achieved in 25 (18.7%) patients, stable disease in 83 (61.9%) patients and disease progression was noted in 26 (19.4%) patients. Post-induction chemotherapy, resectability was achieved in 28 (21%) of 134 patients, but 8 of them did not undergo surgery due to logistic and personal reasons. The median OS of patients who underwent surgery followed by adjuvant local therapy (n = 20) was 18.7 months (95% CI: 16.2-21.5 months) and for those treated with non-surgical local therapy (n = 114) was 7.9 months (95% CI: 6.2-9.2 months) (log-rank p = 0.000).

Conclusions
IC may improve the resectability in our patients with T4b OSCC with a manageable toxicity profile. Patients underwent resection had a significantly better median OS than those who received non-surgical local treatment.

Clinical trial identification
1076P - Concurrent chemoradiotherapy (CCRT) versus induction docetaxel, cisplatin and 5-fluorouracil (TPF) followed by CCRT in locally advanced hypopharyngeal and base of tongue cancer: A randomized phase II study

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Background
To date, clinical trials have not consistently supported the use of induction chemotherapy (IC) for locally advanced head and neck squamous cell cancer (LASCC). Hypopharynx and base of tongue (BOT) cancer has shown relatively poor survival compared to other LASCC. We tried to investigate the role of IC for improvement over current chemoradiotherapy (CRT) in patients with locally advanced hypopharynx and BOT cancer.

Methods
Treatment-naïve patients with nonmetastatic stage III/IV hypopharyngeal or BOT cancer were randomly assigned to receive CRT alone (CRT arm: cisplatin 100mg/m² 3-weekly for 2 times plus radiotherapy 68.4Gy/30fraction on weekday) versus two 21-day cycles of IC (docetaxel 75mg/m² on day 1, cisplatin 75mg/m² on day 1, and fluorouracil 750mg/m² over days 1 to 4) followed by same CRT regimen (IC arm). The primary endpoint was progression-free survival (PFS) and 90 patients are required to show the superiority of IC arm with one-sided alpha 0.1 and power of 0.85.

Results
This study closed early after enrollment of 36 patients (19 in CRT arm and 17 in IC arm) because of slow accrual. After a median follow up of 47.2 months, there was no significant difference in PFS: the median PFS were 26.8 months for CRT arm and not reached for IC arm (Hazard ratio: 0.55, 95% CI 0.19-1.60). However, the survival curves widely separated with a plateau after 3-years, suggesting the survival benefit from induction chemotherapy: 3-year PFS rates were 45% and 68%, and 3-year overall survival rates were 56% and 86% (HR: 0.35, 95% CI: 0.07-1.69), in CRT and IC arms, respectively. In both subgroups with BOT and hypopharyngeal cancer, survival outcomes of IC arm were also insignificantly superior to those of CRT arm. All adverse events were manageable and there was no grade 3/4 toxicity except one patient had Gr3 stomatitis in IC arm.

Conclusions
This study failed to demonstrate that induction TPF chemotherapy improves survival in patients with BOT and hypopharyngeal cancer, possibly due to small number of subjects. However, it suggested favorable outcome with induction chemotherapy, and further large randomized studies are needed to this population.
**Clinical trial identification**
NCT01312350

**Legal entity responsible for the study**
Samsung medical center

**Funding**
None

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

**1077P - Do patients over 70 years with advanced head and neck squamous cell carcinoma tolerate curative intent concurrent chemo-radiation? Predictors of oncological outcomes**

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**Background**
Survival benefit of adding chemotherapy to radiotherapy (RT) in patients (pts) age > 70 yrs of head and neck squamous cell carcinoma (HNSCC) has not been found in literature. Our institutional policy is to offer concurrent chemoradiation (CCRT) to patients > 70 years with a good ECOG status.

**Methods**
Retrospective analysis of stage III/IV HNSCC in pts > 70 years who received linac based radical CCRT with dose equivalent to 70Gy in conventional fractionation (n = 57) between 2006 to 2014 were included.

**Results**
Pts with stage III/IV (25.6%/75.4%) HNSCC (n = 57) of oropharynx (n = 15), larynx (n = 18) or hypopharynx (n = 24) underwent radical CCRT having mean age 75.18 yrs (range 70-86 years) and male to female ratio of 10.4:1. Pts on CCRT who got cisplatin (CIS) (n = 35) and carboplatin(CARBO) (n = 22) had mean weight loss of 3.53 (range 0-10) kgs. 61.4% completed chemotherapy (defined as cumulative dose of 200mg/m2 of CIS and 5 weekly dose of CARBO at AUC 2) and 98.2% completed RT without any treatment related death. Higher grades of neutropenia (33.3%) and hyponatremia (17.5%) with CIS and hypercreatinemia (10.5%) with CARBO was noted. Tube dependence (gastrostomy/tracheostomy) had 2.7-fold increase in risk of death in pts (n = 25; 44%) with hypopharynx/larynx cancer, compared with stage and subsite matched pair analysis in pts < 60 years. Factors predicting good PFS were ECOG (1 vs 2) HR = 0.25 (95%CI:0.09-0.70), Completion of treatment without any breaks while on CCRT, HR = 2.54 (95%CI:1.02-6.32, p = 0.04), and age in 70-75 years, HR = 1.09 (adjusted for alcohol and smoking) (95%CI: 1.01-1.20, p = 0.08). Factors suggestive of poor PFS were hyponatremia, hypercreatinemia and weight loss > 3kgs from their baseline. PFS (80%) in pts with stage III and IV disease was 22 (95%CI: 12.4-87.2) months and 15.53 (95%CI: 8.6-20.6) months respectively.

**Conclusions**
Curative intent CCRT should be considered as standard of care in elderly patients > 70
years with good ECOG status. Both cisplatin and carboplatin showed significant benefit in PFS with fewer side effects. Aggressive swallowing rehabilitation, abstinence from smoking and alcohol are likely to improve outcomes.

**Clinical trial identification**
This is a retrospective study and not a clinical trial

**Legal entity responsible for the study**
Amrita Institute of Medical Sciences

**Funding**
None

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

1078P - Multidisciplinary team management in head and neck cancer: The real life experience

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**Background**
Multidisciplinary team (MDT) management in oncology is integrated in a legal framework in France. This practice is essential in Head and Neck cancer management with its complex and multimodal treatments. Some trials report a positive impact of MDT on overall survival of advanced head and neck cancers. The objective of this study was to report the experience of MDT management in Head and Neck Cancer in the Lucien Neuwirth Cancer Institute over the past 6 years.

**Methods**
Records from bi-monthly MDT meeting from 2010 to 2015 were selected for this study. Number of medical cases and type of present medical specialists were noticed. Data from MDT records were reported: clinical characteristics (performans status, weight), anatomical localisation, TNM and pathological classification, and the treatment plan decision. Impact of MDT meeting on treatment delay was also analysed.

**Results**
As of December 2015, 1848 clinical cases were discussed with 1786 patients and 138 MDT meetings. Majority of patients were discussed only once in meeting, and 3% (52) patients were discussed twice. An average of 16 patient’s cases were discussed per-meeting. 1368 patients (74.1%) were presented at primo-diagnosis status and 481 (25.9%) in a recurrence status. 81% of patients were at stage III or IV. 969 (52.4%) patients had a treatment before MDT. Surgery (73.2%) was the main treatment operated before meeting. Radiation therapy delay after MDT was 9.8 days for dosimetric planification CT and 21 days for first radiation treatment session.

**Conclusions**
The percentage of presented recurrent patients is reasonable regarding epidemiologic data in head and neck location. MDT seems not delay radiation treatment occurring within 21 days after MDT. Unfortunately we underlined a majority of patients surgically treated
before MDT discussion.

Legal entity responsible for the study
Nicolas Magné

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1079P - Long-term response to second-line afatinib in patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Analysis of the LUX-Head & Neck 1 (LHN1) trial

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Background
In the Phase III LHN1 trial, second-line afatinib (A) significantly improved PFS (primary endpoint) vs methotrexate (MTX) in pts with R/M HNSCC. Tumour biomarker analyses have shown that survival benefit with A vs MTX was more pronounced in pts with p16/ErbB3-negative, EGFR-amplified, PTEN-positive disease. We present post-hoc analyses of A long-term responders (LTRs).

Methods
Pts with incurable R/M HNSCC who had received first-line platinum-based therapy were randomised to A (40mg/day) or MTX (40mg/m²/week) and treated until progression/intolerable AE. LTRs were defined as pts treated with A ≥ 12 mos. Tumour biomarkers were assessed by IHC (p16, ErbB3, PTEN, cMET) and FISH (EGFR amplification); pre-treatment (tx) serum samples were analysed with the VeriStrat® (VS) test and classified as VS-Good/Poor.

Results
11/322 (3%) pts treated with A were LTRs with a median (range) tx-duration of 16 (12–39) mos. All pts had stopped tx at analysis. Baseline characteristics in LTRs were similar to the overall dataset, except (LTRs/overall): oral cavity primary tumour site (45%/29%); M1 disease (45%/66%); previous therapy with EGFR-antibodies (18%/59%). Median OS was 18.1 mos; median PFS (central independent review) was 14.9 mos. ORR was 45% (CR: 18%; n = 2). The frequency of pts who received ≥1 subsequent therapy was similar to the overall dataset (LTRs, 45%; overall, 51%). In LTRs with available biomarker data, 3/3 (100%) pts were p16-negative, 4/4 (100%) pts were ErbB3-negative, 2/4 (50%) pts were PTEN-positive, 3/3 (100%) pts were cMET-positive, 2/3 (67%) pts had EGFR-amplification, and 5/5 (100%) pts were VS-Good. Tolerability-guided dose reductions were more frequent among LTRs (55% vs 32% overall).

Conclusions
In the LHN1 study, some platinum-pre-treated pts with R/M HNSCC derived a long-term
survival benefit from A; median OS was 1.5 yrs and >11 mos longer than in the overall dataset. Limited biomarker data available in these LTRs suggests that p16/ErbB3-negativity and EGFR-amplification might be potential predictive biomarkers for long-term benefit from A; however, results were not conclusive due to small sample size.

Clinical trial identification
NCT01345682

Legal entity responsible for the study
Boehringer Ingelheim

Funding
Boehringer Ingelheim

Disclosure

1081P - Benefit of cetuximab addition to a platinum-fluorouracil-based chemotherapy in an unselected population of metastatic head and neck cancer patients and effect of KRAS Lcs6 variation on cetuximab response

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Background
While the EXTREME protocol, including platinum (P) fluorouracil (FU) and cetuximab (Cx), is the gold-standard first line chemotherapy for metastatic head neck cancer patients (MHNC), its benefit in an unselected population has never been evaluated. Furthermore, KRAS Lcs6 variation was reported as a potential marker for greater efficacy of EGFR-targeted therapy. We investigated the benefit on progression-free survival (PFS) and overall survival (OS) of adding Cx to PFU as first line treatment for MHNC in an unselected population. We also assessed if there was a differential efficacy of Cx according to KRAS Lcs6 status.

Methods
This monocentric retrospective study included all the patients treated by at least two cycles of PFU+/-Cx between 2005 and 2014 as first line of palliative chemotherapy for MHNC. When tumor samples were available, the KRAS LCS6 variant status (rs61764370) was determined by pyrosequencing, and the p16 status by immuno-histo-chemistry.
Results
134 patients were included: 59 (44%) treated with PFU and 75 (56%) with PFUCx. Baseline characteristics were comparable between the two groups. Of note 30% of the patients had a stage 2 or 3 performance status (PS). In univariate analysis, a longer median PFS was observed with PFUCx compared to PFU (6.1 vs 4.4 months respectively, HR 0.68, p = 0.02). Median OS were not different (11.1 months with PFUCx versus 9.1 with PFU, p = 0.2). Among the 110 tumor samples available, 29 (25%) had a KRAS-variant and 14 (12.7%) were p16 positive. No differences in OS nor PFS were observed according to the KRAS-variant status. When considering only the patients treated with PFUCx, presence of the KRAS-variant (n = 17) was not associated with a better response (p = 0.5). In a multivariate analysis including PS ≤ 1, addition of Cx, KRAS status, p16 status and age ≤ 55 as variables; addition of Cx to PFU was the only factor related to a better PFS (p = 0.008).

Conclusions
This retrospective study confirmed the effectiveness of the EXTREME protocol on PFS in an unselected population of MHNC patients. KRAS LCS6 variant was not related to a differential response to Cetuximab in MHNC population.

Legal entity responsible for the study
Centre Henri Becquerel

Funding
IRON - Centre Henri Becquerel

Disclosure
All authors have declared no conflicts of interest.

1082P - A pilot study of apatinib in heavily pretreated metastatic adenocarcinoma of the head and neck
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Background
Although antiangiogenic therapy is effective in advanced lung, breast, renal, hepatic, and colon cancers, limited is known about its value in the cancer of the Head and Neck. Apatinib is an oral, highly potent tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR-2). This prospective phase II study (NCT02989259) aims to investigate the efficacy and safety of apatinib in heavily pretreated patients (pts) with metastatic adenocarcinoma of the Head and Neck.

Methods
This study enrolled pts with metastatic adenocarcinoma of the Head and Neck, who failed in the metastatic setting at least one prior chemotherapy regimen. The primary end point of this study was progression free survival (PFS). Secondary end points included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. Patients were treated with apatinib 500 mg daily. Efficacy was assessed every 6 weeks.

Results
From December 2016, we recruited 10 pts, including 8 males and 2 females, with a median age of 53 years (26-71). Median number of previous chemotherapy regimens for the metastatic diseases was 2 (1-3). Median follow-up time was 4.3 months. 8 pts were eligible for efficacy analysis. ORR was 25% (2/8). DCR was 87.5% (7/8). Median PFS and
median OS were not reached. The most common adverse events (AEs) of all grade were hypertension (n = 5), nausea (n = 4), fatigue (n = 4) and hand-foot syndrome (n = 3). The most common grade 3/4 AEs were hypertension (n = 2), thrombocytopenia (n = 1) and oral mucositis (n = 1). Toxicities were tolerable and manageable.

Conclusions
Our results so far indicated that apatinib exhibited objective efficacy in heavily pretreated, metastatic adenocarcinoma of the Head and Neck with acceptable safety.

Clinical trial identification
the trial protocol number: NCT02989259 release date: December 2016

Legal entity responsible for the study
The Institutional Review Board of the Cancer Institute/Hospital, CAMS & PUMC

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1083P - Natural history and prognostic factors of head and neck cancer patients with bone metastases: A retrospective Italian study

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Background
We performed a retrospective survey to study the natural history and the prognostic factors of patients (pts) with bone metastases (BM) from head and neck cancers (HNCs).

Methods
Clinical records of pts treated at 11 oncologic centers across Italy were retrieved. All pts were selected on the base of BM either at diagnosis or at subsequent time points. Pts with a diagnosis of nasopharyngeal carcinoma (NPC) were analyzed separately. The time-to-first bone metastasis was calculated from initial diagnosis. The skeletal-related events (SREs) (fractures, medullary compression, hypercalcemia) were recorded from the date of BM diagnosis.

Results
From 2008 to 2016, 192 HNC pts with BMs (64 NPCs and 128 other-HNCs) were collected. Median time to first BM was 9 and 12 months for NPCs and other-HNCs, respectively. SREs occurred in 9% and 27% NPC and other-HNC pts, respectively. Pts received specific antineoplastic treatments (92%) or best supportive care (8%). Median progression free survival (PFS) and overall survival (OS) were 11 and 25 months in NPC-BM pts and only 5 and 6 months in other-HNC-BM pts, respectively. SRE did not affect the pt prognosis except for hypercalcemia that was associated with a poorer prognosis (not significant). Biphosphonates and/or denosumab were administered in 34% NPC and 33% other-HNC pts, respectively. The administration of bone-directed therapies, also including radiation therapy and surgery on BMs, was associated with a better survival
at univariate analysis in both NPC and other-HNC (Hazard Ratio [HR]: 0.43, 95% confidence interval [CI] .008-.237, p <.0005 in NPC and HR 0.37, 95% CI: .191-.735, p .004 in other HNC, respectively).

Conclusions
In HNC pts destined to develop BMs, these events occur early in the natural history of these diseases. The onset of BMs predicts a poor survival in non-NPC HNC pts. SREs are more frequent in non-NPC HNC pts. Bone directed therapies are correlated with better outcome.

Clinical trial identification
Id NP1848 - Study SURMOS - Release date: 11 Dec 2014

Legal entity responsible for the study
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Funding
None

Disclosure
All authors have declared no conflicts of interest.

1084P - Prognostic impact of the neutrophil-to-lymphocyte ratio (NLR) on overall survival in patients treated with chemoradiotherapy for head and neck cancer
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Background
The neutrophil-to-lymphocyte ratio (NLR), a marker of the systemic inflammatory response, has been reported to have prognostic value in different cancer settings. In this study we aimed to assess the prognostic impact of NLR in a cohort of patients with head and neck cancers.

Methods
Patients with head and neck cancer treated with concurrent chemo-radiotherapy (Cisplatin) between 01/2013 and 12/2015 were included in this study. NLR was analyzed as a continuous variable and as dichotomous variable (≤ 5 vs. > 5). The primary end point was overall survival (OS). Progression free survival (PFS) was the secondary endpoint. Univariate analysis was used to identify associations and to select variables included in multivariate Cox regression analysis to determine prognostic value.

Results
146 patients (132 squamous cell carcinomas (SCC), 10 undifferencied nasopharyngeal carcinomas (UCNT) and 4 neuroendocrine carcinomas) were included in this analysis. The median follow up was 20.6 months (2.4-37.0 months). 1-year and 2-year OS were 87.1% and 82.3%, respectively. 1-year and 2-year PFS were 75.9% and 68.0%, respectively. On univariate analysis, OS significantly differed between groups NLR ≤ 5 vs. > 5. In the overall population (OP) (HR: 2.6; IC95%: [1.05-6.53]; p = 0036) and in non-oropharyngeal subpopulation (HR: 3.67; IC95%: [1.19-11.4]; p = 0.016) but not in the oropharyngeal subpopulation (p = 0.51). In multivariate analysis NLR >5 was significantly associated with a poorer OS in the OP (HR: 2.89; IC95%: [1.14-7.33]; p = 0.025) and in...
non-oropharyngeal subpopulation (HR: 4.53; IC95%: [1.34-13.5]; p = 0.014). Body Mass Index (BMI) <18.5kg/m2 and poor performans status (PS: 1-2 vs 0) were also significantly associated with a shortened OS (p = 0.010 and 0.021, respectively). Only the BMI was found to be significantly associated with PFS (p = 0.006) in the OP.

Conclusions
In this cohort of patients treated with chemo-radiotherapy for head and neck cancer, pre-treatment NLR >5 was predictive of shorter overall survival. Further prospective clinical investigations are required to confirm these results and determine the clinical applicability as prognostic factor.

Legal entity responsible for the study
Centre Oscar Lambret

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1085P - Association of ERP29 genetic polymorphism in microRNA-binding site with oropharynx cancer risk and prognosis

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Background
Our previous large-scale genotyping study identified more than 6,000 single nucleotide polymorphisms (SNPs) associated with base of tongue (BT) squamous cell carcinoma (SCC) risk in 49 patients and 49 controls. The SNP c.*293A>G of the ERP29, a tumor-suppressor chaperone, was selected for further analyses. An in silico analysis showed that microRNA (miR)-4421 shared binding site with 3’-untranslated region of variant allele of referred SNP while wild-type allele disrupt this target site. However, the role of this SNP in the risk and prognosis of oropharynx SCC (OPSCC) patients is still unknown. We aimed to verify whether the distinct genotypes or ERP29 c.*293A>G SNP influence the OPSCC risk and prognosis, and the ERP29 and miR-4421 expressions.

Methods
DNA from 250 OPSCC patients and 250 controls was analyzed by RT-PCR. The patients were treated with surgery, radiotherapy and/or platinum based agents. The ERP29 and miR-4421 levels were evaluated by qPCR using RNA of 58 controls. The differences between groups were calculated by chi-square, logistic regression model and Mann-Whitney tests. Progression-free survival (PFS) and overall survival (OS) times were calculated by Kaplan-Meier and Cox regression methods.

Results
ERP29 variant GG genotype was more common in OPSCC patients than in controls (6.4% vs. 3.6%, P = 0.002). Individuals with GG genotype were under 8.86-fold increased risk of OPSCC than others (95% CI: 2.20-35.69). Considering only the BTSCC patients, at 36 months of follow-up, shorter PFS were seen in patients with variant GG genotype (0.0% vs. 39.1%, P = 0.01, Cox: HR: 2.68, 95% CI: 1.21-5.95, P = 0.01). Individuals with ERP29 wild-type genotype showed higher levels of ERP29 mRNA when compared to
others (1.44 vs. 1.10 arbitrary units AUs, P = 0.005). In addition, lower miR-4421 expression was observed in individuals with ERP29 AA genotype when compared to those with AG or GG genotypes (0.42 vs. 0.73 AUs, P = 0.05).

Conclusions
Our data present, for the first time, that ERP29 c.*293A>G SNP is associated with increased risk of OPSCC and with worst survival of BTSCC patients, possibly due to variation of ERP29 mRNA levels modulated by miR-4421.

Legal entity responsible for the study
University of Campinas

Funding
São Paulo Research Foundation (FAPESP) and Coordination for the Improvement of Higher Education Personnel (CAPES)

Disclosure
All authors have declared no conflicts of interest.

1086P - Diagnostic and prognostic impact of plasma osteopontin in nasopharyngeal carcinoma

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Background
We investigated the diagnostic and prognostic impact of plasma osteopontin (pOPN) concentrations in advanced nasopharyngeal carcinoma (NPC).

Methods
Pre-treatment plasma samples from 138 patients with previously untreated and biopsy-proven NPC were collected. Plasma samples from another 70 healthy volunteer were served as control. OPN concentrations were measured by the enzyme-linked immunosorbent assay (ELISA). The patient characteristics were- age range 24-83 and median 48 years, male/female=97/41, WHO pathology type I/II/III=1/105/32, stage III/IV(M0)/IVC(M1) = 57/73/8. The treatment consisted of radiotherapy alone (2), concurrent chemoradiotherapy (28), and neoadjuvant chemotherapy plus radiotherapy (100) for M0 patients, and systemic chemotherapy with or without radiotherapy for M1 patients (8).

Results
NPC patients (median 97.2 ng/mL; interquartile range 72.1-130.4) had significantly higher pOPN level than normal control (median 61.6 copies/ml; interquartile range 44.9-88.1), P<0.0001. The area under ROC curve is 0.754, P=0.0001. The median concentrations of stage III, IV(M0), and IV(M1) were 85.4, 104.2, and 217.7 ng/mL respectively (P=0.0002).

We divided patients into two groups by pretreatment pOPN concentration and found that patients with higher pOPN (>100 ng/mL) correlated with some clinically poor prognostic factors, such as older age, male gender, advanced T-stage, and advanced overall stage. Pretreatment pOPN affected patients’ survival as well as rates of distant failure. The 5-year overall survival (56.6% vs. 81.4%, P=0.0036) and metastasis-free survival (66.3% vs. 81.2%, P=0.0726) were significantly lower in patients with pretreatment pOPN > 100 ng/mL than in those with pOPN < 100 ng/mL.

Conclusions
Pretreatment pOPN levels can serve as a useful diagnostic and prognostic marker for
1087P - Head and neck cancer (HNC) and synchronous lung cancer: Impact of the lung cancer on the management and prognosis of these patients. Data from the SYNCHRON GFPC 15-04 Study

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Background
Management of synchronous head and neck and lung cancer is almost difficult. The aim of this observational study was to describe the impact of the lung cancer on the management and prognosis of HNC.

Methods
Inclusion criteria were: consecutive patients diagnosed between January 2011 and December 2015 in 19 French centers with HNC and synchronous lung cancer (all stages). We describe: clinical characteristics, management and outcomes. Patient characteristics and treatment information was analyzed descriptively. Kaplan-Meier estimation was used to assess median overall survival.

Results
The study included 132 patients: men: 83%; 63,7 years old, current smokers: 59,8%; performans status: 0 and 1 for 22% and 66% of the patients respectively; high rate of comorbidities: cardiovascular: 63%, COPD: 33%. Main histology for HNC was squamous: 98%, (in oral cavity: 24%, oropharyngeal: 26%, hypo-pharyngeal: 22% and laryngeal: 28%) T classification was T1, T2, T3 and T4 in 16%, 24%, 28% and 18% of cases respectively, and N classification was N0, N1, N2, N3, for 36%, 18%, 20% and 8% of cases respectively. The main treatment was surgery, 37,1%, and chemo-radiotherapy, 35,6%. The diagnosis of lung cancer impacts the HNC management in 38% of the cases. Median delay between HNC and first day treatment was 54 days. HNC progressive free survival rate was 68% at 2 years. Lung cancers were mostly localized (stages I: 46%, stages II: 10%), squamous: 39%, or adeno-carcinomas: 39%. Main treatments were surgery: 29%, mainly lobectomy, radiotherapy: 13%, radio-chemotherapy: 14% and chemotherapy alone: 35%. Seven patients didn’t receive active treatment. Median delay of treatment was 82,3 days. Lung cancer progressive free survival rate was 35% at 2 years. OS was 40% at 2 years, better for stage I - II lung cancers (55%).

Conclusions
Synchronous lung cancer at HNC diagnosis significantly impacts the management and outcomes of HNC. Specific recommendations and multidisciplinary approach should be elaborate to improve the management of these patients.

Legal entity responsible for the study
Taichung Veteran General Hospital

Disclosure
All authors have declared no conflicts of interest.
1088P - An estimation of the population survival benefit of first-course chemotherapy for head and neck cancers

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Background
Randomised clinical trials describe the benefit of chemotherapy for specific head and neck patients with selected patient and tumour characteristics. This study estimates the overall survival benefit of chemotherapy above all other modalities for the whole population of head and neck cancer patients in Australia, if evidence-guidelines were followed.

Methods
Decision trees with evidence-based indications for chemotherapy have been previously defined. For all defined indications, the highest level of clinical evidence available was identified. Multiple electronic citation databases were systematically queried, including Medline and Cochrane library. The benefits of first-course chemotherapy were estimated for 1-year and 5-year overall survivals. To assess the robustness of our estimates, univariate and multivariate analyses were performed.

Results
The estimated 1-year and 5-year absolute population-based survival benefits of optimally utilised chemotherapy for head and neck cancer patients in Australia are 5.5% (95% Confidence Interval, CI, 4.5%-6.8%) and 4.2% (95% CI, 3.6%-5.0%), respectively.

Conclusions
First-course chemotherapy improved population-based survival in head and neck cancer patients, when used in accordance with guidelines recommendations. Measurement of population survival benefits of cancer treatment is important as these can provide salient inputs for economic analyses, aid in priority setting in cancer program and guide quality improvement according to evidence-based guidelines.

Legal entity responsible for the study
CCORE, Ingham Institute for Applied Medical Research, Sydney, Australia.

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Disclosure
All authors have declared no conflicts of interest.

1089P - GSTP1 c.313A>G, XPD c.934G>A, XPF c.2505T>C and CASP9 c.-1339A>G polymorphisms and severity of vomiting in head and neck cancer patients treated with cisplatin chemoradiation

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Background

Cisplatin (CDDP) chemotherapy associated with radiation (RT) has been used in head and neck squamous cell carcinoma (HNSCC) patients, and vomiting is a common side effect during treatment. This prospective study aimed to identify the roles of GSTM1 and GSTT1 (presents or nulls), GSTP1 c.313A>G, XPC c.2815A>C, XPD c.934G>A and c.2251A>C, XPF c.2505T>C, ERCC1 c.354C>T, MLH1 c.-93G>A, MSH2 c.211 + 9C>G, MSH3 c.3133G>A, EXO1 c.1765G>A, TP53 c.215G>C, CASP3 c.-1191A>G and c.-1168G>T, CASP9 c.-1339A>G, CASP8 c.-937_-932delAGTAAG, FAS c.-1378G>A and c.-671A>G, and FASL c.-157-687C>T single nucleotide polymorphisms, involved in CDDP metabolism, in vomiting severity in HNSCC patients treated with CDDP and RT.

Methods

We evaluated 88 HNSCC patients diagnosed June 2011-February 2014 which receive CDDP chemoradiation. Ondansetron and dexamethasone were administered as antiemetic therapy and evaluated using National Cancer Institute criteria. Genotypes were analyzed in genomic DNA by polymerase chain reaction based methods. The logistic regression model was used to identify variables influencing toxicities and significant results were validated using a bootstrap (bt) resampling to investigate the stability of risk estimates (1000 replications).

Results

GSTP1 c.313AG or GG genotype alone (46.7% vs 18.6%, P = 0.004) and combined with XPD c.934GA or AA (50.0% vs 16.7%, P = 0.02; P_{bt} = 0.008), XPF c.2505TC or CC (52.2% vs 16.7%, P = 0.02; P_{bt} = 0.007) and CASP9 c.-1339AG or GG (51.9% vs 16.7%, P = 0.02; P_{bt} = 0.01) genotypes were more common in patients with moderate/severe vomiting than other genotypes. Carries with GSTP1 c.313AG or GG genotypes alone and combined with XPD c.934GA or AA, XPF c.2505TC or CC and CASP9 c.-1339AG or GG genotypes had 4.28, 5.00, 5.45, and 5.38 more chances of presenting moderate/severe vomiting than others.

Conclusions

Our data suggest, for the first time, that inherited abnormalities in DNA repair and apoptosis pathways are capable of modulating emesis in HNSCC patients under CDDP chemoradiation, and may be used for selecting patients who deserve to receive distinct doses of antiemetics or association of potent antiemetics in clinical practice.

Legal entity responsible for the study

Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)

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None

Disclosure

All authors have declared no conflicts of interest.

1090P - Analysis of the impact of the tumours committee on the multidisciplinary approach to head and neck epidermoid cancer in our institution

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Background
The objectives are to define the characteristics of people with HNSCC treated in our area and quantify the impact of the committee on the staging, the change in the initial treatment proposed to determine whether the selection of treatment by the multidisciplinary team (MDT) influences therapeutic compliance.

Methods
Observational retrospective study of two cohorts, which aims to analyse the variables in the cohort of patients handled by an MDT with respect to the patients without an MDT. We included all patients with an initial diagnosis of HNSCC at our centre between 2005 and 2012. The MDT cohort comprised those from 01/01/2009 to 31/12/2012. With access to the Pathological Anatomy database, the records of the MDT, the archived and computerised medical history, we collected the endpoints related to the patient (age, sex, ECOG), the tumour (date of diagnosis, location, and TNM stage), the treatment (therapy selected, change in treatment, compliance, reason for default). Definitive sample consists of 408 patients. A descriptive analysis is given of the clinical characteristics of the sample, together with the comparative bivariate analysis of these characteristics in the cohorts.

Results
Our population presents age (mean) 64.2y (SD 12.4), male 82.6%, ECOG<2 89%, 32.1% laryngeal location, tumour stage IVA 31.6%. Treatment with surgery (S) 43.4%, S and radiotherapy (RT) 14.7%, RT 10% and chemo-radiotherapy 9.8%. From our comparative analysis we want to highlight (C1 vs C2) change in stage 26 vs 19.7%, increase 1.5 vs 15.4%(p < 0.001), change of treatment 34.5 vs 39.9% (p < 0.001), organ-preservation without surgery 3 vs 6.3% (p < 0.001) and therapeutic compliance 91 vs 92.3% (p = 0.72).

Conclusions
The population served in our area presents clinical characteristics similar to those of other series published in our and other countries. The MDT improved the staging of the tumour before treatment in a statistically significant way. The change in treatment is higher, so as to be statistically significant, when the therapeutic planning is addressed by an MDT. No statistically significant difference was observed in therapeutic compliance rates when treatment was decided by the MDT.

Legal entity responsible for the study
María José Martínez-Ortiz

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1091P - Prognostic nutritional index (PNI) is an independent prognostic factor in locoregionally advanced squamous cell head and neck cancer (LAHNSCC)

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Background
There is increasing evidence that the presence of an ongoing systemic inflammation response and the nutritional status are a stage-independent predictor of poor outcome in cancer patients. This study aims to investigate association of the Prognostic Nutritional
Index (PNI), a proposed marker of cancer-related inflammation and nutritional status, with survival in LAHNSCC patients (pts).

**Methods**

We included 137 LAHNSCC pts treated with induction chemotherapy (ICT) followed by concurrent chemoradiotherapy (CCRT) at Hospital La Fe (HFV) (n = 50) and Hospital Clínico (HCV) (n = 87) between 2011-2016; they were used as a training (HFV) and validation (HCV) set respectively. Demographic and clinical data were collected. All nutritional factors were measured within 5 days before ICT. PNI was calculated as: 10× serum albumin concentration (g/dL) + 0.005× lymphocyte count (number/mm2) in peripheral blood (Nozoe et al, 2010). Receiver operating characteristic (ROC) curve was used to determine the optimal cutoff for PNI in the HFV set. Cox regression models were used to investigate the association of PNI with OS.

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>0 points</td>
<td>PNI ≥ cutoff = PNI-high group</td>
<td>Normal nutritional status – Low risk</td>
</tr>
<tr>
<td>1 point</td>
<td>PNI &lt; cutoff = PNI-low group</td>
<td>Moderate severe nutritional impairment - High Risk</td>
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**Results**

At baseline, HFV pts were younger with a median age of 54.5 (41-59 years) vs 60.6(43-77 years) and with less advanced stage (stage III 18.8 vs 20.5%; stage IVA: 78.1 vs 62.1%; stage IVB:3.1 vs 17.2%). The optimal cutoff established in the HFV set was 45. According to this cutoff, 10 pts (20%) in HFV set had a low PNI. In HFV set, OS at 12-months follow-up (FU) was 75% in PNI-high group vs 37.5% in PNI-low group (P = 0.032) with a Hazard ratio of (HR) of 2.84 (95%CI 1.04-7.78) in the multivariate analysis. In the HCV set, a low PNI was found in 23 (26.4%) out of 87 pts. OS at 12-months FU was 95% in PNI-high group and 45% in PNI-low group (p = 0.007) with a HR of 3.9 (95% CI 1.45-10.98) in the multivariate analysis.

**Conclusions**

PNI is a valuable prognostic marker in LAHNSCC associated with survival in pts treated with ICT followed by CCRT. PNI could be useful for stratification in future clinical trials.

**Clinical trial identification**

None

**Legal entity responsible for the study**

Gema Bruixola

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1092P - CASP9 c.-1339A>G and CASP3 c.-1191A>G polymorphisms in susceptibility and outcome of head and neck squamous cell carcinoma**

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J. Rinck-Junior (Campinas, Brazil) G. J. Lourenço (Campinas, Brazil) C. S. Lima (Campinas, Brazil)

**Background**
We analyzed herein the roles of CASP9 c.-1339A>G (rs4645978) and CASP3 c.-1191A>G (rs12108497) single nucleotide polymorphisms (SNPs) of intrinsic apoptosis pathway on risk and behavior of head and neck squamous cell carcinoma (HNSCC).

Methods
DNA of 350 HNSCC patients and 350 controls was analyzed by polymerase chain reaction method and enzymatic digestion for genotyping. Patients were treated according to the Institutional protocol, including surgery, radio and chemotherapy. The statistical analyses were realized using chi-square, logistic regression model, multifactor dimensionality reduction (MDR), Kaplan-Meier, and univariate and multivariate Cox analyses.

Results
CASP3 c.-1191AG or GG genotype was more common in patients with overall HNSCC (63.4% versus 53.4%, P= 0.013), male patients with overall HNSCC (65.5% versus 53.4%, P= 0.011), patients with SCC of oral cavity (OCSCC) (68.0% versus 53.4%, P= 0.02) and SCC of pharynx (PSCC) (62.7% versus 53.4%, P = 0.010) than in controls; carriers of genotypes were under 2.15 and 2.34-fold increased risks of overall HNSCC, 2.75 and 2.67-fold increased risks of OCSCC and PSCC, respectively. Interactions of CASP9 and CASP3 SNPs and tobacco on HNSCC, OCSCC, PSCC, and laryngeal SCC risks were evident in study (P< 0.01). At 60 months of follow-up, event-free survival was worst in patients with CASP9 c.-1339GG genotype (35.9% versus 45.1%, P = 0.04) compared to others (Kaplan-Meier estimates). Patients with CASP9 c.-1339GG genotype and CASP9 c.-1339GG plus CASP3 c.-1191GG genotypes had 1.46 more chances of disease progression or relapse and 2.66 more chances of evolving to death in univariate and multivariate analyses, respectively.

Conclusions
We present, for the first time, preliminary evidence that inherited abnormalities in the intrinsic apoptosis pathway, related to CASP9 c.-1339A>G and CASP3 c.-1191A>G SNPs, are important determinants of HNSCC risk and outcome. Financial support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Legal entity responsible for the study
Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1093P - Resource-stratification of national comprehensive cancer network (NCCN®) head and neck cancers guideline

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Background
Resource constraints in low- and middle- income countries (LMICs) often impede critical medical care. 65% of new cases of lip and oral cancer, and 76% of related deaths occur in LMICs, where patients lack access to standard diagnostic tests and/or treatment.
approaches. The development of resource-stratified clinical guidelines promotes access to critical diagnostic and treatment pathways in LMICs.

**Methods**
To address the unmet need in LMICs, a multi-disciplinary committee of NCCN Member Institution experts developed the NCCN Framework™ for Head and Neck Cancers: Lip and Oral. In the evidence-based, resource-stratified Guidelines, recommendations from the NCCN Guidelines for Head and Neck Cancers were assigned to specific resource levels, based on access to various interventions and importance in achieving clinical outcomes. International experts reviewed the resource-stratified Guidelines to assess utility in LMICs and NCCN approved and published the finalized guidelines.

**Results**
The NCCN Framework for Head and Neck Cancers: Lip and Oral has four resource levels: Basic, Core, Enhanced, and Parent guideline. The Framework for Basic Resources identifies essential services required for minimal standard of care for improvement in outcome; the Core Resources lead to improved outcomes but are not cost prohibitive; the Enhanced Resources recommend additional services that may improve outcomes, but may be cost prohibitive in certain settings. For initial treatment of early stage cancer of the oral cavity (T1-2, N0) as an example, the Enhanced Framework recommends surgical resection and radiation therapy (RT), but not sentinel lymph node (SLN) biopsy, which is recommended in the NCCN parent Guidelines and requires more advanced resources. The Basic Framework recommends surgical resection as the only primary treatment option, since RT may not be available at this resource level.

**Conclusions**
The NCCN Framework for Head and Neck Cancers: Lip and Oral provide LMICs with a system to optimize care in limited resource settings, and a map to improve cancer care incrementally as resources become available. Use of this framework facilitates improved patient care in resource-constrained settings.

**Legal entity responsible for the study**
National Comprehensive Cancer Network

**Funding**
None

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

**1094P - Long-term results of chemoradiotherapy for stage III nasopharyngeal carcinoma patients and risk grouping by pretreatment EBV viral load**

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**Background**
No previous study reported the treatment outcome of stage III nasopharyngeal carcinoma (NPC) patients. The aim of this study is to investigate the long-term clinical outcome of stage III NPC patients and do risk grouping by plasma EBV DNA assay for future therapy improvement.

**Methods**
A total of 356 previously untreated, pathologically-proven NPC patients with stage III disease and available pretreatment plasma EBV DNA data were enrolled in this
retrospective study. Initial definitive treatment consisted of concurrent chemoradiotherapy or induction chemotherapy plus radiotherapy. Eighty-four of 356 (23.6%) patients also received post-RT adjuvant chemotherapy. Patients with pretreatment EBV DNA > 1000 copies/mL were defined as a high-risk subgroup (n = 106) and the remaining patients as a low-risk subgroup (n = 250).

Results
After a median follow-up of 90 months, there were 66 recurrences (18.5%) and 57 deaths (16.0%). The 5-year overall survival (OS), progression-free survival (PFS), distant metastasis failure-free survival (DMFFS), and locoregional failure-free survival (LRFFS) for all 356 patients were 88.4%, 83.9%, 90.5%, and 90.5%, respectively. Thirty-five of 105 (33.0%) high-risk patients developed tumor relapse later, whereas only 12.4% (31/250) low-risk patients had tumor relapse (P < 0.0001) Survival analysis revealed that the high-risk subgroup had significantly worse OS (5-year rate, 79.9% vs. 92.8%, P < 0.0001), PFS (73.7% vs. 88.4%, P < 0.0001), DMFFS (80.2% vs. 95.0%, P < 0.0001), and LRFFS (85.6% vs. 92.6%, P = 0.0045) than those of the low-risk subgroup.

Conclusions
Long-term treatment results for Stage III NPC patients were good. Risk grouping identified a subgroup of patients with high pretreatment EBV DNA had a significantly higher relapse rates and worse survivals. Future trial should strengthen treatment intensity for these high-risk patients.

Legal entity responsible for the study
Taichung Veterans General Hospital

Funding
Taichung Veterans General Hospital

Disclosure
All authors have declared no conflicts of interest.

1095P - Nasopharyngeal cancer in children: Long term results the experience of the university hospital of Sfax (Tunisia)

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Background
Nasopharyngeal carcinoma in children is frequent in Mediterranean area. We aimed to report our experience in the treatment of this entity.

Methods
We retrospectively review the records of 76 young patients (<21 years) presenting with nasopharyngeal cancer during the period 1993-2015. Diagnosis was confirmed with histological study of the biopsy of nasopharynx. Initial work-up included nasofibroscopy, CT scan and/or MRI of the nasopharynx and neck, chest X-ray, abdominal ultrasonography and bone scan. TNM 2009 classification was used. Patients treated before 2009 were retrospectively reclassified. Metastatic patients were excluded. Patients had cisplatin based regimen chemotherapy (neoadjuvant, concomitant or both). Radiotherapy was delivered at the dose of 70 to 75 Gy targeting the nasopharynx and involved cervical nodes. Prophylacting dose up to 50 Gy was delivered to the remaining cervical areas. Survival was studied with Kaplan Meier test. Late toxicities were assessed
according to SOMA-LENT and RTOG scales in patients with a minimal follow-up of 24 months.

**Results**

Mean age was 16 years (9 – 20). Sex-ratio was 1,1. Seventy two percent of patients (n = 55) had locally advanced tumor (T3 or T4). Cervical nodal involvement was seen in 95% of cases (n = 71). There were 52 cases (68%) of N2 or N3. Sixty-six patients had neoadjuvant chemotherapy, 10 had concomitant and 5 had both. Five patients had exclusive irradiation. Radiotherapy was monofractionated in 45 cases and bifractionated in the remaining cases. Acute toxicities were tolerable. Mean follow-up was 198 months (28-289). One patient experienced a local failure. Twenty-six presented metastatic failures. Overall survival rate at 10 years is 67,4%. Disease free survival rate at 10 years is 66,7%. Xerostomia was the most frequent late toxicity (97%). Patients experienced endocrine troubles (hypothyroidism in 19%, amenorrhea in 13%), cerebral necrosis (5 cases), osteoradionecrosis (10 cases) and secondary cancer (3 cases).

**Conclusions**

Pediatric nasopharyngeal carcinoma has good prognosis despite frequent locally advanced disease at presentation. Combining radiotherapy and chemotherapy is the standard of care. Late toxicities are often severe and affect the quality of life.

**Legal entity responsible for the study**

University Hospital of Sfax - Tunisia

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1098P - Incidence and impact of DPD mutation on neoadjuvant chemotherapy in head and neck cancers**

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**Background**

Dihydropyrimidine dehydrogenase (DPD) is an enzyme essential for metabolism of 5FU. The incidence of polymorphisms or mutation in variable across different ethnic populations. This study is first report highlighting the high incidence of DPYD mutation is seen in head and neck cancers in India.

**Methods**

Consecutive patients with head and neck cancer undergoing TPF neoadjuvant chemotherapy at our centre between May 2015 - December 2016 underwent DPD mutation analysis. The haematological toxicities consisting of neutropenia and thrombocytopenia while gastrointestinal toxicities consisting of mucositis and diarrhea were considered as 5FU related toxicities for this analysis. Toxicities were graded in accordance with CTCAE (Common terminology criteria for adverse events) version 4.03. DPYD mutation analysis by Sanger sequencing on ABI 3500 platform, for the most prevalent exonic regions (Exon 13 →c1627 A>G (DPYD*5) p1543V (ATA>GTA); Exon 14 – 1845 G>T; (E615D) missense mutation, Exon 14 splice variant G>A and Exon 18
(DPYD*6) pV7321) - c2194 G>A (GTT>ATT}). Descriptive statistics was performed using SPSS version 16 and RStudio. Proportions with 95% CI were described. Fisher's exact test was performed to see the relationship between DPD mutation status and grade 3-5 adverse events.

**Results**

Consecutive 118 patients were included in this analysis. The median age was 45 years (IQR 37.25-54.00 years). The median cycles of TPF received were 2 (range 1-4). DPD mutation was seen in 29 patients (24.59%, 95%CI 16.94-32.23%). The mutations were seen in exon 18 in 17 patients (14.4%), exon 13 in 9 patients (7.6%) and in both exon 13 & 18 in 3 patients (2.5%). 100 patients were eligible for assessment of adverse events (84.7%). The rate of grade 3-5 haematological and gastrointestinal adverse events was 64% and 35% respectively. The rate of grade 3-5 haematological (88.5% versus 55.4%, p=0.002) and gastrointestinal adverse events (57.7% versus 27.0%) were higher in DPYD mutated cohort.

**Conclusions**

This study signifies the importance of ethnic difference in drug polymorphism and mutations. The impact of these adverse events in DPD mutated patients justifies doing a DPD mutation prior to subjecting patient to 5FU in head and neck cancer.

**Legal entity responsible for the study**

Tata Memorial Hospital Centre, Mumbai

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

1099P - Radiotherapy related xerostomia in head and neck oncology: A systematic review

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**Background**

Radiotherapy in the head and neck region can lead to salivary gland hypofunction and as a result dry mouth ensues. We have undertaken this systematic review and meta-analysis to estimate the effectiveness of available interventions for radiotherapy-induced xerostomia and hyposalivation.

**Methods**

A systematic review and meta-synthesis techniques were adopted to identify, appraise and synthesize the relevant literature regarding the experience of nutritional symptoms of HNC patients conducted according to the PRISMA guidelines. Several electronic databases such as PubMed, CINAHL, Scopus, PsycINFO and the Cochrane Library databases were searched.

**Results**

1598 patients from Eighteen studies were included in the systematic review. Cholinergic agonists like Pilocarpine, cevimeline and bethanechol were tested in most studies. Other drugs tested include malic acid, physostigmine, specific monoclonal antibodies like Rituximab, fluoroquinolones, saliva substitutes/mouthcare systems, hyperthermic humidification, acupuncture, acupuncture-like transcutaneous electrical nerve stimulation,
low-level laser therapy and herbal medicine. A recent study evaluated the salivary parameters in 4 phases. Results of meta analysis suggests cholinergic agonists were the most effective to improve salivary flow, compared to placebo, although some aspects of the relevant effect size, duration of the benefit, and clinical meaningfulness remain unclear.

Conclusions
Pilocarpine, bethanechol and cevimeline should represent the first line of therapy in head and neck cancer survivors with radiotherapy-induced xerostomia and hyposalivation. The use of other treatment modalities cannot be supported on the basis of current evidence.

Clinical trial identification
nil

Legal entity responsible for the study
nil

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1100P - The phase II study of HMB/Arg/Gln against oral mucositis induced by chemoradiotherapy for head and neck cancer patients

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Background
Opioid-based pain control and systemic oral care program are effective for the chemoradiotherapy (CRT)-induced severe oral mucositis (OM) in patients with head and neck cancers (HNC). This phase II trial assessed the clinical benefit of beta-Hydroxy-beta-Methylbutyrate, Arginine, and Glutamine (HMB/Arg/Gln) in the prevention of CRT-induced OM in patients with HNC.

Methods
Patients with HNC who were scheduled to receive definitive or postoperative cisplatin-based CRT were enrolled. HMB/Arg/Gln was administered orally or per percutaneous endoscopic gastrostomy from the first day of CRT up to completion of CRT. All patients received opioid-based pain control and oral care programs we previously published. The primary endpoint was the incidence of grade ≥3 OM (functional/symptomatic) according to the Common Terminology Criteria of Adverse Events version 3.0. QOL (EORTC QLQ-C30/PROMS) and intake of nutrition at baseline and 50Gy were also assessed.

Results
From February 2015 to June 2016, 35 patients with HNC were enrolled. Sixteen patients (45.7%) developed grade ≥3 OM (i.e., functional/symptomatic). The incidence of grade ≤1 OM (functional/symptomatic) was 51.5% at 2 weeks and 82.9% at 4 weeks after completion of RT. Clinical examination revealed that 10 patients (28.6%) developed grade ≥3 OM. The incidence of grade ≤1 OM (clinical exam) was 80.0% at 2 weeks and 100% at 4 weeks after completion of RT. Only 5.7% of patients had unplanned breaks in
radiotherapy, and all patients completed treatment. Adverse events related to HMB/Arg/Gln were increase in blood urea nitrogen and diarrhea, but were easily managed.

**Conclusions**

Addition of HMB/Arg/Gln to opioid-based pain control and oral care programs was feasible but still insufficient in reducing the incidence of severe CRT-induced oral mucositis. However, the benefit of HMB/Arg/Gln should not be neglected in terms of findings of clinical examination and the recovery from severe oral mucositis.

**Clinical trial identification**

UMIN000016453

**Legal entity responsible for the study**

None

**Funding**

Public Interest Incorporated Foundation- Shizuoka Industrial Foundation- Pharma Valley Center

**Disclosure**

All authors have declared no conflicts of interest.

**1101P - Oral mucosa dose parameters predicting grade ≥3 acute toxicity in locally advanced nasopharyngeal carcinoma patients treated with concurrent intensity-modulated radiation therapy and chemotherapy**

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**Background**

To determine whether volumes based on the contours of the mucosal surface can be used instead of the contours of the oral cavity to predict for grade ≥3 acute oral mucosa toxicity in patients with locally advanced nasopharyngeal carcinoma (LANPC) treated with concurrent intensity-modulated radiation therapy (IMRT) and chemotherapy.

**Methods**

A standardized method for the oral cavity (oral cavity contours, OCC) and a novel method for the mucosal surface (mucosal surface contours, MSC) were developed for the oral mucosa and prospectively applied to the radiation treatment plans of 92 patients treated with concurrent IMRT and chemotherapy for LANPC. Dose–volume histogram (DVH) data were extracted and analyzed against patient toxicity. Receiver operating characteristic analysis and logistic regression were carried out for both contouring methods.

**Results**

Grade ≥3 oral mucosa toxicity occurred in 20.7% (19/92) of patients in the study. A highly significant dose–volume relationship between oral mucosa irradiation and acute oral mucosa toxicity was supported by using both oral cavity and mucosal surface contouring techniques. In logistic regression, body weight loss was an independent factor related to grade ≥3 toxicity for OCC and MSC (p=0.017 and 0.005, respectively), and the independent factor of dosimetric parameters for OCC and MSC were V30Gy (p=0.003) and V50Gy (p=0.003), respectively. In the receiver operating characteristics curve, the areas under V30Gy of the OCC curves was 0.753 (p=0.001), and the areas under V50Gy of MSC curves was 0.714 (p=0.004); the cut-off value was 73.155% (sensitivity, 0.842; specificity, 0.671) and 14.32% (sensitivity, 0.842; specificity, 0.575), respectively.
Conclusions
DVH analysis of mucosal surface volumes accurately predicts grade ≥3 oral mucosa toxicity in patients with LANPC receiving concurrent IMRT and chemotherapy, but the MSC method is still no better than the OCC method in clinical application.

Clinical trial identification
NCT02945878

Legal entity responsible for the study
Yuanyuan Chen

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1102P - Sinonasal non-glandular cancers relapsing after multimodal treatments
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Background
Multimodality treatment (MMT) is the current approach to advanced sinonasal cancers (SC). We lack salvage treatment standardization especially for pts already receiving MMT. No clinical factors able to predict outcome have been identified in this disease setting.

Methods
We retrospectively analyzed a series of pts with recurrent/metastatic (RM) SC after multimodal curative treatment, consisting in induction chemotherapy (iCT) followed by locoregional therapy. Overall survival (OS) was measured as the interval from relapse to death.

Results
Among 106 pts with SC treated with MMT at our Center from 1997 to 2016, 50 (M/F 31/19) relapsed. Median age was 53 yrs (16-73). Median follow-up was 26 months (m) (5-192). WHO 2005 histotypes were: 36% sinonasal undifferentiated carcinoma (SNUC), 34% squamous cell cancer (SCC), 30% carcinomas with neuroendocrine differentiation (CND). Median time to first relapse after curative treatment was 13.5 m. Median OS was 13 m from recurrence: 19 m in SCC, 16 m in SNUC and 6 m in CND (p = .34). Relapse occurred as distant metastasis in 40%, as nodal recurrence in 6% and at primary site in 54% of cases. First line salvage treatment was surgery in 38% (14 pts received surgery on T, 2 on N and 3 on M), CT in 30%, RT in 8%, best supportive care in the remaining pts. Median OS was 31 m in surgically treated pts and 4.8 m in those receiving CT (p < .0001). In pts with disease control (PR+SD) after iCT, median OS after recurrence was longer than in pts with PD (13.4 vs 1.5 m, p = .07). Median OS from relapse was 29.6 m in pts with CR after definitive treatment, 7.1 m in those with PR and 3.4 m in those with PD (p = .002). Pts with an objective response to palliative CT had a longer median OS than those with PD (20 vs 4 m, p = .002).

Conclusions
Prognosis of SC relapsing after MMT is dismal. With the caveat of a retrospective analysis
and a case series that has been collected in a long time frame, we showed that feasibility of salvage surgery, objective response to prior definitive treatment and response to palliative CT are factors associated with better outcomes. Pts with relapsed or metastatic SC not amenable to salvage surgery should be considered for enrolment in clinical trials.

Legal entity responsible for the study
Fondazione IRCCS Istituto Nazionale Tumori Milano - Università degli Studi di Milano. Italy

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1103P - Survival outcome and optimal treatment of intermediate-grade salivary gland carcinoma
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Background
Histological grade is the most important factor for defining treatment strategies and predicting prognosis for salivary gland carcinoma (SGC). Although several studies have addressed low- and high-grade SGCs, intermediate-grade SGC (IGSGC) has received minimal attention. Therefore, we examined factors affecting long-term recurrence and survival among IGSGC patients to define optimal treatment modalities and outcomes.

Methods
We reviewed the clinical and pathological data of 108 IGSGC patients who underwent definitive surgery with or without postoperative radiotherapy at our tertiary referral center between 1994 and 2014. We performed univariate and multivariate analyses of variables predictive of locoregional control (LRC), distant metastasis-free survival (DMFS), and overall survival (OS). We compared treatment outcomes by treatment strategies such as surgical extent, primary tumor, neck dissection, or postoperative radiotherapy.

Results
During a median 103 (range, 24–282)-month follow-up, local, regional, and distant recurrences were detected in 14 (13.0%), 3 (2.8%), and 21 (19.4%) patients, respectively. The 10-year LRC, DMFS, and OS rates were 83.1%, 76.0%, and 80.1%, respectively. Multivariate analyses identified a non-parotid primary site as an independent prognostic factor for LRC ($P = 0.018$), Adenoid cystic carcinoma and positive pN classification were significantly unfavorable prognostic factors for DMFS ($P = 0.025$ and $P = 0.030$, respectively); overall advanced stage was an independent prognostic factor for OS ($P = 0.020$). Surgical extent, elective neck dissection, and postoperative adjuvant radiotherapy did not significantly affect treatment outcomes.

Conclusions
Patients with early-stage IGSGC of parotid origin can achieve favorable treatment outcomes with conservative surgery alone.

Legal entity responsible for the study
no

Funding
None
Disclosure
All authors have declared no conflicts of interest.

1104P - Incidence and survival of secondary malignances (SM) in oropharingeal squamous cell carcinoma (OPSCC): A homogeneous single report institution

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Background
SM in HNSCC patients (pts) are common, due to the presence of risk factors (smoking habit or alcohol abuse). Aim of this report is to evaluate the incidence and characteristics of SM in a series of OPSCC.

Methods
We retrospectively reviewed clinical data of 266 pts with OPSCC seen at Modena University Hospital between 2006 and 2016. We recorded data from a web platform in which every pt has a personal form filled with clinical information. In particular, we analyzed the rate of SM and described clinical and survival data.

Results
SM was diagnosed in 37 pts (13,9%): 15 NSCLC (5% on all; 40,5% of SM); 7 HNSCC (18,9%), 8 GI (21,6%), 2 prostate (5,4%), 2 thyroid cancer (5,4%), 2 hematologic malignancy (5,4%) and 1 melanoma (2,7%). Clinical features at diagnosis for OPSCC: 30 (81%) male, 7 (19%) female; median age 68 years (range 37-90). Twenty-five pts (67,6%) were current/former smokers, 26 (70,3%) HPV-positive; stage at diagnosis was I-II in 5 (13,5%) and III-IV in 32 pts (86,5%). Eleven pts developed SM < 12 vs 26 ≥12 months (mo) after the diagnosis of OPSCC. Stage at diagnosis for SM was: for lung 10 (66,6%) I-II vs 5 (33,4%) III-IV; for HNSCC 3 (42,8%) I-II vs 4 (57,2%) III-IV; for GI 2 (25%) I-II vs 6 (75%) III-IV. Treatments for SM: 18 surgery, 2 RT, 8 CT, 5 combined treatment; 4 pts did not need or not received therapy. Death occurred in 18 pts (48,6%): SM-related in 12 (66,6%), OPSCC-related in 3 (16,7%) and not cancer-related in 3 (16,7%). mOS from diagnosis of OPSCC vs SM were 68,5 and 21,3 mo, respectively. Pts with lung or HNSCC SM (mOS 6,7 mo) had worse OS than pts with other SM (mOS 20,7 mo), but not statistically significant. Pts with SM diagnosed ≥ 12 mo vs < 12 mo after OPSCC had a significantly better OS (mOS 81 vs 25,1 mo; p < 0.001).

Conclusions
In our retrospective series, we confirmed that secondary lung cancer was the most frequent SM; it was diagnosed at earlier stage, because these pts underwent a periodical follow-up for their previous OPSCC with a chest X-ray/CT. Smokers may benefit from a more intensive follow-up for a higher risk of smoking related SM (lung, HNSCC). Survival is more influenced by the occurrence of SM than by OPSCC. All these considerations should be applied to a larger series.

Legal entity responsible for the study
Modena University Hospital

Funding
None

Disclosure
1105TiP - Pembrolizumab plus chemoradiation (CRT) for the treatment of locally advanced head and neck squamous cell carcinoma (LA-HNSCC): Phase 3 KEYNOTE-412 trial

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Background

Despite significant advancements in oncologic treatment, the outcome for patients with advanced or recurrent HNSCC is poor. Identification of abscopal effects by use of radiotherapy (RT) in combination with immunotherapy in a patient with metastatic melanoma has prompted interest in the use of combination regimens. The objective of the KEYNOTE-412 trial (NCT03040999) is to assess efficacy and safety of pembrolizumab in combination with CRT as maintenance therapy for subjects with LA-HNSCC.

Trial design

KEYNOTE-412 is a phase 3, randomized, placebo-controlled, double-blind trial enrolling subjects with newly diagnosed, treatment-naive, oropharyngeal p16 positive (any T4 or any N3), oropharyngeal p16 negative (any T3-T4, or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4, any N2a-N3) SCC. Approximately 780 subjects will be randomly assigned (1:1) to receive pembrolizumab plus cisplatin-based CRT or placebo plus cisplatin-based CRT. Subjects will be stratified by RT regimen, tumor site/p16 status, and disease stage. Treatment will include a priming dose of pembrolizumab 200 mg or placebo 1 week before initiation of CRT, followed by 7 weeks’ CRT (cisplatin 100 mg/m² every 3 weeks [Q3W] [3 doses]; accelerated RT [70 Gy, 6 fractions/week] or standard RT [70 Gy, 5 fractions/week]) plus pembrolizumab 200 mg Q3W or placebo Q3W. Treatment with pembrolizumab 200 mg Q3W or placebo Q3W will continue up to 1 year (maximum 17 doses). Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, or investigator decision to withdraw the patient. Response will be assessed by computed topography or magnetic resonance imaging 12 weeks after completion of CRT, every 4 months for a subsequent 2 years, and every 6 months thereafter up to year 5. Safety will be monitored throughout the study. The primary end point is event-free survival by blinded independent central review per RECIST v1.1. Secondary end points include overall survival, safety, and quality of life. Exploratory biomarker analyses will be conducted.

Clinical trial identification

NCT03040999, February 1, 2017

Legal entity responsible for the study

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

Funding

Merck & Co., Inc., Kenilworth, NJ, USA Disclosure: J-P. Machiels: Advisory board member: MSD (uncompensated), Innate, AstraZeneca, Nanobiotix, Debio; Research funding: Bayer, Janssen, Novartis. L. Licitra: Travel expenses, including accommodations: Merck-Serono, Debiopharm, Jobi, Bayer, Amger; Consulting or Advisory Role: Eisai, Bristol-Myers Squibb, MSA, Merck-Serono, Debiopharm, Jobi, Novartis, AstraZeneca,
Background

SGCs are rare and heterogeneous tumors (<1% of all malignancies in Europe). Among more than 20 histotypes, only salivary duct carcinoma (SDC) and adenocarcinoma NOS express AR. These variants are aggressive and associated with poor prognosis. Surgery is the main curative treatment, but upon relapse, patients are left with very few options. There is an urgent need to understand their biology to enable progress in this rare disease. This study (NCT01969578) aims to evaluate the efficacy and safety of ADT (experimental arm) vs chemotherapy (standard arm) in patients with recurrent and/or metastatic AR overexpressing SDC and adenocarcinoma, NOS by demonstrating a 15% improvement in Progression Free Survival (PFS) rate at 6 months in favor of ADT.

Trial design

In this multicenter, randomized, phase II intergroup study, a total of 76 treatment naïve patients (Cohort A) are planned to be randomized to receive ADT or platinum-based chemotherapy. Previously treated patients will be enrolled in a separate Cohort B to receive ADT. Patients from Cohort A randomized to chemotherapy can also enter Cohort B at disease progression. The primary endpoint is PFS for Cohort A and best overall response for Cohort B. Central testing of AR expression is based on staining intensity (0 = negative to 3 = strong) and percentage of positive nuclear stained cells (0 = ≤10% to 3 = ≥70%). AR overexpression requires a maximum score of 3 on both scales. Mechanisms of AR activation and resistance will be studied. This study is led by EORTC Head and Neck Cancer with UNICANCER/REFCOR, International Rare Cancer Initiative UK Salivary Gland Cancer Group and RARECARENet. It will run in 35 sites in 10 countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Portugal, The Netherlands, and United Kingdom. Sites from the EURACAN European Reference Network are participating. Currently, 36 patients are registered; 20 have AR overexpression, of which 16 have been randomized in Cohort A. Identification of AR as a treatment target in SGC can be practice changing.

Clinical trial identification

EORTC 1206 HNCG http://clinicaltrials.gov/ct/show/NCT01969578
1107TiP - Phase II trial of abiraterone acetate in patients with relapsed and/or metastatic, castration resistant AR expressing salivary glands carcinomas (SGCs)

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**Background**

Expression of androgen receptors (AR), is reported in more than 80% of salivary duct carcinomas (SDC) and in 50% of adenocarcinomas, NOS. Similarly to prostate cancer (Pca), androgen deprivation therapy (ADT) has been employed with success in patients with metastatic AR-expressing SDC and adenocarcinoma, NOS in so much as an international randomized trial is ongoing to assess the efficacy of ADT over chemotherapy as first line treatment in this setting of patients (NCT01969578). Abiraterone acetate was approved in advanced, castration resistant Pca in 2011. We tested the activity of abiraterone in two patients with AR-positive castration resistant adenocarcinoma, NOS obtaining two partial responses (Locati LD, Cancer Biol Ther 2014).

**Trial design**

This is a phase II trial (NCT02867852) aimed at assessing the activity (CR+ PR) of abiraterone in castration resistant AR-positive SGCs. The drug will be considered effective and worth of further evaluation if the response rate will be at least 20%. The null hypothesis will be RR 5% versus the alternative RR20%. A 2-stage Simon design will be applied. Type I and type II error rates are set at the 10% and 20% levels. If at least 1/9 response will be observed in the first step, patients’ enrolment will go on up to a final overall sample size of 24 subjects. If at least 3/24 responses will be recorded, the null hypothesis will be rejected in favor of the alternative and the drug considered promising and worthy of further investigation. Objective tumor response and time to progression will be measured according to RECIST criteria 1.1 and to PCWG2 recommendations for bone lesions. Twenty four patients with AR-expressing SGC, progressed on ADT, will be enrolled over two years. Four 250 mg tablets of abiraterone acetate will be administered daily to patients until progression of disease or intolerable toxicity. Disease control rate, incidence of adverse events, overall survival and progression free survival will be assessed as well. Tumor samples will be also collected for translational analyses (e.g. CYP17 expression; PI3K mutations). Blood and saliva samples will be collected as well.

**Clinical trial identification**

NCT02867852
1108TiP - Chemoradiotherapy versus radiotherapy in the treatment of salivary glands and nasal tumors: The GORTEC 2016-02 study

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Background
Carcinomas of sinuses and salivary glands are rare and heterogeneous in terms of anatomical sites and histology subtypes. For these reasons and because of the absence of prospective study results, their treatment is still largely extrapolated from data of frequent carcinomas of the upper digestive tract. Treatment is based on surgery and radiotherapy (proof level grade C). Despite the advances, the 5-year overall survival does not exceed 65%, mainly due to locoregional recurrence. In this context, chemotherapy administered concomitantly with radiotherapy could increase the efficacy of locoregional treatment by radiosensitization, regardless of the histology.

Trial design
The GORTEC launched a multicenter, phase III randomized, open-label, study evaluating in case of high-risk of locoregional relapse, the impact of the addition after surgery of cisplatin 100 mg/m² (every 3 weeks; 3 cycles) to radiotherapy. The population is defined as patients with radioresistant histologies (e.g. cystic adenoids carcinomas) or patients with unfavorable histoprognostic criteria (e.g. incomplete resection, T4 tumor, malignant lymph node(s) with capsular rupture, presence of emboli, …). The primary endpoint is the progression free survival. Secondary outcomes are: overall survival, quality of life, time to progression (locoregional and distant) and toxicities. Two hundred and sixty patients will be enrolled in 5 years. Eligible patients are adults, with a performance status ≤ 2 and an adequate hematological and renal function for cisplatin treatment. Recruitment is ongoing in France. The study comprises a quality insurance program in radiotherapy and surgery. Coordinating investigators are Drs Ferrand and Thariat.

Clinical trial identification
NCT02998385.

Legal entity responsible for the study
GORTEC (Groupe Oncologie Radiothérapie Tête et Cou)

Funding
GORTEC

Disclosure
All authors have declared no conflicts of interest.

1109TiP - MEDINDUCTION: Phase I trial evaluating the safety of durvalumab in combination with Docetaxel, Cisplatin and 5-FU (DCF) in induction for locally advanced squamous cell carcinoma of the head and neck (SCCHN)

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Background
SCCHN represents the sixth most common malignancy with 650 000 new cases and 350
000 SCCHN-related deaths reported annually worldwide. A majority of patients present with stage III or IV M0 disease, with a 5 year overall survival from 30% to 50%. Results of recent randomized trials evaluating induction chemotherapy by DCF are conflicting, and benefit on overall survival is uncertain. It is needed to improve efficacy of induction chemotherapy without increase toxicities. Tumours can actively evade destruction by the immune system by exploiting inhibitory checkpoint pathways that suppress antitumour T-cell responses. Antibody therapy to block immune checkpoints activated by the programmed cell death ligand-1 (PD-L1) has shown survival benefit in recurrent or metastatic SCCHN. Durvalumab is a selective, high affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80. Durvalumab has shown encouraging antitumour activity in SCCHN with a manageable safety profile. The aim of this open-label, multi-center, Phase 1-b study is to characterize the safety profile of the combination of DCF with durvalumab.

**Trial design**

Patients aged ≥ 18 yr with histologically confirmed SCC of the oral cavity, oropharynx, larynx or hypopharynx, previously untreated, with indication of induction chemotherapy will be eligible. The primary objective is to determine the recommended Phase 2 dose (RP2D). The secondary objectives are to document any antitumor activity (PFS, ORR, RECISTv1.1 criteria), to estimate the pharmacokinetic parameters of durvalumab, to explore the relationships between immune capacity, specificity, activation state and clinical outcome. The study will be conducted in 2 parts: a dose-deescalation part to determine the RP2D (6 pts), and an expansion part (30 pts). The durvalumab will be administered every 3 weeks for 3 injections at week 1, 4, 7. The durvalumab first dose level is 1120 mg and the dose level -1 is 750 mg Q3W. The chemotherapy will be administered every 3 weeks at week 1, 4, 7 at the following doses: Docetaxel 75mg/m$^2$ on D2, Cisplatin 75mg/m$^2$ on D2, 5 Fluorouracil 750mg/m$^2$/day from D2 to D6.

**Clinical trial identification**

NCT 02997332 Eudract number 2015-004146-25

**Legal entity responsible for the study**

Gustave Roussy

**Funding**

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**Disclosure**


**HEALTH ECONOMICS**

M. J. Ijzerman (Enschede, Netherlands)

**1114P - All.Can initiative: improving efficiency in cancer care**

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Background
In industrialised countries, about 20% of healthcare spending is currently wasted on ineffective interventions. With growing cancer prevalence and the increasing complexity of care, efficiency must improve – defined as delivering better outcomes to patients for the resources available.

Methods
The All.Can initiative was set up as a multi-stakeholder platform to engage policymakers on the need to remove obsolescence and focus resources on what matters most to patients across the cancer care continuum. Members of the group include patient organisations, policymakers, healthcare professionals, research and industry representatives from across Europe and Canada. All.Can has a continued programme of research and policy engagement to achieve its aims.

Results
The group issued the following policy recommendations: focus care on what matters most to patients; invest in data to evaluate and monitor whether care is delivering optimal outcomes; instil accountability mechanisms across the cancer care pathway, creating a cycle of continuous improvement; and build political to drive meaningful change to systematise good practice. As a starting point however, we need clear definitions of waste and inefficiency from the patient perspective. All.Can will conduct a comprehensive qualitative survey of cancer patients to create a patient-relevant conceptual framework for waste and inefficiency. The survey will also be extended to oncology specialists. Findings will help determine where greatest opportunities lie to improve efficiency in cancer care, and serve as a basis for concrete policy proposals that may make the greatest difference to cancer patients.

Conclusions
Improving efficiency across the entire cancer care pathway is a complex and pressing challenge that will require close collaboration between all stakeholders. The All.Can initiative is a promising way forward.

Clinical trial identification
Not applicable

Legal entity responsible for the study
The Health Policy Partnership Ltd

Funding
Bristol-Myers Squibb, Amgen and MSD

Disclosure
A. Roediger: Employment with MSD. T. Rosvall-Puplett: Employment with Bristol-Myers Squibb. K. Steinmann: Employment with Amgen. S. Wait: Received consultancy fees from Amgen, MSD and Bristol-Myers Squibb (the funders of All.Can) through organisation, the Health Policy Partnership, for providing secretariat to All.Can. All other authors have declared no conflicts of interest.

1115P - Cost-effectiveness of nivolumab+ipilimumab in first-line treatment of
advanced melanoma: Analysis using 28-month overall survival from CheckMate 067

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Background
The objective of this study is to evaluate the cost-effectiveness of nivolumab+ipilimumab (NIVO+IPI) versus existing treatments in first-line treatment of patients with advanced melanoma from a US payer perspective using recently reported 28-month survival data from the CheckMate 067 phase III trial.

Methods
This three-state partitioned survival model was developed from projections of overall survival (OS) and progression-free survival (PFS) based on a network meta-analysis that considers time-varying hazard ratios to estimate accrued quality adjusted survival, total drug acquisition, follow-up, and toxicity costs over a lifetime time horizon (30 years). Competing treatments included NIVO, IPI, pembrolizumab (PEM), dabrafenib+trametinib (DAB+TRA), DAB, vemurafenib+cobimetinib (VEM+COB), VEM, and dacarbazine (DTIC). Costs and adverse event frequencies were obtained from expert input, publically available sources, and literature. Utility weights were estimated from the CheckMate 067 trial. Incremental analysis is summarized as incremental cost-utility ratios (ICURs) for NIVO+IPI. A 3.5% discount rate is applied to costs ($US 2016) and utilities.

Results
NIVO+IPI is projected to have the greatest accrued survival among the competing treatments with 6.015 LY and 4.979 QALY and also the highest costs ($291,096 including treatment acquisition, follow-up, management of adverse events, and post-progression costs) over the 30-year time horizon. Pairwise ICURs for NIVO+IPI vs. other treatments ranged from $34,774 per QALY (vs. DAB+TRA) to $92,647 per QALY (vs. NIVO). In extended dominance analysis, DTIC, NIVO, and NIVO+IPI form the cost-effectiveness frontier, showing that these are the most cost-effective options at different willingness to pay thresholds. Probabilistic sensitivity analysis generated results consistent with the base case for NIVO+IPI.

Conclusions
The large survival gains of NIVO+IPI make it a cost-effective option for first-line treatment of advanced melanoma when compared to other immune-oncologic therapies, targeted agents, and chemotherapy.

Clinical trial identification
Cost study based on the 067 trial NCT01844505 protocol number is CA209-067 (CheckMate 067)

Legal entity responsible for the study
Bristol-Myers Squibb

Funding
Bristol-Myers Squibb

Disclosure
Background
The addition of palbociclib to letrozole improves progression free survival (PFS) and response rates compared to letrozole alone in the 1st line treatment of hormone receptor positive advanced breast cancer (ABC). This study assesses the cost-utility of palbociclib from the Canadian healthcare payer perspective.

Methods
To evaluate the cost-utility of palbociclib, a probabilistic discrete event simulation model was developed. The model was parameterized with data from the phase 2 and 3 PALOMA 1 and 2 trials and other sources. The incremental cost per quality-adjusted life-month (QALM) gained for palbociclib was calculated. A time horizon of 15 years was used in the base case with costs and effectiveness discounted 5% annually. The time to progression and death were derived from Weibull and exponential distributions, respectively. Expected costs were based on Ontario fees and other sources. Probabilistic sensitivity analyses were conducted to account for parameter uncertainty.

Results
Compared to letrozole alone, the addition of palbociclib provided an additional 14.7 QALM at an incremental cost of $161,508. The resulting incremental cost-effectiveness ratio was $10,999/QALM gained. Assuming a willingness to pay (WTP) of $4167 per QALM, the addition of palbociclib was not cost-effective and the probability of palbociclib to be cost-effective was 0%. Cost-effectiveness acceptability curves derived from a probabilistic sensitivity analysis showed that at a WTP of $11,667/QALM gained, the probability of palbociclib to be cost-effective was 50%.

Conclusions
Compared with letrozole alone, the addition of palbociclib is unlikely to be cost-effective for the treatment of ABC from a Canadian healthcare perspective with its current price. While ABC patients derive a meaningful clinical benefit from palbociclib, considerations should be given to increase the WTP threshold and reduce the drug pricing, to render this strategy more affordable. Model validation and calibration are needed to confirm those results.

Legal entity responsible for the study
Jacques Raphael

Funding
None

Disclosure
All authors have declared no conflicts of interest.
Background

Contemporary data from the advanced urothelial cancer (UC) setting are scarce. Here, we describe treatment (tx) patterns and outcomes among > 350 patients (pts) in Germany.

Methods

Data were extracted from pt medical records from office-based urologists and urology clinics in Germany. Adult pts (age ≥ 18 y) diagnosed with T4b, N2-3 and/or M1 UC and received first-line (1L) or second-line (2L) palliative chemotherapy from 2009 to 2016 were included. The index date was the start date of first systemic therapy. We described tx patterns and clinical characteristics; Kaplan-Meier method assessed overall survival (OS). Cox regression adjusted for age, Eastern Cooperative Oncology Group performance status (ECOG PS) and liver metastases, stratified by hospital/office, compared tx.

Results

Among 368 included pts, 356 and 107 received 1L and 2L tx, respectively. At the start of 1L therapy, mean age was 68 y, 73% of pts were male, 74% were current/ex-smokers and 63% had metastatic disease. In 1L, 75% of pts received dual-combination tx, most commonly gemcitabine + cisplatin (GemCis; 83%). In 2L, 74% received single-agent tx, most commonly vinflunine (66%). In 1L, 12-month OS was 60%, slightly higher with GemCis (65%) than with other tx (52%). No difference in OS by sex or smoking status was noted. Pts with and without renal impairment (creatinine clearance <≥ 60 mL/min) had a 12-month OS of 47% and 70%, respectively. 12-month OS among pts with ECOG PS 0-1 was 62% vs 54% among pts with ECOG ≥ 2. There was no OS difference between vinflunine and other 2L tx (Table) (hazard ratio, 1.11 [95% CI: 0.65, 1.90]). Median PFS was 6.8 months in 1L pts and 3.3 months in 2L pts.

### Table: 1117P Milestone Overall Survival, %

<table>
<thead>
<tr>
<th></th>
<th>1L n = 356</th>
<th>2L n = 107*</th>
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<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>60%</td>
<td>37%</td>
</tr>
<tr>
<td>24 mo</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>36 mo</td>
<td>21%</td>
<td>5%</td>
</tr>
<tr>
<td>GemCis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1L vs other 1L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>65% vs 52%</td>
<td>—</td>
</tr>
<tr>
<td>24 mo</td>
<td>40% vs 34%</td>
<td>—</td>
</tr>
<tr>
<td>36 mo</td>
<td>20% vs 21%</td>
<td>—</td>
</tr>
<tr>
<td>Vinflunine</td>
<td></td>
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<tr>
<td>2L vs other 2L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>—</td>
<td>38% vs 37%</td>
</tr>
<tr>
<td>24 mo</td>
<td>—</td>
<td>20% vs 16%</td>
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</tbody>
</table>
A total of 368 pts were included; shown here are 356 pts who initiated 1L tx and 107 pts who initiated 2L tx during the study (2009-2016). 88.8% (n = 95) of the 107 pts are a subset of the 356 pts who initiated both 1L and 2L during the study.

Most common tx per line of therapy.

Estimate could not be calculated due to insufficient follow-up time

Conclusions
Outcomes in advanced UC tx in pts in this large real-world data study are comparable with clinical trials. Despite frequent use of cisplatin-based 1L tx and vinflunine 2L tx, per recent guidelines, outcomes are generally still poor.

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

Funding
F. Hoffman-La Roche Ltd.

Disclosure
G. Niegisch: Research funding: 4SC AG Lecturer: Pfizer Pharma GmbH, Pierre Fabre Pharma GmbH, Roche Pharma AG Consulting or Advisory Role: Bristol-Myers Squibb, Roche Parma AG, IMS Health AG, medac GmbH Travel, Accommodations, Expense: Pfizer Pharma GmbH, Roche Pharma AG, Bristol-Myers Squibb. S-W. Lin: Receive salary and stocks from Genentech/Roche. J. Pavlova: Employee: Roche. A. Gondos, A. Rudolph, G. Haas: Employed by QuintilesIMS during the study. M.W. Kramer: Received honories for advisory board memberships and presentations from Roche, Pierre Fabre, Bristol-Myers Squibb, Novartis, Bayer, Astellas, Sanofi, Ipsen and Eisai. All other authors have declared no conflicts of interest.

1118P - Health related quality of life and utility weights of medical oncology inpatients

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Background
Health related quality of life (HRQoL) data and utilities derived from preference-based scales are needed for pharmacoeconomic studies. However, available data for hospitalized Medical Oncology patients are scarce or restricted to specific neoplasms. The aim of this work was to obtain health state utilities (HSU) from a heterogeneous population of cancer inpatients admitted to a Medical Oncology department.

Methods
Between Dec-15 and March-16, we prospectively collected HRQoL data from consecutive patients admitted to a Medical Oncology ward using EuroQoL 5-domains 5-levels instrument (EQ-5D-5L) and EQ-5D-5L visual analogic scale (VAS). Utility weights were assigned according to Spain social tariff using EuroQol crosswalk value sets. Non-parametric tests (Mann Whitney U, Kruskal-Wallis) were used to evaluate differences of HSU between groups.
Results
215 patients were included; median age: 62 (16-88); ECOG: 1 (45%), 2 (43%), 3-4 (12%); site: lung (27%), breast (15%), colorectal (15%), urogenital (15%); stage: I-II (11%), III (15%), IV (74%); active anticancer treatment: 87%; death during admission: 17 (8%). Mean (SD) EQ-5D-5L HSU for all patients was 0.52 (0.41); VAS: 52 (2). Mean (SD) values for EQ-5D-5L domains: mobility, 2.21 (1.24); self-care, 2.23 (1.49); usual activities, 2.89 (1.41); pain/discomfort, 1.94 (1.29); anxiety/depression: 2.12 (0.94). Differences between groups are shown in Table.

Table:

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Patients (n = 215)</th>
<th>EQ-5D-5L utility</th>
<th>p</th>
<th>EQ-5D-5L VAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1 2 3-4</td>
<td>96 92 27</td>
<td>0.77 0.41</td>
<td>&lt;0.001</td>
<td>63 45 34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage I-II III IV</td>
<td>23 32 154</td>
<td>0.79 0.68</td>
<td>&lt;0.001</td>
<td>64 56 49</td>
<td>0.001</td>
</tr>
<tr>
<td>Active treatment Yes No</td>
<td>187 28</td>
<td>0.56 0.26</td>
<td>0.001</td>
<td>53 45</td>
<td>0.04</td>
</tr>
<tr>
<td>Cause of admission</td>
<td>18 53 129</td>
<td>0.81 0.16</td>
<td>&lt;0.001</td>
<td>65 38 55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptom worsening Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Conclusions
Average utility (EQ-5D-5L) for Medical Oncology inpatients is 0.52; lowest scores in this population were obtained for pain/discomfort and anxiety/depression domains. Significant differences were observed between different ECOG levels, tumor stages, admission causes and type of treatment.

Legal entity responsible for the study
Francisco Ayala de la Peña

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1119P - A trial-based EUROQOL EQ-5D health utility analysis in patients with classical Hodgkin’s lymphoma

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Background
Pembrolizumab has shown a high response in patients classic Hodgkin lymphoma (cHL) patients who have experienced disease progression after brentuximab vedotin in KEYNOTE (KN)-087 and the results have been presented. This study aimed to evaluate the health-related quality of life (HRQoL) of the trial patients in KN087.

Methods
METHODS:
KN-087 is an ongoing single-arm multi-center, non-randomized Phase II trial evaluating pembrolizumab 200mg Q3W IV in patients with relapsed or refractory cHL. In KN-087, HRQoL data were collected at baseline and every drug administration over the 18 months
of follow-up. HRQoL was assessed using both the EQ-5D and EORTC QLQ-C30 instruments. The generic health statuses assessed from both instrument were converted to population-based utility values using published algorithms. More specifically, US-based scoring was applied to US patients, UK-based scoring for UK patients and EU-based scoring for all other patients. HRQoL was reported by status of respond and disease progression. Response was defined based upon IWG criteria. Furthermore, stratified analyses were conducted to examine the health disabilities of the patients who experienced grade 3+ adverse events (AEs), and by ECOG performance and the number of prior therapies.

**Results**

**RESULTS:**

Among 210 trial patients, HRQoL data were collected for 205 patients at baseline and the mean health utility score was 0.759 (95% CI 0.730-0.788). Mean health utility score among responders and non-responders was 0.826 (95% CI 0.811-0.842) and 0.760 (95% CI 0.718-0.801), respectively. The difference is considered clinically significant. Mean utility decreased from 0.820 (95% CI 0.807-0.833) for time spent prior to progression to 0.806 (95% CI 0.780-0.832) post disease progression. Progression-free patients who experienced grade 3+ AEs (N=17) had a mean health utility of 0.736 (95% CI 0.662-0.811), compared with 0.825 (95% CI 0.811-0.838) among those did not.

**Conclusions**

**CONCLUSIONS:**

The results showed a substantial HRQoL impact of R/R cHL. Treatment response was associated with significant clinically meaningful improvement in HRQoL. The utility estimates from the study are important for economic evaluations of treatments in R/R cHL patients.

**Clinical trial identification**

NCT02453594

**1120P - Real world comparison of common patient reported symptoms with health utility scores in cancer outpatients**

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**Background**

Health utility scores (HUS), a form of health-related quality of life (HRQoL) assessments useful in economic analyses, such as the EuroQol (EQ-5D) were originally standardized to health state preferences in healthy individuals. To demonstrate clinical appropriateness in cancer patients, we assessed the association of common cancer symptoms with EQ-5D HUS.

**Methods**

Adult cancer outpatients were surveyed cross-sectionally using the Edmonton Symptom Assessment System (ESAS), the EQ-5D-3L, and clinico-demographic variables. ESAS rated symptoms from 0-10. HUS were derived from the EQ-5D-3L (Canadian conversion). ESAS symptoms were correlated with HUS using Spearman correlation coefficients (R). Multivariable regression analyses identified independent variables associated with HUS.
Results

Of 764 patients across multiple cancers, 27% were palliative at assessment. There were significant correlations between each ESAS symptom score and HUS (p < 0.0001 for each comparison; Spearman coefficients: 0.20 to 0.42); the highest were for pain (R = 0.42), fatigue (R = 0.39), and depression (R = 0.35). In multivariable analyses, pain and depression symptom scores remained highly associated with HUS (p < 0.0001 each), while fatigue was of borderline significance (p = 0.059). Despite correlations, prediction of HUS by global ESAS scores was poor, with the highest prediction ability at 0.25. Because ESAS and EQ5D shared common symptom questions (pain, depression/anxiety), we evaluated if we could map and replace these EQ5D questions with ESAS. Spearman correlation of pain symptoms by EQ5D and ESAS was 0.95, while for depression/anxiety, 0.90. Replacing both questions yielded a correlation of 0.83.

Conclusions

HUS is associated with many cancer symptoms, including pain, fatigue, nausea, depression, anxiety, drowsiness, loss of appetite, and shortness of breath. EQ-5D-3L derived HUS have clinical utility. On exploratory analysis, we cannot replace accurately the EQ5D with ESAS, although we can replace two symptom questions within EQ5D with ESAS with high correlation.

Legal entity responsible for the study
Princess Margaret Cancer Centre, UHN, Toronto, Canada

Funding
Cancer Care Ontario

Disclosure
All authors have declared no conflicts of interest.

1121P - Costs of dacomitinib versus placebo in pretreated unselected patients (pts) with advanced NSCLC: CCTG BR.26

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Background
Dacomitinib, a potent irreversible pan-HER kinase inhibitor, has activity in EGFR mutant (mt) lung cancer. BR.26, completed in 2013, compared dacomitinib versus placebo in unselected pts who had received both chemotherapy (1 or 2 lines) and a first-generation EGFR TKI for advanced NSCLC. Dacomitinib pts had significantly improved tumour response rate, PFS, and time to symptom deterioration but not improved survival (OS). A trend towards improved OS was seen in pts with KRAS wildtype (wt) tumours (KRAS unknown in 42%). A prospective economic evaluation was planned for Canadian and Australian pts.

Methods
Resource utilization and utility scores (EQ5D-3L) were collected prospectively in 385 trial participants from Canada and Australia. Direct medical costs were applied to resources in
2015 Canadian dollars (CAD) from the Canadian public health care payer perspective. Dacomitinib is not approved for marketing, thus we used a range of plausible drug costs (0-$120/mg). Restricted mean survival time, utility, and costs per arm were calculated, and explored in KRAS wt and EGFR mt subgroups.

**Results**

Incremental outcomes and costs by treatment arm are shown below. Mean utility scores were similar, although higher in dacomitinib-treated pts with KRAS wt or EGFR mt tumours (range u = 0.41- 0.55). Mean quality-adjusted survival was approximately 1 month longer with dacomitinib in both KRAS wt and EGFR mt subgroups. Direct medical costs excluding dacomitinib were similar between arms. Exploratory estimates of cost-utility ranged from $26,369-$184,701/QALY in KRAS wt, and $2,243-$133,953/QALY in pretreated EGFR mt pts.

**Conclusions**

Dacomitinib in previously treated, unselected NSCLC may yield minor gains in quality-adjusted survival without increasing other costs of care. Analyses of mutation status by ctDNA are ongoing.

### Table: 1121P

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 385)</th>
<th>KRAS wild type (KRAS known n = 165)</th>
<th>EGFR mutant (EGFR known n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (ΔE, years)</td>
<td>0.0014</td>
<td>0.104</td>
<td>0.129</td>
</tr>
<tr>
<td>Quality-adjusted survival (ΔE, QALY)</td>
<td>0.011</td>
<td>0.069</td>
<td>0.088</td>
</tr>
<tr>
<td>Cost (ΔC, 2015 CAD) Set drug price at: $0/mg $40/mg $80/mg $120/mg</td>
<td>$524 $3,944</td>
<td>$1,829 $5,489</td>
<td>$199 $4,083</td>
</tr>
<tr>
<td></td>
<td>$7,363</td>
<td>$9,149 $12,809</td>
<td>$7,968 $11,853</td>
</tr>
<tr>
<td></td>
<td>$10,783</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical trial identification**

2009-016509-41

**Legal entity responsible for the study**

Canadian Clinical Trials Group (CCTG)

**Funding**

Pfizer

**Disclosure**

P. Bradbury: Honorarium from Pfizer and Merck. P. Ellis: In the past two years, received honoraria for talks from Boehringer Ingelheim and Novartis. G. Liu: Honoraria from AstraZeneca, Pfizer, Novartis and Takeda. R. Sangha: Honoraria from: Pfizer, Boehringer Ingelheim, AstraZeneca, Roche, Eli-Lilly, Bristol-Myers Squibb and Merck. M. Boyer: I’ve received Honoraria (paid to my institution) from Pfizer, Boehringer Ingelheim and Astra Zeneca. G. Goss: Honoraria from Pfizer, AstraZeneca, Boehringer Ingelheim, Lilly, Bristol-Myers Squibb, and Celgene. L. Seymour: Pfizer provided funding for the BR.26 trial. N.B. Leighl: Research funding (institution) - Novartis Unrelated CME (not speaker's bureau) - travel/honoraria - AstraZeneca, Merck Sharpe Dohme, Pfizer, Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

**1122P - Feasibility of routine collection of health state utilities using EQ-5D in a**
**Background**

Routine collection of health state utilities in the clinical setting may produce data more representative of the real-world population for use in cost-utility models and guide decision making. We are currently carrying out a cross-sectional study to assess the feasibility of routine administration of EQ-5D to breast cancer patients in a multidisciplinary oncology clinic, in an academic cancer centre in Ontario, Canada.

**Methods**

English literate women undergoing treatment or on follow-up for their breast cancer (stage I to IV), are being recruited during their scheduled visit to the cancer centre, preferably after completing the implemented routine symptom screening using the Edmonton Symptom Assessment System (ESAS). Consenting patients complete EQ-5D-5L in tablets, followed by a socio-demographic questionnaire and feedback questions pertaining to study conduct. Answers are stored in a research database and linked to diagnostic and treatment data. Feasibility will be assessed primarily by the proportion of patients who fully complete EQ-5D and by their willingness to complete the instrument at each clinic visit.

**Results**

To date, 474 women were approached; 262 (55%) were eligible and consented to participate (target enrolment: 341). Median age of participants was 56 years (range:28-90); 24% had metastatic disease. All participants were English literate, but 59% were born outside Canada and speak primarily other languages at home. Ninety-eight percent of recruited patients completed EQ-5D, compared with 84% who completed ESAS on the same day (63% completed ESAS voluntarily prior to enrolment; 21% agreed on completing ESAS for study purposes only). Median time for EQ-5D completion was 84 seconds. Most patients (82%) had no problems using the tablet. Willingness to continue to complete EQ-5D at each clinic visit was not affected by disease status (stage I to III versus stage IV) and 74% would “definitely”/“very likely” continue to answer EQ-5D regularly at each clinic visit.

**Conclusions**

These preliminary results indicate that routine collection of EQ-5D in clinical practice might be feasible, although the completion rate might be overestimated by the cross-sectional design of the study.

**Legal entity responsible for the study**

Sofia Torres

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1123P - The cost of expensive breast cancer drugs**

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L. W. Terstappen (Enschede, Netherlands)S. Sleijfer (Rotterdam, Netherlands)
M. J. Ijzerman (Enschede, Netherlands)
Background

Increasing healthcare costs are a major challenge in medical oncology, since the total costs of oncology can account for up to 30% of the total hospital expenditures. As many novel (expensive) cancer treatments are being developed, it is important to be transparent about drug prices from an early research stage on. To assess the potential financial impact of pipeline drugs, their expected future prices can be deducted from prices of currently used drugs. As an overview of the standard prices of expensive breast cancer treatments in European countries is lacking, this review aimed to synthesize all evidence on costs of approved, expensive breast cancer drugs in the Netherlands.

Methods

A literature review was performed to create an overview of all approved, expensive drugs in the Netherlands. Standard drug costs were retrieved via the Dutch administrative health authority (ZINL). Drugs were considered expensive if the standard price of the drug was more than €10 per unit or if the cost of a treatment with that particular drug exceeded €1000 on average per patient.

Results

In the Netherlands 25 breast cancer drugs are approved with a standard price of more than €10 per unit. After excluding drugs with expected treatment costs less than €1000, 19 drugs were included in the analysis. The standard drug price is €7,943 on average (range €63 - €45,452), and the average number of cycles per patient is 10.5 (range 4 - 25.3 cycles). This results in average treatment costs per patient of expensive drugs of €17,968 (range €1,103 - €87,123). Four drugs that initially ranked low based on standard drug unit prices (rank 10-19), rank substantially higher (rank 1-10) when ranking total treatment costs.

Conclusions

Ranking standard drug prices per unit may not be very informative. It would be valuable to rank drug treatment costs, based on treatment length and dosage estimates. However, in the Netherlands the expected treatment length for a particular drug is not standardly reported in official approval reports. Furthermore, actual prices of expensive drugs may differ from standard drug prices, by which treatment costs might be deviant. Extending standardization of reporting and calculation of drug treatment costs would be valuable and particularly relevant when extending this type of cost calculations to other countries.

Legal entity responsible for the study

University of Twente - Health Technology and Services Research

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1124P_PR - Impact of licensing and reimbursement discrepancies on patient access to cancer treatments across Europe and Canada

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Background
The European Medicines Agency (EMA) grants licenses to safe, effective cancer treatments where access to the drug can improve and prolong life. Subsequent country-specific health technology assessment (HTA) and reimbursement decisions may restrict access to sub-populations of clinically eligible patients. This study is the first to quantify the impact of licensing discrepancies in terms of Years of Life Lost (YLL) across a range of countries.

**Methods**

Oncology drugs approved by the EMA for six cancers (breast, kidney, lung, multiple myeloma, melanoma, prostate) between 2006 and 2016 were identified. Associated HTA reimbursement decisions from 13 agencies (Belgium, Canada, Denmark, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, UK) were classified by degree of restriction between the populations clinically eligible and eligible for reimbursement: "no restriction", "partial restriction" (by percent of clinically eligible population restricted)" or “complete restriction”. Epidemiology data (GLOBOCAN 2012) and population sizes from HTA submissions informed the estimated number of patients impacted. Potential survival gains from pivotal studies were applied to quantify the YLL impact of licensing discrepancies.

**Results**

Overall, 26% of published decisions resulted in complete or partial restriction; the extent of restrictions differed across countries (from 0% in Germany to 4% in Portugal and 63% in Scotland), cancer types and drugs. The restrictions impacted approximately 100,000 clinically eligible patients annually and, result in over 30,000 YLL across the scope countries. Restriction rationale was often not publically available. Results show differences between countries regardless of GDP or timing of HTA assessment.

**Conclusions**

Despite one regulatory system for the approval of new medicines, results suggest that access to cancer therapies remains inequitable across Europe and Canada. Reimbursement decisions appear fragmented, resulting in varying restrictions that impede use of effective medicines among clinically eligible patients and result in substantial YLL burden.

**Legal entity responsible for the study**

Bristol-Myers Squibb Pharmaceuticals Ltd

**Funding**

Bristol-Myers Squibb Pharmaceuticals Ltd

**Disclosure**

J. McKendrick, X. Song: PRMA Consulting was paid to conduct the study and contribute to abstract preparation by Bristol-Myers Squibb. B. Malcolm: Employee of Bristol-Myers Squibb. K. Sheahan: Payment outside the submitted work from Bristol Myers Squibb as a Worldwide Heath Economics and Outcomes Research Fellow. I. Katsoulis, J. van Loon: Employed by PRMA Consulting who were paid to conduct the study and contribute to abstract preparation by Bristol-Myers Squibb.

1125P - The cost-effectiveness of EndoPredict to inform adjuvant chemotherapy decisions in early breast cancer

**S. Hinde** (York, United Kingdom) C. Theriou (Nottingham, United Kingdom) S. May (Brighton, United Kingdom) L. Matthews (Brighton, United Kingdom) A. Arbon (Brighton, United Kingdom) L. Fallowfield (Brighton, United Kingdom)
Background
Chemotherapy alongside endocrine treatment in ER +ve breast cancer patients post resection of a primary tumour has been estimated to reduce mortality rates by up to 30%. However, the high cost of the therapies, heterogeneous nature of the disease and adverse event profile implies that not all patients should receive the treatment. Many existing prognostic tools such as the NPI, PREDICT, and Adjuvant! Online may not definitively estimate the risk profile of patients, resulting in an indeterminate risk classification. In such cases gene expression profiling tests such as EndoPredict can aid the treatment decision. It is important to examine if the test represents a cost-effective use of limited NHS resources in such intermediate risk patients.

Methods
This small (n = 151) multi-centre, two-stage study evaluated the cost-effectiveness of EndoPredict in patients with no clear treatment based on current prognostic criteria. The primary analysis examined whether EndoPredict test results increased or decreased the use and intensity of chemotherapy and the associated direct cost implications. Secondly, a mathematical model was constructed to determine how the change in treatment decisions impacted the long term health of the population, and the future cost implications to the NHS.

Results
A cost increase per patient treated with chemotherapy was identified when EndoPredict test results were available (£149), alongside no significant change in the total number being prescribed chemotherapy. However, chemotherapy was offered to a very different patient population, with 36.9% of patients having a change in treatment decision. The long term analysis found the use of EndoPredict to be associated with greater total costs but a potential increase in population health, resulting in an incremental cost-effectiveness ratio of £26,836 per quality adjusted life year.

Conclusions
While EndoPredict was found to be more expensive overall, the ability of the EPClin score to affect a more optimal allocation of chemotherapy, resulted in long term health gains. However, this result was on the margin of what is conventionally considered a cost-effective use of limited NHS resources and subject to significant uncertainty.

Clinical trial identification
ISRCTN69220108

Legal entity responsible for the study
Sussex Health Outcomes Research and Education in Cancer

Funding
Myriad

Disclosure
S. Hinde C. Theriou, S. May, L. Matthews, A. Arbon, L. Fallowfield, D. Bloomfield: This research was funded through an unrestricted educational grant from Myriad.
The value of drugs will evolve over time as new evidence for risks and benefits emerge and the price of a drug changes.

Methods
A NICE Evidence Search on March 1, 2017 revealed 25 systematic reviews and 55 economic evaluations of filgrastim.¹

Results
Initial Health Technology Assessments (HTA) suggested low value due to high drug cost and no evidence for significant gain in Overall Survival (OS). More recent meta-analyses of placebo-controlled randomized trial data show absolute OS gains of 3.2% (95% CI: 2.1—4.2%) from filgrastim support of cytotoxic chemotherapy² and falling costs due to biosimilar competition.

Conclusions

Clinical trial identification
N/A

Legal entity responsible for the study
N/A

Funding
None

Disclosure

1127P - Tyrosine kinase inhibitors (TKI): Awareness of drug-drug interaction

Background
Since TKI are metabolized with cytochrome P450 system which is a common pathway for drug-drug interactions. However, these interactions might be overlooked by clinicians. The aim of this study is to evaluate the drug-drug interactions in patients receiving TKI.

Methods
Between May 2007 and March 2015, the data of 265 patients receiving TKI for any reason were evaluated retrospectively. All prescribed medications (PMs) received during TKI therapy for 6 months period were noted and drug-drug interactions with TKI were evaluated. Additionally the nature of interaction was described as ‘increase or decrease in TKI level or cautious use of TKI recommended’. The interaction between TKI and PMs was checked from Up-To-Date web site or "medscape.com/drug-interaction checker".

Results
In the study, 265 patients who are taking TKI were noted. 251 patients (94.8%) have been taking PMs additional to TKI. The median age was 56 year (17-87), most common diagnosis was gastrointestinal stromal tumor (27.5%) followed by kidney tumor (26.3%). Most common TKI has been used was Imatinib (21.9%) and Lapatinib (21.9%). The most common PM groups during 6 months period was non-steroidal anti inflammatory and acetaminophen (50.2%), proton pomp inhibitors (41.4%), antibiotics (33.1%), cardiovascular system drugs (33.5%) and narcotic analgesics (21.1%). The interaction rate between TKI and PMs was 54.2%. The nature of interaction was; decrease in TKI level in 39.7% of patients and increase in TKI level in 30.1% of patients. 77.1% of patients have been warned as cautious use of TKI due to increase risk of side effect. The side effect was emphasized as QT prolongation.

Conclusions
TKI drug interaction is usually overlooked by clinicians. Our study revealed that more than 90% of patients who are taking TKI are also prescribed another medication. There is a drug-drug interaction between TKI and prescribed medications in more than half of these patients. TKI-prescribed drug interaction has been caused decrease effectiveness of treatment and increase the rate of side effects and medical cost. The TKI –drug interaction risk might be decreased by increasing the knowledge of the physicians from other specialties about recent molecular treatments.

Legal entity responsible for the study
Ankara Numune Education and Research Hospital

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1128P - Anti-PD1 inhibitors: Assessment of proper use, efficacy and economic impact in daily practice


Background
Nivolumab, an anti-PD-1 inhibitor, has been approved in France in treatment of first-line BRAF wild-type advanced melanoma and of advanced non-small cell lung cancer after platinum-based chemotherapy, with an approximate monthly processing cost of €5,550 per patient. The objective of our study was to evaluate efficacy and correct use of anti-PD1 antibodies in daily practice since its approvals.

Methods
This retrospective study was conducted between July 2015 and December 2016 on 62 patient files at the Pitié-Salpêtrière hospital, using patient medical records and Multidisciplinary Medical Board (MMB) software. According to the Summary of Product Characteristics (SPC), the correct use of nivolumab required compliance with indications, a WHO status <2 and a limit of 10 mg per day of corticosteroids.

**Results**

Sixty patients were treated for lung cancer: 38 patients (62%) with adenocarcinoma, 14 (22%) with squamous cell carcinoma and 8 (13%) with large cell lung cancer. At the cut-off analysis, 28 patients (47%) had a progressive disease, 20 (32%) were still receiving treatment and 41 (65%) were still alive, with a median follow-up of 6.5 months (0.3 to 17.7 months). Thirteen patients received more than 10 injections and 13 received less than 5 injections. The correct use of nivolumab was observed in 45 patients (73%), 12 patients had a WHO status of 2, 1 patient had a WHO status of 3, and 4 patients received concomitant corticosteroids. The poor utilization of treatment for these 17 patients (27%) totaled 149 injections, costing about €410,000 for a total of €1,615,000 of expenditures using this treatment. Survival rates were not statistically different in these patients compared to those respecting SPC criteria (53% versus 70%; p = 0.2).

**Conclusions**

Although a high cost of inappropriate use of nivolumab, there was no significant difference in survival rates in these patients. These preliminary findings highlight the differences between study populations and daily practice, reflecting willingness of practitioners to give patients access to innovative treatments. Cost effectiveness and efficacy/tolerance data will be updated at the meeting presentation to better determine treatment criteria in daily practice.

**Legal entity responsible for the study**

Assistance Publique - Hôpitaux de Paris

**Funding**

None

**Disclosure**

J-P. Spano: Received fees and has been member of advisory board of Bristol-Myers Squibb, MSD and Roche. All other authors have declared no conflicts of interest.

**1129P - Real world treatment costs and resource utilization among patients with metastatic bladder cancer**

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**Background**

First-line (1L) cisplatin, followed by second-line (2L) taxane or other systemic chemotherapy, has been the historic standard of care in metastatic bladder cancer (mBC). Little is known regarding longitudinal costs and resources consumed during treatment of mBC patient (pts). This study investigated drug utilization, health care (HC) resource use, and disease-related costs among pts with mBC.

**Methods**

Pts with an initial diagnosis of mBC between Jan 2007 - Dec 2011 were retrospectively
identified using SEER-Medicare linked data. Annual survival rates were calculated for treated and untreated pts. Total costs were estimated during the treatment exposure window for HC visits and treatment for mBC-related, AE-related, and other costs; all costs were converted to 2016 US dollars.

**Results**

Overall, 411 eligible pts received 1L therapy and 189 (46.0%) subsequently received 2L therapy. For all 1L treated pts, the 1, 2, and 3-year survival rates from mBC diagnosis were 56.5%, 25.6%, and 15.5%, compared to 12.9%, 6.0%, and 4.7% for untreated pts (n = 804). For 2L pts, the 1, 2, and 3-year survival rates from 2L treatment initiation were 32.8%, 14.9%, and 7.7%. For all regimens, the highest per-patient cost occurred in the outpatient setting, followed closely by emergency, then inpatient, SNF, and lastly by hospice. Table:

1129P Costs Incurred During the Treatment Exposure Window for 1L and 2L mBC Therapies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
<th>Overall</th>
<th>Cisplatin-based regimen</th>
<th>Carboplatin-based regimen</th>
<th>Non-platinum-based regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1L</td>
<td>2L</td>
<td>1L</td>
<td>2L</td>
</tr>
<tr>
<td>Sample size, n (%)</td>
<td></td>
<td>411</td>
<td>189</td>
<td>162</td>
<td>22</td>
</tr>
<tr>
<td>Total cost per patient, mean (SD)</td>
<td></td>
<td>$36,793</td>
<td>$26,732</td>
<td>$35,570</td>
<td>$25,267</td>
</tr>
<tr>
<td>mBC-related cost per patient, mean (SD)</td>
<td></td>
<td>$18,246</td>
<td>$12,939</td>
<td>$19,316</td>
<td>$13,529</td>
</tr>
<tr>
<td>AE-related cost per patient, mean (SD)</td>
<td></td>
<td>$7,629</td>
<td>$4,988</td>
<td>$6,240</td>
<td>$4,170</td>
</tr>
<tr>
<td>Other costs per patient, mean (SD)</td>
<td></td>
<td>$12,990</td>
<td>$10,363</td>
<td>$11,900</td>
<td>$7,992</td>
</tr>
</tbody>
</table>

**Conclusions**

In general, mBC pts had poor survival outcomes, particularly for untreated pts. Less than half of mBC pts received guideline-endorsed 1L cis-combo therapy. mBC-related outpatient and emergency HC utilization were primary drivers of the per-patient economic burden. During the treatment exposure window, total costs were considerable across treatment regimens, with the average total cost during 1L and 2L treatment exceeding sixty thousand dollars per patient.

**Legal entity responsible for the study**

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study, yet the authors take full responsibility for the work as a whole, including the study design, access to data reported in the manuscript, and the decision to submit and publish the manuscript. All authors approved the final manuscript to be published.

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**Disclosure**
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1130P - Investigating discrepancies in assessments of PFS by study investigators and independent review

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G. Monnickendam (Fleet, United Kingdom)

**Background**
OS is considered the gold standard trial endpoint, particularly for health technology assessment. However OS faces challenges – from subsequent therapy bias to needing long trials that delay patients’ access to promising medicines. PFS is often used either instead of, or alongside, OS – by regulators, clinicians, payers, and more recently, value frameworks in oncology. PFS is without a standardized measure. We examine the extent of differences between independent central review (ICR) and investigator assessed (INV) PFS. We aim to increase understanding of potential variability in PFS measurement, relevant associations and possible causal factors to inform appropriate use of PFS in payer and clinician decision-making.

**Methods**
We searched Clinicaltrials.gov for ‘progression free survival’ and ‘cancer’, filtering for interventional phase 2 or 3 studies with results. Studies were extracted and the primary and secondary outcomes filtered for ICR and INV based PFS. We searched PubMed with the same criteria; full articles were reviewed and studies reporting for ICR and INV based PFS included. For comparative trials, we calculated difference in median PFS between intervention and control arms for ICR and INV based PFS. For single arm trials, the difference between ICR and INV based PFS was calculated where both were reported.

**Results**
Of 365 studies from clinical trials.gov; 48 reported ICR based PFS and 45 reported INV. 6 studies reporting both were included. Of 49 studies from PubMed; 21 were included. There was 1 duplicate. The majority of studies were comparative (23/26), in solid tumors (21/26), and published in the last 5 years (21/26).
Calculating the PFS gain at the median, the difference between the ICR based gain and the INV based gain ranged from 0.1 to 4.3 months. In 9 comparisons the gain with ICR was greater than the gain with INV. In 6 comparisons the difference in PFS gain was ≥2 months, a difference of up to 54% of the gains alone.

**Conclusions**
ICR and INV based PFS produce different estimates of PFS gain in clinical trials, but it remains uncommon for studies to report both ICR and INV based PFS. Both measures
should be required, to improve consistency of comparison across trials and transfer of trial results to real world practices and decision-making.

**Legal entity responsible for the study**
PRMA Consulting Ltd

**Funding**
PRMA Consulting

**Disclosure**

1131P - Medical costs and health care resource use (HCRU) in elderly US patients (pts) with newly diagnosed metastatic or surgically unresectable urothelial carcinoma (mUC) using surveillance, epidemiology, and end results (SEER) medicare data

A. Aly (Bethesda, United States of America) C. Johnson (Bethesda, United States of America)
S. Yang (Princeton, United States of America) S. Rao (Princeton, United States of America)
M. Botteman (Bethesda, United States of America) A. Hussain (Baltimore, United States of America)

**Background**
Most elderly mUC pts receive platinum-based therapy as first line of treatment (LOT) but invariably progress, requiring additional LOT and HCRU. This analysis estimated medical costs and HCRU associated with each LOT in US elderly pts.

**Methods**
Pts ≥66 years of age newly diagnosed with mUC (urothelial transitional cell carcinoma) between 2004 and 2011 were identified from the SEER-Medicare database. Pts were followed from diagnosis to death, Medicare disenrollment, HMO enrollment, or till 31 December 2013 to characterize treatments by LOT (first [1L], second [2L], and third + [3L+] LOT). The per-pt HCRU was examined. Cumulative mean costs (overall and by type of LOT) were reported.

**Results**
Among 1,873 eligible mUC pts (median age, 77 years; male, 63%; Charlson comorbidity index ≥2, 29%; median follow-up, 7.5 months), 1,035 (55%) pts did not receive any chemotherapy. Among the 838 chemotherapy-treated pts, 510 (61%), 204 (24%), and 124 (15%) received 1L, 2L, and 3L+ LOT, respectively. Compared with 2L, 3L+ pts had significantly higher mean (standard deviation) per-pt hospital admissions (4.1 [2.9] vs 4.8 [3.3]), computed tomography (CT) scans (7.4 [4.4] vs 9.9 [5.8]), positron emission tomography–CT scans (1.0 [1.5] vs 2.0 [2.9]), and bone scans (1.1 [1.1] vs 1.8 [2.3]). Pts who received 3L+ LOT had significantly higher cumulative mean costs than 2L pts, mostly attributed to physician and outpatient services where chemotherapy is administered (Table). Table:

<table>
<thead>
<tr>
<th>Cost category</th>
<th>All patients (N = 1,873)</th>
<th>No chemotherapy (N = 1,035)</th>
<th>1L only (N = 510)</th>
<th>2L only (N = 204)</th>
<th>3L+ (N = 124) P-value (3L+ vs 2L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>7.5</td>
<td>3.8</td>
<td>11.8</td>
<td>16.1</td>
<td>26.5</td>
</tr>
<tr>
<td>Time, months</td>
<td>Mean costs (%)</td>
<td>$US</td>
<td>99,422 (100)</td>
<td>123,262 (100)</td>
<td>162,549 (100)</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>-----</td>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Inpatient</td>
<td>43,990 (53)</td>
<td>57,208 (64)</td>
<td>51,358 (52)</td>
<td>54,698 (44)</td>
<td>55,575 (34)</td>
</tr>
<tr>
<td>Physician (incl. chemo for treated pts)</td>
<td>21,426 (26)</td>
<td>10,087 (18)</td>
<td>26,735 (27)</td>
<td>39,955 (32)</td>
<td>63,476 (39)</td>
</tr>
<tr>
<td>Outpatient (incl. chemo for treated pts)</td>
<td>9,189 (11)</td>
<td>3,367 (6)</td>
<td>12,199 (12)</td>
<td>18,626 (15)</td>
<td>29,742 (18)</td>
</tr>
<tr>
<td>Home health</td>
<td>2,631 (3)</td>
<td>2,042 (4)</td>
<td>3,256 (3)</td>
<td>3,018 (2)</td>
<td>4,329 (3)</td>
</tr>
<tr>
<td>Hospice</td>
<td>3,208 (4)</td>
<td>3,624 (6)</td>
<td>2,337 (2)</td>
<td>2,671 (2)</td>
<td>4,211 (3)</td>
</tr>
<tr>
<td>Durable medical equipment</td>
<td>1,117 (1)</td>
<td>550 (1)</td>
<td>1,771 (2)</td>
<td>1,627 (1)</td>
<td>2,303 (1)</td>
</tr>
<tr>
<td>Prescription drugs (not incl. chemo)</td>
<td>1,351 (2)</td>
<td>698 (1)</td>
<td>1,767 (2)</td>
<td>2,668 (2)</td>
<td>2,912 (2)</td>
</tr>
</tbody>
</table>

a Physician costs are non-institutional claims largely from physicians who bill for services provided in the office

b Outpatient costs are claims from institutional outpatient providers

**Conclusions**

For pts with mUC, cumulative mean costs increased with additional LOT, although further analysis of cumulative costs over the treatment duration of each LOT is warranted. As the treatment landscape evolves to include immunotherapy, this analysis provides a benchmark for the relative costs associated with mUC treatment across different traditional LOT in the United States.

**Clinical trial identification**

N/A

**Legal entity responsible for the study**

Bristol-Myers Squibb

**Funding**

Bristol-Myers Squibb

**Disclosure**

A. Aly: Reports grants from Bristol-Myers Squibb, during the conduct of the study; grants from Bristol-Myers Squibb, Celldex, Celgene, Daiichi Sankyo, Pharmacyclics, and Amgen, outside the submitted work. C. Johnson: Reports grants from Bristol-Myers Squibb, during the conduct of the study. S. Yang, S. Rao: Reports personal fees from Bristol-Myers Squibb, during the conduct of the study; personal fees from Bristol-Myers Squibb, outside the submitted work. M. Botteman: Reports grants from Bristol-Myers Squib, during the
1132P - Chasing the survival curve tail: The effect on cost-effectiveness of nivolumab for second-line treatment of advanced renal cell carcinoma

M. Sarfaty (Petah Tikva, Israel) A. Moore (Petach Tikva, Israel) V. Neiman (Petah Tikva, Israel) E. Rosenbaum (Petah Tikva, Israel) D. Goldstein (Petah Tikva, Israel)

Background

Treatment of metastatic cancer has been revolutionized in recent years with the incorporation of immunotherapy. In some metastatic settings there is a clear plateau in the overall survival curve, representing long-term survivors. As survival data is still immature with immunotherapy in most cancers it is unclear how to tackle the unknown tail of the survival curve, as it greatly affects the presumed effectiveness. To further understand this issue we present here the example of CEA of nivolumab in 2nd line RCC.

Methods

A Markov model was developed to compare the costs and effectiveness of nivolumab with those of everolimus or placebo in the second-line treatment of advanced RCC. Health outcomes were measured in life-years and quality-adjusted life-years (QALYs). Drug costs were based on Medicare reimbursement rates in 2016. Model robustness was addressed in univariable and probabilistic sensitivity analyses. We examined the effect of different anticipated ends of the survival curve on the cost effectiveness.

Results

The total mean cost per-patient of nivolumab versus everolimus was $101,070 and $50,935, respectfully. Nivolumab generated a gain of 0.24 LYS (0.34 QALYs) over everolimus and 0.89 LYS (0.96 QALYs) over placebo. The incremental cost-effectiveness ratio (ICER) for nivolumab was $146,532/QALY versus everolimus. A theoretical durable response in 10%, 15% or 20% of patients treated with nivolumab reduced the ICER to $86,660/QALY, $64,809/QALY or $48,493/QALY, respectively, compared with everolimus.

Conclusions

Our analysis shows that any durable response changes the ICER dramatically and improves the likelihood that a drug will be considered cost effective. Therefore, we must strive to understand the long term benefit of immunotherapy in different cancers.

Legal entity responsible for the study

Michal Sarfaty

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1133P - Non-elective admissions in cancer care - A review of acute oncology services (AOS) implementation in a north-west region of England

S. Chow (Manchester, United Kingdom) R. Leach (Manchester, United Kingdom) C. Mitchell (Manchester, United Kingdom)

Background
Parallel to advances in cancer therapeutics in the clinics, high quality and patient-centred management of cancer or treatment-related complications during non-elective attendance especially to a non-specialist hospital is crucial in achieving excellent patient outcome. AOS was innovated in the UK to meet this need and has rapidly expanded in recent years. Here, we describe findings of an on-going audit of this expanding networked service within Greater Manchester and Cheshire East County consisting of 10 district general hospitals in collaboration with a regional specialist cancer centre (The Christie NHS Foundation Trust).

Methods
Information related to any hospital episodes warranting AOS input was collated from all participating hospitals using standardised proforma and analysed.

Results
Between Jan 2015 - Sep 2016, 7638 non-elective hospital attendances were recorded of which 58% occurred within working hours. Common cancer sites were lung 16%, breast 15%, lower GI 12%, urology 12%, upper GI and HPB 9%, haematology 7%, gynaecology 6%, cancer of unknown primary (CUP) 6%, and others 7%. Majority were related to cancer complication 40% (Type III), treatment-related 32% (Type II), new cancer diagnosis 10% (Type I) and others 17%. 94% of AOS involvement occurred within 24hr of attendance. Level of intervention by AOS was considered major in 60% while 30% and <10% was intermediate or minor respectively. Median length of stay (LOS) is 4 days, 20% of episodes lasted <24hr (11.2% admission avoidance), 50% 1-7 days, and 30% 2-6 weeks (predominantly type I and III).

Conclusions
This large multi-sites audit documented the service delivery pattern of a growing oncology subspecialty at the same time provided a glimpse into the healthcare implication of unplanned admission in the current era of advancing oncology landscape. Excellent median LOS in this region compared to national average likely a reflection of pertinent AOS team involvement in a timely manner. AOS is now an integral component to the cancer care in the UK and its role in the non-elective setting serves to ensure excellent patient experience as well as providing far-reaching potential in healthcare efficiency.

Clinical trial identification
not applicable

Legal entity responsible for the study
not applicable

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1134P - Changing treatment patterns in metastatic colorectal cancer in EU5 countries from 2014 to 2016
N. Schmidt (Frankfurt am Main, Germany) L. Hoyer (Frankfurt am Main, Germany)

Background
Colorectal cancer is the third most common cancer type nowadays in Europe. Lately however, no treatment has been approved for 1st or 2nd line treatment in metastatic...
colorectal cancer, only a new treatment option in 3rd line for pretreated patients is available. Therefore it will be interesting to see whether also the existing treatment patterns and testing results have not changed over time.

Methods
This study is based on IMS Oncology Analyzer®, a quarterly survey among a physician panel covering retrospective patient data about the disease and the treatment (tx) history across all types of cancer. Metastatic colorectal cancer patients treated in the EU5 countries (France, Germany, Spain, Italy and UK) within 2014, 2015 and 2016 were analyzed.

Results
Comparing the tx guidelines to the tx patterns derived from IMS Oncology Analyzer®, it shows that physicians are following the guidelines for K-RAS wildtype and K-RAS mutant colorectal cancer patients. An analysis of the K-RAS testing shows, that the share of wildtype patients remains almost stable from 2014 to 2016. Unlike in Germany, here the shares of wildtype patients are shrinking from 57.2% to 51.3%. A similar trend accounts for UK. In Spain, France and Italy however, the number of patients, who are wildtype is increasing. Accordingly to the decreasing rate of wildtype patients, the share of Anti-EGFR-therapies is going down in Germany from 38.8% to 25.3%. Also in Italy and Spain the trend of the K-RAS testing is mirrored in the usage of Anti-EGFR-therapies. However, in UK, the use of these therapies increases drastically from 23.9% to 77.8%, despite the decreasing number of K-RAS wildtype patients. In France Anti-EGFR-therapies only lose 1.7% in terms of market shares, even though the K-RAS wildtype population is increasing.

Conclusions
While the general tx guidelines are still followed, some tx patterns have changed due to a difference in K-RAS test results. Further research needs to investigate why there are changes in K-RAS test results. Also studies have shown that tumor localization (right, left, transversum) has an impact on the efficacy. Future studies therefore need to evaluate whether the tumor localization is impacting the tx pattern as well.

Legal entity responsible for the study
QuintilesIMS

Funding
None

Disclosure
All authors have declared no conflicts of interest.

IMMUNOTHERAPY OF CANCER
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1149P - Results of the randomized, placebo-controlled phase I/IIB trial of CV9104, an mRNA based cancer immunotherapy, in patients with metastatic castration-resistant prostate cancer (mCRPC)
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Background

CV9104 is a novel prostate cancer immunotherapy based on sequence-optimized, free and protamine-complexed mRNA encoding the antigens PSA, PSMA, PSCA, STEAP1, PAP and MUC1. Safety and immune responses to the predecessor therapy CV9103 encoding 4 of the antigens have been described previously. We assessed whether immunotherapy with CV9104 on top of standard of care (SOC) results in longer overall survival than placebo plus standard of care in patients with mCRPC.

Methods

After completion of a safety lead-in phase I, men with chemo-naïve, oligosymptomatic/asymptomatic mCRPC without visceral metastases were randomized 2:1 to intradermal CV9104 or placebo (P). Double-blinded treatment was continued beyond initial progression until progression under first subsequent SOC therapy or toxicity. The primary endpoint (EP) was overall survival (OS). Key secondary EPs included radiographic progression-free survival (rPFS1/rSPFS from randomization until initial progression/second progression on SOC therapy and rPFS2 from start of SOC therapy to second progression), time to symptom progression and cellular and humoral immune responses.

Results

197 patients (pt) were randomized 2:1 to either CV9104 (n = 134) or P (n = 63). Pt characteristics, median number of administrations and first subsequent SOC therapies were well balanced between the arms. No significant difference in OS was found, median (m) OS was 35.5 months (mo) [28.-NE] in the CV9104 arm vs. 33.7 mo [28.7-NE] in the P arm (hazard ratio [HR] 1.1, 95% CI 0.70-1.76; one-sided p = 0.33). There were also no significant differences in the rPFS endpoints and time to symptom progression. Incidence of Grade ≥3 AEs (51.1% vs. 59.7%) and serious AEs (44.5% vs. 43.5%) was similar in both arms, injection site reactions and flu like symptoms were more frequent in the CV9104 arm.

Conclusions

CV9104 did not improve OS compared to placebo. Additional clinical outcomes and analyses of cellular and humoral immune responses will be presented and impact on further development will be discussed.

Clinical trial identification

EudraCT number: 2011-006314-14

Legal entity responsible for the study

CureVac AG

Funding

Study Sponsor: CureVac AG

Disclosure

1150P - Phase II clinical trial of peptide vaccination for advanced head and neck cancer patients induced immune responses and prolonged OS

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Background
The peptides derived from ideal cancer-testis antigens, including LY6K, CDCA1 and IMP3 (identified using genome-wide cDNA microarray analyses), were utilized in immunotherapy for head and neck squamous cell cancer (HNSCC). In this trial, we analyzed the immune response to and safety and efficacy of vaccine therapy.

Methods
A total of 40 patients with advanced HNSCC were enrolled in this trial of peptide vaccine therapy, and the OS, PFS and immunological response were evaluated using enzyme-linked ImmunoSpot (ELISPOT) and pentamer assays. The peptides were subcutaneously administered weekly with IFA. The primary endpoints were evaluated based on differences between HLA-A*2402-positive (A24(+)) patients treated with peptide vaccine therapy and –negative (A24(-)) patients treated without peptide vaccine therapy among those with advanced HNSCC.

Results
Our cancer vaccine therapy was well tolerated. The OS of the A24(+) vaccinated group (n = 40) was statistically significantly longer than that of the A24(-) group (n = 18) (MST 4.9 vs. 3.5 month, respectively, p < 0.05). One of the patients exhibited a complete response. In the A24(+) vaccinated group, the ELISPOT assay identified LY6K-, CDCA1- and IMP3-specific CTL responses in 85.7%, 64.3% and 42.9% of the patients, respectively. The patients showing LY6K- and CDCA1-specific CTL responses demonstrated a longer OS than those without CTL induction. Moreover, the patients exhibiting CTL induction for multiple peptides demonstrated better clinical responses.

Conclusions
The immune response induced by this peptides vaccine may improve the prognosis of patients with advanced HNSCC.

Legal entity responsible for the study
Yoshihiro Yoshitake
1151P - Phase I study of glypican-3-derived peptide vaccine therapy for patients with refractory pediatric solid tumors

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Background
The carcinoembryonic antigen glypican-3 (GPC3) is a good target of anticancer immunotherapy against pediatric solid tumors expressing GPC3. In this non-randomized, open-label, phase I clinical trial, we analyzed the safety and efficacy of GPC3-peptide vaccination in patients with pediatric solid tumors.

Methods
We conducted a phase I study of pediatric patients with solid tumors. GPC3 is a target of anticancer immunotherapy against some pediatric solid tumor especially hepatoblastoma. Vaccinations were carried out biweekly from the first until disease progression with the primary endpoint being the safety of GPC3-peptide vaccination and the secondary endpoints being immune response, as measured by interferon (IFN)-γ enzyme-linked immunospot assay and Dextramer staining, and the clinical outcomes of tumor response, progression free survival (PFS), and overall survival (OS).

Results
A total of 18 patients (7 hepatoblastoma, 4 rhabdomyosarcoma, 3 brain tumor, 1 MRT, 1 pancreatoblastoma, 1 Wilms tumor, 1 germ cell tumor) were enrolled from 5 hospitals, all cases showed no dose-limiting toxicity (DLT), which was the primary endpoint of this trial. No grade 3-4 hematological and non-hematological toxicity due to GPC3 vaccine therapy occurred. Clinical benefit ratio was 66.7% with six long SD (SD during more than 24 weeks; 5 hepatoblastoma, 1 MRT) The GPC3-peptide vaccine induced a GPC3-specific CTL response in seven patients, with PFS and OS significantly longer in patients with high GPC3-specific CTL frequencies than in those with low frequencies. Furthermore, we established GPC3-peptide-specific CTL clones from a resected-recurrent tumor from one patient, with these cells exhibiting GPC3-peptide-specific cytokine secretion.

Conclusions
GPC3 peptide vaccine therapy is well tolerated in heavily pretreated pediatric patients with refractory solid tumors especially hepatoblastoma with acceptable toxicities in outpatient setting and keep good QOL.

Legal entity responsible for the study
AKO hosono

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1152P - Phase 1 study of HSP105-derived peptide vaccine for patients with
Background
The HSP105 protein has been identified in pancreatic cancer by the SEREX method, and this protein has also been reported to play a role in controlling apoptosis in cancer cells. HSP105 is highly expressed in various human cancers, including colorectal cancer, esophageal cancer, pharyngeal cancer, pancreatic cancer, breast cancer, and melanoma. We have therefore identified the respective HSP105-derived peptides that bind to HLA-A24 and HLA-A2 (EP1536006, JP5112615, JP5291641, US9,404,925). We investigated the safety and efficacy of HSP105-derived peptide vaccine for patients (pts) with advanced esophageal cancer/colo-rectal cancer.

Methods
We conducted a multicenter phase 1 study of HSP105-derived peptide vaccine for pts with advanced esophageal cancer/colo-rectal cancer. The recommended dose is determined based on the incidence of dose-limiting toxicity (DLT) during phase 1a (P1a). Pts will then be added in phase 1b (P1b) to investigate the safety and efficacy of the vaccine. The vaccine was injected intradermally every 7 days. The primary objective of this study was to evaluate DLT (P1a), response rate (P1b). Progression-free survival, treatment failure rate, and toxicity were also evaluated as secondary objectives. As exploratory endpoint, immunological effect was investigated.

Results
A total 30 pts (HLA-24 group 15pts, HLA-02 group 15 pts) were enrolled and grouped into level 1 which received intradermally administration of peptide vaccine (emulsifying agent: Montanide ISA 51 VG) 3 mg/body. No DLT occurred and no major safety problems were reported throughout the trial. Although pts with objective clinical efficacy was not apparent, 7 pts showed stable disease 2 months after initiation of treatment. The HSP105-derived peptide vaccine induced HSP105-specific CTL response in 15 pts (50%) of 30 pts. Additionally, we established several HSP105 peptide-specific CTL clones from PBMCs and tumor of pts vaccinated with HSP105 peptide by single cell sorting using Dextramer or anti-CD107a antibody.

Conclusions
Although objective clinical efficacy was not apparent, HSP105-derived peptide vaccine appears safe and well tolerated with minimal local toxicity.

Clinical trial identification
Protocol number: UMIN000017809, Release date: Jun 22, 2015

Legal entity responsible for the study
National Cancer Center

Funding
1153P - An observational clinical study with RAS peptide vaccine TG01 evaluating immune response, safety and overall survival in patients with non-resectable pancreatic cancer

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Background
The study evaluated the immune response, safety and survival of the TG01/GM-CSF vaccine, an antigen-specific cancer immunotherapy consisting of 7 RAS peptides targeted to KRAS mutated pancreatic adenocarcinoma, in treatment naive non-resectable pancreatic cancer patients (pts). TG01/GM-CSF was recently reported to elicit immune response and increased survival in resectable pancreatic pts (ASCO 2017).

Methods
25 treatment naive non-resectable pancreatic cancer pts were immunised with TG01/GM-CSF at week 1, 2, 3, 4, 6, 10 (immunisation period) followed, after a 3 months pause, by a booster period of four weekly administrations. Pts were followed up for up to 12 months from 1st dose of TG01/GM-CSF. Immune response was evaluated by Delayed Type Hypersensitivity (DTH) skin reaction test, (S)AEs recorded throughout the study and survival data calculated using Kaplan-Meier.

Results
14/25 pts (56%) had a positive DTH by week 10. The TG01/GM-CSF treatment was well tolerated with no reports of allergic or other adverse hypersensitivity reactions. 13 pts experienced 19 SAEs; 5 were due to disease progression, 13 were deaths due to disease progression, and one was treatment related (hypoglycaemia). Median survival (MS) from first administration of TG01/GM-CSF was for all treated pts (n = 25) 4.5 months, for DTH responders (n = 14) 5.1 months and for DTH non-responders (n = 11) 3.6 months. For the DTH responders the result compares favorably with untreated patients (MS ≈ 3.7 months). At 1 year, 4 pts of whom three DTH responders were alive. 1. Palmer KR et al., Br J Surg: 81, 882-885 (1994).

Conclusions
In pts treated with TG01/GM-CSF monotherapy, immune response was recorded in 56% of the pts, results that correspond with data from a Phase I/II trial with a similar RAS peptide vaccine in non-resectable pancreatic pts. Even though not statistically significant, the results indicate increased survival for the immune responders. In the otherwise incurable disease, the non-resectable pancreatic pts may therefore benefit from immunisation with TG01/GM-CSF RAS peptide vaccine with few side effects. 2. Gjertsen M et al., Int J Can: 92, 441-450 (2001).

Clinical trial identification
Protocol CTN RAS 98010, 20.05.1998, Norway

Legal entity responsible for the study
Norsk Hydro ASA, Oslo, Norway

Funding
1154P - Telomerase peptide vaccine combined with ipilimumab in metastatic melanoma: Reports from a phase I trial

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Background
The checkpoint inhibitor ipilimumab has improved survival for a proportion of patients with metastatic melanoma. However, most patients do not benefit from single agent immunotherapy. Patients lacking a spontaneous immune response may benefit from combining checkpoint blockade with a tumor-specific vaccine. UV1 is a therapeutic cancer vaccine consisting of three long synthetic peptides of the enzyme telomerase (hTERT). The UV1 peptides comprise epitopes recognized by T cells from cancer patients experiencing long-term survival following vaccination with a first-generation hTERT vaccine. The aim of this trial was to investigate the safety and efficacy of combining UV1 and ipilimumab in the treatment of patients with metastatic melanoma.

Methods
In a phase I, single center trial [EudraCT No. 2013-005582-39], patients with metastatic melanoma received treatment with UV1 (300 µg) + GM-CSF (75 µg) as adjuvant, combined with ipilimumab (3 mg/kg). Safety was assessed according to CTCAE v. 4.0, and tumor responses according to RECIST v.1.1. Immune responses against UV1 peptides were monitored in peripheral mononuclear blood cells by using 3H-thymidine proliferation and IFN-γ ELISPOT assays.

Results
12 patients were recruited from Jan to Oct 2015. Treatment was generally well tolerated. Adverse events mainly included injection site reactions and diarrhea. Eleven serious adverse events (SAEs) were reported; nine treatment-related and two not related. Ten out of twelve patients showed an immune response (one negative, one not evaluable). Three patients obtained a partial response. Overall survival at 18 months was 75%. A comparison to a reference population from a phase IV ipilimumab trial in our center will be made.

Conclusions
Combining UV1 and ipilimumab is safe and induces clinical responses. The high proportion of immune responders and early induction of detectable immune responses suggest a synergistic effect due to de novo tumor-specific immune responses, likely due to blockage of CTLA-4, allowing expansion of hTERT-specific T-cell clones.

Clinical trial identification
EudraCT No. 2013-005582-39 Start date 16 Jan 2015

Legal entity responsible for the study
Ultimovacs AS Ullernschausséen 64 NO-0379 Oslo Norway Ultimovacs AS Ullernschausséen 64
1155P - Results of an open label randomized phase II trial of CV9104, an mRNA-based multivalent cancer immunotherapy in patients (pts) with intermediate or high risk localized prostate cancer (PC) undergoing radical prostatectomy (RPE)

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Background

CV9104 is a multivalent mRNA-based active cancer immunotherapy containing sequence-optimized free and protamine complexed mRNA coding for six prostate cancer associated antigens (PSA, PSMA, PSCA, STEAP1, PAP and MUC1). CV9104 has been investigated in a placebo controlled Phase IIb study in pts with metastatic castrate-resistant PC. Administration of mRNA based immunotherapy by needle free jet devices has been shown to improve antigen expression and immunogenicity vs needle injection in preclinical models. The purpose of this study was to evaluate immune responses and safety of CV9104 administered by conventional intradermal (cID) injection or with a needle-free ID (nfID) injection device in pts with intermediate/high-risk localized PC.

Methods

48 pts with intermediate or high risk localized PC and an indication to undergo RPE were randomized in a 1:1:1 ratio to receive presurgical CV9104 by nfID injection (960 µg mRNA per administration) (A), or cID injection (1920 µg mRNA per administration) (B), or no treatment (C). CV9104 was administered in weeks 1, 2, 3 and 5 before RPE was performed in week 6-7. Postoperative CV9104 was offered to all pts with high-risk PC. Cellular (against all antigens) and humoral immune responders (against PSA, STEAP1, PAP, MUC1) were determined in blood at week 6-7 before RPE and 8 weeks after surgery. Further samples (prostatectomy, exprimate urine, serum) were collected for exploratory biomarker analyses.

Results

48 pts were randomized (A: 15; B: 17; C: 16); Treatment with CV9104 was well tolerated using either nfID or cID injection. Most frequent adverse events (AEs) in Arms A and B were Grade 1-2 injection side reactions, transient flu-like symptoms (FLS) and AEs related
to RPE. There were no CV9104 related Grade ≥3 AEs or SAEs. FLS were most frequent in Arm B (76.5%) vs Arm A (37.5%) and Arm C (6.3%).

Conclusions
CV9104 was well tolerated using either nflD or cID injection, with a safety profile similar to other previous mRNA-based cancer immunotherapies. Cellular and humoral immune responses including responses per antigen and additional biomarker results will be presented.

Clinical trial identification
EudraCT Number: 2013-004489-32

Legal entity responsible for the study
CureVac AG

Funding
Sponsor Clinical Trial: CureVac AG

Disclosure

1156P - Italian nivolumab expanded access programme: real-world results in non-squamous non-small cell lung cancer patients
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Background
Nivolumab monotherapy has shown survival benefit in patients (pts) with different tumors, including melanoma, lung cancer, renal cell carcinoma and head and neck cancer. The experience of pts and physicians in routine clinical practice is often different from that in a controlled clinical trial setting. Here, we report efficacy and safety of nivolumab monotherapy in pts with non-squamous non-small cell lung cancer (NSCLC) treated in the nivolumab Expanded Access Programme in Italy.

Methods
Nivolumab was available upon physician request for pts aged ≥18 years who had relapsed after a minimum of one prior systemic treatment for stage IIIB/stage IV non-Squamous NSCLC. Nivolumab 3 mg/kg was administered intravenously every 2 weeks to a maximum of 24 months. Pts included in the analysis had received at least 1 dose of nivolumab and were monitored for adverse events (AE) using Common Terminology Criteria for Adverse Events.

Results
In total, 1588 Italian pts participated in the EAP across 168 centers. Baseline characteristics of pts were representative of the population with non-squamous NSCLC, in the advanced disease setting. With a median follow-up of 7.8 months (1-21.9) and a
median of 7 doses, the overall response rate (ORR) was 18%, including 10 pts (<1%) with complete response and 280 pts (17%) with partial response. Stable disease has been defined for 414 pts (26%) and totally 279 patients were treated beyond progression. As of March 2017, median overall survival (OS) was 11 months (range: 10.0-12.0). Response rates and survival were comparable among pts regardless age (< and ≥ 75 years), presence of brain metastasis and number of prior therapies. Overall, among 1588 pts, 1254 discontinued treatment for any reason, with only 80 pts (5%) who discontinued treatment due to related adverse events.

**Conclusions**

To date, this is the largest clinical experience with nivolumab in a real-world setting. These preliminary EAP data confirm that nivolumab seems to be an effective and safe therapy for pre-treated patients with non-squamous NCSLC, supporting its use in current clinical practice.

**Clinical trial identification**

CA209-966

**Legal entity responsible for the study**

Prof. Lucio Crinò

**Funding**

Bristol-Myers Squibb

**Disclosure**


1157P - Correlation and differences in Effect sizes between Progression Free Survival (PFS) and Overall Survival (OS) among PD-1 inhibitors

**Background**

Programmed death 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab, have now been approved for various cancers based on results from pivotal randomized controlled trials (RCTs). These drugs are known for unconventional response patterns with varying effects on PFS and OS. We aimed to compare the correlation between PFS and OS and evaluate the differences in treatment size between PFS and OS for PD-1 inhibitors.

**Methods**

We carried out a systematic search on PubMed and conference abstracts for RCTs of
nivolumab and pembrolizumab versus non-immunotherapy control and obtained data on median PFS, median OS for both arms and hazard ratio (HR) and confidence intervals (CIs) for PFS and OS. We evaluated the correlation between PFS and OS as well as between Delta (PFS) and Delta (OS). We also evaluated the ratio of HR of PFS to HR of OS for each trial (rHR) and obtained a summary rHR by random-effects meta-analysis across trials.

**Results**

Of 52 studies identified, a total of 11 phase 3 RCTs met the eligibility criteria. However, 2 trials didn’t have data on OS. So our analysis includes 9 RCTs that had data on both PFS and OS (6 Nivolumab, 3 Pembrolizumab). There was no significant correlation between PFS and OS ($r = 0.676$, $R^2 = 0.457$, $P = 0.095$) or between Delta (PFS) and Delta (OS) ($r = 0.474$, $R^2 = 0.225$, $P = 0.282$). Using random-effects meta-analysis, treatment effects were in general 19% higher for OS than PFS (rHR 1.19, 95% CI 1.07 to 1.32, $p = 0.001$). There was no statistical evidence for lack of homogeneity ($I^2 = 0.0\%$, $p = 0.850$) and thus, subgroup analysis were not conducted. PFS and OS were discordant for 5 RCTs (3 Nivolumab, 2 Pembrolizumab) and in all these 5 RCTs, OS was significant but PFS was not. All RCTs ($n = 3$) showing benefit for PFS also showed benefit for OS. Only one RCT was negative for OS.

**Conclusions**

Unlike targeted therapies where benefit in PFS mayn't translate to OS, treatment effect sizes in RCTs of PD-1 inhibitors were greater for OS than PFS. The benefit in OS was poorly captured by PFS. There was no correlation between PFS and OS. OS should remain the standard endpoint for PD-1 inhibitor RCTs unless better surrogate endpoints such as immune-criteria based PFS are introduced and validated.

**Legal entity responsible for the study**

The authors

**Funding**

None

**Disclosure**

Y. Ando: Reports grants and personal fees from Taiho Pharmaceutical Co., Ltd., and personal fees from Merck Serono Co., Ltd., Ono Pharmaceutical Co., Ltd and Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1158P - Is objective response rate (ORR) a valid primary endpoint in phase 2 trials (Ph2t) of immune checkpoint inhibitors (ICI) for advanced solid cancers?

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**Background**

ORR is commonly used as the primary endpoint in Ph2t. ICI have different mechanisms of action to chemotherapy or molecular targeted agents (MTA). The validity of ORR as a surrogate for progression-free survival (PFS) and overall survival (OS) with ICI is uncertain and may differ by tumor type. We performed a meta-analysis of randomized controlled trials (RCTs) in advanced solid cancers that compared ICI to chemotherapy, MTA or placebo to address this question.

**Methods**
We performed a literature search to determine the current Ph2t designs used in ICI trials. Efficacy data from single-arm trials and RCTs were extracted. Amongst the RCTs, correlations between ORR odds ratio (OR) with PFS hazard ratio (HR) and OS HR were examined for between randomized arms comparisons. Correlations within ICI treatment arms of the RCTs between ORR with PFS and OS rates were also studied. Using data from the RCTs, multivariable models that examined the relationships between ORR, 6-month PFS and 12-month OS rates were developed and their predictive performances validated in the single-arm trials.

Results

Of 87 Ph2ts identified, most were single arm design (68%), and only 10% were RCTs with concurrent standard of care arms. ORR was the most common (60%) primary endpoint and PFS was uncommon (8%). A total of 20 RCTs (4 Ph2t and 16 phase 3 trials) with mature data were examined. There were 25 treatment comparisons in 8 different tumors (non-small cell lung cancer 44%, melanoma 24%). For RCTs in all tumors, the correlations (r) between ORR OR with PFS HR, ORR OR with OS HR, and PFS HR with OS HR were 0.63, 0.57 and 0.42 respectively. Within the ICI arms, r between ORR with 6-month PFS, ORR with 12-month OS, and 6-month PFS with 12-month OS were 0.37, 0.08 and 0.74 respectively. In the single-arm trials dataset, we were able to accurately predict 12-month OS using the actual 6-month PFS with the multivariate model developed from our RCTs dataset. Conversely, when ORR was used to predict 6-month PFS or 12-month OS, there was poor agreement between actual and predicted results.

Conclusions

These data do not support the use of ORR as a surrogate for OS in ICI trials. In future ICI Ph2t, 6-month PFS should be the primary endpoint rather than ORR.

Clinical trial identification

Not applicable

Legal entity responsible for the study

Not applicable

Funding

None

Disclosure

M. Friedlander: Receives personal fees and grants with an advisory board position with AstraZeneca. Does not have any patents planned, pending or issued, broadly relevant to the work. All other authors have declared no conflicts of interest.

1159P - Long term survival in patients responding to an Anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation

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Background

The long-term outcome of cancer patients responding to an anti-PD-1/PD-L1 immunotherapy (IT) remains unknown. This study aimed to describe the long-term survival...
of patients responding to anti-PD-1/PD-L1 monotherapy across multiple cancer types.

**Methods**

306 patients treated with an anti-PD-1 or PD-L1 monotherapy in a phase 1 trial at Gustave Roussy were retrospectively analyzed over a period of 5 years. Major inclusion criteria were: at least 18 years-old, performance status 0-1, at least 1 infusion, evaluation by RECIST 1.1 and/or irRC. Multiple myeloma patients were excluded as they do not respond to anti-PD-1 monotherapy. All other cancer types (n = 19) were included.

**Results**

The overall objective response rate within this cohort of 262 patients was 29% (n = 76; 77% being evaluated by irRC). The median PFS of responders was 22 months and the median OS was not reached. The OS of patients responding to IT at 3 years was 76% and at 5 years was 63%. Long responders (patients with enough follow up to have tumor responses lasting more than 2 years) represented 11.8% of the cohort (31 patients). No death occurred in the 21 complete responders over this long term follow up. The median duration of response was not reached. Out of the 33 patients who discontinued immunotherapy, 9 patients showed a disease relapse (median response duration after treatment discontinuation: 6 months). Clinical and biological factors associated with response, long term survival, and secondary refractory disease will be reported at the ESMO meeting.

**Conclusions**

This study shows that, across cancer types, patients with objective tumor responses under anti-PD-1/PD-L1 immunotherapy have a high level of overall survival. Best survivals are seen with complete responses (no deaths in our cohort). Complete response rate might be a good short term surrogate marker for overall survival benefits. Clinical trials aiming at putting patients with partial responses under immunotherapy into complete responses should be assessed in a near future.

**Clinical trial identification**

N/A

**Legal entity responsible for the study**

Gustave Roussy

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1160P - Meta-Analysis of Anti-PD-1/PD-L1 Therapy Related Adverse Events in Clinical Trials**

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**Background**

Anti-PD-1/PD-L1 immunotherapy is a major breakthrough in cancer treatment. With
increasing use, its adverse event (AE) profile continues to be defined. We performed a meta-analysis to summarize AEs of anti-PD-1/PD-L1 therapy in clinical trials.

Methods
Clinical trials involving monotherapy with PD-1 or PD-L1 antibody in cancer patients published before April 1, 2017 were reviewed, and treatment related AE data were extracted. Meta-analysis of AE rates was done by Comprehensive Meta-Analysis (v2) using a random effects model. Average AE rate (Total AE No./Total Patient No.) was calculated in Microsoft Excel.

Results
63 studies involving 10592 patients were included: 27 on nivolumab, 23 on pembrolizumab, 8 on atezolizumab, 4 on avelumab, and 1 on BMS-936559. Treatment related AE rates were summarized in the Table. In meta-analysis, all grade AE (AEx) rate was 71.5%, and grade 3-4 AE (AE3) rate was 14.9%. Common AEx included fatigue (>20%), pruritus, rash, diarrhea, nausea (10-20%), decreased appetite, arthralgia, vitiligo, pyrexia, hypothyroidism, and asthenia (5-10%). Most common AE3 included hyponatremia, lymphopenia, and fatigue (>1%). Average immune-mediated AEx/AE3 rates (%) were uveitis 0.9/0.0, pneumonitis 2.9/0.8, colitis 1.4/0.9, ALT increase 3.7/0.9, AST increase 4.0/0.8, pancreatitis 1.7/0.4, vitiligo 8.2/0.1, alopecia 1.0/0.0, asthenia 7.3/0.4, paresthesia 1.0/0.0, dysgeusia 2.2/0.0, peripheral neuropathy 1.5/0.0, hypothyroidism 7.0/0.1, hyperthyroidism 3.0/0.1, hypophysitis 0.5/0.4, and adrenal insufficiency 1.2/0.5. 31 (0.3%) treatment related deaths were reported. Pulmonary causes were most common, including 11 pneumonitis, 3 pneumonia and 1 respiratory failure.

Conclusions
Common AEs of anti-PD-1/PD-L1 therapy were primarily constitutional and gastrointestinal. Most grade 3-4 AE rates were < 1%. Rates of immune-related AE were low. Treatment related death was rare, and pneumonitis was the most common cause.

Clinical trial identification
Not applicable.

Legal entity responsible for the study
Yucai Wang

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1161P - A standardized comparison of outcomes in patients (pts) with refractory, aggressive non-hodgkin Lymphoma (rNHL) from the SCHOLAR-1 analysis and the ZUMA-1 study of axicabtagene ciloleucel (axi-cel)

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Background
SCHOLAR-1 (Crump, ASCO 2016) is a large, pooled analysis of rNHL and demonstrated poor outcomes: objective response rate (ORR)= 26%; complete response (CR)=8%.
ZUMA-1 is the first, multicenter trial of anti-CD19 CAR T cells (axi-cel) in rNHL and reported positive results: ORR= 82%; CR= 54%. This is a comparative analysis of outcomes from ZUMA-1 and SCHOLAR-1 after adjusting for imbalances in key covariates of patients enrolled.

Methods
Eligible pts for both studies had rNHL (stable disease ≤6 mos with ≥4 cycles frontline or ≥ 2 cycles later-line therapy, progressive disease as best response, or relapse ≤12 mos post autologous stem cell transplant). Standardized analyses were performed to account for other baseline covariates that were imbalanced between the studies despite similar inclusion criteria. These analyses equally weighted the proportions of patients with select prognostic covariates between the two studies. The pre-specified covariates selected for weighting were refractory subgroup and occurrence of SCT after refractory status. Sensitivity analyses included additional covariates.

Results
101 ZUMA-1 pts received axi-cel; SCHOLAR-1 included data from 508 pts. Baseline characteristics for each study are listed in the Table. ZUMA-1 median follow-up was 8.7 mos. Using the standardized analysis, the estimated ORR and CR rates in SCHOLAR-1 were 20% and 6%, respectively. Standardized 6-mo survival rate for SCHOLAR-1 was 35%. Risk of death in ZUMA-1 was reduced by 77% relative to SCHOLAR-1 (P < .0001).

Table:

<table>
<thead>
<tr>
<th>ZUMA-1 mITT SCHOLAR-1 Response</th>
<th>N = 101</th>
<th>N = 508</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ≥65 y, n (%)</td>
<td>24 (24)</td>
<td>74 (15)</td>
</tr>
<tr>
<td>Refractory subgroup, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary refractory</td>
<td>2 (2)</td>
<td>101 (20)</td>
</tr>
<tr>
<td>Refractory to ≥ 2L</td>
<td>78 (77)</td>
<td>316 (62)</td>
</tr>
<tr>
<td>Relapse &lt;12 mo post-ASCT</td>
<td>21 (21)</td>
<td>91 (18)</td>
</tr>
<tr>
<td>Received stem cell transplant*, n (%)</td>
<td>11 (11)</td>
<td>161 (32)</td>
</tr>
<tr>
<td>Prior lines of chemotherapy &amp; ASCT</td>
<td>n = 101</td>
<td>n = 417</td>
</tr>
<tr>
<td>Median prior lines, n</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ECOG performance score</td>
<td>n = 101</td>
<td>n = 288</td>
</tr>
<tr>
<td>0-1, n (%)</td>
<td>101 (100)</td>
<td>230 (80)</td>
</tr>
<tr>
<td>IPI Score</td>
<td>n = 101</td>
<td>n = 215</td>
</tr>
<tr>
<td>≥2, n (%)</td>
<td>74 (73)</td>
<td>142 (66)</td>
</tr>
</tbody>
</table>

* Autologous or allogeneic SCT at any time after determination of refractory status. ASCT,
Conclusions
Despite the imbalances between the ZUMA-1 and SCHOLAR-1 studies, axi-cel appears to represent a significantly improved treatment option for pts with rNHL compared with currently available therapies as used in the SCHOLAR-1 study.

Clinical trial identification
NCT02348216

Legal entity responsible for the study
Kite Pharma

Funding
Kite Pharma

Disclosure

1162P - Predictive factors for poor progression-free survival in patients with non-small-cell lung cancer treated with nivolumab

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Background
Nivolumab (Nivo) has shown promising effects in patients with non-small-cell lung cancer (NSCLC) as a second- or later-line treatment. However, owing to the inclusion of random patients, the observed progression-free survival (PFS) in a clinical setting may be shorter than that in a clinical trial. For treatment effectiveness, it is important to clarify which patients may not experience any benefit from Nivo treatment. Therefore, in this multicenter retrospective study, we aimed to identify which patients would not be eligible for Nivo treatment.

Methods
In this study, data for 201 patients treated with Nivo during 17 December 2015 to 31 July 2016 at three respiratory medical centers in Japan were retrospectively reviewed. We
collected clinical data including age, sex, smoking history, performance status (PS) score, body mass index (BMI), histological types, epidermal growth factor receptor (EGFR) mutation status, number of previous treatment, steroid use and laboratory data (Lactate Dehydrogenase (LDH) and C-reactive protein) at the time of Nivo treatment commencement. We investigated relationship between PFS and patient characteristics. Patients were followed-up for disease status until September 2016.

**Results**

The median age at the time of administration Nivo was 68 years, 135 patients were male, 157 patients had smoking history, 153 patients had a PS score of 0–1, and 23 patients received steroids. For all participants, median PFS was 2.9 months, over all response rate was 15.9% and disease control rate was 51.7%. In the univariate analysis, PS score ≥2, steroid use at baseline, and LDH level >240 IU/L was significantly associated with poor PFS. Furthermore, in the multivariate analysis, PS score ≥2 (hazard ratio [HR]: 1.57; 95% confidence interval (CI): 1.06–2.29; p = 0.027), steroid use at baseline (HR: 2.37; 95% CI: 1.44–3.74; p = 0.001) and LDH level >240 IU/L (HR: 1.63; 95% CI: 1.15–2.31; p = 0.007) were significantly associated with poor PFS.

**Conclusions**

PS score ≥2, steroid use at baseline, and high LDH levels were predictive of poor PFS in patients with NSCLC treated with Nivo. Careful monitoring is recommended for treating such patients with Nivo.

**Legal entity responsible for the study**
Fumio Imamura

**Funding**
Ono pharmaceutical Co., Ltd. Bristol-Myers Squibb Co., Ltd.

**Disclosure**
tumours: The Gustave Roussy experience

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Background

More than half of new cases of cancer are diagnosed in patients over 65 years. However, only few elderly patients have so far been included into trials, despite general awareness of the need. The revolution of immune checkpoint blocker development brings new hope in older patients because of clinical efficacy and low toxicity. Clinical indications are rising steadily but very few data are available in this population where co-morbidities, reduced functional reserve and immunosenescence may affect efficacy and tolerance.

Methods

All cases of patients enrolled in immunotherapy phase I trial between January 2012 and December 2016 in the Drug Development Department (DITEP) at Gustave Roussy were retrospectively reviewed. Case-control analysis was performed in a group of patients ≥ 70 years (elderly patients EP) matched to a group of patients < 70 years (younger patients YP) by trial and treatment dose. We compared cumulative incidence, grade and type of adverse events (AEs) and survival outcomes. Cumulative incidence was calculated according to Fine and Gray method and survivals using Kaplan-Meier method.

Results

Median age of EP and YP were respectively 75 (70 - 88) and 55 (22 - 70). Among the 46 EP and the 174 YP enrolled in 13 protocols, 10 (22%) and 23 (13%) patients experienced grade 3-4 AEs. Cumulative incidence of grade 1-2 AEs was significantly higher in EP versus YP (p < 0.05). For grade 1 AEs, median time of occurrence was 0.67 for EP versus 2.67 months for YP. For grade 2 AEs, median was not reached. No difference was observed between the two groups for grade 3-4 AEs (p = 0.50). Older age was not associated with lower dose intensity of treatment (p = 0.14). The response rate was respectively 14% for EP and 18.5% YP (p = 0.52). Median overall survival and median progression free survival were similar between the two groups (10.1 months, HR 0.93 [0.58-1.48] p = 0.77; 6.2 months, HR 1.41 [0.94-2.11] p = 0.09 for EP and YP, respectively).

Conclusions

Immune checkpoint blockade appears to be a practicable option of treatment for elderly patients. The toxicity and efficacy profiles appear similar to the ones in younger patients. Dedicated studies in this population are warranted.

Legal entity responsible for the study

Gustave Roussy

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1164P - Patterns of progression under antiPD1/PDL1 in advanced NSCLC patients
allow discriminating pseudo-progression from real progression

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**Background**

Immunotherapy (IT) is now a standard of care in advanced NSCLC patients. However, patients may present with various patterns of response, including initial progression followed by long stabilization or response, making it difficult to decide whether or not we should continue the treatment at the occurrence of progression. Our aim was to explore the patterns of responses based on CT-scans in order to differentiate real progression (PD) from pseudoprogression (PsPD).

**Methods**

We conducted a retrospective analysis of all NSCLC patients treated with IT in our Institution. All CT-scans were reviewed and the responses were assessed by RECIST 1.1 and iRECIST criteria. Seven different patterns of PD were considered based on the combination of target (T) and/or non-target (NT) and/or new lesions (NL). A confirmatory CT scan was performed at 4 weeks to discriminate real progression from PsPD. PsPD was defined as any decrease or stable disease for at least 6 months following an initial progression. Dissociated responses (DR) were defined as concomitant progressing and responding lesions for patients treated at least 6 months. Patterns of PD were correlated with overall survival (OS).

**Results**

Out of 202 patients treated by IT, 39 patients (19%) were excluded due to the absence of confirmatory CT. 87 patients (53%) had an initial PD, confirmed by a subsequent CT, or by death related to tumor progression. 14 patients (9%) experienced PsPD or DR. PsPD or DR patients had higher OS than PD patients \( (p = <.05) \). The pattern which was the most likely to confer PsPD or DR was the appearance of NL in the thoracic area (lung, pleura) or lymph nodes. The concomitant increase of T, NT and appearance of NL was only observed in real PD. New extra-thoracic visceral lesions (especially liver and brain) were very unlikely related to PsPD. New liver lesions occurring during IO were detrimental on OS \( (p = <.05) \).

**Conclusions**

On the first occurrence of progression upon IT, a concomitant increase of T, NT and appearance of NL or appearance of extra-thoracic visceral lesions were strongly suggestive of real PD. IT should be stopped in these patients, and a confirmatory CT scan should be avoided.

**Legal entity responsible for the study**

Gustave Roussy

**Funding**

None

**Disclosure**

A. Marabelle: Reports personal fees from Roche/Genentech, personal fees from Bristol-Myers Squibb, personal fees from Merck, personal fees from Pfizer, personal fees from AstraZeneca, outside the submitted work. D. Planchard: Reports consultancy for
Background
MITF translocation renal cell carcinoma (tRCC) is a rare RCC subtype harbouring TFE3/TFEB translocations with poor prognosis and no standard of care in metastatic setting. Program death ligand-1 (PDL-1) expression was reported in 90% of cases prompting us to analysed the benefit of immune checkpoint inhibitors (ICI) in this population.

Methods
A multicenter retrospective study was conducted to identify patients with MITF family tRCC who had received ICI in referral centres in France and USA. In the majority of cases, the diagnosis was confirmed by FISH. Overall response rate (ORR) according to RECIST criteria, progression-free survival (PFS) and overall survival (OS) were analyzed.

Results
Overall, 23 patients (4 males and 19 females) with metastatic disease were identified in 12 institutions (median age 33.5 years), all receiving ICIs as 2nd or later line. For first-line treatment, 19 (82.6%) patients received vascular endothelial growth factor receptor (VEGFR) inhibitors with a median PFS on therapy of 3 months (range, 1-22 months) and 2 (10.5%) responders. Regarding ICI, 19 patients received Nivolumab, 3 patients Ipilimumab and 4 patients combinations of ICIs +/- VEGFR inhibitors. Median PFS for patients under first ICI administered was 2.45 months (range, 1-40 months); among those, 4 patients experienced partial responses (17.4%) and 2 patients (9.5%) a stable disease with a median PFS of those responders under ICI of 9 months (range 8,3-30), similar to the first line PFS with VEGFR inhibitors [9 months, (range 1-22)]. One patient with partial response to Ipilimumab lasting for 9 months showed hyperprogressive disease following treatment by Nivolumab. With a median follow-up of 19 months, median OS was 23.5 months.

Conclusions
MITF family tRCC is an aggressive disease with occasional responses to ICI. Valid targets and clinical trials remain warranted in this disease.
Background
In the last decade, TFR was described as a side-effect associated with immunomodulatory agents IMiDs (thalidomide and lenalidomide), and as a specific condition to chronic lymphocytic leukemia (CLL). However, this phenomenon is seen with the use of new immunotherapy (checkpoints inhibitors) in solid tumors, in addition, cases of TFR were reported in advanced gynecologic, prostate cancer and lymphoid malignancies. TFR is defined as an increase of lesion size related to treatment which simulates disease progression. This phenomenon that occurs after initiating cancer therapy is poorly understood and incidence is under-estimated, since not captured by Recist. It has been suggested that TFR may be the results of immune system activation and may precede tumor shrinkage. TFR is associated with morbidity, severe cases were reported, some of them life-threatening or leading to death. So, early recognition and initial management of patients presenting with TFR, is critical.

Methods
From 1985 to 2016, a search was performed in the Pubmed, ASCO and ASH abstracts to identify publications reporting TFR or pseudoprogression.

Results
The incidence of all grades of TFR in CLL, ranged from 28% in a study to 58% in another trial. In CLL, painful lymph nodes and/or spleen enlargement were reported with a sudden onset after the first dose. Following initial progression (TFR), tumor response in patients treated beyond progression, was reported in melanoma trials: 9.7% with ipilimumab, 10% with nivolumab, 6.7% and 12% with pembrolizumab, and in renal cell carcinoma 69% with nivolumab. Even if rare cases of life-threatening or fatal TFR were reported, symptoms are usually mild. While correct diagnosis and adequate management are critical, it is important to better recognize TFR, and avoid an effective treatment discontinuation. Some studies showed that treating patients beyond progression yielded tumor responses, considering TFR as predictive of response.

Conclusions
Treatment with immunomodulatory agents is associated with TFR. This is likely to be
misinterpreted as progression, hence the need to identify appropriate clinical benefit criteria and the use of immune-related RECIST (irRC) in prospective trials for a better understanding.

Legal entity responsible for the study
Amina TALEB MD

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1167P - Melanoma brain metastases patients treated with stereotactic radiosurgery and ipilimumab versus stereotactic radiosurgery alone: a systematic review with meta-analysis

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Background
The synergistic effects of radiotherapy and novel immunotherapy agents have shown renewed interest in cancer management. We examined survival outcomes in melanoma brain metastases (MBM) patients treated with stereotactic radiosurgery (SRS) and ipilimumab immunotherapy. We compared these outcomes with those of MBM patients receiving SRS without added immunotherapy.

Methods
We conducted the first systematic review with meta-analysis of studies comparing combined SRS and ipilimumab with SRS only in MBM. The protocol was published in the PROSPERO register for systematic reviews. MEDLINE and CENTRAL databases were searched using PRISMA method by three separate reviewers. Studies that examined SRS and ipilimumab compared to SRS without ipilimumab in MBM were included. Newcastle-Ottawa Scale Risk of Bias Assessment and the GRADE evidence quality rating method were used for qualitative appraisal. Statistical analysis was performed using Review Manager.

Results
We found 37 publications in our search and identified 4 retrospective studies to further assess; 3 studies were chosen for pooled-analysis. Evidence for survival benefits with combined treatment was rated “low”, per GRADE method. Meta-analysis of 222 patients confirmed significant survival advantage for SRS and ipilimumab (pooled median survival: 16.8 vs. 6.2 months; HR 0.38, 95% CI: [0.28 – 0.52]; p < 0.01). One study’s cohorts (n = 58) demonstrated non-significant trend for improved local and distant brain control. Otherwise, we found no differences in local control, distant brain control, radiation necrosis, or intracranial bleeding in our analysis.

Conclusions
Combining stereotactic radiosurgery and ipilimumab in melanoma brain metastases can dramatically improve survival rate compared to stereotactic radiosurgery without immunotherapy. There is no increased risk of radiation necrosis and/or intracranial bleeding with combining radiation and immunotherapy in this setting.

Legal entity responsible for the study
Background
There is a current need to broadly evaluate the ability of RNA sequencing (RNAseq) to identify patients that will respond or not to PD-1 or PDL-1 immune checkpoint blockers (ICB) across metastatic tumor types.

Methods
RNA sequencing analysis were prospectively performed by a unique platform on patients’ fresh frozen biopsies collected in the MOSCATO (NCT01566019) and MATCH-R (NCT02517892) prospective trials, ongoing at Gustave Roussy. We have analyzed more than 100 signatures related to immune cell types or immune mechanisms with several methods, and have evaluated their relation to PFS and OS under ICB, up to January 2017.

Results
RNAseq performed on a frozen tumor biopsy before receiving an ICB were available for 67 patients. The median time between the biopsy and start of the ICB was 41 days. The results of RNAseq analysis were available within a median of 42 days. The majority of patients were affected by either head-and-neck carcinomas (N = 12), bladder carcinomas (N = 11) or lung adenocarcinomas (N = 11). The majority of patients were treated with PD-1 (N = 41) or PD-L1 (N = 28) inhibitors either in monotherapy or in combination. The immune infiltrate was heterogeneous across patients and neither related to the histology nor to the location of the biopsy. The top RNAseq pipeline of analysis related to PFS were GSVA enrichment method and the combination of GSEA on Z transformed log TPM pipeline. Taken individually, 60% of the tested signatures had a significant relation to PFS under ICB whatever the pipeline used (logrank FDR<0.05). Using the best pipeline of analysis, the signatures with a significant continuous relation with PFS and OS were represented by 7 different T cells signatures, antigen processing and presentation, and PD-1 signaling (min-max ranges for PFS; HR 0.19-0.39, FDR = 0.0008-0.02 and for OS; HR = 0.17-0.32, FDR = 0.04 for all). An independent cohort is under constitution to validate these findings.

Conclusions
The use of RNAseq to orient patients to ICB is feasible. Estimation of immune infiltrate and function from RNAseq may be associated with treatment benefice either in term of PFS or in term of OS.
Clinical trial identification
MOSCATO (NCT01566019) and MATCH-R (NCT02517892)

Legal entity responsible for the study
Jean Charles Soria

Funding
None

Disclosure
L. Verlingue: Consultant for Adaptherapy. J-C. Soria: Consultancy fees from AstraZeneca, Astex, Clovis, GSK, Gammmamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. All other authors have declared no conflicts of interest.

1169P - Topography of Tumor Mutational Burden (TMB) and Immune-related Genomic Alterations (GA) Across Gastrointestinal Malignancies (GIm): A Study of 22,570 Cases

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Background
Response to immune checkpoint inhibitors (ICPIs) is mediated in part by tumor neoantigens. TMB has emerged as a predictive biomarker, but data is lacking in GIm. We examined TMB and concurrent GA across GIm to identify patient subsets for further study.

Methods
Comprehensive genomic profiling was used to determine TMB, microsatellite instability (MSI), and additional GA using previously described methods. GA were compared among anatomically defined tumor types and stratified by TMB status (mutations/DNA megabase), and those associated with response or resistance to ICPIs were compared to identify patient subsets.

Results
Median TMB was higher for tubular vs. non-tubular GIm (p = 0.032). Among the entire cohort, 3.5% and 7.4% of samples had a TMB >20 and >10, respectively. The proportion of tumors with TMB ≥10 was greatest within tubular foregut structures (esophagus, stomach, duodenum; 11.2%). MSI was observed across all anatomic subtypes (range: 0.2-6%). Overall 1.2% of cases harbored receptor tyrosine kinase (RTK) fusions; colon and biliary tumors with RTK fusions had high (11) and low (2.5) median TMB, respectively. Validated immunoresponsive GA including PD-L1 amplification and POLE mutations were mutually exclusive and enriched in tubular GI structures [esophagus (0.5%), stomach (0.8%), colon (0.9%), duodenum (1.3%) and rectum (0.9%)]. POLE mutation, but not PD-L1 amplification, correlated with high TMB (median 100 and 5.4, respectively). PIK3CA catalytic (H1047R) vs. helical (E545K) domain GA were strongly associated with high TMB (p < 0.0001), and similar findings were observed within MSI vs. MSS samples.
(p < 0.0001). Pre-existing GA that may decrease ICPI responsiveness including or JAK1 inactivating GA were rare (4.7% and 0.3% of cases, respectively). Representative clinical cases will be presented.

Conclusions
GAs associated with increased sensitivity and/or resistance to ICPIs are observed across GI cancers. Baseline genomic profiling may inform rational patient selection for immunotherapy treatment. The observation that high TMB and MSI are strongly enriched for PIK3CA H1047R, and whereas low TMB and MSS are enriched for E545K, warrants further study.

Legal entity responsible for the study
Samuel J. Klempner

Funding
None

Disclosure

1170P - Analysis of POLE mutation and tumor mutational burden (TMB) across 80,853 tumors: Implications for immune checkpoint inhibitors (ICPIs)
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Background
Mutations of the DNA polymerase epsilon (POLE) can lead to a hypermutated tumor phenotype, in the absence of microsatellite instability (MSI). Exceptional responses to ICPIs in POLE-mutated endometrial adenocarcinoma (EA), colorectal (CRC), and glioblastoma (GBM) are described, but detailed pan-tumor POLE analyses are lacking.

Methods
We prospectively analyzed 80,853 primarily advanced solid tumors using hybrid-capture based comprehensive genomic profiling. TMB (mutations/Mb) was calculated from 1.11 Mb of sequenced DNA (PMID: 28420421). Known genomic alterations (kGA) were defined as those reported as somatic in the COSMIC database or with published evidence indicating loss of function.

Results
POLE GA were identified in 5.0% of cases: melanoma (10%), duodenal adeno (DA, 7.8%), uterus carcinosarcoma (CS, 6.9%), EA (6.4%), unknown primary carcinoma (CUP, 6.3%), NSCLC (6.1%), CRC (5.1%), prostate adeno (5.0%), and GBM (4.6%). Most POLE GA were variants of unknown significance (VUS). POLE kGA were found in only 259 (0.3%) total cases, including ovary or uterus CS (2.2%), DA (1.3%), EA (1.2%), CRC
(0.7%), GBM (0.6%), and CUP (0.6%). Patients with POLE kGA had a median age of 58 yrs (range 7-95); 53% were male. Median TMB in cases with POLE kGA, VUS and wild-type was 31, 9 and 3.6, respectively (each p < 0.0001). Of cases with POLE kGA, 54% had high TMB (>20), while 28% had low TMB (<5). The most common POLE kGA were R446Q (n = 77), P286R (n = 41), V411L (n = 29) and L424X (n = 17). R446Q, which is uncharacterized, was associated with low TMB (p < 0.0001) and predominantly germline, while P286R and V411L were associated with high TMB (each p < 0.0001), predominantly somatic, and enriched in CRC and EA. Inactivating GA in mismatch repair genes co-occurred with POLE kGA in 28% of cases; these cases had low MSI (7% vs. 5% for all kGA POLE cases), but very high TMB (median 230). PD-L1 IHC and outcomes will be presented for a subset of cases.

Conclusions
POLE GA are found across tumor types, but functionally significant GA may be less frequent than previously reported, particularly in advanced tumors. Identification of specific POLE GA associated with a hypermutated phenotype may be important to identify likely responders to ICPIs.

Legal entity responsible for the study
Foundation Medicine

Funding
Foundation Medicine

Disclosure

1171P - Checkpoint inhibitors in MSI tumors: Lessons from a monocentric experience
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Background
Microsatellite unstable (MSI) tumors have showed high response rates to checkpoint inhibitors. Nonetheless, patterns of response and characteristics of responders remain poorly understood. We hereby report preliminary results of response to immunotherapy in a cohort of patients (pts) with metastatic MSI tumors.

Methods
We included all pts with metastatic MSI tumors of various histologic types treated at our institute with checkpoint inhibitors as monotherapy or combinations. Somatic MSI status has been identified by immunohistochemistry with PCR at diagnosis and/or whole-exome sequencing in molecular screening trials at metastatic stage. Pts not previously known to have Lynch syndrome (LS) have been tested for inherited germline defect.

Results
From November 2014 through April 2017, 43 pts were enrolled. Main pts characteristics
were as follow [median (range)]: age at treatment was 56.4 years (26-78) and number of previous treatment lines was 2 (1-5). The most frequently treated histologic types were gastro-intestinal (22/43: 15 colorectal (CRC), 2 small bowel, 2 biliary, 2 pancreatic, 1 duodenal) and gynecologic (11/43: 8 endometrial, 3 ovarian) tumors. Diagnosis of hereditary LS has been confirmed in 12 pts (28%) and screening results are awaited in 6 pts. After a median follow-up of 5.6 months and treatment with a median of 7 cycles (Range 1-47), median overall survival was not reached (NR) and median progression-free survival (PFS) was 11.1 months (95% CI 2.8-19.5). In the 38 evaluable pts who received more than 2 cycles, overall objective response (ORR) and stable disease rates were 31.6% (12/38; 4 complete responses (CR), 8 partial responses (PR)) and 18.4% (7/38) respectively. ORR was 33.3% (5/15; 4 CR, 1 PR) in CRC and 30.4% (7 PR/23) in non-CRC. PFS was significantly better in confirmed LS than sporadic tumors (NR and 5 months, respectively, p = 0.028) and in CRC than non-CRC (NR and 5.6 months, respectively, p = 0.025) in univariate analysis.

Conclusions
We reported high response rates and survival benefit with checkpoint inhibitors in pts with MSI tumors remarkably in CRC and LS. A comprehensive analysis of immune microenvironment would be of clinical interest to characterize responders and non-responders.

Legal entity responsible for the study
Gustave Roussy Cancer Campus

Funding
Gustave Roussy Cancer Campus

Disclosure
All authors have declared no conflicts of interest.

1172P - Single nucleotide polymorphisms in PD-L1 and outcome in nivolumab-treated advanced non-small-cell lung cancer patients
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Background
Nivolumab is an established agent in the management of non-small-cell lung cancer (NSCLC); however, while some patients with lung cancer have marked responses to nivolumab, others do not respond. To determine the efficacy of nivolumab, we retrospectively evaluated treatment response with respect to PD-1/PD-L1 SNPs among patients with NSCLC.

Methods
Between December 2015 and October 2016, a total of 68 patients with histologically or cytologically confirmed NSCLC were treated with nivolumab. Among these 68 patients, all of whom were registered at Kyoto University Hospital. Genomic DNA was extracted from peripheral blood and genotyping was performed using real-time PCR method. We investigated the possible correlation of PD-1/PD-L1 SNPs with PFS (progression-free survival) using Kaplan-Meier method.

Results
A total of 68 patients were evaluated for clinical response. The G allele of PD-L1 rs2282055 was significantly associated with better clinical response. The median PFS time was 4.2 months (95% confidence interval [CI], 1.7 months to 3.9 months) for the G/G and G/T genotypes of rs2282055 and 2.0 months (95% confidence interval [CI], 0.9 months to 2.2 months) for the T/T genotype (P = 0.0388). Moreover, the T/T and C/T genotypes of PD-L1 rs1411262 were significantly associated with better PFS in NSCLC patients treated with nivolumab.

Conclusions
The G/G and G/T genotypes of PD-L1 rs2282055 were significantly associated with better ORR and PFS in NSCLC patients treated with nivolumab. These results suggest that PD-L1 SNPs may be a biomarker for the efficacy of nivolumab.

Legal entity responsible for the study
Kyoto University

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1173P - Efficient identification of neoantigens for personalized cancer immunotherapy in advanced refractory epithelial cancer patients
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Background
Recent genomic and bioinformatic technological advances have made it possible to dissect the immune response to personalized neoantigens encoded by tumor-specific mutations. However, rapid and efficient identification of neoantigens is still fraught with difficulty, and a systematic evaluation of personalized neoantigens based immunotherapy in advanced refractory epithelial tumors is lacking.

Methods
Tumor and ctDNA samples from 16 advanced epithelial cancer patients were underwent mutational profiling by cancer-associated genes panel. Neoantigens identification were performed by two strategies: (1) As classic mode, somatic mutations were subjected to in silico analysis to predict potential high-affinity epitopes and mutated peptides were denovo synthesized; (2) Hotspot mutations were matched to our customized driver mutation-derived neoantigens peptide library. Candidate neoepitopes were identified. Approximately $10^8$ neoantigen loaded DC vaccine and $10^{10}$ bulk T cells composed of $10^9$ neoantigen reactive CD8+T cells were generated for personlized immunotherapy.

Results
Among the sequenced patients, 12 neoantigens recognized by autologous T cells have been successfully identified in 3 of 4 patients who utilized the classic mode and 6 of 12 patients who performed customized neoantigens library, respectively. Subsequently, a total number of 6 patients received immunotherapy targeting personalized neoantigen following immunomodulatory chemotherapy or radiotherapy. One patient with metastatic thymoma is achieving a complete and durable response beyond 12 months. In addition, immune related partial response was observed in another advanced pancreatic cancer
patient. The remaining 4 patients achieved prolonged stabilization of disease with median PFS of 8.6 months.

Conclusions

Our customized neoantigens library can provide a novel approach for neoantigens screening in advanced epithelial cancer patients. Besides, targeted sequencing is sufficient for somatic variant and neoantigen identification. The combination of two strategies can accelerate the neoantigen-based translational immunotherapy research into the paradigm of precision medicine.

Legal entity responsible for the study

Baorui Liu

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1174P - KRAS mutations (KRAS-mut) and antiPD1/PDL1 therapy in a cohort of non-small cell lung cancer (NSCLC) patients (p): Experience from a single institution

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P. Torres (Badalona, Spain) E. Lopez (Badalona, Spain) R. Muriel (Badalona, Spain)
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E. Carcereny Costa (Badalona, Spain)

Background

AntiPD1/antiPDL1-based immunotherapy has changed dramatically the prognosis of NSCLC p with a substantial improvement of overall survival (OS) and even presenting long lasting responses in a subset of p. Several factors have been associated with the likelihood of better survival, which include the smoking exposure and the presence of KRAS-mut according to data from randomized clinical trials that compared chemotherapy to these immunotherapeutic agents.

Methods

By reviewing the clinical records of all stage IV NSCLC p treated with antiPD1/antiPDL1 agents, we identified p with KRAS-mut and evaluated their clinical outcomes.

Results

129 p with advanced NSCLC were treated with nivolumab, pembrolizumab or atezolizumab (65.1%, 17.1% and 17.8%, respectively) from November 2013 to April 2017. 14 p were identified as adenocarcinomas with KRAS-mut (20.3%) of all non-squamous NSCLC (60p) once squamous cell carcinoma (39 p), p with Kras status unknown (15p), or due to other reasons (6p) were excluded. Kras-mut subgroup included 28.5% of female, with median age of 62.3 years, 92.8% of ever smokers, and PS0 and 1 in 21.4 and 78.6%, respectively. The immunotherapy consisted of nivolumab (71.4%) and pembrolizumab and atezolizumab (14.3% each) and was administered as 1st, 2nd and ≥3rd therapy in 7.1, 78.6 and 14.3% of p, respectively. 71.4% of p responded to therapy (64.3% were evaluated as
partial response) and in 42.8% of p this response lasted ≥12 months (range 12-32). For this cohort of p median progression-free survival was 7.65 months and median OS was 58 months. At the time of analysis 57.1% were still receiving treatment.

Conclusions
Although the number of p is small, KRAS-mut p represent a subgroup of p that seem to substantially benefit from antiPD1/PDL1 agents in terms of both response and survival.

Clinical trial identification
Not applicable

Legal entity responsible for the study
Medical Oncology Department, Catalan Institute of Oncology Badalona

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1175P - Comparability of programmed death-ligand 1 (PD-L1) expression on tumor-infiltrating immune cells (IC) and tumor cells (TC) in advanced urothelial bladder cancer (UBC) using clinically relevant immunohistochemistry (IHC) assays

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Background
PD-L1/PD-1 checkpoint inhibitors have shown clinical activity in UBC. It has been shown that PD-L1 expression on TC and/or IC correlates with clinical efficacy. In this study (ML39708) we examined technical comparability and inter-reader agreement of 4 clinically relevant assays for PD-L1 expression on IC and TC in locally advanced UBC.

Methods
Archived formalin-fixed paraffin-embedded sections from 30 patients with locally advanced UBC (70% cystectomies, 30% transurothelial resections) were selected from 150 cases based on PD-L1 status per VENTANA SP142 IC < 1%, 1–5% or > 5% (10 cases each). The study cohort was stained for PD-L1 using SP142, SP263 (VENTANA), 22C3, and 28-8 (DAKO) assays at two sites according to manufacturer protocols. Stainings were blinded and scored at 5 sites for the PD-L1 expression on IC (% per tumor area) and TC (%). All readers were trained on scoring IC with SP142.

Results
Percentage of IC cells staining for PD-L1 varied from 6.54 to 8.18%, and TC from 5.46 to 15.85%, depending on the assay used (Table). For each assay, IC staining varied slightly to moderately between readers, with small non-significant differences between assays. Results for TC were comparable except for significantly lower staining with SP142. Pairwise comparison revealed −0.3 to 1.6% differences in adjusted means between assays for IC, and for TC, −10.5 to −7.8% (SP142 vs other assays) and −1.9 to 2.7%
(other comparisons). Retrospective allocation to binary cut-offs (1%, 5% and 10%) for IC or TC only predominantly showed substantial or high Kappa agreement scores (0.6–0.8) for IC and TC between assays for each reader.

Table:

<table>
<thead>
<tr>
<th>Assay</th>
<th>PD-L1 on IC % (95% CI)*</th>
<th>Reader ICC†</th>
<th>PD-L1 on TC % (95% CI)*</th>
<th>Reader ICC†</th>
</tr>
</thead>
<tbody>
<tr>
<td>VENTANA SP142</td>
<td>8.18 (7.32–9.03)</td>
<td>0.699</td>
<td>5.46 (2.85–8.07)</td>
<td>0.609</td>
</tr>
<tr>
<td>VENTANA SP263</td>
<td>7.08 (6.22–7.94)</td>
<td>0.729</td>
<td>15.85 (13.24–18.47)</td>
<td>0.805</td>
</tr>
<tr>
<td>DAKO 22C3</td>
<td>6.54 (5.68–7.39)</td>
<td>0.532</td>
<td>13.19 (10.57–15.80)</td>
<td>0.883</td>
</tr>
<tr>
<td>DAKO 28-8</td>
<td>6.88 (6.02–7.74)</td>
<td>0.573</td>
<td>15.15 (12.54–17.77)</td>
<td>0.845</td>
</tr>
</tbody>
</table>

* Adjusted means for each assay;
† Intra-class correlation per test between 5 readers

Conclusions
This is the first multicenter study for analytical comparison of PD-L1 IHC staining on IC and TC in UBC. High concordance rates across all assays were achieved between trained readers for scoring PD-L1 on IC and TC.

Clinical trial identification
ML39708

Legal entity responsible for the study
Roche Pharma AG

Funding
Roche Pharma AG

Disclosure
A. Hartmann: Membership of an advisory board: Roche, MSD, AstraZeneca
Corporate-sponsored research: Novartis, Biontech, Illumina, Nanostring, Quiagen. G. Baretton: Membership of an advisory board Roche, Bristol-Myers Squibb, AstraZeneca
Corporate-sponsored research Roche, Bristol-Myers Squibb. F. Lasitschka: Membership of an advisory board: Roche NSCLC regional advisory board. Bristol-Myers Squibb NSCLC regional advisory board Corporate-sponsored research: Roche PLACU study. P. Schirmacher: Roche (Research, Honorarium) Bristol-Myers Squibb (Research, Honorarium), MSD (Research, Honorarium), AstraZeneca (Research, Honorarium), Novartis (Research, Honorarium). T. Braunschweig: Membership of an advisory board and invited guest speaker: Bristol-Myers Squibb Invited guest speaker: MSD
Corporate-sponsored research: Roche. R. Tauber: Membership of an advisory board: Roche, Sanofi, Bristol-Myers Squibb) Corporate-sponsored Research: conduct as subinvestigator of clinical trials. S. Hieke-Schulz: Employee Roche Pharma AG. J. Ammann: Stock ownership: Roche Pharmaceuticals Other substantive relationships: Employee of Roche Pharma AG. W. Weichert: Conflicts of interest Advisory boards for Roche, AstraZeneca, MSD, Bristol-Myers Squibb, Pfizer, Novartis, Boehringer. Collaborative research with Roche, Novartis, AstraZeneca, Boehringer. All other authors have declared no conflicts of interest.

1176P - IDO-1 and PD-L1 predict response to immunotherapy in advanced non
small cell lung cancer: An NGS and multiplex IHC analysis

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Background
PD1/PD-L1 inhibitors (IO) can be prescribed as first line treatment in high PD-L1 positive NSCLC pts. There is an important need for additional predictive factors to identify pts with PDL1 weak or negative NSCLC that could benefit from these.

Methods
In this retrospective study, pts with stage III/IV NSCLC eligible for an IO were selected. All pts consented for tissue analysis. Pt characteristics and outcome were collected. A NGS panel on 52 genes was performed with an immunochemistry analysis (PDL-1 with the SP-263 clone, CD8, PTEN, beta-catenine, MSI, FOXP3, IDO-1 and CD163). We used image analysis with density results. PD-L1 was classified as negative/weak/positive if 0/1-9%/10%+ of tumor cells were stained.

Results
Sixty-seven pts were enrolled. Median age was 64 years, 8 pts were never smokers, 90% had PS 0-1, 11.3%/58.1%/30.6% received an IO as 1st/2nd/3rd line or more, 69% had a non-squamous carcinoma. 38.7% of the tumors were PD-L1 positive, and 15% weak. Median progression-free survival (PFS) was 3.5 months (IC95%, 1.9-7.6), 12 months overall survival rate was 63.3% (IC 95% 46.6-76.1). The objective response rate (ORR) was 50.8%. In univariate analysis PS, line of IO, positivity for PD-L1 (cut off 10%), CD8 (H-SCORE ≥ 284,4), FOXP3 (H-SCORE ≥ 155,4) and IDO-1 (H-SCORE ≥ 0,4) were significantly correlated with ORR and PFS. ORR was 77% in IDO-1 positive (n = 26), 32% in IDO-1 negative (n = 25) NSCLC pts. KRAS mutation, smoking status, histological type, response to platinum-based chemotherapy were not correlated with PFS and ORR. In multivariate analysis, positive PD-L1 and IDO-1 were the only factors correlated with ORR. ORR was 87.5% if both positive (n = 16), 60% if one of them was positive, 22.7% if both negative. Only IDO-1 was correlated with PFS.

Conclusions
Along with PD-L1, IDO-1 appears as a promising predictive factor for IO. A prospective validation is ongoing.

Legal entity responsible for the study
Sylvestre Le Moulec

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1177P - Undiscovered immune heterogeneity in pancreatic adenocarcinoma (PDAC)

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Background
Our group previously identified three subtypes of human PDAC based on gene expression (PDAassigner, classical, quasi-mesenchymal (QM) and exocrine-like subtypes). Recently Bailey et al. published four subtypes that were concordant with our three subtypes except that their immunogenic subtype (enriched for immune genes) is a sub-subtype of the classical subtype. Here we applied our published prognostic/predictive colorectal cancer gene expression subtype classifier (CRCassigner) to PDAC patient samples to establish if these subtypes existed in PDAC and if they could be used to further refine our original PDAC subtypes.

**Methods**

CRCassigner signatures were used to classify 123 PDAC patient samples. Comparisons between different subtype classifications were performed using hypergeometric test. Patient survival analysis were performed using Kaplan-Meier plots and log-rank test. Pathway enrichment analysis was performed using gene set enrichment analysis (GSEA) on RNAseq expression profiles.

**Results**

We confirmed the existence of the five CRCassigner subtypes – enterocyte, goblet-like, inflammatory, stem-like and transit-amplifying (TA) - in PDAC. These subtypes were found to be sub-groups of original three PDAassigner subtypes. By combining our subtype classification with Bailey et al.’s we classified PDAC into six sub-subgroups of three published subtypes – classical (pancreatic progenitors and immunogenic); QM/squamous (stem-like and inflammatory) and exocrine-like/ADEX (TA and enterocyte). Interestingly, we observed differences in the distribution of immune cells between Bailey’s immunogenic and our inflammatory subtypes. We noted a significant increase in the expression of most of the immune regulatory genes in the inflammatory (n = 7) subtype compared to the immunogenic subtype (n = 13).

**Conclusions**

This study further refines our published PDAC subtypes. The data reveals a new subgroups with a different immune and stromal profiles associated with different overall survival in this small data set. Further validation of these results is warranted to determine if subtype classifier can stratify patient samples for treatment with immunotherapy or immunotherapy combinations in PDAC.

**Legal entity responsible for the study**

The Institute of Cancer Research

**Funding**

National institute for health research

**Disclosure**

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1178P - Optimized protocols to determine PD-L1 expression on tumor tissue and cytology samples from non–small cell lung cancer (NSCLC) patients using the 22C3 antibody with various immunohistochemistry (IHC) autostainers
Background

Pembrolizumab (pembro) is approved for treatment of PD-L1–expressing NSCLC in both treatment-naive patients with a PD-L1 expression tumor proportion score (TPS) ≥50% and previously treated patients with a PD-L1 TPS ≥1%. Testing for PD-L1 expression is mostly carried out using the PD-L1 IHC 22C3 pharmDx companion diagnostic test on the Dako Autostainer Link 48 (ASL48) platform. We developed optimized protocols for laboratory-developed tests (LDTs) that use the 22C3 antibody (Ab) concentrate on more widely available IHC autostainers for tumor tissue. We are also developing LDT protocols for cytology specimens.

Methods

PD-L1 expression was evaluated using the 22C3 Ab concentrate on 3 commercially available autostainers: ASL48, Ventana BenchMark ULTRA, and Leica BOND-III. Staining results were compared with the PD-L1 IHC 22C3 pharmDx kit on the ASL48 platform. PD-L1 expression was evaluated in tonsil specimens and a training set of 3 NSCLC specimens. Optimized protocols were validated in 120 NSCLC tumor tissue specimens. Cytology staining is being evaluated in 70 cell blocks from bronchial washes and pleural effusions with >100 tumor cells using the 22C3 Ab concentrate and optimized protocols.

Results

Protocols for LDTs were established on both BenchMark ULTRA and ASL48; the BOND-III autostainer protocol could not be optimized without a prohibitively high concentration of 22C3 Ab. Intraclass correlation coefficients, which measure the correlation of TPS score as a continuous variable, were 98.7% to 99.9% for the 22C3 Ab concentrate on the ASL48 and ULTRA platforms relative to the PD-L1 IHC 22C3 pharmDx kit on the ASL48. Interpathologist agreement was high for both LDTs and for the PD-L1 IHC 22C3 pharmDx kit. Optimized protocols for evaluation of PD-L1 expression in cytology specimens will also be presented.

Conclusions

Optimized protocols to determine PD-L1 expression in tumor tissue and cytology specimens using the 22C3 Ab concentrate on multiple autostainer platforms will expand the ability of laboratories to assess eligibility of patients with NSCLC for treatment with pembro in a reliable and reproducible manner.

Legal entity responsible for the study

Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding

Merck & Co., Inc., Kenilworth, New Jersey, USA

Disclosure

S. Khambata-Ford: Employment with Merck; stock ownership with Bristol-Myers Squibb. L. Huang: Employment with Merck; stock ownership with Merck and GSK R. Mogg: Employment with Merck Sharpe and Dohme; stock ownership with Merck Sharpe and Dohme. J. Juco: Employment with Merck & Co., Inc.; stock ownership with Merck, Illumina, and Regeneron All other authors have declared no conflicts of interest.
Background
Ovarian cancer is a malignancy with a complex immune suppressive microenvironment mediated by the recruitment or induction of CD4+ regulatory T cell. The purpose of this study was to assess the effect of neoadjuvant chemotherapy (NACT) on immune activation in stage IIic/IV of high-grade serous ovarian carcinoma (HGSOC), and its relationship to treatment response.

Methods
We retrospectively identified 33 patients diagnosed with HGSOC and treated with neoadjuvant platinum-paclitaxel from 2005-2014. Pre and post-neoadjuvant treatment tissue samples were submitted to immunohistochemical analyses with anti-CD3, CD4 and CD8 antibodies for the identification of tumor-infiltrating lymphocytes (TILs). Pathological response classification to NACT was made according to Steffen Bohm (JCO 2015). Response score system (CRS) was explicitly defined (CRS-1; No or minimal tumor response, CRS-2; Appreciable tumor response amid viable tumor that is readily identifiable, CRS-3; Complete or near-complete response).

Results
The average age of patients was 63.44 years (46.53-84.14). BRCA-mutation status was negative in 78.8% of patients (26/33); BRCA-mutation was positive in 6.1% (2/33); and variant of uncertain significance was found in 15.1% (5/33). The majority of patients (78.8%) were stage IIic. The area under the ROC curve of post-surgery TILs for complete pathological response were: CD4 (epithelial): [0.73 (0.5; 0.97), p: 0.084]; CD4 (stromal): [0.74 (0.51; 0.97), p: 0.077] and CD8 (epithelial): [0.81 (0.63; 1.0), p: 0.02]. The expression of epithelial CD4 TILs in pre-surgery samples (≤ 0.5 [OR: 0.7(0.01; 0.86), p: 0.038]) and epithelial CD8 TILs in post-surgery samples (≤ 5.4 [OR: 0.1(0.01; 1.19, p: 0.06]) proved to be a marker of good prognosis for pathological response. Survival analysis demonstrated that the expression of epithelial CD3 ≤ 4.3 in pre-surgery samples is a marker of poor prognosis.

Conclusions
The high number of tumor-infiltrating lymphocytes in post-surgery samples was significantly associated with higher rates of complete pathological response and better prognosis. It is convenient to carry out further and multicentric studies to validate these results.

Legal entity responsible for the study
Hospital 12 de Octubre.

Funding
None

Disclosure
All authors have declared no conflicts of interest.
Background
Clinical success of PD-1/PD-L1 and CTLA-4 checkpoint inhibitors demonstrated that reactivation of anti-tumor immunity provides strong clinical benefits including curative responses. However, only a fraction of patients demonstrate long-lasting therapeutic effects prompting efforts to target additional pathways regulating antitumor immune response. Depletion of arginine inhibits proliferation and activation of T cells and is an important mechanism of immunosuppression. High plasma and tumor arginase (ARG) activity has been found in patients with a wide spectrum of cancers correlating with a poor prognosis. Therefore, we developed ARG inhibitors and report the immunoregulatory and antitumor activity of the lead compound (OAT-1746) alone or in combination.

Methods
The IC$_{50}$ of the compounds was determined against the recombinant ARG1/2. M2-polarized, bone marrow derived murine macrophages and CHO cells transfected with human ARG1 were used to assess the cellular activity. Murine and human CD4+/CD8+ T cells were negatively isolated and incubated with anti-CD3/CD28 beads to trigger proliferation, CD3ζ levels were measured. The in vivo antitumor efficacy was evaluated in syngeneic mouse models after oral administration at 50 mg/kg bid.

Results
We have developed potent, selective, orally active inhibitors of ARG1 and 2. Our lead compound, OAT-1746, has a low nanomolar activity against ARG1/2 and < 50 nM cellular activity. It reversed the ARG1-inhibited proliferation of human and murine T cells and restored CD3ζ expression in ex vivo assays. In vivo, OAT-1746 showed good pharmacological properties with significant antitumor efficacy in multiple tumor models as a monotherapy and in combinations with checkpoint inhibitors and gemcitabine. The efficacy correlated with sustained PD effects: suppression of tumor arginase activity and 3-6 fold increase in plasma and tumor arginine concentrations that exceeded those required for the maximal stimulation of T cell proliferation. Induction of inflammatory markers in tumors confirmed reversal of immunosuppression. No toxicity was observed after multiple oral dosing in mono- or combinatorial therapies.

Conclusions
These results support the clinical development of OAT-1746 for cancer therapy.

Legal entity responsible for the study
OncoArendi Therapeutics SA

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Disclosure
1181P - Pharmacokinetics (PK) and Pharmacodynamics (PD) of cergutuzumab amunaleukin (CA), a carcinoembryonic antigen (CEA)-targeted interleukin 2 variant (IL2v) with abolished binding to CD25

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Background
CA is a CEA-specific antibody fused to IL2v with abolished CD25 binding. Compared to wildtype (wt) IL-2, CA was designed to preferentially expand natural killer (NK) and CD8 T cells but not T regulatory cells (Tregs), to be retained within CEA+ tumors, and for improved PK.

Methods
In this FIH phase I study, PK/PD analyses were performed using samples from solid tumor patients treated weekly (QW) or biweekly (Q2W) with 6 – 40 mg CA monotherapy IV. Methods: PK - population modeling; PD analysis of baseline (BL) and on-treatment (OT) samples; flow cytometry of peripheral blood monocytes (PBMCs); immunohistochemistry (IHC) on tumor biopsies; PD-L1 expression using SP142 assay; measurement of plasma cytokines and sCD25.

Results
During cycle 1, CA exhibited prolonged exposure (8-fold) vs. wt IL2. Following multiple cycles, serum exposure showed typical target-mediated drug disposition kinetics, likely due to clearance by IL-2 receptor-expressing cells. In PBMCs from patients treated QW x 4, a significant increase in the absolute number of NK cells and CD8 T cells was seen (median of 13- and 2.3-fold, respectively). By contrast, moderate or no increase was seen in the absolute number of CD4 T or Tregs (median of 1.5- and 1.2-fold). Similar but less prominent changes were observed in patients treated Q2W. Treatment was accompanied by upregulation of the activation marker CD314 (NKG2D), which was undetectable on more than 20% of NK cells in 9 of 39 patients at BL, suggesting increased functional activity of NK cells in the affected patients. A transient increase in the level of various cytokines was seen, peaking 24 hours after administration. Changes in the level of sCD25 correlated with drug exposure. OT biopsies showed an increase in the number of infiltrating Ki67+ CD8 T cells and PD-L1+ immune cells (median of 3.5- and 3-fold, n = 11).

Conclusions
PK data confirmed that CA has longer exposure than wt IL2. PD data demonstrated preferential expansion and reinvigoration of NK and CD8+ T cells in both PBMCs and tumors. This data suggest that CA can be a potent combination partner for cancer immunotherapies targeting CEA+ solid tumors.

Clinical trial identification
NCT02004106

Legal entity responsible for the study
All authors have declared no conflicts of interest.
F. Hoffmann-La Roche Ltd

Funding
F. Hoffmann-La Roche Ltd

Disclosure

1182P - A first-in-human study of a novel monoclonal antibody INCSHR01210 directed against programmed cell death protein 1 (PD-1) in patients with advanced or metastatic cancer

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Background
INCSHR01210 is a novel PD-1 inhibitor with a safety and activity profile that may be different from that of other PD-1 inhibitors.

Methods
This is an ongoing, open-label, Phase1, dose-escalation/tumor-expansion study to evaluate the safety of INCSHR01210 in patients (pts) with relapsed/refractory solid tumors (NCT02492789). In Part 1, INCSHR01210 was administered IV at 1, 3, 6, or 10 mg/kg, initially on Day 1 of a 28-day cycle (for safety, PK and PD) and then Q2W, in a standard 3 + 3 dose-escalation design. Based on Part 1 data, Part 2 consisted of different tumor expansion cohorts, in which fixed doses of INCSHR01210 (600 mg and 200 mg Q4W) were evaluated.

Results
As of data cutoff (3Feb2017), 23 pts were treated in Part 1 (median age, 62 y [range, 32–73]; 74% women). Treatment-related AEs in ≥ 20% of pts (all Gr; Gr3/4) were skin capillary hemangioma (61%; 0%) and diarrhea (26%; 4%). Skin capillary hemangiomas were scattered and typically: <1 cm in diameter; on the face and upper chest; considered Gr1/2; regressed after stopping INCSHR01210. Immune-related AEs were consistent with other PD-1 inhibitors and observed in 3 (13%) pts. Treatment discontinuation due to AEs was reported in 1 pt (10 mg/kg; Gr1 skin hemangioma [resolved after stopping treatment]). The PK profile showed a dose-dependent increase in half-life from 3 days at 1 mg/kg to 7
days at 10 mg/kg. The receptor occupancy (RO) assessment at 10 mg/kg showed a target PD-1 inhibition of 80% for up to 28 days. Of 21 efficacy evaluable pts, 5 (24%) had PR (median DOR, 163 days [range, 36–316]) and 4 (19%) had SD. Pts with PR included 1 pt each with SCC of the parotid gland (1 mg/kg), breast cancer (1 mg/kg), RCC (6 mg/kg), bladder cancer (10 mg/kg) and ovarian cancer (10 mg/kg). Based on the safety (including tolerability of hemangioma), PK and RO data from Part 1 and from Part 2 at 600 mg Q4W flat dosing, the remainder of Part 2 patients were treated at the 200 mg Q4W flat dose; Part 2 data will be presented.

Conclusions
INCSHR01210 demonstrated manageable toxicity, but with Gr1/2 hemangioma not seen with prior PD-1 inhibitors. The recommended Phase 2 dose/schedule is 200 mg Q4W.

Clinical trial identification
NCT02492789

Legal entity responsible for the study
Incyte Europe Sàrl, Geneva, Switzerland

Funding
Incyte Europe Sàrl, Geneva, Switzerland

Disclosure
P. Grimison: Corporate-sponsored research: Tilray, Incyte, Gilead, Tigermed, Pfizer, Merck, Boston Biomedical, Medimmune, Halozyme, Specialised Therapeutics Australia. H. Kallender, K. Sun, X. Chen: Employee at Incyte Corporation. A. Behren: CSL Ltd: Stock ownership, Corporate-sponsored research. P. Fernandez-Penas: Advisory board member: Roche, Janssen, Abbvie, Lilly, Novartis Employee: The University of Sydney, Westmead Hospital Corporate-sponsored research: Incyte. K. Woods: Corporate-sponsored research: CSL Ltd. All other authors have declared no conflicts of interest.

1183P - Safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of PF 06801591, an anti-PD1 antibody administered intravenously (IV) or subcutaneously (SC)

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Background
PF-06801591, a humanized IgG4 monoclonal antibody, blocks the Programmed Cell Death (PD-1) pathway by binding with high affinity to PD-1 and preventing its interaction with its ligands. A phase 1 study to assess the safety and tolerability of PF-06801591 after IV or SC administration is ongoing in patients (pts) with locally advanced or metastatic solid tumors.

Methods
PF-06801591 was administered at 0.5, 1, 3, or 10 mg/kg IV once every 3 weeks (q3w), or 300 mg SC once every 4 weeks (q4w). Dose escalation occurred after the first 2-4 pts at each dose cohort, with additional pts then enrolled to each cohort for further PD assessment. Safety, tolerability, PK, and PD were assessed for all pts.
Results
As of January 31, 2017, 26 pts (ovarian cancer, n = 12; sarcoma, n = 6; head and neck cancer [SCCHN]; n = 5; melanoma, n = 1; small cell lung cancer, n = 1; and malignant peritoneal neoplasm, n = 1) were treated in the dose-escalation phase: 0.5 (n = 2), 1 (n = 8), 3 (n = 7), 10 (n = 5) mg/kg IV, and 300 mg (n = 4) SC. Maximum tolerated dose was not reached. No drug-related SAEs or dose-limiting toxicities were observed. All drug-related AEs were Grade 1 or 2, and the most frequently reported in > 15% of pts include nausea (15.4%) and fatigue (15.4%). No dose-dependency of AEs was observed during IV dose escalation nor serious skin toxicity with SC administration. Four pts had partial response at 0.5, 1, and 10 mg/kg IV (ovarian pts) and 300 mg SC (SCCHN pt) and 3 pts had stable disease lasting >24 wks. There was a dose-dependent increase in the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) after IV administration. Following SC administration, PF-06801591 was slowly absorbed, with a median time to C_{max} of 182 hours. The mean average concentration (C_{av}) after the first SC dose at 300 mg q4w was approximately 50% of the mean C_{av} following IV administration at 3 mg/kg q3w. Full receptor occupancy of PD-1 was seen in all dose cohorts.

Conclusions
Preliminary results demonstrate that PF-06801591 is well-tolerated with objective responses observed across the dose levels tested in both IV and SC forms. PK data confirmed the appropriateness of the dosing frequency.

Clinical trial identification
NCT02573259

Legal entity responsible for the study
Pfizer Inc.

Funding
Pfizer Inc.

Disclosure
S. Hu-Lieskovan: Consulting: Amgen, Merck, Novartis, Vaccinex, Emergent BioSolutions
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Speaker and advisor/consultant for Pfizer. J. Grilley-Olson: Only disclosures are for
Institutional research funding from: Pfizer, Genentech, Novartis, Seattle Genetics,
Medimmune, Nanocarrier. J. Chou J. Davda, B. Jin, A. Forgie: Employed by Pfizer and

1148P - A phase I/II safety study of tisotumab vedotin (HuMax®-TF-ADC) in patients
with solid tumors

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Background

Tisotumab vedotin (Tv) is an antibody-drug conjugate composed of a Tissue Factor (TF) specific human IgG1 monoclonal antibody conjugated to a microtubule disrupting agent Monomethyl Auristatin E (MMAE). Tv is being tested in an ongoing Ph I/II dose-escalation study (NCT02001623) in patients (pts) with locally advanced and/or metastatic solid tumors known to express TF. Preliminary data were presented at ASCO 2015, abstract #2570; here, we present the full data set from the dose-escalation part.

Methods

Key eligibility criteria include PS 0-1, normal organ function and no bleeding disorder or invasion of large vessels. Pts were treated with a classic 3 + 3 dose escalation regimen of Tv once every 3 weeks (q3Wk). The primary study objective was to assess tolerability of Tv. Safety was reported according to CTCAE 4.03. Responses were evaluated according to RECIST 1.1.

Results

Twenty-seven pts were enrolled across 8 dose cohorts (0.3-2.2 mg/kg). Demography: mean age 61 yrs (range 43-73); gender 9 males and 18 females; median number of prior lines of therapy 3 (range 1-14). Three dose-limiting toxicities (diabetes mellitus type II, mucositis and neutropenic fever, all Gr 3) were seen in 3 pts in the 2.2 mg/kg dose cohort. The most common AEs seen in ≥ 20%: epistaxis (48%), fatigue (48%), anemia (41%), alopecia (30%), constipation (30%), nausea (30%), pyrexia (30%), decreased appetite (26%), abdominal pain (22%) and diarrhea (22%). SAEs (all pts): 29 events in 15 pts (56%), 1 SCCHN pt in the 0.6 mg/kg cohort died from tumor related bleeding. AEs Gr ≥ 3: 19 pts (70%) experienced 41 events. Efficacy: 14 pts (52%) achieved SD or better; 1 cervical cancer pt dosed 1.2 mg/kg with 2 prior treatment lines before trial entry achieved and maintained PR during entire study period. After study period, the pt was transferred to named patient use. Immunohistochemistry (IHC): Samples from 25 pts were evaluable. TF expression was present in 20 (80%) samples.

Conclusions

Tisotumab vedotin demonstrated a manageable toxicity profile. Recommended Ph II dose was identified as 2.0 mg/kg q3Wk. Biological activity included SD in 13 pts and 1 pt with prolonged PR (cervical cancer). TF was found widely expressed across investigated indications by IHC. Data warrant further exploration in solid tumors.

Clinical trial identification

NCT02001623, release date November 14, 2013

Legal entity responsible for the study

Genmab A/S

Funding

Genmab A/S

Disclosure

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have served as advisor on advisory boards for multiple industry partners incl. AstraZeneca, Daiichi-Sankyo, Genentech, GSK, Merck, Pfizer, Sanofi, Taiho a.o. S. Lisby, L. Basse: Employee of Genmab and hold stocks in the company. All other authors have declared no conflicts of interest.

1185P - Safety, pharmacodynamic, and pharmacokinetic profile of TSR-042, an anti–PD–1 monoclonal antibody, in patients (pts) with advanced solid tumors

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Background
TSR-042, an immunoglobulin G4k humanized monoclonal antibody targeting programmed death (PD)–1, is being evaluated in a phase 1 study (NCT02715284) in pts with advanced solid tumors. We present preliminary safety, efficacy, receptor occupancy (RO), and pharmacokinetic (PK) data.

Methods
Pts were ≥18 years old with recurrent and advanced solid tumors, and adequate organ function. In part 1, pts received intravenous (IV) weight based doses of TSR-042 (1, 3, or 10 mg/kg every 2 weeks [Q2W]). Additionally, based on a PK predictive model from part 1, pts received 500 mg Q3W or 1000 mg Q6W TSR-042 IV in part 2A. Serum was collected for PK and RO analyses.

Results
33 pts received TSR-042 in parts 1 (N = 21) and 2A (N = 12). No DLTs were observed. In part 1, all pts had ≥1 treatment-emergent adverse event (TEAE) with grade ≥3 TEAEs in 9/21 pts; most common TEAEs were fatigue (9 pts), nausea (7 pts), decreased appetite (6 pts), and dehydration (6 pts); 17/21 pts had treatment related TEAEs (TRTEAEs); 7/21 pts had serious TEAEs; 1 case of grade 3 TEAE (AST/ALT elevation) was deemed treatment related. In part 2A, 10/12 pts had ≥1 TEAE with grade ≥3 TEAEs in 1/12 pts; most common TEAEs were abdominal pain, fatigue, nausea, tachycardia and influenza like illness (each in 2 pts); 6/12 pts had TRTEAEs; no serious TEAE occurred. In part 1, 2 pts had a partial response (ovarian cancer [OC], small cell lung cancer) and 5 had stable disease (parotid gland, fallopian tube, anal canal, OC [2 pts]). Pts in part 2A have not yet been evaluated for clinical activity. TSR-042 PK was dose proportional for all dose groups in both parts. The mean trough serum concentrations were 40 (500 mg Q3W) and 50 mg/mL (1000 mg Q6W) after a single dose, which exceeds the 2.4 µg/mL required for 100% receptor occupancy in part 1.

Conclusions
TSR-042 is safe and well tolerated, with a safety profile expected for an agent targeting the PD-1 pathway, with evidence of linear PK and sustained target engagement at
administration intervals up to 6 weeks. TSR-042 showed clinical benefit in heavily pretreated pts in the initial phase 1 study and will be further evaluated in defined tumor types in part 2B. Updated results will be presented.

**Clinical trial identification**
NCT02715284

**Legal entity responsible for the study**
TESARO, Inc.

**Funding**
TESARO, Inc.

**Disclosure**

1186P - Phase Ia study of a humanized anti-PD-1 monoclonal antibody (JS001) in Chinese patients with refractory solid tumors

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**Background**
JS001, a recombinant humanized IgG4 antibody, selectively blocks the interactions of PD-1 with its ligands PD-L1 and PD-L2, and promotes host immune response against Cancer.

**Methods**
A Phase I open-label study is designed to evaluate the safety and tolerability of JS001 in solid tumor patients who are refractory to standard therapy. The study has a traditional 3 + 3 dose escalation design with planned cohorts at 0.3, 1.0, 3.0, 10 mg/kg Q2W and a fixed-dose 240 mg Q2W followed by a dose expansion.

**Results**
Enrollment was completed by October 2016 with 25 patients enrolled including 6 esophageal, 5 gastric, 6 nasopharyngeal, 2 pancreatic, 2 head and neck, and 1 Cholangio carcinoma and 3 melanomas. No dose limit toxicity was observed and no maximum tolerated dose was identified. Adverse events (AEs) occurred in 21/25 patients (84%),
which were mostly grade 1/2, including fatigue (72%), elevation of liver enzymes (52%),
proteinuria (40%), anemia (40%), rash (32%), fever (24%), hyponatremia (24%), hyper-
or hypo-thyroidism (20%), and hypokalemia (20%). The emergence of AEs appeared
unrelated to dose levels. JS001 PK analysis shows linear dose-dependent exposure with
the elimination half-life of 6 to 15 days. Among 13 patients who had underwent at least
one scheduled radiographic evaluation, 1 has confirmed complete response (melanoma),
2 have confirmed partial response (1 Head and neck and 1 esophageal), and 2 achieved
stable disease. PD-L1 expression by IHC on pretreatment biopsy samples was correlated
with the clinical response. Patients with positive PD-L1 staining (> 1%) observed a 30%
response rate (n = 10, 1 CR and 2 PR) and a 50% DCR. Whole exon sequencing was
performed on selected biopsy samples. Mutations on p53, MDM2, TAP2 et al, might
contribute to the favorable response to immunotherapy. Interestingly, a divergent
spectrum of mutations from mixed response patients were observed on tumor cells from
different metastases, which at the time of biopsy had drastically different clinical response
to the treatment.

Conclusions
JS001 demonstrated an acceptable safety profile in solid tumor patients. Additional phase
II studies to evaluate the safety and clinical activity of JS001 in selected tumor types are
ongoing.

Clinical trial identification
Clinical Trial ID: NCT02857166

Legal entity responsible for the study
Sun Yat-sen University Cancer Center

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1187P - A Phase 1/2 trial of intratumoral (i.t.) IMO-2125 (IMO) in combination with
checkpoint inhibitors (CPI) in PD-(L)1-refractory melanoma

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Background
CPI have transformed melanoma treatment, however many patients remain refractory and
subsequent treatment options are limited. IMO, a Toll-like receptor 9 agonist, may improve
response to CPI by activating innate and adaptive immune responses to overcome
immune escape. Initial clinical experience with IMO + ipi is promising (Uemera,
ASCO-SITC 2017). Dose-finding is now complete and is the basis for this updated report.
Methods
Adults with unresectable or metastatic melanoma refractory to a PD-(L)1 inhibitor are eligible if they have tumor accessible to biopsy. IMO is administered i.t. to a single tumor at escalating doses during weeks 1, 2, 3, 5, 8, and 11 along with ipi or pem per the product label. The primary endpoint of Phase 1 is safety and for Phase 2 is overall response rate using a 2-stage design. Serial biopsies are obtained from both the injected and a non-injected lesion for immune analysis.

Results
A total of 22 subjects have been treated with either IMO-ipi (N = 18) or IMO-pem (N = 4) and dose-escalation is now complete for the IMO-ipi arm. Dose-limiting toxicities have not been reported. Immune-related AE were observed in 4 IMO-ipi subjects [hypophysitis (N = 2), hepatitis (1), colitis (1)]. These responded well to standard measures. Of 9 patients treated at the RP2D of 8mg, 6 have experienced clinical benefit (1CR, 1PR, 1uPR, 3 SD). Biopsies show maturation of the mDC1 subset (CD1c+CD303+), upregulation of PD-L1 by malignant cells, and an IFNα response gene signature. Biopsies of uninjected tumors show expression of CD56+ and Ki67+ effector CD8+ T cells in responding patients, indicative of an abscopal effect. Phase 2 accrual using the 8 mg IMO dose is ongoing.

Conclusions
IMO + ipi is a viable strategy to revive the immune response in CPI-resistant tumors and shows preliminary clinical activity worthy of further development.

Clinical trial identification
NCT02644967

Legal entity responsible for the study
Idera Pharmaceuticals

Funding
Idera Pharmaceuticals

Disclosure
J. Geib, S. Swann: Employment by Idera Pharmaceuticals. M. Cornfeld: Employment at Idera Pharmaceuticals. All other authors have declared no conflicts of interest.

1188P - Clinical and immune effects patients with progressive disease treated with low dose of anti-CTLA-4, bortezomib, gemcitabine, naproxen and meloxicam

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Background
Several patients progressed with their cancer disease despite treatment and eventually they become refractory. We selected patients from several malignancies with PD despite standard of care treatment (n = 30) and performed a pilot clinical study to evaluate the
effect of two intravenously, two oral and one subcutaneously agent. With this in mind and with a systematic review and immunomodulatory, anti-angiogenic and anti-tumoral validation of each drug was studied. We tested the preexisting CD8 and Th1 antigen specific immune response against several clinically relevant peptides from bad prognosis proteins.

**Methods**

30 subjects were included after the CICS ethics committee approved the protocol. The inclusion criteria include ECOG=0, complete CT scan from neck, thorax, abdomen and pelvis, laboratory tests such as CBC, phase acute proteins, etc. The patients were accepted after initial IFN-gamma and Elispot assays were done to make sure we have only patients with Th1 and CD8 immune response, as we know that ipilimumab unleashes every T cell. The tumors included were PDAC (n = 5), HGSOC (n = 12), TNBC (n = 10) and MM (3). The patients received the oral and the IV treatment biweekly for 4 months.

**Results**

We had 60% of CR and 40% of PR. The tumor with more significant response was ovarian (90%). There was an immunological correlation of CD8 immune response between in both CR (p = 0.001) and PR (p = 0.05). The combination was well tolerated and after 16 months of stopping the treatment some patients have persistent CD8 antigen specific immune response.

**Conclusions**

The combination is clinically feasible, looks promising and we now understand the importance of preserving the immune response and the use of biomarkers to improve the rational and generate new combinations with this approach to improve clinical outcomes.

**Clinical trial identification**

DOES NOT APPLY

**Legal entity responsible for the study**

CENTRO DE INVESTIGACION DE CANCER EN SONORA CAMPUS CIUDAD OBREGON, SONORA, MEXICO

**Funding**

Fundacion del centro de investigacion de cancer en sonora (cics) campus ciudad obregon, sonora, Mexico.

**Disclosure**

All authors have declared no conflicts of interest.

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**1189P - 4SC-202 plus anti-PD1: Breaking PD1-refractoriness to increase efficacy of checkpoint inhibition in patients with advanced melanoma**

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**Background**

Despite successes in the treatment of melanoma patients with checkpoint inhibitors (CI), majority of patients do not respond to CI alone and a high unmet medical need remains for these patients. One promising approach is to enhance the immunogenicity and alter the tumor microenvironment from an immune-deserted to an inflamed phenotype with combination therapy. Epigenetic modulation has been reported as one key determining factor in shaping the immune microenvironment and compounds altering these processes (e.g. histone deacetylases (HDAC) inhibitors) are particularly promising.
Methods
Tumor bearing animals (CT26 & C38 syngenic models) were treated with 4SC-202, an oral clinical stage combined HDAC class I/LSD1 inhibitor, or CIs PD-(L)-1 alone and in combination. Tumor growth was assessed continuously and after approx. 2 weeks of treatment tumors were excised and analyzed by flow cytometry and gene expression profiling. Additionally, animals not intended for these analyses were further monitored and tumor growth/survival was monitored.

Results
4SC-202 treatment led to an increase of MHC molecules and enhanced expression of inflammatory markers like IFN-γ and various chemokines in tumors. Detailed analysis of the tumors revealed that 4SC-202 strongly altered the immune cell composition; particularly the number of cytotoxic T cells (CTL) was markedly increased. Importantly, subsequent combination treatment of 4SC-202 with CIs in syngenic animal models showed a strong synergistic effect resulting in significant longer survival in both models leading to 55% of tumor free animals (C38 model).

Conclusions
In an upcoming study, patients with advanced melanoma who are refractory/non-responding to anti-PD-1 antibodies will be treated with 4SC-202 plus anti-PD1. These patients do not only represent a population with a high unmet medical need but melanoma also represents a model tumor for immunotherapy in general and CI in particular. We hypothesize that addition of 4SC-202 to anti-PD-1 antibody treatment may lead to increased immunogenicity of the tumor, an inflamed tumor microenvironment and ultimately to clinical benefit in anti-PD-1 refractory/non-responding advanced-stage melanoma patients.

Clinical trial identification
Not available.

Legal entity responsible for the study
4SC AG

Funding
4SC AG

Disclosure
F. Hermann: Employee of 4SC AG, Planegg-Martinsried, Germany.

1192P - Cytomegalovirus reactivation in patients with refractory checkpoint inhibitor-induced colitis

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Background
Objectives: Immune checkpoint inhibitors have become a standard treatment in patients with metastatic malignant melanoma. Showing significant anti-tumor effects by unleashing the immune-system, checkpoint inhibitors can also cause high-grade immune-related adverse events, with immune-related diarrhea and colitis (irColitis) being amongst the most frequent ones. While the majority of patients with irColitis respond well when treated
according to standard treatment algorithms with corticosteroids +/- other immunomodulatory drugs such as infliximab, some patients do not show resolution of diarrhea and colitis. In the present study, we analyzed the frequency of therapy-refractory irColitis, the underlying cause and useful diagnostic measures.

**Methods**

In this retrospective, monocenter study we collected data of 370 patients with metastatic malignant melanoma. All patients had been treated with checkpoint inhibitors at the skin cancer unit of the Department of Dermatology at the University Hospital Essen from 2006-2016. Demographic and clinical data of all patients were collected. Digital patient records of all 370 patients were searched for the terms “diarrhea” and “colitis”.

**Results**

We identified 41 patients with irColitis, the majority occurring during treatment with ipilimumab. Amongst these patients, 5 (12.2%) were refractory to standard immunomodulatory treatment with corticosteroids and infliximab. Therapy-refractory cases tended to show more severe inflammation in colonic biopsies performed during colonoscopy (p = 0.04). CMV-DNA in colonic biopsies and in plasma was significantly more often detectable in therapy-refractory cases (80% vs. 6.75% in non-refractory cases in biopsies, 80% vs. 0% in plasma). Presence of serum CMV IgM as well as positive immunohistochemical stainings of colon biopsies for CMV were also strongly associated with refractory colitis (40% in refractory vs. 0% in non-refractory cases), but not reliable markers in the majority of refractory patients.

**Conclusions**

This report on CMV reactivation during management of checkpoint inhibitor induced colitis emphasizes the need for repetitive diagnostic measures in treatment-refractory irColitis.

**Legal entity responsible for the study**

Ethics committee of the University Hospital Essen, University of Duisburg-Essen

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1193P - Pooled data analysis of the safety and tolerability of intravenous pelareorep in combination with chemotherapy in 500 + cancer patients**

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**Background**

Oncolytic viruses are promising cancer immunotherapies but questions have been raised regarding their safety. Pelareorep (REOLYSIN, R), an unmodified Reovirus Dearing strain, selectively replicates and lyses cancer cells and induces anti-tumor immunity. To date, 900+ patients (pts) have been treated with intravenous (IV) pelareorep. In a phase 2 trial, its combination with paclitaxel improved overall survival (17.4m) vs paclitaxel (10.4m) in
metastatic breast cancer (MBC) pts (HR 0.65, 80% CI 0.46-0.91, p = 0.1; Berstein et.al. AACR2017). A pooled analysis was thus conducted to better characterize pelareorep’s safety profile in combinations with paclitaxel.

Methods
1417 pts have been enrolled in 36 trials: 934 pts received IV pelareorep and 359 were in control arms. Data from 8 trials with paclitaxel (P), paclitaxel + pelareorep (PR), carboplatin + paclitaxel (CP) or carboplatin + paclitaxel + pelareorep (CPR) were pooled. Standard doses of P (weekly) and CP were administered. Pelareorep IV dose was 3x10^10 TCID50 (5-6 doses q21-28 d). Various advanced solid tumors were evaluated, including the 81 pts with MBC.

Results
A total of 563 pts were included in P (86), PR (95), CP (118) or CPR (264) groups. Median age (59-62 y) and ECOG 0-1 status (90-96%) were similar across the groups. All pts in P or PR had received prior chemo but only 26% in CP and 38% in CPR. Fatigue was the most common grade ≥3 treatment related adverse event (TRAE) in PR (9.5%) and CPR (8.3%) vs P (8.1%) and CP (2.5%). Grade ≥3 neutrophil count decreased and/or WBC decreased were more frequent in PR (15.8%/17.9%) than in P (5.8%/3.5%), but addition of pelareorep did not increase the frequency or severity of other grade ≥3 TRAEs with P or CP. Serious TRAEs (%) of interest in P vs PR and CP vs. CPR, included: fever (0 vs 3.2 & 0 vs 3.8), febrile neutropenia (0 vs 1.1 & 3.4 vs 3.4), sepsis (1.2 vs 0 & 0 vs 1.5) and flu-like syndrome (0 vs 1.1 & 0 vs 0.8).

Conclusions
This is the largest database reported to date examining the safety of an IV viral agent. Pelareorep’s administration, in combination with paclitaxel or carboplatin-paclitaxel, is safe and well tolerated. Continued evaluation in a registration trial is planned.

Clinical trial identification
NCI-US
NCI-GOG 0186H (NCT01199263). Ongoing, but not recruiting
NCI-8601 (NCT01280058). Ongoing, but not recruiting NCI- Canada (CCTG)
NCIC-CTG IND.213 (NCT01656538). Ongoing, but not recruiting Oncolytics Biotech Inc:
REO011 – UK (Karapanagiotou et al. CCR 2012) Completed
REO015 (NCT00753038) Completed
REO016 (NCT00861627) Completed
REO018 (NCT01166542). Completed
REO021 (NCT00998192) Completed

Legal entity responsible for the study
Studies were sponsored/conducted by NCI-US, NCI-Canada (CCTG) or Oncolytics Biotech Inc. See section of Clinical Trial Identification

Funding
NCI-US and NCI- Canada conducted their own studies and Oncolytics Biotech only provided the drug. Some studies were fully supported and conducted by Oncolytics. Details can be found in the Clinical Trial Identification section

Disclosure
A.A. Gutierrez: Chief Medical Officer and an employee of Oncolytics Biotech Inc. (or one of its affiliated corporations). Own shares in or have options to purchase shares in
Background
Immune checkpoint inhibitors (ICI) are used increasingly and earlier to treat multiple cancers. Although rates of on-treatment myelotoxicity are low, there are no published data on the long-term effects of ICI. This is a pilot study to evaluate the impact of prior ICI exposure on chemotherapy-related myelotoxicity in patients in the Phase I setting.

Methods
We conducted a retrospective chart review of patients treated between 2012 and 2016 in the Drug Development Unit, The Royal Marsden Hospital. Multivariate logistic regression (including number of previous treatment lines and type of chemotherapy) was used to assess possible relationships between G3/4 neutropenia or thrombocytopenia and previous treatment with immunotherapy in patients receiving combination chemotherapy and targeted agents.

Results
We identified 99 patients (median age 62 years [range 34-79]; chemotherapy partners: cisplatin, carboplatin and paclitaxel). Fourteen patients (14%) received prior immunotherapy (PI) and 85 (86%) had no prior immunotherapy (NPI). Patient characteristics, including baseline full blood count, previous pelvic radiotherapy, sites of metastasis and serum albumin, were comparable between the 2 groups, apart from number of previous treatment lines, which was lower in the PI patients (median 1.5 vs 2, p = 0.003). The odds of G4 neutropenia were higher in the PI group (OR = 7.1, 95% CI = 1.7-29.6, p = 0.007). PI was associated with significantly increased odds of G3/4 thrombocytopenia (OR = 14.4, 95% CI = 2.7-77.4, p = 0.002) on chemotherapy. In multivariate analysis, incorporating lines of prior chemotherapy (OR 1.3, 95% CI = 1.0-1.5, p = 0.037) and type of chemotherapy (carboplatin vs others: OR 2.3, 95% CI = 0.9-6.2, p = 0.094), the odds of developing G3/4 myelotoxicity were significantly higher in PI patients (OR 4.3, 95% CI: 1.3-14.4, p = 0.02).

Conclusions
In our small cohort, previous treatment with immunotherapy was associated with the
development of G3/4 myelotoxicity, especially thrombocytopenia, on subsequent chemotherapy. These preliminary data require further prospective validation but may impact on decision making regarding optimal sequencing of systemic therapy.

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

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None

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1195P - Compromised efficacy of PD-L1 blockade therapy in axenic (germ-free) mice with syngeneic tumors

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Background
The microbiome can have profound effects on the innate immune system. Since the innate immune system regulates the adaptive immune response to antigens, we hypothesized that the microbiome may influence anti-tumor responses to immune checkpoint inhibitors. Accordingly, we sought to characterize the anti-tumor effects of PD-L1 blockade therapy between mice with syngeneic tumors in conventional (specific pathogen-free, SPF) and germ-free (GF) environments.

Methods
B16-OVA or Lewis Lung Cancer (LLC) cell lines were injected subcutaneously into the flanks of 10-12 week-old C57BL/6 mice in both SPF and germ-free (axenic) environments. Mice with B16-OVA tumors in SPF (n = 6) and GF (n = 12, 6 females and 6 males) environments, and mice with LLC tumors in GF (n = 6) environments were randomized to receive the murine PD-L1 blocking antibody 10B5 or an isotype control. Tumor growth was evaluated every 2-3 days until days 35-40 when all mice were euthanized. Tumor size was compared between treatment groups in each environment at day 24 with the Mann Whitney U test. This project was approved by Mayo Clinic’s Institutional Review Board and Institutional Animal Care and Use Committee. Funding was provided by the NIH (K12 CA90628) and Mayo Clinic’s Center for Individualizing Medicine’s Microbiome Project.

Results
Whereas injection of the anti-PD-L1 antibody (clone 10B5) controlled tumor growth compared to treatment with an isotype control in SPF female mice with B16-OVA (p = 0.05), PD-L1 blockade had no effect on tumor growth in female axenic mice with B16-OVA (p = 0.20) or male axenic mice with B16-OVA (p = 0.34) or axenic mice with LLC (p = 0.56).

Conclusions
PD-L1 blockade therapy loses its anti-tumor efficacy in axenic mice. The microbiome may influence the efficacy of PD-L1 blockade through its effects on both innate and adaptive immune responses to tumors.

Legal entity responsible for the study
Aaron Mansfield at Mayo Clinic

Funding
National Institutes of Health; Mayo Clinic's Center for Individualizing Medicine Microbiome Project

Disclosure
All authors have declared no conflicts of interest.

1197P - iRGD enhances T cells infiltration and augments response to PD-1 gene knockout immunotherapy in gastric cancer

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Background
Poor infiltration of activated lymphocytes into tumors can be a fundamental factor limiting their efficacy and impeding the therapeutic effect of the checkpoint blockade immunotherapy. A tumor-penetrating peptide, iRGD, has a well-defined role in delivering drugs into extravascular tumor tissues in both the combination regimen and conjugated pattern. Here, we explored for the first time whether this cycled peptide could facilitate the infiltration of lymphocytes into tumor and furtherly overcome resistance to PD1 gene knockout immunotherapy.

Methods
We used polyethylene glycol-conjugated phospholipid (PEG-lipid) derivatives, a time-efficient and versatile platform, to immobilize iRGD on T cell membrane. The ability of iRGD modified or co-applied lymphocytes infiltration was detected in both the 3D tumor spheroids in vitro and subcutaneous tumor model and peritoneal tumor model of gastric cancer in vivo. Furthermore, the synergistic effect of iRGD modification and PD-1 gene knockout in adoptive T cell transfer immunotherapy was examined in a xenograft model of EBV-associated gastric cancer.

Results
In this study, we showed that T cells could be modified by the synthetic iRGD-PEG-lipid without compromising their vitality, expansion, phenotype and effector function. In vitro, co-administration of iRGD could promote the infiltration of T cells while iRGD modification made T cells spread more extensively throughout the multicellular spheroids. Near infrared results showed that iRGD modification made a tenfold improvement infiltration of T cells into tumors without a parallel increase in normal tissues. Most importantly, we demonstrated that iRGD modified T cells had superior antitumor efficiency owing to sufficiently increased T cells infiltration, and exhibited robust synergistic effect with PD-1 gene knockout immunotherapy.

Conclusions
Our study indicates that modification of T cell membrane with iRGD might be a potent strategy to increase T cells infiltration, thereby overcome the bottleneck of solid tumor immunotherapy.
Background
Regorafenib is a small molecule inhibitor of multiple kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, angiogenesis, and tumor immunity. Regorafenib is approved for the treatment of advanced colorectal cancer (CRC) and gastrointestinal stromal tumors. In addition, an overall survival benefit has recently been shown in patients with hepatocellular carcinoma who had previously progressed on sorafenib (RESORCE trial). Immuno-oncology treatment strategies have recently expanded the arsenal of highly effective cancer therapies. In addition to their activity in monotherapy, they are being tested in combination with other therapies, including those inhibiting angiogenesis, to further improve their antitumor activity. We investigated the immunomodulatory effect of regorafenib alone and in combination with a mouse-reactive anti PD1 antibody in mouse models of CRC.

Methods
CT26 or MC38 syngeneic tumors were treated with regorafenib alone and in combination with anti PD1. We monitored tumor growth and analyzed the immune status of tumors ex vivo at the end of the study. Immune infiltrates were characterized by flow cytometry, intratumoral cytokines by multiplex ELISA, and expression of immunologically relevant genes by qPCR.

Results
Both regorafenib and anti PD1 inhibited the growth of MC38 tumors vs control, and this effect was significantly enhanced by concomitant treatment or when regorafenib was given after anti PD1. Regorafenib treatment most consistently reduced tumor-infiltrating macrophages in both MC38 and CT26 tumors in a dose-dependent manner. Additionally, signs of M1-type macrophage conversion were detected by elevated inducible NO synthase and reduced arginase expression. This may be due to a regorafenib-mediated inhibition of the CSF1 receptor, as shown in vitro in the murine macrophage cell line RAW264.7. Anti PD1 treatment was associated with elevated interferon-g levels, indicative of enhanced T cell activation.

Conclusions
These results warrant further exploration of a combination of regorafenib and PD1 for the treatment of colorectal cancer.
Background
Understanding of cancer-immune system interaction led to development of immunotherapy; anti-programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibodies are now used in non small cell lung cancer (NSCLC) treatment. MAPK cascade is a key intracellular network for tumor proliferation and recent data suggest that it is implicated in interplay of tumor and T-CD8+ cytotoxic lymphocytes (CTL).

Methods
We evaluated PD-L1 mRNA level by Real Time qPCR (RT-qPCR) and its protein production, together with MAPK proteins, by western blot (WB), in NSCLC cell lines. Then, we studied the changes in PD-L1 and major histocompatibility complex class-I (MHC-I) expression and cytokines’ production, after MAPK-inhibition or -stimulation, by MEK-inhibitor, cobimetinib, or phorbol 12-myristate 13-acetate (PMA), respectively. In addition, we explored the effect of cobimetinib on cytokines’ genes by RT-qPCR on cDNA, obtained from retro-transcription of RNA extracted from T-lymphocytes, derived from Peripheral blood mononuclear cells (PBMC) of healthy volunteers, by density gradient separation, and activated with anti-CD3/anti-CD28 coated beads.

Results
WB and RT-qPCR for PD-L1 in NSCLC cells revealed a consistent correlation between mRNA and protein levels, together with activated MAPK and MEK1/2 signals, and suggested that ectopic PD-L1 mainly depends on transcriptional regulation. PDL-1 levels were significantly decreased by cobimetinib and increased by PMA, suggesting that MAPK can regulate PD-L1. Moreover, MEK-inhibition resulted on cancer cells in increased synthesis of MHC-I, IFN-gamma, IL-6, IL-1B, and TNFalpha, involved in CTL activation, and on activated human peripheral T-lymphocytes in increment of mRNA levels of IL-12, TNFalpha and IFNgamma, that are pro-inflammatory cytokines typical of CTL subset, that seems more involved in immune response against cancer.

Conclusions
These results demonstrate that MEK-inhibitor induces the establishment of a pro-inflammatory microenvironment and may represent a potential mechanism to convert otherwise resistant cancers through treatment combination strategies of MEK-inhibitors and anti-PD-L1/PD-1 antibodies in NSCLC.

Clinical trial identification
Not applicable

Legal entity responsible for the study
AOU Università della Campania “Luigi Vanvitelli”
Background
Adoptive T cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) can induce prolonged clinical responses in selected patients with gastrointestinal tumors while a significant fraction of patients do not respond. The association between immune profiles and antigenic specificity of TIL and clinical responses remains unclear. We addressed these issues, including the recognition of neoantigens, in order to explore the potential of personalized cell-based and vaccine therapy in colorectal cancer (CRC).

Methods
Tumor specimens of primary (n = 11) and metastatic (n = 12) colon adenocarcinoma were dissected in fragments and cultured with IL-2 (6000U/ml) for 17-28 days. TIL were analyzed by multiparametric flow cytometric analyses and interrogated with private sets of predicted neoepitopes derived from non-synonymous mutations. T-cell responses against neoepitopes were detected by IFNγ ELISpot and validated with peptide-MHC multimers.

Results
TIL (i.e.>50x10^6 cells, mean±SEM 239±52x10^6) were obtained from 7 and 8 patients with primary and metastatic colon adenocarcinoma, respectively. In primary tumors, the highest potential for TIL expansion was observed for microsatellite-instable tumors as opposed to microsatellite-stable (MSS) tumors (mean±SEM 435±194x10^6 vs. 84±34x10^6 cells; p = 0.05, Mann-U). TIL yield was similar in primary and metastatic tumors, however in metastatic tumors the CD4/CD8 T cells ratio was higher (median 11 vs. 1; p = 0.002, Mann-U) and inversely correlated with TIL expansion (r_s -0.8; p = 0.005). Most (>90%) Tcells had a phenotype of effector-memory (CCR7^CD45RA^- activated (HLADR^PD1^- TIM3^+) cells. Mutational load (ranging from 23 to 2760) and potential neoepitopes (from 25 to 2373) were determined and, of interest, initial screening experiments identified 2% of neoantigen specific-TIL (mutMALT1; V380A) in a representative MSS metastatic tumor harboring only 47 missense mutations.

Conclusions
We demonstrate the spectrum of TIL expansion across CRC subtypes and stages, including the validation of neoepitopes in a non-hypermutated advanced tumor. These observations stress the potential of CRC patients for different strategies of personalized immunotherapy.

Legal entity responsible for the study
1203P - Functional screening of B7H6-based chimeric antigen receptor (CAR) designs

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Background
B7H6, a stress-induced ligand for the NK-activating receptor Nkp30, is widely expressed at the surface of transformed cells yet absent in healthy tissues. This makes B7H6 an attractive target for a CAR T-cell therapy with broad clinical applicability, including colon cancer and neuroblastoma. CARs are artificial receptors comprising an extracellular antigen-binding region (often a single chain variable fragment (scFv)) fused to an intracellular T-cell activation tail (usually CD3ζ in tandem with one or two costimulatory domain(s)). Here, we report the in vitro screening of various B7H6-based CAR designs differing by either the origin of their targeting moiety (murine versus humanized scFv), the costimulatory signaling module (either CD28 or 4-1BB as a 2nd generation CAR) or a combination of CD28 and 4-1BB in a 3rd generation CAR context.

Methods
Primary human T-cell populations expressing the diverse B7H6-specific CAR constructs were compared for viability and fold expansion at the end of manufacturing as well as in vitro functionality (IFNg secretion and cytolytic activity when challenged with B7H6 expressing cell lines).

Results
All B7H6-based CAR T-cells yielded comparable fold expansion with high viability suggesting that the CAR design has no impact on process parameters. CARs with targeting moiety of murine scFv origin were functionally superior to humanized versions in terms of killing and IFNg release potentially due to a difference in target affinity between the scFv. Second generation CARs containing CD28 endowed CAR T-cells possessed superior in vitro anti-tumor activity compared to all other constructs. Cryopreservation of these 2nd generation CAR T-cells did not significantly reduce viability and potency post-thawing.
Conclusions

In these studies, a B7H6-based CAR comprised of murine scFv fused to CD28-CD3ζ signaling tail represented the best choice candidate after in vitro testing warranting further investigation. Subsequent studies will include in vivo xenograft models of colon cancer and neuroblastoma as well as target profiling through immunohistochemistry assessing B7H6 expression in a wide panel of tumor and normal tissues. This work focuses upon developing a package to support the clinical testing of B7H6 targeted CAR T-cell therapy.

Legal entity responsible for the study

Celyad SA

Funding

Celyad SA

Disclosure


1204P - Concurrent immuno-radiotherapy in lung and renal cancer- a new treatment paradigm


Background

Concurrent administration of checkpoint inhibitors and radiotherapy (Immuno-RT) remains investigational and is the subject of multiple clinical trials. Nivolumab is an anti-programmed death-1 receptor monoclonal antibody that exhibits checkpoint-mediated immune response against tumor cells. Nivolumab has received regulatory approval for the second-line management of metastatic non-small cell lung cancer (NSCLC) & renal cell carcinoma (RCC). Ionising radiation could increase the diversity & quantity of tumoral antigen presentation, thereby augmenting anti-tumour immune response achieved with checkpoint inhibitors. The aim of this study was to assess the efficacy & toxicity of concurrent administration of nivolumab and radiotherapy.

Methods

We identified 6 patients that received concurrent nivolumab and radiotherapy to 19 lesions; metastatic NSCLC (n = 4), metastatic RCC (n = 2). Treatment-related toxicities were identified by retrospective review of patient notes. Measurable lesions were assessed by RECIST 1.1 criteria. Pain score was used to assess symptomatic responses.

Results

Stereotactic and conformal radiotherapy were delivered to 9 and 10 lesions, respectively. Treatment sites (number of lesions): lung (n = 8), hip (n = 3), brain (n = 4), shoulder, scalp, ethmoid and adrenal. The gap between radiotherapy & nivolumab did not exceed 2 weeks for all patients. No grade 3-4 toxicities were observed. Two of the lung cancer patients developed grade 1 pneumonitis. Fractionation schedules included 48Gy/4 fractions (#), 40Gy/4#, 34Gy/4#, 22Gy/1#, 30Gy/10#, 25Gy/5#, 20Gy/4# and 20Gy/5#. Of the 14 measurable lesions, 86% had excellent response including complete response of 3 lesions. Symptomatic benefit was observed in 4 out of 6 treatment sites (66%).
Conclusions
The role of concurrent nivolumab & radiotherapy in patients with metastatic NSCLC and RCC has never been reported previously. In our study, concurrent administration of nivolumab and radiotherapy appears to be well tolerated with excellent radiological and symptomatic responses. Ongoing clinical trials may help determine the future role of Immuno-RT in the rapidly evolving treatment paradigm of metastatic NSCLC and RCC management.

Legal entity responsible for the study
Jawaher Ansari

Funding
None

Disclosure
J. Ansari: Paid honoraria for lectures and/or advisory boards for Amjen, AstraZeneca, Pfizer, Novartis, Boehringer Ingleheim, Bristol-Myers Squibb, Roche and Sanofi. A. Shaukat: lecture fees and advisory board for Bristol-Myers Squibb. A. Alhamad: Advisory board for Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

1205P - Optimum fractionation of radiation dose to combine anti-PD-1 mAb in MC38 mice model
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Background
The irradiated tumor cell death can enhance antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes. Radiotherapy (RT) combined with immunotherapy has revealed promising outcomes in various animal models. However, the optimum fractionation of radiation for priming immune response is controversial. This study aimed to explore the fractionation of radiation to maximize immunity in combinatorial treatment.

Methods
Mice bearing MC38 murine colon cancer were treated with up to 24Gy radiation given in various sized fractions as 24Gy x 1f, 8Gy x 3f, 8Gy x 1f followed by 2Gy x 8f and 2Gy x 12f, and tumor growth followed. The immune response in the tumor, drainage lymph node (dLN) and spleen at 48h after radiation were assessed. 8Gy x 3f was chosen to combine anti-PD-1 immunotherapy. The abscopal effects and immune response were assessed by flow cytometry and immunohistochemistry (IHC).

Results
Single dose of 24Gy and 8Gy x 3f brought best tumor control. No abscopal effects was observed after radiotherapy alone. Fractionation of 8Gy x 3f increased the irradiated tumor infiltrating lymphocytes (TILs). However, conventional 2Gy doses decreased CD4+TILs and CD8+TILs and increased myeloid myeloid-derived suppressor cell (MDSC) in spleen significantly. As the optimal fractionation to maximize immunity, 8Gy x 3f was chosen to combine anti-PD-1 mAb. Compared to radiotherapy or anti-PD-1 mAb alone, 8Gy x 3f combining with anti-PD-1 mAb brought obvious abscopal effect. CD8+ T cells in the dLNs of the irradiated tumors were increased significantly in the combining group. Also, the
combining treatment regimen increased CD4⁺T cells and CD8⁺T cells and decreased MDSC in the spleen. No serious toxicity of heart, liver, spleen, lung and kidney in each group was observed by using IHC.

Conclusions
Hypofractionation of 8Gy x 3f was the fractionation of radiation dose to maximize immunity, compared to single dose of 24Gy and conventional 2Gy doses. Radiation with 8Gy x 3f combining with anti-PD-1 mAb had synergistic antitumor effect.

Legal entity responsible for the study
Jinming Yu

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1206P - Efficacy of tumor treating fields (TTFields) and anti-PD-1 in non-small-cell lung cancer (NSCLC) preclinical models

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Background
Tumor Treating Fields (TTFields) are an effective anti-neoplastic treatment modality delivered via non-invasive application of low intensity, intermediate frequency, alternating electric fields. TTFields is approved for the treatment of both newly diagnosed and recurrent glioblastoma. TTFields interrupt mitosis in cancer cells by disrupting microtubules and septin filaments, which play key roles in mitosis. The mitotic effects of TTFields include abnormal chromosome segregation that trigger different forms of cell death. We evaluated TTFields’ effect on immunogenic cell death and its efficacy when combined with an immune checkpoint inhibitor (αPD1) in NSCLC.

Methods
Murine Lewis lung carcinoma (LLC) cells were treated with TTFields using the inovitro™ system. Levels of cell surface calreticulin (CRT) and intracellular ATP levels were evaluated using flow cytometry. High mobility group box 1 (HMGB1) secretion was measured using an ELISA assay. Mice inoculated with LLC cells were treated with isotype control, TTFields, αPD-1, or TTFields + αPD-1. Tumor volume monitoring and intra-tumor immune cell profiling were performed.

Results
TTFields induced elevated cell surface expression of CRT, decreased ATP levels, and promoted HMGB1 secretion. In vivo, the combined treatment of TTFields + α-PD-1 led to a significant decrease in lung tumor volume compared to all three other groups (P < 0.001). Significant increase in CD45+ tumor infiltrating cells was observed in the TTFields + αPD-1-treated mice. Infiltrating cells demonstrated a significant upregulation of surface PD-L1 expression. Both F4/80+CD11b+ cells and CD11c+ cells exhibited higher tumor infiltration and elevated PD-L1 expression, as compared to the control group. These findings indicate enhanced inflammatory antitumor environment conferred by the combination of TTFields + αPD-1.

Conclusions
Our results demonstrate that TTFields treatment potentiates immunogenic cell death in NSCLC cancer cells. Combining TTFields with specific immunotherapies such as anti-PD-1 may enhance antitumor immunity and result in increased tumor control. A phase III clinical study on TTFields in combination with either PD-1 inhibitors or docetaxel in NSCLC is underway.

Legal entity responsible for the study
Novocure

Funding
Novocure

Disclosure

1207TiP - An open-label, Phase IB study of NEO-PV-01 + Adjuvant with Nivolumab in Patients with Melanoma, Non-Small Cell Lung Carcinoma, or Transitional Cell Carcinoma of the Bladder

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Background
Cancer cells harbor DNA mutations that encode altered amino acid sequences known as neoantigens. Absent from normal tissues and highly specific for tumors, neoantigens bypass central tolerance and have been established as critical targets for tumor directed T cell responses. Tumor mutational burden and neoantigen load have been associated with anti-tumor activity of immune checkpoint inhibitors. Vaccines targeting neoantigens have the potential to induce de novo and expand existing tumor directed T cell responses. NEO-PV-01 is a personalized neoantigen long peptide vaccine designed specifically for the molecular profile of an individual patient’s tumor.

Trial design
NT-001 is a single-arm, phase IB study evaluating the safety of administering NEO-PV-01 + adjuvant (Poly-ICLC) with the PD-1 directed antibody, nivolumab, in patients with advanced melanoma, smoking-associated non-small cell lung carcinoma, or transitional cell carcinoma of the bladder who have received no more than one prior systemic treatment. NEO-PV-01 is custom designed and generated for each patient by DNA and RNA sequencing of a recently biopsied tumor, HLA typing, selection of neoantigen epitopes, and synthesis of up to 20 peptides (14-35 amino acids in length). Patients receive treatment with nivolumab at a dose of 240 mg IV q2 weeks while their vaccine is produced. These peptides are formulated into four distinct pools, mixed with Poly-ICLC, and administered subcutaneously into up to 4 non-rotating anatomical sites. Beginning at Week 12, patients receive five priming immunizations over a three-week period followed by booster vaccinations at Weeks 19 and 23 while continuing nivolumab. The primary endpoint is safety. Secondary endpoints are ORR, CBR, PFS, and assessment of response conversion between Week 12 and Week 24. Exploratory endpoints include extensive immune monitoring. The study is open as of October 2016 with estimated enrollment of 90 patients.

Clinical trial identification
NCT02897765

Legal entity responsible for the study
Neon Therapeutics, Inc.

Funding
Neon Therapeutics, Inc.

Disclosure
P.A. Ott: Reports grants and personal fees from Bristol-Myers Squibb, CytomX, Celldex, and Merck, personal fees from Neon Therapeutics, Amgen, Novartis, Pfizer, and Roche/Genentech, and grants from AstraZeneca/MedImmune, outside of the submitted work. G. Ramaswamy: Reports advisory board or consulting work for Merck, Genentech, Baxalta, Roche, Boehringer Ingelheim, Novartis, Ariad, Astellas, Bristol-Myers Squibb, Pfizer, Celgene, AstraZeneca, INC Research, AbbVie, and MSKCC. M. Moles, R. Gaynor, M.J. Goldstein: Employee of Neon Therapeutics, Inc. S. Hu-Lieskovan: Consulting: Amgen, Merck, Novartis, Vaccinex, Emergent BioSolutions. Contracted Research: Pfizer, Plexxikon, Genentech, Neon Therapeutics. Research Support: Bristol-Myers Squibb, Merck. Travel: Amgen, Merck, Novartis, Vaccinex, Emergent BioSolutions, Neon Therapeutics. All other authors have declared no conflicts of interest.

1208TIp - A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors

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Background
Although acquired immunodeficiency syndrome-related mortality is decreasing with the introduction of effective antiretroviral therapy, it has been reported a significant increase in the proportion of non-acquired immunodeficiency syndrome defining malignancies in HIV infected patients, often associated with premature immunosenescence and exhaustion. It has been shown in murine models and humans that programmed cell death ligand 1 (PD-L1) and its receptor, programmed cell death 1 (PD-1) play an active and reversible role mediating T-cell exhaustion both in cancer and in chronic infections. Binding PD-1 to its ligand PD-L1 negatively regulates T-cell response, leading to an exhausted phenotype on CD8+ T cells. Therefore, there is a potential of immunotherapeutic intervention targeting PD-1/PD-L1 in order to enhance anti tumoral immune responses as well as to facilitate viral eradication. Durvalumab (MEDI4736) is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1k) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab has demonstrated in cancer patients a favorable safety profile with encouraging antitumor activity, but there are no data about tolerance or anti retroviral activity in HIV patients.

Trial design
This is an ongoing multicenter, open-label, phase 2 study (EUDRACT: 2016-004524-38) whose primary objective is to assess the feasibility of durvalumab at the recommended
dose of 1500 mg every 4 weeks in HIV-infected patients with solid tumors for which no additional oncologic standard treatment is available. As secondary objectives the response rate (RECIST 1.1 and irRECIST), duration of response, PFS and OS will be measured. Exploratory objectives include the assessment of antiviral activity by measuring the changes in the HIV viral reservoir, the residual viral replication and the composition and function of circulating T lymphocytes and the study of molecular predictive factors of antitumoral activity on pretreatment tumor samples.

Clinical trial identification
EUDRACT: 2016-004524-38

Legal entity responsible for the study
Spanish Lung Cancer Group

Funding
AZ Spain

Disclosure
All authors have declared no conflicts of interest.

1209TiP - A first-in-human, open-label, multicenter phase 1/2a study to evaluate the safety and efficacy of increased repeated doses of the first in class RORγ agonist LYC-55716 in treating locally advanced or metastatic solid tumors

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Background
LYC-55716, a first-in-class oral, small-molecule agonist of nuclear receptor retinoic acid–related orphan receptor γ (RORγ), has been shown in preclinical models to modulate gene expression to reprogram immune cell antitumor effector function and decrease immunosuppressive mechanisms, resulting in immune-mediated tumor growth control and enhanced survival. Data suggest that LYC-55716 acts via well-known antitumor mechanisms by increasing immune cell trafficking and recruitment to tumors, enhancing T cell effector function and memory development, and promoting T cell survival. LYC-55716 may enhance immune-mediated antitumor responses via its effects on T effector/Treg cell ratios, PD-1 expression, and sensitivity to PD-L1 inhibition of T cell proliferation. A first-in-human, single-arm, open-label multicenter Phase 1/2a study is ongoing to evaluate the safety and tolerability of LYC-55716 and determine the maximum tolerated dose and objective response rate. All adult subjects enrolled will have relapsed or refractory metastatic cancer and have failed to responded to standard therapies.

Trial design
The Phase 1 portion of the study will follow a dose-escalation design to evaluate the occurrence of dose-limiting toxicities (DLTs) and determine the maximum tolerated dose and recommended Phase 2 dose of LYC-55716. Following a screening period, adults with locally advanced or metastatic solid tumors will receive 28-day treatment cycles of LYC-55716 BID (n = 4–6/cohort). Dosing escalation considers dose and dosing regimen and is determined by PK profile and safety. Primary endpoints include safety (monitoring of adverse events, physical examination, and lab results) and incidence of DLTs (Grade 3 or 4 toxicities) during the first 28-day treatment cycle. Secondary endpoints include objective tumor response rate as assessed via response evaluation criteria in solid tumors
Background
Because of its increasingly demonstrative successes, CAR-T therapy has been well recognized as one of the most promising therapies for cancer. We have developed a novel autologous CAR-T, NKR-2, incorporating the full-length human natural killer receptor NKG2D fused with the human CD3 zeta signaling domain. When expressed in T-cells, the naturally-expressed DAP10 provides the co-stimulatory signals to NKR-2 to be fully activated. NKR-2 selectively target tumor cells upon recognition of up to eight different NKG2D ligands expressed in many distinct cancer indications. In preclinical studies, NKR-2 demonstrated long-term anti-tumor activity towards multiple solid and hematologic tumors deploying multiple mechanisms of action targeting tumor cells and cells from the neo-vasculature and tumor suppressive immune environment, resulting in an adaptive response. In our recently completed Phase 1 study in hematologic cancers, a single administration of autologous NKR-2 was safe with initial signs of clinical benefit. Likewise, to overcome the operational challenges, our trial design incorporates strategies to harmonize multiple clinical and manufacturing processes while also enhancing patient safety and clinical outcomes.

Trial design
THINK trial (THerapeutic Immunotherapy with NKR-2) is a EU/US open-label Phase I study to assess the safety and clinical activity of NKR-2 therapy administered in three infusions, two weeks apart in five solid tumor indications (CRC, urothelial, TNBC, pancreatic, ovarian) and two hematologic indications (AML/MDS and MM). No lymphodepleting conditioning is required in this study. The study contains two consecutive segments. The dose escalation segment will enroll 18 patients in two separate
hematologic and solid malignancy arms, and evaluate 3 dose levels of NKR-2 (3x10^8, 1x10^9 and 3x10^9 cells per injection) following a 3 + 3 design. The expansion segment will then enroll 96 additional patients in 7 separate cohorts for each indication with 3 steps of statistical analysis (overall futility, futility within each cohort and final evaluation). At time of submission, the trial has completed enrollment in its first cohort among solid indications.

**Clinical trial identification**

FDA: CYAD-N2T-002

**Legal entity responsible for the study**

CELYAD

**Funding**

CELYAD

**Disclosure**


**1211Tip - FAK-PD1: a phase I/IIa trial of FAK (defactinib) & PD-1 (pembrolizumab) inhibition**

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**Background**

Focal Adhesion Kinase (FAK) is a pivotal intracellular mediator of extracellular contact interactions. It is over-expressed in cancer, with a long-established role in migration, invasion & survival, and is associated with poor prognosis. Recently FAK has been found to have a similar activity in recruitment of immunosuppressive cells to the tumour. We have shown that FAK inhibition can re-model the tumour immune microenvironment in vivo, shifting the balance from inhibitory Tregs, macrophages, fibroblasts and myeloid progenitors, to one which supports an active CD8+ adaptive immune response, resulting in tumour clearance and lasting immunity. FAK inhibition synergises with Programmed cell death receptor 1 (PD-1) blockade in more resistant models. Defactinib (VS-6063, Verastem) is a small molecule FAK inhibitor in Phase II development with an encouraging safety profile and biological activity. Pembrolizumab (MK-3475, MSD) is a humanized IgG4/kappa monoclonal antibody to PD-1, licensed for the treatment of an increasing number of tumour types. This recently open trial will assess the safety, tolerability and preliminary activity of defactinib plus pembrolizumab in patients with advanced solid malignancies.

**Trial design**

FAK-PD1 is an open label, phase I/IIa clinical trial, combining 200 mg pembrolizumab as a 3-weekly IV infusion, with defactinib given orally twice daily at either 200 mg or 400 mg, before leading into three tumour-specific expansions (non-small cell lung cancer, mesothelioma and pancreatic cancer) at the selected dose. Up to 60 patients, PS 0-1, with
adequate blood parameters, measurable disease, baseline tissue, and without contraindications to either agent, will be treated for up to 2 years until clear clinical progression, unacceptable toxicity, or withdrawal. Primary endpoint is safety (NCI-CTCAE v4.03); secondary endpoints include objective response rate (irRECIST), progression-free survival, FAK Y397 phosphorylation and immune cell infiltrate effects. Exploratory endpoints include comprehensive cellular and molecular characterisation of baseline and on-treatment tumour samples, and serial blood immune cell and cytokine profiling. Positive data will support further development of the combination.

Clinical trial identification
FAK-PD1 EudraCT number: 2015-003928-31

Legal entity responsible for the study
University of Glasgow & NHS Greater Glasgow and Clyde

Funding
Cancer Research UK, Verastem Inc, and Merck Sharp and Dohme Ltd •Verastem Inc (via the Combinations Alliance program) and Cancer Research UK

Disclosure
All authors have declared no conflicts of interest.

1212TiP - PIVOT-02: A phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 and nivolumab in patients with select, locally advanced or metastatic solid tumor malignancies

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Background
Abundance and functional quality of tumor infiltrating lymphocytes are positively linked with tumor response and improved survival with checkpoint inhibitors. NKTR-214 is a CD122-biased agonist that targets the IL2 pathway and is designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2Rβγ) to preferentially activate and expand NK and effector CD8+ T cells over CD4+ T regulatory cells within the tumor microenvironment. NKTR-214 has been administered to 28 patients with advanced cancers. NKTR-214 as a single agent demonstrated a substantial increase in both CD8+ T and NK cells within the tumor microenvironment in patients with prior immune checkpoint therapy (Bernatchez et al 2016). Given the favorable safety profile and strong biomarker data, a trial combining NKTR-214 and nivolumab was initiated.

Trial design
PIVOT-02 is a phase 1/2 open-label trial in patients (pts) with locally advanced or metastatic melanoma (mM), non-small cell lung cancer (NSCLC), renal cell carcinoma...
(RCC), urothelial carcinoma, or triple-negative breast cancer (TNBC). The primary objectives are to evaluate safety and tolerability, determine the recommended phase 2 dose (RP2D), and assess tumor response by RECIST 1.1. In an outpatient setting, NKTR-214 is administered at dose levels of 0.003, 0.006 and 0.009 mg/kg in combination with nivolumab at two flat dose schedules of either 240 mg @ q2w or 360 mg @ q3w. As of May 8, 17 pts (7 mM, 8 RCC, and 2 NSCLC) have been enrolled into 4 cohorts in the dose-escalation phase. In the dose-expansion phase, approximately 250 pts will be enrolled in five tumor types and eight indications; immunotherapy naïve patients and patients who are relapsed/refractory to checkpoint therapy are being studied separately. Extensive blood and tumor tissue samples are being collected to measure immune activation using immunophenotyping including flow cytometry, immunohistochemistry (IHC), T cell clonality and gene expression analyses. Enrollment is ongoing.

Clinical trial identification
NCT02983045

Legal entity responsible for the study
Nektar Therapeutics

Funding
Nektar Therapeutics

Disclosure
A. Diab: Consulting or Advisory Role - Celgene; CureVac; Nektar Research Funding - Celgene (Inst); Idera (Inst); Nektar (Inst); Pfizer (Inst) Travel, Accommodations, Expenses – Nektar. M.E. Hurwitz: Employment - Pfizer Consulting or Advisory Role – Nektar. N. Tannir: Honoraria - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis; Pfizer Advisory Role - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis Research Funding - Bristol-Myers Squibb; Epizyme; Exelixis; Novartis Travel - Bristol-Myers Squibb; Exelixis; GSK; Nektar; Novartis; Pfizer. C. Bernatchez: Employment - Lexicon (I) Stock - Lexicon (I) Advisory Role - Lion Biotechnologies Research Funding - Idera; Nektar Patents - Patent pending on BTLa as a marker for better CD8 T cells for adoptive immunotherapy. C. Haymaker: Cara L. Haymaker Research Funding - Idera; Nektar. B.D. Curti: Honoraria - Prometheus Speakers' Bureau - Prometheus Research Funding - Bristol-Myers Squibb; Galectin Therapeutics; MedImmune; Prometheus; Viralytics Travel, Accommodations, Expenses - Agonox; MedImmune; Nektar; Prometheus. I. Gergel: Employment - Nektar Leadership - Corium International; Nektar Stock and Other Ownership Interests - Corium International; Nektar. M. Tagliaferri: Employment - Nektar Travel, Accommodations, Expenses - Nektar J. Zalevsky: Employment - Nektar. U. Hoch, S. Aung, M. Imperiale: Employment - Nektar Stock and Other Ownership Interests - Nektar D. Cho: Honoraria - Bristol-Myers Squibb; Exelixis; Roche/Genentech Consulting or Advisory Role - Pfizer; Prometheus. S.S. Tykodi: Consulting or Advisory Role - Amgen; Prometheus Research Funding - Argos Therapeutics (Inst); Bristol-Myers Squibb (Inst); Exelixis (Inst); Genentech (Inst); GlaxoSmithKline (Inst); Prometheus (Inst). I. Puzanov: Consulting or Advisory Role - Amgen; Bristol-Myers Squibb; Roche/Genentech. H. Kluger: Honoraria - Merck Consulting or Advisory Role - Alexion Pharmaceuticals; Prometheus; Regeneron Research Funding - Merck (Inst) Travel, Accommodations, Expenses - Bristol-Myers Squib P. Hwu: Stock and Other Ownership Interests - immatics; Lion Biotechnologies Consulting or Advisory Role - Lion Biotechnologies Research Funding - Bristol-Myers Squibb (Inst); Genentech (Inst). M. Sznol: Stock - Adaptive Bio; Amphivena; Intensity Thera Advisor - Adapimmune; Alexion; Amgen; AstraZeneca; Biodesix; Bristol-Myers Squibb; Genentech; Immune
MELANOMA AND OTHER SKIN TUMOURS
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1227P - Avelumab treatment in chemotherapy-naïve patients with distant metastatic Merkel cell carcinoma (mMCC)
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Background
MCC is a rare, aggressive skin cancer. In a phase 2 study of patients with mMCC progressed on or after chemotherapy (JAVELIN Merkel 200; NCT02155647), avelumab (a human anti–PD-L1 antibody) showed durable responses and a manageable safety profile, including an objective response rate (ORR) of 33.0%, proportion of responses with ≥1-year duration of 74% (Kaplan-Meier estimate), and estimated 1-year overall survival (OS) rate of 52%. Based on these results, avelumab was approved by the US FDA in March 2017 and is the only approved treatment for patients with mMCC. Here, we report early interim results from patients with mMCC receiving first-line avelumab.

Methods
Eligible patients with mMCC and no prior systemic treatment for metastatic disease received avelumab 10 mg/kg Q2W. Tumors were assessed every 6 weeks (RECIST v1.1) by independent review committee (IRC). Adverse events (AEs) were assessed by NCI CTCAE v4.0.

Results
At data cutoff on Dec 30, 2016, 29 of 112 planned patients had been enrolled. Median follow-up was 3.1 months (range 0.3–8.5) and median duration of treatment was 8.1 weeks (range 2.0–37.9). Of 16 patients with ≥13 weeks of follow-up, confirmed ORR by IRC was 62.5% (95% CI 35.4–84.8) with response ongoing in all 10 patients, including in all 5 patients with ≥6 months of follow-up. Of 25 patients with ≥6 weeks of follow-up, unconfirmed ORR by IRC was 68.0% (95% CI 46.5–85.1); responses were ongoing at last follow-up in 16 of 17 responders (94.1%; 1 censored due to other therapy). 23 of 29 patients (79.3%) had a treatment-related AE (TRAE), including 5 (17.2%) with a grade 3 or 4 TRAE. There was 1 immune-mediated TRAE (grade 1 rash). 5 patients (17.2%) discontinued avelumab due to a TRAE. There were no treatment-related deaths. Updated analyses of 39 patients will be presented (n = 29 and n = 14 with ≥13 weeks and ≥6 months of follow-up, respectively; data cutoff Mar 24, 2017), including PFS and OS analyses.

Conclusions
First-line avelumab treatment resulted in early responses and a high ORR in distant mMCC, substantiating prior findings with second-line or later avelumab treatment. Most responses were ongoing, including all responders with ≥6 months of follow-up. Enrollment
1228P - Long-term effects of sonidegib on tumor burden: 30-month results from the phase 2 randomized bolt trial

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Background
Sonidegib, a hedgehog pathway inhibitor (HPI), is approved in the United States and European Union for locally advanced basal cell carcinoma (laBCC) based on primary results from the BOLT trial (Migden, Lancet, 2015). Updated data from 30-months analysis demonstrated continued efficacy and manageable safety (Dummer ASCO 2016). Here we present 30-month tumor burden results, which have not previously been presented or published.

Methods
Eligible HPI-treatment-naïve patients with laBCC not amenable to curative surgery/radiotherapy or patients with metastatic BCC (mBCC) were randomized 1:2 to receive sonedegib 200 or 800 mg QD. For all patients, tumor burden was assessed as decrease of best percentage change from baseline by central review. For patients with
laBCC, tumor lesions were assessed by photography and modified RECIST criteria; for patients with mBCC, photography or MRI/computed tomography (CT) and RECIST 1.1 were used.

Results
Evaluable patients at 30 months were from the primary efficacy analysis set (pEAS) for laBCC patients (200 mg, n = 32; 800 mg, n = 74) and mBCC patients (200 mg, n = 12; 800 mg, n = 19). Consistent with the primary, 12- and 18-month analyses, 96.9% (n = 31) and 94.6% (n = 70) of patients with laBCC experienced a substantial reduction in tumor size with sonidegib 200 and 800 mg, respectively. Reduction in target lesions for patients with mBCC receiving 200 mg was 91.7% (n = 11) across all time points; for the 800 mg group, 84.2% (n = 16) of patients experienced reduction in tumor lesions in the primary, 12-, 18-month analyses and 89.5% (n = 17) at 30 months. Sonidegib 200 mg had a more favorable safety profile compared to 800 mg, with lower rates of grade 3/4 adverse events (AEs; 43.0% vs 64.0%) and AESs events leading to discontinuation (30.4% vs 40.0%).

Conclusions
Sonidegib 200 and 800 mg in patients with laBCC and mBCC demonstrated substantial target tumor lesion reduction across 30 months. Safety/tolerability was manageable and similar across 30 months with no new side effects emerging following the primary analysis.

Clinical trial identification
NCT01327053

Legal entity responsible for the study
Novartis Pharmaceuticals

Funding
Sun Pharmaceutical Industries Ltd.

Disclosure
R. Dummer: Received research funding from Novartis, Merck, Bristol-Myers Squibb, Roche, and GlaxoSmithKline and has served as a consultant/advisory board for Novartis, Merck, Bristol-Myers Squibb, Roche, GlaxoSmithKline, Amgen, and Takeda. M. Migden: Participated on advisory boards and received honoraria from Genentech, Inc.; Novartis Pharmaceuticals Corporation; Eli Lilly and Company; and Sun Pharmaceuticals

1230P - Modulation of Risk and Prognosis of Cutaneous Melanoma Patients by Genetic Polymorphisms on PDCD1 Gene

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Background
This study aimed to evaluate whether PD1.1 (c.-606G>A), PD1 (c.627 + 252C>T), PD1.5 (c.804C>T) and PD1.9 (c.644C>T) single nucleotide polymorphisms (SNPs) on PDCD1 gene influence risk, clinicopathological aspects and survival of patients with cutaneous melanoma (CM).

Methods
We evaluated 250 CM patients diagnosed at the University of Campinas and 250 blood donors (controls). DNA was analyzed by real-time polymerase chain reaction (PCR) for
genotyping. PDCD1 gene expression and PD1 protein expression were assessed by quantitative PCR and flow cytometry, respectively. The statistical significance of differences between groups was calculated using the Fisher’s exact or chi-square test. Bonferroni method was used in multiple comparisons. PDCD1 expression and PD1 expression on T lymphocytes were calculated, using Kruskal-Wallis and Mann-Whitney test, respectively. The prognostic impact of SNPs on recurrence-free survival (RFS) and overall survival (OS) of CM patients were examined using the Kaplan Meier and Cox analyses.

Results

Individuals with PD1 CC genotype isolated and associated with PD1.5 CC genotype were under 2.20 (95% CI: 1.00-4.82, P= 0.04) and 2.51 (95% CI: 1.04-6.03, P= 0.03) times greater risks of developing CM, respectively. Individuals with phototype I or II and PD1 CC genotype or PD1 CC plus PD1.5 CC genotype had 5.89 and 6.71 more chances of presenting CM than others, respectively. PD1.5 TT genotype was associated with increased expression of PDCD1 gene when compared with CT or CC genotype (P= 0.03). PD1.5 CT or TT genotypes and T allele increased expression of PD1 protein in CD4+ lymphocytes (P= 0.01, P= 0.006; respectively). At 60 months of follow-up, shorter RFS was observed in patients with PD1.1 AA genotype (33.3% vs 72.5%, P= 0.02). Patients with PD1.1 AA genotype had 4.39 more chances of presenting tumor progression or relapse in univariate Cox analysis (P= 0.04) and patients with PD1.5 CC genotype had 2.38-fold increased risk of evolving to death in multivariate Cox analysis (P= 0.02).

Conclusions

The data suggest, for the first time, preliminary evidence that inherited abnormalities in regulation of T lymphocyte activities, related to PD1.1, PD1 and PD1.5 SNPs, alter CM risk and prognosis.

Legal entity responsible for the study

Faculty of Medical Sciences, University of Campinas

Funding

São Paulo Research Foundation (FAPESP)

Disclosure

All authors have declared no conflicts of interest.

1231P - Role of an intronic polymorphism in the CREB1 gene, involved in melanogenesis, with the risk and the aggressiveness of cutaneous melanoma

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Background

Recently, we observed 12,882 new single nucleotide polymorphisms (SNPs) associated with cutaneous melanoma (CM) risk in 103 patients and 103 controls, using large-scale genotyping with microarrays. CREB1 c.303 + 373G>A, involved in melanogenesis and located in regulatory sequence of mRNA processing (splicing), was selected for further analyses. An in silico analysis showed that referred SNP may alters the binding sites of splicing regulatory proteins, such as SF1 and hnRNP A1. However, the role of this SNP in
the risk, aggressiveness and prognosis of CM is unknown. Verify whether the distinct genotypes of CREB1 c.303 + 373G>A influence the CM risk and prognosis, clinicopathological aspects, and CREB1, SF1 and HNRNPA1 mRNA levels.

**Methods**

Genomic DNA of 262 patients and 280 controls was analyzed by RT-PCR. Patients were treated with conventional procedures. Gene expressions were determined by qPCR using total RNA of 56 controls. Chi-square, logistic regression model, Mann-Whitney and Student’s t tests analyzed the differences between groups. Progression-free survival (PFS) and overall survival (OS) times were calculated using Kaplan-Meier and Cox regression analyses.

**Results**

CREB1 GA or AA genotypes were more frequent in CM patients than in controls (72.0% vs. 61.1%, P = 0.02). Carriers of the genotypes were under 1.61-fold increased risk of CM (95% CI: 1.07-2.41) than others. An excess of CREB1 AA variant genotype was seen in patients with Breslow’s thickness higher than 1.5mm (28.2% vs. 18.5%, P = 0.04) and high Clark’s level (26.2% vs. 13.3%, P = 0.02). The median of follow-up of CM patients was 76 months; no association of referred SNP and patients' PFS and OS was observed in this study. Individuals with CREB1 GA or AA genotypes presented higher mRNA expression of CREB1 (0.94 vs. 0.60 arbitrary units (UAs), P = 0.007), SF1 (1.33 vs. 1.05 UAs, P = 0.03) and HNRNPA1 (0.77 vs. 0.57 UAs, P = 0.02) than those with GG wild-type genotype.

**Conclusions**

Our data suggest, for the first time, that CREB1 c.303 + 373G>A SNP is an important hereditary factor for the risk and aggressiveness of CM, possibly due to variation of the splicing factors.

**Legal entity responsible for the study**

University of Campinas

**Funding**

Foundation for protection of research in the state of São Paulo (FAPESP)

**Disclosure**

All authors have declared no conflicts of interest.

**1232P - Investigation of AMBRA1 as a melanoma susceptibility gene**

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**Background**

Melanoma is the most lethal form of skin cancer, which shows a rapid increase in incidence in many countries including Sweden. To date, the annual increase is over 5% and there is an urgent need to improve possibilities for prevention and early diagnoses when the prognosis is far favorable compared to disseminated disease. Melanoma is caused by an interplay of environmental and genetic factors and is one of the cancer forms showing highest heritability. Still a substantial extent of the genes underlying melanoma susceptibility is unknown.

**Methods**

We have executed whole-exome sequencing of melanoma-prone families to identify novel melanoma predisposing genes. Further genetic and functional studies of strong candidate
genes using patient samples and melanoma cell lines has been performed. Various in vitro assays have been used to determine the role of these genes in, for example, autophagy and cell proliferation.

**Results**

One gene discovered was the autophagy/beclin-1 regulator 1 (AMBRA1), where a putative splice variant was co-segregating with the melanoma phenotype in a 4-case family. This mutation was not found among over 6000 Swedish population-based controls nor in any additional melanoma patients. AMBRA1 is essential in the regulation of autophagy and apoptosis and has been suggested to function as a tumor suppressor. By gene expression analysis, we identified several transcripts of AMBRA1, with differential expression in melanoma tumors and in various melanoma cell lines. In tumor material from the splice variant carrier, AMBRA1 showed low levels of expression. In melanoma cell lines, AMBRA1 was up-regulated when adding an autophagy activating reagent while down-regulated when treating the cells with Chloroquine, a drug inhibiting autophagy. AMBRA1 was also significantly up-regulated when treating the cells with Crizotinib, a drug that targets the tyrosine kinase receptor c-MET and may induce autophagy, whereas no effect was seen when using the BRAF-inhibitor Vemurafenib. Thus, AMBRA1 may be involved in the Crizotinib-induced autophagy pathway.

**Conclusions**

Preliminary data suggest AMBRA1 as a candidate melanoma susceptibility gene with a role during autophagy in melanoma cells. Further studies are needed to elucidate the specific role of this gene in melanoma development.

**Legal entity responsible for the study**

Karolinska Institutet

**Funding**

The Swedish Cancer Society, The Swedish Research Council, Regnérs foundation

**Disclosure**

All authors have declared no conflicts of interest.

1233P - Influence of an intronic polymorphism in the MITF gene, of melanogenic pathway, in the risk and the prognosis of cutaneous melanoma

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C. S. Lima (Campinas, Brazil) G. J. Lourenço (Campinas, Brazil)

**Background**

We identified more than 12,000 new single nucleotide polymorphisms (SNPs) associated with cutaneous melanoma (CM) risk in 103 patients and 103 controls, using large-scale genotyping with DNA microarrays. A bioinformatics analysis showed that MITF c.938-325G>A SNP, involved in melanogenesis and located in regulatory sequence of mRNA processing (splicing), may alter the binding sites of splicing proteins, such as SF1 and hnRNP A1. However, the role of this SNP in the risk and prognosis of CM patients is still unknown. We aim to evaluate the influence of this SNP on the risk and prognosis of CM, clinical and tumor characteristics, and MITF, SF1 and HNRNPA1 levels.

**Methods**
MITF genotypes of 262 CM patients and 280 controls were identified in DNA by RT-PCR. Patients were treated with conventional protocols. Gene expressions were evaluated by qPCR using RNA of 73 controls. The differences between groups were assessed by chi-square, logistic regression, t test and ANOVA. Progression-free (PFS) and overall survival (OS) times were estimated by Kaplan-Meier and Cox methods.

Results

The frequency of the AA variant genotype was higher in patients than in controls (26.8% vs. 21.1%, P = 0.03). Individuals with referred genotype were under 1.60-fold increased risk of CM (95% CI: 1.02-2.52) than others. The frequency of GA or AA genotypes was more common in patients with lower phototype (I-III) (90.8% vs. 80.9%, P = 0.04) and with vertical tumors (83.7% vs. 67.5%, P = 0.04). The median of follow-up was 76 months. At 60 months, PFS (53.4% vs. 71.6%, P = 0.005, Cox: HR: 1.84, P = 0.006) and OS (76.2% vs. 82.4%, P = 0.02, Cox: HR: 1.79, P = 0.03) were shorter in patients with AA genotype than others. We observed similar frequencies of MITF (1.2 vs. 1.1 vs. 1.0 arbitrary units (AUs), P = 0.30), SF1 (1.1 vs. 1.2 vs. 1.0 AUs, P = 0.94) and HNRNPA1 (1.1 vs. 1.3 vs. 1.3 AUs, P = 0.61) mRNA levels in individuals with distinct genotypes.

Conclusions

Our results suggest, for the first time, that MITF c.938-325G> SNP is an important inherited factor for the risk and prognosis of CM. Our findings, once validated in additional studies, will contribute to personalize the therapy of CM patients.

Legal entity responsible for the study

University of Campinas (UNICAMP)

Funding

São Paulo Research Foundation (FAPESP)

Disclosure

All authors have declared no conflicts of interest.

1234P - Hybrid-capture based genomic profiling identifies BRAF V600 and non-V600 alterations in melanoma samples negative by prior testing

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Background

BRAF and MEK inhibitors are approved for V600-mutated melanoma, and response rates of up to 70% are seen for patients with V600 mutations. Responses to targeted therapies have also been observed for a variety of non-V600 BRAF alterations. Thus, sensitive, accurate, and broad detection of BRAF alterations is critical to match patients with available targeted therapies.

Methods

Pathology reports were reviewed for 385 consecutive melanoma cases (Mar 2016 - Mar 2017) with BRAF mutations or rearrangements identified using a hybrid-capture based next generation sequencing (NGS) assay during the course of clinical care.
Results

Records of prior BRAF molecular testing were available for 79 (21%) cases, utilizing PCR (n = 30), Sanger sequencing (n = 13), IHC (n = 10), non-hybrid capture based NGS (n = 9), or other or unspecified methodology (n = 17). Of cases with BRAF V600 mutations 11/57 (19%) with available data were negative by prior BRAF testing, including 2/11 (18%) with confirmation that the same biopsy was tested. In cases with BRAF V600 mutations, there was no significant difference in mutant allele frequencies (median 35% vs. 40%, p = 0.25) or percentage of tumor nuclei (median 50% for both, p = 0.97) between samples with prior negative and prior positive results. Prior negative results were also identified in 16/20 (80%) cases with non-V600 mutations, two of which harbored multiple BRAF alterations [K601E (4), D594A/G/N (4), S467L (2), L584F (2), G464V, G466V, G469V, E586K, N581I, L597Q, A589_T599insT]. Two of 2 (100%) cases with activating BRAF fusions also had prior negative BRAF results. Clinical outcomes for a subset of patients will be presented.

Conclusions

Despite approved companion diagnostics, significant variability exists in methods for BRAF testing in the clinical setting. Hybrid-capture based NGS identifies diverse activating mutations and fusions, including BRAF V600E, in a significant fraction of cases for which prior BRAF testing returned negative results. Given the proven clinical benefit in patients with BRAF alterations treated with match targeted therapies, hybrid-capture based NGS should be considered for patients with metastatic melanoma, particularly if other testing is negative.

Legal entity responsible for the study

Foundation Medicine, Inc.

Funding

Foundation Medicine, Inc.

Disclosure

A. Wang, J.S. Ross, P.J. Stephens, S.M. Ali, A.B. Schrock, V.A. Miller: Employee with stock ownership in Foundation Medicine, Inc. All other authors have declared no conflicts of interest.

1235P - Post-transcriptional regulation of immune checkpoint genes by mir-16 in melanoma

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Background

The complex interface between T lymphocytes and cancer ('the immunological synapse') comprises of both co-stimulatory and co-inhibitory proteins that modulate lymphocytes towards activation or anergy. 'Checkpoint inhibitors' have impressive activity in melanoma, but not all patients respond and drug resistance often develops. MiRNAs are master regulators of gene expression. Our aim is to study the regulation of the immunological synapse by miRNAs in melanoma.

Methods

Bioinformatic analyses of mRNAs and miRNA expression in 451 samples from the melanoma TCGA database was performed. Spearman rho correlation coefficients were calculated and survival analysis was performed using the Kaplan-Meier method. Direct mRNA targets of miRNAs were found using luciferase reporter assays, and mRNA/miRNA
expression was assessed by qRT-PCR following either ectopic expression or depletion of specific miRNAs.

Results
Of 15 checkpoint mRNAs and 8 miRNAs examined, nine checkpoint mRNAs showed a highly statistically significant positive correlation to each other and, to a lesser extent, to mir-16. These results were fully corroborated in vitro. Mir-16 may potentially target the 3'UTR of 3 of these mRNAs. CD80 (B7.1) was found to a direct target of mir16 in vitro. Overexpression of mir-16 in melanoma cell lines led to downregulation of CD80, CD274 (PD-L1) and CD40, while downregulation of mir-16 increased the expression of these genes. Survival data from 163 stage III melanoma patients show that high levels of mir-16 and low levels of any of six checkpoint mRNAs (among them CD80) is significantly associated with poor prognosis.

Conclusions
Our results suggest that mir-16 and many checkpoint mRNAs are generally under a strict joint transcriptional regulation. The ability of mir-16 to decrease CD80 expression suggests that it serves as a key regulator of the immunological sample. We hypothesize that in vivo, an aberrantly high expression of mir-16 decreases the expression of the co-stimulatory checkpoint CD80 in melanoma and other checkpoint mRNAs, leading to immune evasion and compromised outcome. Further elucidation of both the transcriptional and post-transcriptional regulation of the immunological synapse may help point to novel targets and means for immune modulation.

Legal entity responsible for the study
Raya Leibowitz-Amit

Funding
Israeli Scientific Foundation (ISF)

Disclosure
All authors have declared no conflicts of interest.

1236P - Does melanoma or other skin cancers belong to the BRCA2 phenotype?
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Background
The BRCA2 phenotype includes breast (BC) and ovarian cancer (OC) as well as, less frequently, prostate (PC), gastric (GC) and pancreatic cancer. The association with melanoma remains unclear, because previous studies were retrospective and included non-confirmed carriers. With this study we intend to determine the rate of melanoma and nonmelanoma skin cancers diagnoses in a consecutive prospective cohort of confirmed BRCA2 carriers.

Methods
Review of all skin cancer diagnoses in BRCA2 carriers under prospective surveillance.

Results
Four hundred and eighty six BRCA2 carriers (376 female, 110 male) belonging to 216 families were identified. The median age for genetic diagnosis was 48.3yrs with the
BRCA2 c.156_157inAlu being the mutation most frequently observed (43.6%). Most carriers (359/486) had yearly full skin examinations. Although a majority of women (226/376) were cancer survivors (209 BC, 29 OC and 12 with breast/ovarian cancer), only 30/110 men had a previous cancer diagnosis (20 BC, 8 PC and 2 GCs). For a median follow up of 4 yrs, melanoma diagnoses were 3 in 2 female with bilateral BC. The patient with 2 melanomas had the first melanoma at 28yrs before BC diagnoses. Other skin cancers: 14 squamous cell carcinoma (SCC) (8 invasive, 6 in situ SCC) and 14 pts with basal cell carcinoma (BCC), 6 of which with multiple BCC. Four pts were diagnosed with actinic keratosis (AK). The rate for melanoma is 0.4% and for nonmelanoma skin cancers 5%. The rate for skin cancer in BRCA2 carriers with a previous cancer diagnosis is 2%. No statistical significance was found either for the association of skin cancer (p = 0.221) or melanoma (p = 0.9) with specific BRCA2 mutations.

**Conclusions**
The low rates of melanoma diagnosis in our prospective confirmed BRCA2 cohort, raises questions about the previously described association of melanoma and BRCA2 mutations. Also, no association was found between the Portuguese founder mutation and melanoma or other skin cancers. Although more follow up may be needed, there is insufficient evidence to warrant increased skin surveillance of BRCA2 carriers in the absence of standard skin cancer risk factors.

**Legal entity responsible for the study**
IPOL FG, E.P.E.

**Funding**
None

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

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**1237P - Resected malignant melanoma at high risk of recurrence in SEER-Medicare**

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A. Hernandez (South San Francisco, United States of America)
D. Colburn (South San Francisco, United States of America)
G. Goodman (South San Francisco, United States of America)

**Background**
While surgery remains a mainstay in the management of high-risk resectable malignant melanoma (MM), there is a high chance of recurrence. Utilization of approved adjuvant therapies (e.g. interferon α and ipilimumab) are limited by the common occurrence of debilitating side effects. The objective of our study was to describe characteristics of patients (pts) with resected MM at high risk of recurrence in the older US population.

**Methods**
A retrospective cohort study was undertaken using the Surveillance, Epidemiology, and End Results (SEER)-Medicare population-based linked database. The study population included pts with Stage IIC-IIIC surgically resected MM diagnosed between 2004 and 2011. Demographic and clinical characteristics, adjuvant therapies, including radiation (XRT) and/or systemic therapy (eg, interferon α, interleukin, pegylated interferon), and overall survival (OS) were evaluated.

**Results**
We identified 1016 pts; the mean age was 75.2 years (interquartile range [IQR], 72–82)
and 66.2% were males. The majority of pts had Stage IIC-IIIB disease at diagnosis (Cohort 1; n = 877 [86.3%]); the remainder had stage IIIC disease (Cohort 2; n = 139 [13.7%]). Adjuvant therapy was utilized in 27.3% (n = 239) and 43.2% (n = 60) of pts in Cohorts 1 and 2, respectively, and consisted of XRT in 74% and 78% of pts, systemic therapy in 16% and 10% of pts (with interferon α representing 98.6% of systemic therapies), and a combination of XRT and systemic therapy in 10% and 12% of pts. OS differed between cohorts, with a median of 32.3 months (IQR, 17.9–53.3) for Cohort 1 and 19.8 months (IQR, 11.5–36.2) for Cohort 2. Landmark OS at 5 years was 20.8% for Cohort 1 and 12.2% for Cohort 2.

Conclusions
Among pts with resected MM at high risk of recurrence in the older US population, utilization of adjuvant therapy and OS varied based on disease stage at diagnosis. Pts with Stage IIIC disease were exposed to more medical interventions; however, use of highly toxic systemic therapy available during the study period was limited in both cohorts. As more therapies for the adjuvant setting are being developed, the evaluation of clinical and demographic characteristics may help tailor treatment regimens.

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

Funding
F. Hoffmann-La Roche Ltd.

Disclosure
N. Sadetsky, A. Hernandez, D. Colburn: Employee, Genentech, Inc. G. Goodman: Employee, Genentech, Inc.; owns stock in Roche. All other authors have declared no conflicts of interest.

1238P - Independent prognostic impact of lympho-vascular invasion in cutaneous melanoma patients with sentinel lymph node biopsy

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Background
Incidence of cutaneous melanoma (CM) is increasing worldwide. The primary treatment of CM is surgery. Prognosis is determined by characteristics of the lesion such as depth of invasion, ulceration and sentinel lymph node (SLN) status. The aim of this study was to analyze the prognostic impact of lympho-vascular invasion (LVI) in CM patients (pts) undergoing SLN biopsy since LVI has not been established as a clear prognostic factor in the current AJCC 8th ed. cancer staging system.

Methods
Retrospective, descriptive and observational analytical study. We used the institutional database of pts with diagnosis of CM, submitted to SLN biopsy between November 1994 and August 2016. The association between pathological characteristics and SLN were analyzed using Chi2 and logistic regression model. Kaplan Meier and Log rank were used for disease free survival (DFS) analysis.

Results
385 pts with a diagnosis of CM were analyzed. Median follow-up 45.2 months (IQR: 15.66-91.77). Median age: 52 years (IQR 42-65). Evaluated prognostic factors: Breslow (Br) 1.5 mm md (IQR 1-2.67), ulceration + 94/385 (24.4%), LVI + 32/144 (22.2%). Relapse 86/367 (23.4%). In the univariate analysis we found association between relapse and the following factors: LVI + (OR: 2.97, p = 0.0125), SLN + (OR: 3.97, p < 0.01), Br ≥ 1mm (OR: 4.13, p = 0.01) and ulceration + (OR: 2.08, p < 0.01). There was no association with age and sex. In the multivariate analysis LVI + (OR: 2.47, p = 0.049) and SLN + (OR: 3.91, p = 0.048) were associated with relapse, whereas neither Br ≥ 1 mm, sex nor ulceration were associated with relapses. 5-year-DFS was higher in SLN - (79.3% vs 56.1%, p < 0.01), LVI - (80.7% vs 57.9%, p 0.019), Br < 1 mm (89.5% vs 71%, p < 0.01) and ulceration - (80.4% vs 59.7%, p < 0.01).

Conclusions
In our retrospective series, after a long period of follow-up, the presence of LVI as an independent factor was associated with relapse and DFS. Within CM pts the best candidate for adjuvant therapy is yet to be defined, LVI + as a prognostic factor should be validated in prospective trials in this scenario.

Legal entity responsible for the study
Instituto Alexander Fleming

Funding
Instituto Alexander Fleming

Disclosure
All authors have declared no conflicts of interest.
PMN) median PFS was 4m (95% CI 4-5) for normal LDH and ECOG 0, 7 (3-9) for normal LDH and ECOG > 0, 2.6 (2-3) for elevated LDH and ECOG 0 and 2.5 (2-3) for elevated LDH and ECOG > 0. Corresponding median OS was 17m (95%CI 15-18), 12.7 (95%CI 10-19), 7.4 (95%CI 6.3-8.9) and 5.3 (95%CI 3.8-6.1). CCI were PFS 0.72 (SE 0.02, 95% CI 0.69-0.75), OS 0.73 (SE 0.02, 95% CI 0.7-0.76).

Table:

<table>
<thead>
<tr>
<th>Variable (n = 463) (n (%), median, range)</th>
<th>$7^{th}$ AJCC</th>
<th>HUCH</th>
<th>PMN</th>
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<tbody>
<tr>
<td>ECOG</td>
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<td>0</td>
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<td>&gt; 2</td>
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<tr>
<td>Diameter in cm of largest metastasis</td>
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<tr>
<td>&lt; 3 cm</td>
<td>1.9 (0-2.9)</td>
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<tr>
<td>3-8 cm</td>
<td>4.4 (3-8)</td>
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<tr>
<td>&gt; 8 cm</td>
<td>10.8 (8.1-22.5)</td>
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<tr>
<td>Diameter of largest liver lesion</td>
<td>3.8 (0-22.5)</td>
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<tr>
<td>% liver involvement</td>
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<tr>
<td>&lt; 20</td>
<td>3 (0-65) 5 (1) 3 (1)</td>
<td>452 (98)</td>
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<td>20-50</td>
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<td></td>
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<tr>
<td>&gt; 50</td>
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<tr>
<td>LDH</td>
<td>344 (39-8198)</td>
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<tr>
<td>ALP</td>
<td>89 (24-1178)</td>
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<tr>
<td>Disease free interval</td>
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<tr>
<td>OS (%), 95% CI</td>
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<td>M1a</td>
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<td>6</td>
<td>68 (62-74) 48 (39-57)</td>
<td>48</td>
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<td>12</td>
<td>38 (31-44) 17 (11-24)</td>
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<tr>
<td>24</td>
<td>14 (94-19) 5 (2-1)</td>
<td>5</td>
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<tr>
<td>M1b</td>
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<tr>
<td>6</td>
<td>45 (33-57) 8 (0-29)</td>
<td>8</td>
<td></td>
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<tr>
<td>12</td>
<td>19 (10-29) 0</td>
<td>0</td>
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<tr>
<td>24</td>
<td>78 (27-17) 0</td>
<td>0</td>
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</table>

Conclusions
Prognostic models in MUM remain imprecise in an externally validated dataset. Further validation is needed to find clinical utility

Clinical trial identification
not applicable
1240P - Impact of an active surveillance programme on outcome of patients (pts) with uveal melanoma (UM) after primary curative therapy (PTx): results of a single-institution experience

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Background
About 30% of pts with UM develop metastatic disease (MUM) despite PTx. Liver is by far the commonest site of metastases. MUM has poor prognosis and no systemic treatment (STx) has been proven to improve overall survival (OS). However, the role of active surveillance for metastatic disease is still controversial.

Methods
We performed an outcome analysis of all UM pts prospectively registered onto our active surveillance programme after PTx. All pts had systemic staging at initial diagnosis of UM and then 6-monthly liver imaging (CT triple-phase or ultrasound) and clinical review for the first 5 years and 12-monthly afterwards. Progression-free survival (PFS) was calculated from time of first systemic relapse to first disease progression, OS from time of first systemic relapse to death or latest FU.

Results
Out of 166 pts registered between April 2009 and April 2017, 36 (22%) developed MUM: 14 pts relapsed <2 yrs, 17 between 2 and 5 yrs, 5 >5 yrs from PTx. MUM pts characteristics: males 19 (53%); median age 58 (range 34-85); median tumour thickness at diagnosis 9mm (2-22); sites of metastases: liver only 13 (36%), liver + other sites 21 (58%), extra-hepatic only 2 (6%). Relapses were asymptomatic and detected on surveillance imaging in 29 (80%) pts. Nine pts (7 detected from surveillance) underwent primary hepatic metastasectomy (HM), 27 (75%) pts were non-resectable (NR) and underwent STx (n = 18), locoregional Tx (n = 4), best supportive care (n = 5). Overall, 29/36 MUM pts received immunotherapy with either ipilimumab or nivolumab/pembrolizumab. At a median FU of 36.5 mos (1-103), 27 pts have died and the median OS is 16.6 mos (95%CI: 7.8-25.3). Both PFS and OS were statistically significantly longer for HM pts compared to NR pts (PFS: 10.8 vs 4.4mos, p = 0.01/OS: 24.9 vs 13.4mos, p = 0.04). Eight out of 9 pts developed further disease relapse after HM.

Conclusions
Our data indicate that active surveillance after PTx of UM can allow detection of asymptomatic potentially resectable liver metastases, especially in pts with high risk UM (i.e. tumour thickness >5mm). Although durable remission after HM is rare PFS and OS may be significantly prolonged.
1241P - Impact of duration of response (DOR) on overall survival (OS) in patients with metastatic melanoma treated with dacarbazine (DTIC), vemurafenib (V), or cobimetinib plus vemurafenib (C+V): a pooled analysis

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E. McKenna (South San Francisco, United States of America) Q. Zhu (South San Francisco, United States of America)
Y. Mun (South San Francisco, United States of America) A. Hauschild (Kiel, Germany)

Background
Evaluation of treatment efficacy in oncology using OS is confounded by survival benefit from post-progression treatment. We pooled data from the BRIM-2, -3, -7, and coBRIM studies (BRAF inhibitor–naive patients with BRAF V600-mutated metastatic melanoma) to evaluate whether DOR could be a surrogate for OS.

Methods
Time-dependent Cox proportional hazards regression was used to model the association of DOR (interval from date of first RECIST response to progressive disease [PD] or death) with OS. The risk of death for DORs of 1–10 months (in 1-month increments) was evaluated. Patients with best response of stable disease or PD [nonresponders (NR)] were assigned a DOR of zero. Models were adjusted for time-fixed baseline covariates (ECOG status, demographics, disease covariates, and first-line treatment), and time-dependent covariates (DOR and post-progression treatment [immunotherapy, targeted therapy, or other]).

Results
This analysis included 1365 patients (DTIC = 338; V = 717; C+V = 310). Objective response was 47.5% for the overall population and 11.5%, 53.6%, and 72.9% for the DTIC, V, and C+V cohorts, respectively. Median DOR was 9.3 months in the overall population and 6.4, 7.6, and 14.6 months in the DTIC, V, and C+V cohorts, respectively. Cox proportional hazards adjusted for time-dependent covariates showed a significant and progressive reduction in the risk of death with increasing DOR vs NR. The absolute risk of death decreased by a mean of 6.3–7.7% per month increase in DOR in the overall population and across treatment cohorts (Table). Sensitivity analyses in responders only showed similar results.

<table>
<thead>
<tr>
<th>Patient cohort</th>
<th>DOR of 1 month HR (95% CI)</th>
<th>DOR of 10 months HR (95% CI)</th>
<th>Mean per month HR decrease</th>
<th>Range of HR decrease</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.85 (0.82–0.87)</td>
<td>0.19 (0.14–0.25)</td>
<td>0.073</td>
<td>0.034–0.130</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-value</td>
<td>Hazard Ratio</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>V</td>
<td>0.80 (0.77–0.84)</td>
<td>0.077</td>
<td>0.028–0.157 &lt;0.0001</td>
<td></td>
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<tr>
<td>C+V</td>
<td>0.89 (0.86–0.93)</td>
<td>0.063</td>
<td>0.039–0.095 &lt;0.0001</td>
<td></td>
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<tr>
<td>DTIC</td>
<td>0.81 (0.71–0.92)</td>
<td>0.076</td>
<td>0.029–0.154 0.0016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All responders</td>
<td>0.88 (0.85–0.90)</td>
<td>0.068</td>
<td>0.038–0.108 &lt;0.0001</td>
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<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
<th>Hazard Ratio</th>
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<tr>
<td>V</td>
<td>0.84 (0.80–0.88)</td>
<td>0.074</td>
<td>0.033–0.135 &lt;0.0001</td>
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<tr>
<td>C+V</td>
<td>0.91 (0.88–0.94)</td>
<td>0.059</td>
<td>0.039–0.086 &lt;0.0001</td>
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<tr>
<td>DTIC</td>
<td>0.87 (0.78–0.97)</td>
<td>0.069</td>
<td>0.037–0.111 0.0148</td>
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</table>

HR, hazard ratio.

a Association of DOR with risk of death.
b Patients with complete or partial response.

**Conclusions**

These exploratory analyses suggest that DOR is independently associated with OS outcomes regardless of treatment and merits further exploration as a surrogate endpoint to assess long-term treatment benefit.

**Legal entity responsible for the study**

F. Hoffmann-La Roche Ltd.

**Funding**

F. Hoffmann-LaRoche Ltd.

**Disclosure**

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1242P - Neutrophil to Lymphocyte Ratio (NLR) as an independent prognostic measure in patients receiving targeted therapy or immunotherapy for stage IV melanoma

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Background

Treatment of metastatic melanoma has rapidly evolved with the introduction of targeted and immunotherapies in recent years. An elevated NLR (neutrophil-lymphocyte ratio) has been shown to be an independent marker of poor prognosis in malignancies including melanoma. Here we present an updated survival analysis demonstrating the utility of NLR as a marker of prognosis in patients with metastatic melanoma receiving targeted and immunotherapy.

Methods

We identified patients with stage 4 melanoma who received systemic therapy with targeted therapy (BRAF +/- MEK inhibitor) or immunotherapy (Anti-CTLA-4 or Anti-PD-1) at our institution. Patients not receiving any systemic therapy were excluded. We retrospectively reviewed all medical records collecting data on baseline demographics, prognostic factors (stage, LDH, CNS and Liver metastases), treatments received, pre-treatment NLR and outcomes. Overall survival (OS) and Progression-free survival (PFS) were measured from date of first dose received.

Results

174 patients were treated between August 2010 to November 2016, 74 received targeting therapy and 100 receiving immunotherapy. Median follow up was 10 months. At time of interim analysis median OS for patients with NLR < 5 was 11.7 months compared to 4.8 months in NLR >5 (HR 0.45, 95% C.I. 0.31-0.67, p = 0.00007), this was seen in patients treated with both targeted therapies (HR 0.48, p = 0.012) and immunotherapies (HR 0.40, p = 0.0009). Median PFS was also longer in patients with NLR <5 4.8 vs. 3.6 months (HR 0.65, p = 0.02). Multivariate analysis including age, sex, M stage, baseline LDH and CNS/Liver metastases, demonstrated NLR was the strongest predictor of OS (HR 0.39 95% C.I. 0.25-0.60, p = 0.00002).

Conclusions

NLR >5 is a strong independent predictor of poor outcome in patients with metastatic melanoma regardless of targeted or immunotherapy. We hypothesis that at final data lock in July 2017 this association will remain strong given it was a clear predictor of outcome at the time of interim analysis. NLR may assist selection of initial therapy, for example, a favourable ratio may indicate suitability for single agent rather than doublet immunotherapy with its greater toxicity profile.

Legal entity responsible for the study

Alfred Health

Funding

None
Disclosures
All authors have declared no conflicts of interest.

1243P - The prognostic significance of distant metastasis free interval (DMFI) in BRAF mutant advanced melanoma patients treated with first line targeted therapy

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Background
Prognostic models are investigated for advanced melanoma patients treated with targeted therapy. This study aims to identify the relationship between DMFI and outcome of first line targeted therapy in BRAF mutant (BRAFmut) patients.

Methods
BRAFmut patients identified from 2 referral centres were assigned to 3 prognostic groups: A (PS 0, Metastatic sites ≤3, LDH normal, CNS not involved), B (PS 1, Metastatic sites ≤3, LDH >1-2ULN, CNS not involved), C (PS 2, Metastatic sites >3, LDH ≥2ULN, CNS involved or not). Factors analysed: Distant Metastasis Free Interval (DMFI from primary melanoma to first distant metastasis), Post Relapse Progression Free Survival (PRPFS post relapse to BRAFi), Post Relapse Survival (PRS), number of metastatic sites, LDH, CNS involvement, PS. Univariate and multivariate Cox regression analysis was used adjusted with the 3 prognostic groups. Statistical analysis with STATA/SE V13.0.

Results
From 380 advanced melanoma patients, 161 BRAFmut patients received first line BRAFi only (101) or BRAFi+MEKi (60). Patients relapsed from primary at a median DMFI 12 months (range 0-185) and were included in the 3 prognostic groups (Group A 27, Group B 72, Group C 56). To study DMFI significance, we defined 2 patient groups according to DMFI: DMFI <24 months Group 1, DMFI ≥24 months Group 2. Median PRPFS was 5 months for Group 1 and 8 months for Group 2 with statistically significant difference (HR = 1.45, 95%CI 1.01-2.09, p = 0.046). In multivariate analysis, DMFI also emerged as an independent prognostic factor (HR 1.44, 95% CI 0.99-2.10, p = 0.059). Prognostic Group (C vs A), number of metastatic sites (≥3 vs < 3), PS (0 vs 1-2), and LDH (>2ULN vs normal) were confirmed as independent prognostic factors for PRPFS and PRS. ROC analysis on progression showed best DMFI cut-off at 26 months (9 vs 5), HR 1.6 (95%CI 1.10-2.33), p = 0.014 [sen 46.2%, spec 69.6%]. No difference in median PRS between the 2 groups (14 vs 16 months, p = 0.517), possibly reflecting effect of therapies after BRAFi.

Conclusions
Patients with BRAFmut advanced melanoma and DMFI <2 years have significantly worse post relapse PFS after first line targeted therapy. Our results indicate DMFI as an independent prognostic factor for BRAFmut patients.

Legal entity responsible for the study
A’ Oncology Dept, Metropolitan Hospital

Funding
None

Disclosure
All authors have declared no conflicts of interest.
Background
Part 1 of the COLUMBUS study demonstrated that the BRAF inhibitor ENCO 450 mg once daily (QD) + the MEK inhibitor BINI 45 mg twice daily (BID; COMBO450) improved progression-free survival vs VEM 960 mg BID alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced BRAF V600−mutant melanoma. Tolerability of COMBO450 was favorable compared with VEM or ENCO300. Here we evaluate resource utilization based on hospitalization data (ClinicalTrials.gov, NCT01909453; EudraCT, 2013-001176-38).

Methods
Pts were randomized 1:1:1 to receive COMBO450, VEM, or ENCO300. Efficacy endpoints, including the number of pts hospitalized and number of hospitalizations, were described. Time to first occurrence of hospitalization was assessed by the Kaplan-Meier method. Hospitalization endpoints were adjusted per 100 pt-months (pt-mo) of exposure to study drug.

Results
Among 577 pts, 192 were randomized to COMBO450, 191 were randomized to VEM, and 194 were randomized ENCO300. Exposure-adjusted hospitalization rates (per 100 pt-mo) were 3.5% in the COMBO450 arm compared with 4.3% and 6.2% in the ENCO300 and VEM arms, respectively. Exposure-adjusted mean duration of hospitalization per 100 pt-mo was 32.5, 38.2, and 53.7 days in the COMBO450, ENCO300, and VEM arms, respectively. Median (95% CI) time to first hospitalization for pts with ≥1 event was 5.1 (2.6–6.1) mo in the COMBO450 arm compared with 2.8 (0.8–4.2) and 2.8 (2.0–3.8) mo in the ENCO300 and VEM arms, respectively.

Conclusions
Resource utilization, as determined by hospitalization data in COLUMBUS Part 1, was lower with COMBO450 compared with VEM or ENCO300 monotherapy.
A. Arance: Honoraria from and consulting/advisory role and speakers bureaus for Novartis, Roche, MSD, and Bristol-Myers Squibb; travel expenses from Roche and Bristol-Myers Squibb. R. Dummer: Honoraria from and consulting/advisory role for Roche, Bristol-Myers Squibb, GSK, MSD, Novartis, and Amgen; research funding from Roche, Bristol-Myers Squibb, GSK, MSD, and Novartis. P.A. Ascierto: Consulting fees from Bristol-Myers Squibb, Roche/Genentech, MSD, Ventana, Novartis, Amgen, and Array BioPharma; research funding from Bristol-Myers Squibb, Roche/Genentech, Ventana, and Array BioPharma. H. Gogas: Consultant for Roche, Bristol-Myers Squibb, MSD, Novartis, and Amgen. M. Mandala: Honoraria from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureaus for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, and Bristol-Myers Squibb; research funding from Roche. C. Garbe: Honoraria and travel expenses from and served in a consulting/advisory role and as speakers bureau member for Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche, and Philogen; has received research funding for University Hospital Tuebingen from Bristol-Myers Squibb, Novartis, and Roche. D. Schadendorf: Honoraria and travel expenses from and consulting/advisory role and speakers bureaus for Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD; research funding for University Hospital Essen from Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD. I. Krajsrová: Advisory board member for Bristol-Myers Squibb, Novartis, Roche, MSD; travel expenses from Bristol-Myers Squibb and MSD. R. Gutzmer: Consulting fees and/or honoraria from Roche, Bristol-Myers Squibb, MSD, GSK, Novartis, Almirall, LEO, Amgen, Pfizer, Pierre Fabre, Merck Serono, Boehringer Ingelheim; research funding from Roche, Novartis, Pfizer, Johnson & Johnson; travel expenses from Bristol-Myers Squibb, Roche. V. Chiarion Sileni: Honoraria received from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureaus for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, Bristol-Myers Squibb, and Roche. J.W.B. de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, Bristol-Myers Squibb, GSK, MSD, and Merck Serono N. Yamazaki: Advisory role for Chugai Pharma, Bristol-Myers Squibb Japan, and Ono Pharmaceutical; honoraria from Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstraZeneca Japan, Boehringer Ingelheim, and Maruho C. Loquai: Advisory board member for Roche, Novartis, Bristol-Myers Squibb, MSD, BioNTech, Pierre Fabre, and Amgen; speakers fees from Roche, Novartis, Bristol-Myers Squibb, and MSD; travel expenses from Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. L.A. de Parseval: Employee of Novartis Pharma AG; may own stock or stock options M. Pickard: Employee of Array BioPharma; may own stock or stock options V. Sandor: Employee/leadership role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp. C. Robert: Consultant for Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. K.T. Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis. All other authors have declared no conflicts of interest.

1245P - Quality-of-life (QoL) in COLUMBUS part 1: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in braf-mutant melanoma

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Background

In COLUMBUS Part 1, the BRAF inhibitor ENCO 450 mg once daily (QD) + the mitogen-activated protein kinase kinase (MEK) inhibitor BINI 45 mg twice daily (BID; COMBO450) improved progression-free survival vs VEM 960 mg BID alone and ENCO 300 mg QD (ENCO300) alone in patients (pts) with advanced BRAF V600-mutant melanoma. Tolerability of COMBO450 was favorable compared with VEM or ENCO300. Here we compare patient-reported health-related QoL between the treatment arms.

Methods

Pts were randomized 1:1:1 to receive COMBO450, VEM, or ENCO300. Patient-reported health-related QoL was assessed by 2 validated instruments, the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) questionnaire and the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). Higher scores represent better QoL on both instruments. A mixed-effect model for repeated measures was used to compare the change from baseline (BL) in the domain scores over time.

Results

Among 577 pts, 192 were randomized to COMBO450, 191 were randomized to VEM, and 194 were randomized ENCO300. Compliance of pts completing the FACT-M and EORTC QLQ-C30 questionnaires was equivalent; approximately 80%–90% of pts still at risk completed the assessment from BL through cycle 25. Mean BL FACT-M scores were similar between arms (52.39, 52.01, and 52.84 in the COMBO450, VEM, and ENCO300 arms, respectively). FACT-M subscale change over time indicated that COMBO450 was associated with an estimated 2.98 point higher post-BL score vs VEM (95% confidence interval [CI] 1.34–4.63) and a 4.01 pt higher post-BL score vs ENCO300 (95% CI 2.47–5.54). Mean EORTC QLQ-C30 scores at BL were 66.72, 64.74, and 66.10 with COMBO450, VEM, and ENCO300, respectively. Evaluation of change over time found that COMBO450 was associated with an estimated 5.25 point higher post-BL score vs VEM (95% CI 1.21–9.29) and an 8.32 higher post-BL score vs ENCO300 (95% CI 4.54–12.11).

Conclusions

Patient-reported health-related QoL was rated consistently and significantly better with COMBO450 vs VEM or ENCO monotherapy.

Clinical trial identification

Trial protocol number, CMEK162B2301 (release date, July 13, 2015)

Legal entity responsible for the study

Array BioPharma Inc

Funding

Array BioPharma Inc and Novartis Pharmaceuticals Corporation

Disclosure
H. Gogas: Consultant for Roche, Bristol-Myers Squibb, MSD, Novartis, and Amgen. R. Dummer: Honoraria from and consulting/advisory role for Roche, Bristol-Myers Squibb, GSK, MSD, Novartis, and Amgen; research funding from Roche, Bristol-Myers Squibb, GSK, MSD, and Novartis. P.A. Ascierto: Consulting fees from Bristol-Myers Squibb, Roche/Genentech, MSD, Ventana, Novartis, Amgen, and Array BioPharma; research funding from Bristol-Myers Squibb, Roche/Genentech, Ventana, and Array BioPharma. A. Arance: Honoraria from and consulting/advisory role and speakers bureau for Novartis, Roche, MSD, and Bristol-Myers Squibb; travel expenses from Roche and Bristol-Myers Squibb. M. Mandala: Honoraria from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, and Bristol-Myers Squibb; research funding from Roche. C. Garbe: Honoraria and travel expenses from and served in a consulting/advisory role and speakers bureau member for Amgen, Bristol-Myers Squibb, MSD, Novartis, Roche, and Philogen; has received research funding for University Hospital Tübingen from Bristol-Myers Squibb, Novartis, and Roche. D. Schadendorf: Honoraria and travel expenses from and consulting/advisory role and speakers bureau for Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD; research funding for University Hospital Essen from Amgen, Bristol-Myers Squibb, Novartis, Roche, and MSD. I. Krajsová: Advisory board member for Bristol-Myers Squibb, Novartis, Roche, and MSD; travel expenses from Bristol-Myers Squibb and MSD. R. Gutzmer: Consulting fees and/or honoraria from Roche, Bristol-Myers Squibb, MSD, GSK, Novartis, Almirall, LEO, Amgen, Pfizer, Pierre Fabre Merck Serono, Boehringer Ingelheim; research funding from Roche, Novartis, Pfizer, Johnson & Johnson; travel expenses from Bristol-Myers Squibb, Roche. V. Chiarion Sileni: Honoraria received from Novartis, GSK, Bristol-Myers Squibb, MSD, and Roche; speakers bureau for Novartis, GSK, Roche, and Bristol-Myers Squibb; advisory board member for Novartis, Amgen, MSD, Bristol-Myers Squibb, and Roche. J.W.B. de Groot: Consulting/advisory role for Amgen, Bayer, Celgene, Roche, Bristol-Myers Squibb, GSK, MSD, and Merck Serono. N. Yamazaki: Advisory role for Chugai Pharma, Bristol-Myers Squibb Japan, and Ono Pharmaceutical; honoraria from Chugai Pharma, Bristol-Myers Squibb Japan, Ono Pharmaceutical, GlaxoSmithKline, Takeda, AstraZeneca Japan, Boehringer Ingelheim, and Maruho. C. Loquai: Advisory board member for Roche, Novartis, Bristol-Myers Squibb, MSD, Biotech, Amgen, and Pierre Fabre; speakers fees from Roche, Novartis, Bristol-Myers Squibb, and MSD; travel expenses from Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. L.A. de Parseval: Employee of Novartis Pharma AG; may own stock or stock options. M. Pickard: Employee of Array BioPharma; may own stock or stock options. V. Sandor: Employee/leadership role at Array BioPharma; stock or other ownership of Array BioPharma and Incyte Corp. C. Robert: Consultant for Roche, Novartis, Bristol-Myers Squibb, MSD, and Amgen. K.T. Flaherty: Honoraria from and consulting/advisory role for Novartis and Array BioPharma; research funding from Novartis. All other authors have declared no conflicts of interest.

1246P - Loss of USP28 drives resistance to BRAF targeted therapy in melanoma

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V. Serra (Barcelona, Spain) P. J. Eichhorn (Singapore, Singapore)
Background
Metastatic melanoma is a lethal malignancy leading to an estimated 65,000 deaths annually worldwide. The serine threonine kinase BRAF is mutated in 40-60% of all melanoma patients frequently at a single hotspot BRAF V600E, which results in hyperactivation of MAPK pathway. RAF kinase inhibitors are clinically active in patients with BRAF (V600E) mutant melanoma. However, rarely do tumours regress completely with the majority of responses being partial and short-lived. Several mechanisms of resistance to RAF inhibitors have been suggested in melanoma. In addition to somatic genomic alterations recent studies have revealed the importance of ubiquitination in the role of MAPK signaling. Yet very little is known about the deubiquitinating enzymes that counteract ubiquitination mediated functions. Our study identified loss of deubiquitinating enzyme, USP28 as a novel mechanism of resistance to vemurafenib in BRAF mutant melanoma.

Methods
A genome wide shRNA screen targeting all known deubiquitinating enzymes was performed and level of phosphorylated ERK as the representative of MAPK pathway was assessed by western blotting. Significant hits of the screen were validated and mechanism of action in regulation of MAPK pathway and resistance to MAPK inhibitors in melanoma has been investigated.

Results
Using a functional RNAi screen targeting all known human deubiquitinating enzymes, we identified USP28 as a critical regulator of MAPK pathway. It is known that USP28 binds to and stabilizes the E3 ligase substrate recognition subunit, FBW7 to regulate stability of various proteins. We showed that the USP28/FBW7 complex directly ubiquitinates BRAF and targets BRAF for ubiquitin mediated degradation. Importantly, TCGA datasets indicates that USP28 is deleted in 9% of melanoma patients. Using Kaplan-Meier analysis, we showed that loss of USP28 confers poorer overall survival in melanoma patients. We showed that loss of USP28 enhances MAPK activity through the stabilization of BRAF. Our results revealed the Loss of USP28 drives resistance to RAF inhibitor therapy in BRAF(V600E) tumors both in vitro and in vivo.

Conclusions
Taken together we showed loss of USP28 as a potential biomarker for MAPK activation and vemurafenib resistance in BRAF 600E mutant melanoma.

Legal entity responsible for the study
National University of Singapore

Funding
Cancer Science Institute of Singapore, National University of Singapore

Disclosure
All authors have declared no conflicts of interest.

1247P - Patterns of progression in metastatic melanoma patients treated with Braf and Mek inhibitors: an Italian Melanoma Intergroup (IMI) study
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Background
Patterns of progression after BRAF+MEK inhibitors (I) could help clinicians in understanding the best treatment strategy among the multiple available options in the BRAFv600 melanoma setting. We analysed outcomes in patients (pts) treated with BRAF+MEK I to characterize pts with rapid progression.

Methods
In this multicenter retrospective analisis, 164 consecutive pts affected by BRAFv600 metastatic melanoma and treated with BRAF+MEK I from February 2012 to April 2017 were included.

Results
Overall, 164 patients were enrolled. Baseline LDH was elevated in 68 (41%) pts, baseline number of metastatic organs were 1, 2, 3 and more in 52 (32%), 52 (32%), 29 (18%), and 32 (19%) pts. BRAF+MEK I administered were dabrafenib+trametinib in 151 pts and vemurafenib+cobimetinib in 13 pts, and they were administered in first line in 129 (79%) pts. Best response was CR, PR, SD and PD in 27 (16%), 87 (53%), 17 (10%) and 27 (16%) pts. On cutoff date, progression was observed in 104 (63%) pts; 60 (37%) pts still on treatment. mPFS was 9.83 (1-54.7+) months: significant difference in PFS was showed in pts with normal baseline LDH or high LDH (13.2 vs 6.3 months, p < 0.0001), and in pts with number of metastatic organs lower or higher then 2 (13.4 vs 7 months, p < 0.0001). mOS was 18.3(1-62.5+) months: significant difference in OS was showed in pts with normal baseline LDH or high LDH had (24.7 vs 10 months, p < 0.0006), and in pts with number of metastatic organs lower or higher then 2 (25.9 vs 10 months, p < 0.0003).

Among 104 progressed pts, 72 (69%) pts died, mOS after progression was 2.5 months (0.5-42+ months); Subsequent treatments were administered in 44 (42%) pts. Duration of response (DR) was defined as time from BRAF+MEK I best response to progression of disease. Significant difference in OS after BRAF+MEK I progression was observed in pts with DR < 6 months(77 pts -74%) or > 6 months (27 pts - 26%) (2 vs 8.3 months, p < 0.0023) and in pts with number of metastatic organs after progression lower or higher then 3 (4.5 vs 2 months, p < 0.022).

Conclusions
DR and extension of progression during BRAF+MEK I are factors that can be useful to identify pts with lower OS after progression, in addiction to known parameters like LDH and baseline number of metastatic organs.

Legal entity responsible for the study
IMI
Funding
None
Disclosure
R. Marconcini: Received payment for consultancy and honoraria for speaking from Bristol-Myers Squibb, MSD, Roche, Novartis. All other authors have declared no conflicts of interest.

1248P - Tumor-stroma interactions as a determinant of drug resistance in BRAF-mut melanoma

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Background
In BRAF-mut melanoma combined BRAF/MEK inhibition increases survival; however, pharmacological effects on the genetically “normal” tumor microenvironment (i.e. paradox MAPK activation) may set the stage for the development of drug resistance.

Methods
GFP-labeled cutaneous fibroblasts (HFF) were co-cultured with melanoma cells, in the presence or absence of direct cell-cell contact, and response to Dabrafenib (D) and Trametinib (T), alone or combined, was monitored over time. SEMA6A and AXL were preliminarily evaluated as potential mediators of such interactions.

Results
HFF significantly protected (60-100% protection at the lowest two drug concentrations) BRAF-mut M14 melanoma cells from the growth inhibitory activity of D and T, alone or combined; however, combined D+T at the highest concentrations overcame stroma-mediated protection and eliminated both cell populations. Thus, combined BRAF/MEK inhibition resulted in strongly synergistic interactions, as compared to single agent treatments, only under co-culture conditions (CI 0.6 and 0.2 for M14 and HFF cells, respectively). Protective melanoma/stroma interactions were mediated by direct cell-cell contact, as co-cultures in trans-well Boyden chambers or isolated cultures using conditioned medium (HFF-conditioned medium for M14; M14-conditioned medium for HFF), did not affect pharmacological response. As SEMA6A expression is tightly controlled by MAPK and AXL mediates resistance to MAPK inhibition in melanoma, we assessed their potential as mediators of stroma-mediated melanoma protection: interestingly, SEMA6A and AXL expression in a panel of melanoma cell lines were inversely correlated; moreover, in cell lines derived by primary and cutaneous metastases of the same patient, AXL expression was upregulated at the mRNA and protein level in cells derived from metastatic lesions.

Conclusions
Tumor-stroma interactions protect BRAF-mut melanoma from MAPK inhibition; such functional protection is mediated by cell-cell contact. SEMA6A and AXL are possible mediators of this interaction and their reciprocal relationships are being studied in melanoma cell line models and clinical series.

Legal entity responsible for the study
Regina Elena Cancer Institute- San Gallicano Dermatologic Institute

Funding
AIRC (18622-14362-9979)

Disclosure
All authors have declared no conflicts of interest.

1249P - Extended survival analysis of ipilimumab for the treatment of advanced malignant melanoma in pretreated patients: Five-year long-term follow-up of the South African expanded access program

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Background
Ipilimumab is a human monoclonal IgG1 antibody against CTLA-4 that has been shown to prolong the overall survival of patients with advanced pretreated melanoma. In 2015, a retrospective, multi-centre, non-interventional analysis was performed on data collected from the ipilimumab expanded access programme in South Africa, with last follow-up date (or death) in December 2014. The current study extends this analysis by follow-up on the long-term survival of pre-treated metastatic patients up to September 2016.

Methods
Follow-up questions were sent to participating investigators, who had patients who were still alive (29) or for whom it was not known whether they were still alive (11) following the last ipilimumab infusion. Investigators had to confirm whether patients were still alive, the date of death or last contact, clinical response at last contact, and whether the patient was still responding to ipilimumab.

Results
Of the 108 patients, 84 (78%) had cutaneous melanoma and 24 patients (22%) had non-cutaneous melanoma, including uveal, mucosal, and melanoma of unknown primary. Twenty patients previously received two or more lines of treatment for metastatic melanoma. The median age was 59 years (range 27 – 86) and there were 73 (68%) males and 35 (32%) females. Baseline ECOG PS was 0 in 33%, PS 1 in 58% and PS 2 in 6% of patients. The longest follow-up time available was 5.4 years. The median OS was 9.36 months (95% CI 7.48 – 11.84). One-year survival was 39% (95% CI 29% - 48%), 2-year survival was 22% (95% CI 15% - 30%), 3-year survival was 19% (95% CI 12% - 27%), 4- and 5-year survival was 15% (95% CI 8% - 21%). In the group of cutaneous melanoma patients, the 4- and 5-year survival was 17% (95% CI 9% - 25%) while in the non-cutaneous group the 4- and 5-year survival was 6% (95% CI 0% - 16%).

Conclusions
Ipilimumab at a dose of 3mg/kg is an effective treatment for patients with pre-treated advanced (unresectable or metastatic) melanoma and is associated with durable remissions and long-term survival.

Clinical trial identification
Protocol number: CA184-515 Ethics approval extended on protocol REC 2/21/05/14

Legal entity responsible for the study
Dr Bernardo L Rapoport

Funding
Investigator Sponsored Research (ISR) trough Bristol-Myers Squibb

Disclosure
H. Duvenhage: Head of Medical at Bristol-Myers Squibb All other authors have declared no conflicts of interest.

1250P - Real-world use of ipilimumab and nivolumab monotherapy or in combination in patients with advanced melanoma: results from a retrospective chart review

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C. Atzinger (Bethesda, United States of America)K. Gupte-Singh (Princeton, United States of America)
C. Solem (Bethesda, United States of America)S. Rao (Princeton, United States of America)
Background
The advanced melanoma treatment landscape has significantly changed with approval of ipilimumab (IPI) and nivolumab (NIVO). This analysis aimed to describe real-world characteristics and treatment patterns of patients (pts) prescribed IPI, NIVO, or NIVO+IPI.

Methods
This interim analysis of an observational, retrospective, multisite study collected data for US pts diagnosed with unresectable or metastatic melanoma who received IPI, NIVO, or NIVO+IPI (index) between January 2015 and May 2016. Demographics and treatment patterns were abstracted from medical records through most recent visit (≥6 months). Data were descriptively reported.

Results
Of 115 pts from 20 sites in the USA, 43 received IPI (mean±SD age 61.5±11.3 years, 51.2% female, 86.0% ECOG PS ≤ 1), 41 NIVO (age 65.9±13.7 years, 48.8% female, 90.3% ECOG PS ≤ 1), and 31 NIVO+IPI (age 57.1±11.3 years, 48.4% female, 100% ECOG PS ≤ 1). Tests for BRAF and PD-L1 were conducted in 98.3% and 39.1% of pts, respectively; 14.3%, 6.7%, and 12.2% of tested IPI, NIVO, and NIVO+IPI patients had a BRAF mutation, and 60%, 50%, and 79.0% of IPI, NIVO, and NIVO+IPI patients had a positive PD-L1 status. The index treatment was first line for 98.3% of pts; mean±SD days from advanced diagnosis to treatment initiation was 21.5±16.1 days for IPI, 55.1±68.6 for NIVO, and 41.5±68.6 for NIVO+IPI. The most common rationales for treatment initiation across treatments were improved efficacy (73.9%) and documented survival benefit (44.4%). Dose delays occurred in 9.3% of IPI pts (mean delay 12.7 days) and 6.5% of NIVO pts (mean delay 45 days); no NIVO+IPI pts had dose delays. At 6 months, 16% of pts remained on IPI, 85% remained on NIVO, and 71% remained on the NIVO portion of the NIVO+IPI regimen. Permanent discontinuation of treatment prior to completing planned courses of therapy was relatively infrequent (IPI: 16%, NIVO: 26%, NIVO+IPI: 19%), possibly reflecting improved experience in toxicity assessment and management.

Conclusions
Within this real-world cohort, a minority of pts discontinued NIVO or NIVO+IPI by 6 months. This research sheds light on current treatment patterns for IPI, NIVO, and their combination.

Clinical trial identification
CA209-983

Legal entity responsible for the study
Bristol-Myers Squibb

Funding
Bristol-Myers Squibb

Disclosure
A. Tarhini: Served as a consultant or advisor for Bristol-Myers Squibb; received institutional research funding from Amgen, Bristol-Myers Squibb, Incyte, MSD, Novartis, and Prometheus Laboratories. C. Macahilig: Employed by Medical Data Analytics, where she provides study design and data collection. C. Atzinger: Received personal fees from Bristol-Myers Squibb; employee of Pharmerit International. K. Gupte-Singh: Employee of Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squib. C. Solem: Institution received consulting fees from Bristol-Myers Squibb to conduct this research. S. Rao: Employed of Bristol-Myers Squibb and has stock/ownership in Bristol-Myers Squib.
Background
Neutrophil-to-lymphocyte ratio (N/L) was shown to be prognostic in several solid malignancies. There are limited data about changes of N/L ratios during immunotherapy. The aim of the study was to assess a clinical value of this ratio and its association with tumour response in patients with advanced melanoma.

Methods
Between June 2011 and March 2017, 308 patients with metastatic/unresectable melanoma were included in the analysis. Patients' age was 58.4±17.3 years (mean), 43 cases had brain metastases. BRAF mutation was present in 107 cases, and 98 patients with positive mutation received targeted therapies with BRAF+/- MEK followed by ipilimumab and/or anti-PD1 therapy. Patients with BRAF negative mutation received immunotherapy (pembrolizumab or nivolumab with/without ipilimumab). In all patients the N/L ratio was assessed at the baseline and monitored during treatment until disease progression or last observation. The cut off for ratio N/L was set at 3. Logistic GEE and Kaplan-Meier survival probability estimation were used for analysis.

Results
N/L ratio ≥3 at baseline was significantly associated with poorer overall survival (OS) (p < 0.001 in log-rank test). Median overall survival time was 25.8 months (95%CI 20.4-31.2) for N/L ratio <3 vs. 14.0 months (95%CI 10.7-17.3) for N/L ratio ≥3. In repeated measurements analysis, increased N/L ratio was significantly associated the confirmed disease progression, both in univariate random effect model (p < 0.001) and multivariate model adjusted for age, gender, presence of BRAF mutation and LDH>URL (p < 0.001). N/L ratio in all 6 patient who had pseudo-progression on immunotherapy was not elevated over time.

Conclusions
Our results confirm the usefulness of N/L ratio as a prognostic and predictive marker in patients with metastatic melanoma, and monitoring of the N/L ratio over immunotherapy may be helpful for assessment of the disease progression, response, as well as pseudoprogression, thus likely contributes to an optimization of treatment and resource allocation in patients with metastatic melanoma.

Clinical trial identification
not applicable

Legal entity responsible for the study
Maria Sklodowska-Curie Institute and Oncology Center, Warsaw, Poland

Funding
None

Disclosure
Background

T-VEC is the first FDA-approved oncolytic immunotherapy designed to activate antitumor immune responses. Pembro is a mAb against human programmed death receptor-1 that can stimulate inactivated anticancer T cells and is approved for the treatment (tx) of SCCHN. This combination of agents may further enhance antitumor immune response. This phase 1b/3 study will evaluate the safety and efficacy of T-VEC and pembro in patients (pts) with R/M SCCHN progressing after platinum (NCT02626000).

Methods

The primary objective for phase 1b is to assess dose-limiting toxicities (DLTs). Key secondary objectives include objective response rate, best overall response, and safety. Key eligibility criteria include histologically confirmed R/M SCCHN unsuitable for resection/radiotherapy, progressing after platinum tx, and injectable lesions. T-VEC was given by intralesional injection ≤ 8 mL of 10^6 PFU/mL on day 1, then after 3 w, ≤ 8 mL of 10^8 PFU/mL Q3W; pembro was given IV at 200 mg Q3W. Approximately 18 pts in the safety cohort and an additional 22 pts for long-term safety and efficacy will be enrolled into phase 1b.

Results

28 pts have been enrolled; 16 are DLT evaluable: 12 (75%) male, median age 57.5 y (range: 35, 77), ECOG 1 (75%). There was a DLT in 1 pt after 2 doses of both drugs: fatal arterial hemorrhage (AH). Grade 3/4 AEs were seen in 6 (38%) of pts - none led to tx discontinuation. There were 2 grade 5 AEs: AH (DLT) and disease progression. Incidence of SAEs possibly related to T-VEC was 5 (31.3%: chills, pyrexia, stridor, odynophagia, AH) and to pembro was 2 (12.5%: eczema, pyrexia) - none led to tx discontinuation.

Table: 1252P

<table>
<thead>
<tr>
<th></th>
<th>All DLT Evaluable* (N = 16)</th>
<th>Non-DLT Evaluable (N = 12)</th>
<th>All Pts (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tx-emergent AEs</td>
<td>15 (93.8)</td>
<td>11 (91.7)</td>
<td>26 (92.9)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (31.2)</td>
<td>2 (16.7)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (6.3)</td>
<td>1 (8.3)</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>
Grade 5  2 (12.5)  7 (58.3)  9 (32.1)
AEs related to T-VEC
Grade 3  4 (25)  1 (8.3)  5 (17.9)
Grade 4  0 (0)  0 (0)  0 (0)
AEs related to pembro
Grade 3  1 (6.3)  1 (8.3)  2 (7.1)
Grade 4  0 (0)  0 (0)  0 (0)

* To be DLT evaluable, pt must have had ≥ 6 w of follow up from the initial dosing and have received ≥ 2 doses of T-VEC and pembro in combination, or have a DLT during the DLT evaluation period after at least 1 dose of T-VEC and pembro.

Conclusions
There was 1 DLT of 16 evaluable pts. The combination regimen was deemed safe to continue into the phase 1b efficacy portion. The protocol was amended to exclude pts who have received reirradiation to the neck and are at high risk for AH.

Clinical trial identification
NCT02626000

Legal entity responsible for the study
Amgen Inc.

Funding
Amgen Inc. and Merck

Disclosure
K. Harrington: Corporate-sponsored research from AstraZeneca, Merck Sharp Dohme; Consulting fees from Amgen, AstraZeneca, Bristol-Myers Squib, Merck, Merck Sharp Dohme, Pfizer; Speakers Bureau from Amgen, AstraZeneca, Bristol-Myers Squib, Merck, Merck Sharp Dohme. S. Treichel, J.J. Kim: Employee and stock shareholder of Amgen Inc. J. Cheng: Employee and stock shareholder of Merck. J. Chesney: Consulting fees from Amgen Inc. All other authors have declared no conflicts of interest.

1253P - Characteristics of metastatic melanoma (MM) patients with leptomeningeal disease (LMD) and survival of > 1 year

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Background
Several studies have demonstrated that the presence of LMD correlates with very short overall survival (OS) in metastatic melanoma patients (pts). However, a subset of pts have OS > 12 months (mts). We reviewed the outcomes of a large cohort of patients with LMD to identify predictors of improved outcomes.

Methods
The clinical features, treatments, and OS of MM pts diagnosed with LMD by CSF cytology and/or radiographic findings from 2000 to 2015 were reviewed. Landmark Cox
proportional hazard regression models were used to identify factors significantly associated with OS > 12 mts.

**Results**

178 pts with LMD were identified. For these, median age at diagnosis (dx) was 51.2 years, 62% were male, 75% pts had a performance status of ECOG 0-1, 39% had elevated LDH, extracranial disease present in 75% and concurrent brain metastasis in 77%. 56% of pts were tested for BRAF mutation, and 37% (of those tested?) were positive. 61% of pts had CSF analysis done, but 49% of these had positive cytology. Neurological deficits were reported in 49%. Median OS from LMD diagnosis was 4.27 mts (95%CI: 3.12-5.55), and 12-, 36-, and 60-mts cumulative OS was 0.22 (95%CI: 0.163-0.290), 0.11 (95%CI: 0.069-0.169), and 0.09 (95% CI: 0.054-0.151), respectively. Compared to those who died within 3 mts, pts who lived longer than 12 mts (n = 36) were more likely to have: ECOG of 0 (57.1% versus 15.3%), previous surgery (55.6% versus 25.3%), systemic disease controlled (41.7% versus 33.3), intrathecal therapy (69.4% versus 21.6%), systemic therapy with targeted therapy (55.6% versus 18.9%) or chemotherapy (61.1% versus 37.8%); and were less likely to have neurological deficits (27.8% versus 62.7%), previous systemic therapy (63.9% versus 88.0%), and LDH above normal (19.4% versus 45.9%). Positive CSF cytology (HR = 3.06, 95% CI 1.02-9.17) and concomitant systemic disease (HR = 2.65, 95%CI 1.03-6.82) were associated with significantly shorter OS.

**Conclusions**

Long term survival in MM pts with LMD is rare, but possible. Features significantly associated with OS may help strengthen the design and interpretation of future trials for pts with LMD.

**Legal entity responsible for the study**

Isabella C Glitza

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

1254P - Tolerance and outcomes of stereotactic radiosurgery combined with anti-PD1 (pembrolizumab) for melanoma brain metastases

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**Background**

Anti-PD1 antibodies are currently the first-line treatment for patients with metastatic BRAF wild-type melanoma, alone or combined with the anti-CTLA4 mAb, ipilimumab. To date, data on safety and the outcomes of patients treated with the anti-PD1 mAbs, pembrolizumab (PB) or nivolumab, combined with stereotactic radiosurgery (SRS) for melanoma brain metastases (MBM) are lacking.

**Methods**

Patients with MBM treated with PB combined with SRS between 2012 and 2015 were retrospectively reviewed. The primary endpoint was neurotoxicity. The secondary endpoints were local control, distant intracranial control and overall survival (OS).
Results
Among 74 patients with MBM treated with SRS, 25 patients with a total of 58 MBM treated with PB combined with SRS within 6 months were included. Radionecrosis, occurring within a median time of 6.5 months, was observed in four metastases (6.8%) in four different patients. No significant other SRS-related adverse event had been reported. After a median follow-up of 8.4 months, local control had been achieved in 46 metastases (80%). The median time to local progression was 2 months. Perilesional oedema and intratumour haemorrhage appearing or increasing after SRS were mostly associated with local progression (P < 0.001). Median OS was 15.3 months (95% CI 4.6-26). The timing between SRS and PB administration did not seem to influence radionecrosis, intracranial control or OS.

Conclusions
SRS combined with PB was well tolerated and achieved high local control as recently described with SRS and nivolumab. Prolonged OS were achieved compared to that currently yielded with recommended treatments. Prospective studies are required to confirm these results and define the best timing between SRS and PB for the management of MBM.

Legal entity responsible for the study
Caroline Robert, Gustave Roussy

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1255P - Dabrafenib and Trametinib combination in real life patients including brain metastases: French experience within MelBase

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Background
Combining BRAF and MEK inhibitors is a standard of care in BRAF-mutated advanced melanoma patients. Dabrafenib (D) and Trametinib (T) have led to a 3-year overall survival (OS) rate around 44% in patients without active brain metastases (BMs) at enrollment. Recently, T received French Health Authority approval but little information is available in D+T combination use in real life, especially with active BMs patients. We report the first results of efficacy and tolerance in real life patients treated with D+T, including BMs, within national French MelBase cohort.

Methods
MelBase is a French multicentric clinical biobank dedicated to the prospective follow-up (FU) of adults with unresectable stage III or stage IV melanoma. Since March 2013, 1168 patients were included (26 centers). Available data were collected (April 2017) and analyzed (demography, OS, progression-free survival (PFS), response rate, safety).
Results

2 groups are presented: all patients treated with D+T (g1) and patients with BMs treated with D+T (g2). The characteristics at baseline are: - g1 (n = 135): mean age 57 years, PS 0-1 87%, elevated LDH 33%, BRAF V600E mutated 78%, brain metastases 29%, treated in first line 79%. After median FU 11.2 months, median OS and PFS were respectively 17.8 months (95%CI: 15.5-Not Reached (NR)) and 8.1 months (95%CI: 6.2-11.2). Best overall response (BORR) was 63% and disease control rate (DCR) 79%. - g2 (n = 39): mean age 55 years, PS 0-1 87%, elevated LDH 46%, BRAF V600E mutated 72%, treated in first line 73%. After median FU 10.3 months, median OS and PFS were respectively 15.5 months (95%CI: 13.3-NR) and 5.9 months (95%CI: 4.3-10.7). BORR was 56% and DCR 72%.

Conclusions

We report the first real life D+T data in France. Even though our results still need to mature with a longer FU, BORR is similar to COMBI-d updated data (63% g1 versus 69%). In addition, our results point out for the first time D+T efficacy in patients with active BMs. Indeed the combination appears more efficient in patients with BMs compared to D alone in already published clinical data (BREAK-MB).

Legal entity responsible for the study

Assistance Publique des Hôpitaux de Paris (AP-HP), Direction Clinique de la Recherche et de l'Innovation (DRCI)

Funding

French National Cancer Institute (INCa), Novartis, Roche, Bristol-Myers Squib, MSD

Disclosure

C. Allayous: Travel, accommodations, expenses: Amgen, Bristol-Myers Squib, Roche. S. Dalac Rat: - Consulting or advisory role: Roche - Travel, accommodations, expenses: Roche, Bristol-Myers Squib, GSK, MSD, Novartis. L. Mortier: Roche, GSK, Novartis, Bristol-Myers Squib, MSD, Amgen. S. Dalle: - Research funding: Bristol-Myers Squib - Travel, accommodations, expenses: MSD, Bristol-Myers Squib P. Saiag: - Honoraria: Bristol-Myers Squib, MSD, Roche, Novartis, Amgen - consulting or advisory role: Bristol-Myers Squib, MSD, Roche, Novartis, Amgen - Research funding: Bristol-Myers Squib, Novartis, Roche - Travel, accommodations, expenses: Bristol-Myers Squib, MSD, Roche Novartis. M. Beylot-Barry: - Consulting or advisory role: Roche, Bristol-Myers Squib - Travel, accommodations, expenses: Roche. F. Aubin: - Honoraria: Abbvie, LéoPharma, MSD, Novartis, Celgène - Consulting or advisory role: Janssen, Celgène, MSD, Roche, Novartis - Travel, accommodations, expenses: Janssen, MSD, Abbvie, Novartis. T. Lesimple: - Consulting or advisory role: Roche, Bristol-Myers Squib - Research funding (Institution): Roche - Travel, accommodations, expenses: Roche, MSD. C. Lebbe: - Consultancy, Honoraria, Speakers bureau: Roche, Bristol-Myers Squib, Novartis MSD - Research funding (Institution): Roche - Travel accommodations-Meetings: Roche, Bristol-Myers Squib, Novartis, Amgen - Advisory role: Roche, Bristol-Myers Squib, Novartis, MSD, Amgen, GSK. All other authors have declared no conflicts of interest.

1256TiP - A Phase II, Randomised, Open Label Study of Neoadjuvant Pembrolizumab with/without Dabrafenib and Trametinib (D+T) in BRAF V600 Mutant Resectable Stage IIIb/C/D Melanoma (NeoTrio Trial)
Background
BRAF targeted and CTLA-4/PD-1 immunotherapies have high response rates and improve survival for patients (pts) with metastatic melanoma, however, most still die of this disease. It is hypothesised the activated cytotoxic T cell infiltrate that occurs early during treatment with BRAF/MEK inhibitors is potentiated by adding checkpoint inhibitors, resulting in improved response and survival. While trials combining BRAF/MEK inhibitors and anti-PD-1/L1 antibodies are underway in the metastatic setting, the neoadjuvant setting provides an opportunity to test different treatment schedules in small cohorts of pts. Tissue and blood biomarkers can be drawn at several timepoints and correlated to clinical and pathological endpoints to explore mechanisms of response, biomarkers of efficacy, and to select the best schedules to take forward to larger-scale trials.

Trial design
Eligible pts with BRAF V600 mutant, stage IIIIB/C/D, resectable and measurable (RECIST 1.1) metastatic melanoma are evenly assigned to 3 cohorts (n = 60). All pts undergo complete macroscopic resection (RES) at week 12 and receive neoadjuvant therapy for 12 weeks preceding RES, followed by 40 weeks of adjuvant therapy. Cohort 1 receive sequential therapy with D+T for 2 weeks, followed by 4 pembrolizumab (pembro) doses until week 12, and 3 weekly pembro after RES. Cohort 2 receive concurrent D+T and 3 weekly pembro before and after RES. Cohort 3 receive 3 weekly pembro for the entire treatment course. Pembro is given at a flat dose of 200mg. Ultrasound surveillance of known disease areas is undertaken during the neoadjuvant period. Serial CT and FDG PET/CT are used to measure response and exclude progression in the neoadjuvant phase, and to monitor for recurrence during adjuvant and post treatment phases. Blood and tumour samples are collected at baseline, week 1, 4 and 12. The primary endpoint is the complete pathological response rate at RES following 12 weeks of therapy. Secondary endpoints include RECIST response, metabolic response, OS, RFS, safety/tolerability, surgical outcomes, quality of life, as well as biomarker analysis.

Clinical trial identification
NCT02858921

Legal entity responsible for the study
Melanoma Institute Australia

Funding
Merck Sharp & Dohme

Disclosure
All authors have declared no conflicts of interest.
Background

Standard-dose pembro (2 mg/kg Q3W) + reduced-dose ipi (1 mg/kg Q3W × 4 doses) showed preliminary efficacy in patients (pts) with melanoma in part 1B of the phase 1/2 KEYNOTE-029 study (NCT02089685), but 42% of pts had treatment-related AEs (TRAEs). In part 1C, 2 more dosing regimens of this combination will be evaluated to further assess efficacy and aim to reduce the toxicity seen in part 1B.

Trial design

Pts aged ≥18 y with histologically confirmed unresectable stage III/IV melanoma not amenable to local therapy; no prior treatment ([neo]adjuvant treatment, excluding PD-1/PD-L1 or BRAF/MEK inhibitors, was allowed if pts did not discontinue for TRAEs, all TRAEs returned to baseline/stabilized, and relapse did not occur within 6 mo of discontinuation for anti–CTLA-4 therapy); measurable disease per RECIST v1.1; ECOG PS 0/1; tumor sample for determination of PD-L1 status; no active brain metastases (baseline brain MRI required) were eligible. 100 pts will be randomized 1:1 to pembro 200 mg Q3W + ipi 50 mg Q6W (arm 1) or 100 mg Q12W (arm 2). Combination therapy will continue for ≤24 wk in arm 1 and ≤48 wk in arm 2, followed by pembro monotherapy for ≤24 mo or until PD, intolerable toxicity, or patient/physician decision. Tumor imaging will occur every 6 wk until wk 24, and every 12 wk thereafter. Response will be assessed per RECIST v1.1 by independent central review (for efficacy) and modified RECIST v1.1 by investigator review (for treatment decisions). Survival follow-up will occur every 12 wk. AEs will be graded per CTCAE v4.0. Pts with investigator-determined, confirmed CR who received ≥24 wk pembro and ≥2 doses after initial CR may discontinue pembro; pts with investigator-determined, confirmed CR or very good PR (percentage change from baseline in tumor size >60%) who received ≥1 ipi dose may discontinue ipi. Pts with SD or better who subsequently have PD may be eligible for a second course of pembro + ipi or pembro monotherapy (maximum 17 doses pembro and 4 doses ipi). Eligible pts with PD may remain on treatment until a confirmatory scan ≥4 wk later. Primary end points are safety and ORR; secondary end points include PFS, OS, and DOR. Enrollment is ongoing in the US, Australia, and New Zealand.

Clinical trial identification

NCT02089685

Legal entity responsible for the study

Merck & Co., Inc., Kenilworth, New Jersey, USA

Funding

Merck & Co., Inc., Kenilworth, New Jersey, USA

Disclosure

M.B. Atkins: Advisory board member for Bristol-Myers Squibb, Merck, Roche, Novartis,
1258TiP - Phase 2 Study Comparing Pembrolizumab with Intermittent/short-term dual MAPK pathway inhibition plus Pembrolizumab(PEM) in patients harboring the BRAFV600 mutation (IMPemBra Trial)

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Background
Continuous combinations of targeted therapy (TT), e.g. BRAF+MEK inhibitors(BRAFi+MEKi), with immunotherapy (IT), e.g. CTLA-4 or PD-1 blockade are currently tested in several phase1/2 trials with the aim to improve response rate and response duration in melanoma patients with a BRAFV600 mutation. However, high toxicity rates have been observed, revealing PD-1 blockade currently being the only possible combination partner for TT. Recently we have published preclinical data, showing that short-time TT induces strong T cell infiltration and is synergistic with PD-1 blockade. Analysis of biopsies of patients during TT indicate that long-term TT might be counterproductive, as T cell infiltration decreases in some patients already beyond 2 weeks. This raises the question which time period of MAPK pathway inhibition is optimal for combination with anti-PD-1. The IMPemBra trial will address this question, comparing PEM monotherapy with combination schemes of intermittent/short-term BRAFi + MEKi plus PEM. The primary objective is to explore safety, feasibility and the immune-activating capacity of the different regimens.

Trial design
Stage IV BRAFV600E/K mutation positive melanoma patients, naïve for IT and TT, will start treatment with PEM 200mg q3wk. After 6 wks the patients will be randomized (stratified according their LDH level) to continue PEM for up to 2 years (cohort 1), or to
one of the experimental cohorts receiving either dabrafenib 150mg BID + trametinib 2mg QD two times intermittent for 1 wk (cohort 2), two times intermittent for 2 wks (cohort 3), or continuous for 6 wks (cohort 4). All cohorts continue afterwards with PEM for up to 2 years. Each cohort will consist of 8 patients. Primary endpoints are SUSARs and adherence to the study timeline, the intra-patient alteration in intratumoral CD8+ T cells and the percentage PD1+ CD8+ T cells in the peripheral blood. Tumor biopsies and blood samples including PBMCs are taken at baseline, wk 6, 9, 12, 18 and in case of progression. Secondary endpoints are objective response rate and progression free survival. Enrollment started in May 2016, 11 patients have been included so far.

Clinical trial identification
NCT02625337

Legal entity responsible for the study
NKI-AVL

Funding
MSD

Disclosure
J.V. Thienen: Advisory board: MSD and Bristol-Myers Squib. J.B. Haanen: Advisory role: Bristol-Myers Squib. MSD, Pfizer, Roche, Novartis, Neon Therapeutics Research grants: Bristol-Myers Squib, MSD, Novartis, GSK. C.U. Blank: Advisory board: Bristol-Myers Squib, MSD, Novartis, GSK, Pfizer, Lilly, Roche Research grants: Bristol-Myers Squib, Novartis. All other authors have declared no conflicts of interest.

1259TiP - A randomized, double-blind, placebo-controlled, phase III study comparing the combination of PDR001, dabrafenib and trametinib versus placebo, dabrafenib and trametinib in previously untreated patients with unresectable or metastatic BRAF V600–mutant melanoma (COMBI-i)

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Background
Checkpoint inhibitor and targeted therapies are both important tools in the management of BRAF V600–mutated unresectable or metastatic melanoma. Although these therapies have improved responses and overall survival, many patients still progress and die from this disease. Thus, additional treatment strategies are needed to improve durability of responses and related long-term outcomes in these patients. Based on preclinical and preliminary clinical data, BRAF and MEK inhibitors can reverse the oncogenic BRAF-induced immune-suppressive phenotype through enhanced melanoma antigen expression and enhanced tumor antigen-specific T-lymphocyte recognition in vivo. These data suggest that there is potential clinical benefit in combining dabrafenib and trametinib with checkpoint inhibitor therapy.
Trial design

The 3-part COMBI-i phase 3 study (NCT02967692) will evaluate the safety and efficacy of PDR001, an investigational anti–programmed death 1 antibody, in combination with dabrafenib and trametinib in previously untreated patients with BRAF V600–mutated unresectable or metastatic melanoma. In part 1, a safety run-in will establish the recommended phase 3 regimen (RP3R) for use in part 3 using an adaptive Bayesian logistic regression model. In part 2, tissue and blood samples from the biomarker cohort will be used to characterize baseline immune markers and explore potential immune marker modulation by the triplet therapy. Part 3 is the randomized, double-blind, placebo-controlled portion that will open once the RP3R has been determined. Approximately 500 patients will be randomized 1:1 to receive either PDR001 in combination with dabrafenib and trametinib or placebo in combination with dabrafenib and trametinib, with randomization stratified based on Eastern Cooperative Oncology Group performance status and lactate dehydrogenase level. The primary endpoint will be progression-free survival per investigator’s assessment according to RECIST v1.1. Overall survival will be a key secondary endpoint.

Clinical trial identification

NCT02967692 First received: November 16, 2016

Legal entity responsible for the study

Novartis Pharmaceuticals Corporation

Funding

Novartis Pharmaceuticals Corporation

Disclosure

Background

After the introduction of ipilimumab, an anti-CTLA-4 monoclonal antibody, durable, long-term survival has become a possibility for a subgroup of advanced melanoma patients. Since ipilimumab is a relatively novel drug there are limited data on the long-term physical, psychological, and social functioning of these patients. This study will evaluate the long-term physical and psychosocial performances and the information needs of advanced melanoma survivors who have been treated with ipilimumab.

Trial design

This is a prospectively enrolling, multicentre cohort study. Objectives: To assess health-related quality of life (HRQoL), anxiety, depression, fatigue, fear of cancer recurrence, sexual health and generic health status in patients with advanced melanoma who have survived at least 2 years after ipilimumab treatment (without subsequent other systemic therapies) as compared with healthy controls, and to describe the melanoma-specific HRQoL, impact of cancer, social functioning and information needs in patients with advanced melanoma who have survived at least 2 years after ipilimumab
treatment. Patients and healthy control population: Patients with advanced (stage IV or unresectable stage III) melanoma who survived at least 2 years and were treated with ipilimumab between 2011 and 2015 in 14 hospitals in the Netherlands are included. The patient population consists of 3 treatment groups based on time since ipilimumab treatment: 24 to < 36 months, ≥ 36 to < 48 months and ≥ 48 months post-ipilimumab treatment. The healthy control population will be selected from 'Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES)'. PROFILES contains a reference cohort of more than 2000 healthy individuals and is designed to be representative of the Dutch-speaking population in the Netherlands. Measurements: The primary and secondary study outcomes will be measured by questionnaires, at 3 time-points in patients 24 to < 36 months and at 1 time-point in patients ≥ 36 months post-ipilimumab treatment. The primary outcome, HRQoL will be assessed with the European Organisation for Research and Treatment of Cancer quality of life questionnaire-C30 (EORTC QLQ-C30).

Clinical trial identification
Date of release: November 2016
Legal entity responsible for the study
Netherlands Cancer Institute
Funding
Bristol-Myers Squibb
Disclosure
A.H. Boekhout: Employee of Bristol-Myers Squibb. M. Lee, KJM Janssen: Employee of and receiving stock from Bristol-Myers Squibb, during the conduct of the study. All other authors have declared no conflicts of interest.

PALLIATIVE CARE
F. Scotté (Paris, France)

1390P - Efficacy of anamorelin in advanced non-small cell lung cancer (NSCLC) patients with anorexia/cachexia and modified Glasgow Prognostic Score (mGPS) of 2: Pooled analysis of two phase 3 trials
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Background
Anorexia/cachexia occurs in patients with advanced NSCLC. In 2 randomized, double-blind, placebo-controlled phase 3 trials in cachectic NSCLC patients, the ghrelin receptor agonist anamorelin was well tolerated and significantly improved body composition parameters and anorexia/cachexia symptoms over 12 weeks (Temel JS et al, Lancet Oncol 2016). The mGPS (0–2) has independent prognostic value; patients with mGPS 2 have worse prognosis. This analysis determined anamorelin’s efficacy in cachectic NSCLC patients with mGPS 2 (C-reactive protein levels >10mg/L and albumin levels <3.5g/dL).

Methods
Stage III/IV NSCLC patients with cachexia (BMI<20 kg/m² or ≥ 5% weight loss during prior
6 months) were randomized 2:1 to once-daily oral anamorelin 100 mg or placebo up to 12 weeks. An ad-hoc efficacy analysis was performed in the modified intent-to-treat population (N = 829) to assess whether mGPS score at baseline may predict differences in anamorelin treatment effect size at end of study (or last observation carried forward since week 6 or 9).

Results
Anamorelin treatment effect was statistically significantly better, compared with placebo, for all body composition parameters in all mGPS subgroups. This effect was numerically larger in patients with mGPS 2 and statistically significant, compared with placebo, for all analyzed parameters, except fatigue subscale score (Table). In patients with mGPS 2, the placebo-adjusted mean increase in body weight exceeded the 5% weight loss cutoff used as an official criterion for cancer cachexia diagnosis.

Table: 1390P

<table>
<thead>
<tr>
<th>Treatment Effect of Anamorelin in patients with mGPS 2 (n = 123)</th>
<th>Mean 95% Cl</th>
<th>P value, compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>3.07</td>
<td>1.47–4.68</td>
</tr>
<tr>
<td>Body weight change, %</td>
<td>5.40</td>
<td>2.82–7.97</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>1.84</td>
<td>0.62–3.06</td>
</tr>
<tr>
<td>Appendicular lean body mass, kg</td>
<td>1.04</td>
<td>0.32–1.77</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>1.35</td>
<td>0.38–2.31</td>
</tr>
<tr>
<td>Handgrip strength, kg</td>
<td>2.44</td>
<td>0.35–4.52</td>
</tr>
<tr>
<td>FAACT Anorexia/Cachexia subscale score</td>
<td>5.23</td>
<td>1.55–8.90</td>
</tr>
<tr>
<td>Fatigue subscale score</td>
<td>0.67</td>
<td>–3.24–4.58</td>
</tr>
</tbody>
</table>

CI, confidence interval; FAACT, Functional Assessment of Anorexia/Cachexia Therapy.

Conclusions
In cachectic NSCLC patients with mGPS 2, anamorelin leads to significant improvements in body composition parameters and symptom burden. The extent of weight improvement in this population suggests that treatment with anamorelin may on average reverse pathologic weight loss.

Clinical trial identification
ROMANA 1: NCT01387269 ROMANA 2: NCT01387282

Legal entity responsible for the study
Helsinn

Funding
Helsinn

Disclosure
S. Kaasa: Stock ownership: Eir solutions AS. B. Laird: Advisory board membership: Chugai Pharma. R. Skipworth: Corporate-sponsored research: Research grant/agreement with Novartis. D. Currow: Unpaid advisory board member for Helsinn. Paid consultant and
Background

Novel, complex, resource intensive, radiation technology is increasingly used for palliative therapy even though they are not cost effective in poor prognosis pts. (Kim IJROBP 2015;556). Since nearly half of all radiotherapy (RT) activity is palliative (Hoskin CI Onc 2013;531), objective, validated prognostic tools are urgently needed to guide cost effective utilisation of RT. As advanced cancer is associated with poor nutritional status and immune dysfunction, we assessed prognostic role of PNI-which is based on serum albumin & peripheral blood lymphocytes.

Methods

Mortality of 233 unselected cancer pts treated over a 3 month at Nottingham was assessed. All tumour sites & histology were included. Overall Median age 68 yrs. Sites of RT field: Chest=29% Vertebrae=26% Pelvis=20% Brain=12% Limbs=6% Abd=3% Miscell=3%. 95% completed RT as planned. 93% had stage 4 cancer. PNI available for 131 pts. Majority not suitable for systemic therapy following palliative RT; only 15% and 28% had further hormones and chemo respectively.

Results

Overall Median survival was 5.82 months; 38% died within 90 days of completing RT; Pts with low PNI (<38) had statistically significant higher 30 day and 90-day mortality (table). On Cox regression, low PNI was strongly predictive of poor survival, (p 0.01; Exp(B) 0.538; [95.0% CI for Exp(B) 0.336 to 0.862]. Pts who received systemic therapy following palliative RT had better survival. (Hormones and chemo P values <0.005 & <0.001 respectively). By contrast, total RT dose, and number of RT fractions were not predictive of survival (p values 0.213 and 0.379 respectively). No survival advantage for multifraction over single fraction RT.

Conclusions

For terminally ill cancer patients, who are not fit for further systemic therapy and whose PNI is < 38, Single fraction RT should be the standard of care.

<table>
<thead>
<tr>
<th></th>
<th>&lt;38</th>
<th>&gt;38</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age -Yrs</td>
<td>68</td>
<td>66</td>
<td>0.26*</td>
</tr>
<tr>
<td>Median RT dose-Gy</td>
<td>20</td>
<td>20</td>
<td>0.21#</td>
</tr>
<tr>
<td>Median No RT fractions</td>
<td>5</td>
<td>5</td>
<td>0.37</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>10%</td>
<td>4%</td>
<td>0.05^</td>
</tr>
</tbody>
</table>
Background
Patients with advanced NSCLC often develop anorexia/cachexia, a comorbidity characterized by decreased body weight or low body mass index (BMI), which negatively impacts quality of life and life expectancy. Weight loss and BMI were suggested to have independent prognostic value (Martin L et al, JCO 2015). The mGPS (0–2) has independent prognostic value, where patients with mGPS 2 (C-reactive protein levels >10mg/L and albumin levels <3.5g/dL) have worse prognosis. Here, we investigated the characteristics of NSCLC patients with cachexia according to their mGPS, and whether mGPS can be used to differentiate patients with cachexia.

Methods
Patients with unresectable stage III/IV NSCLC and cachexia (BMI<20 kg/m² or ≥5% weight loss during prior 6 months) were enrolled in two phase 3 studies of the ghrelin receptor agonist anamorelin (ROMANA 1 and ROMANA 2). A pooled post-hoc data analysis was performed in the modified intent-to-treat population (N = 829), irrespective of treatment arm, to investigate the baseline characteristics of patients with mGPS 0–2.

Results
At baseline, 36% patients had mGPS 0 (n = 296), 49% mGPS 1 (n = 396) and 15% mGPS 2 (n = 123). Patients who lost <10% body weight during the prior 6 months had mainly mGPS 0–1; in contrast, among patients who lost >10% body weight, a higher percentage had mGPS 2. Patients with mGPS 2 had on average substantially lower values of body weight, body composition parameters, handgrip strength and anorexia/cachexia and fatigue scores than the other mGPS subgroups (Table).

Table:
Baseline characteristics based on mGPS score

<table>
<thead>
<tr>
<th></th>
<th>mGPS 0 (n = 296)</th>
<th>mGPS 1 (n = 396)</th>
<th>mGPS 2 (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight loss, n (%) ≤ 10% &gt; 10%</td>
<td>205 (43.0) 92 (27.1)</td>
<td>218 (45.7) 178 (52.5)</td>
<td>54 (11.3) 69 (20.4)</td>
</tr>
<tr>
<td>Mean body weight, kg (SD)</td>
<td>66.9 (13.66)</td>
<td>67.4 (12.73)</td>
<td>63.0 (13.77)</td>
</tr>
<tr>
<td>Mean lean body mass, kg (SD)</td>
<td>44.9 (8.64)</td>
<td>46.2 (7.78)</td>
<td>44.5 (8.54)</td>
</tr>
<tr>
<td>Mean appendicular lean body mass, kg (SD)</td>
<td>19.3 (4.59)</td>
<td>19.7 (3.95)</td>
<td>18.4 (4.25)</td>
</tr>
<tr>
<td>Mean fat mass, kg (SD)</td>
<td>19.4 (8.06)</td>
<td>19.0 (7.80)</td>
<td>16.3 (8.01)</td>
</tr>
<tr>
<td>Mean handgrip strength, kg (SD)</td>
<td>32.2 (11.74)</td>
<td>32.7 (10.92)</td>
<td>27.2 (9.91)</td>
</tr>
<tr>
<td>Mean FAACT Anorexia/Cachexia subscale score (SD)</td>
<td>31.6 (7.92)</td>
<td>29.5 (8.16)</td>
<td>25.5 (8.77)</td>
</tr>
<tr>
<td>Mean fatigue subscale score (SD)</td>
<td>32.4 (9.74)</td>
<td>30.6 (10.21)</td>
<td>25.4 (10.95)</td>
</tr>
</tbody>
</table>

FAACT, Functional Assessment of Anorexia/Cachexia Therapy; mGPS, modified Glasgow prognostic score; SD, standard deviation.

**Conclusions**

While patients with cachexia present mGPS scores that vary from 0–2, a higher percentage of patients with mGPS 2 was observed among those with >10% body weight loss. The baseline characteristics observed in patients with mGPS 2 are worse than in the other mGPS subgroups, suggesting that mGPS may be helpful in identifying patients with more-advanced cachexia.

**Clinical trial identification**

ROMANA 1: NCT01387269
ROMANA 2: NCT01387282

**Legal entity responsible for the study**

Helsinn

**Funding**

Helsinn

**Disclosure**

B. Laird: Advisory board membership: Chugai Pharma. S. Kaasa: Stock ownership: Eir solutions AS. R. Skipworth: Corporate-sponsored research: Research grant/agreement with Novartis. D. Currow: Unpaid advisory board member for Helsinn. Paid consultant and receive payment for intellectual property with Mayne Pharma and am a consultant with Specialist Therapeutics Australia Pty. Ltd. R. Giorgino: Helsinn Healthcare employee. All other authors have declared no conflicts of interest.

**1393P - Chemotherapy in advanced cancer patients with poor performance status (PS) initiated in an integrated oncology and palliative care (PC) setting: an observational comparative study**

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Background
Advanced cancer patients (ACP) with poor PS often get systemic anticancer treatment (SAT). A combined PC and medical oncology structured approach involving double boarded palliative oncologists (PallOnc) is investigated.

Methods
Medical chart review over 2½ years, with locally developed (adapted from Blum D JPSM 2014) tool, of all ACP PS > 1 in a tertiary PC unit (330 pts/year, death rate 40%, length of stay [LOS] 12 days) receiving intravenous SAT (pharmacy orders). ACP with new initiated SAT were compared with continued SAT for tumor history, PS, and outcomes; in new SAT the PallOnc processes decisional process, Palliative Interventions (PIs), and primary dose reduction were analysed.

Results
Of 95 ACP receiving SAT 65 (68%) were PS > 1. In 36 ACP a new SAT was initiated, in 29 continued. Comparable were age (years, mean: 65 vs 63), gender (% female: 39 vs 43), PS (PS3/4: 64% vs 65%), time since diagnosis of stage 4 (months, mean: 16 vs 14), number of anticancer treatment lines (mean: 2 vs 2) and LOS (days, mean: 26 vs 24). New vs continued SAT differed for tumors not responding (never PR or SD) to last chemotherapy (55% [7 PS2, 4 PS3] vs 27% [1 PS2, 2 PS3], monotherapies (67% vs 45%), death at PC unit (14% vs 41%), overall survival (1 patient alive, 1 lost-to-follow-up; days, median: 83 vs 58, mean 152 vs 128), PS at demission compared to admission (stable PS: 33% vs 24%; improved PS: 50% vs 24%), and ACP who died ≤14 days after last SAT (22% vs 14%). No G3/4 non-hematological toxicity was reported. In the new SAT group the decisional process took 11 days (median, range 0-48), explicit goals of SAT were documented in 81% (44% specific tumour-related symptoms), attitude towards SAT in 86% ACP (unwilling, ambiguous 4/31, wants, imperative 17) and 42% physicians (0, 15). Of 5 PIs Illness understanding, symptom control, end-of-life preparation, network & family support, spiritual needs) all were delivered in 21 ACP (58%), 4 and 3 in 7, 2 in 1. Primary dose reduction was applied in 2/4 PS4 patients (1: 5-25%,1: 26-50%), 13/19 PS3 (5, 8) and 11/13 PS2 (7, 4) ACP.

Conclusions
In a setting with PallOnc anticancer treatment in poor PS patients seems feasible. The encouraging data may foster prospective research.

Legal entity responsible for the study
Cantonal Hospital St.Gallen, Switzerland

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1394P - Previous palliative care encounter is associated with lower total hospital charge and shorter length of stay in patients with metastatic cancer
Y. Liu (New York, United States of America)

Background
Patients with metastatic cancer require substantial health care resources. Palliative care has been increasingly recognized for improvement of quality of life and reducing
healthcare costs. Here, we examined the effect of prior palliative care encounters on the total hospital charges (TOTCHG) and length of stay (LOS) during the subsequent hospitalization.

Methods

We used National Inpatient Sample (NIS) 2014 to extract data for patients non-electively hospitalized with corresponding ICD9 code of previous palliative care visit (ICD9 code V667) and metastatic cancer. NIS is a nationally representative survey of hospitalizations conducted by Heathcare Cost and Utilization project. It represents 20% of all hospital data in the US. Univariate regression screening (threshold P > 0.1) and hybrid selection were used to create multivariate regression models. Relationship between TOTCHG and previous palliative care encounter as well as LOS and previous palliative care encounter were analyzed by using established models.

Results

A total number of 136591 patients admitted non-electively with metastatic cancer was identified among which 24736 had been coded for previous palliative care encounter. Teaching hospital admission, rural hospital admission, self-pay, increased age and increased Charlson score were associated with higher rate of previous palliative encounter. The multivariate regression model for LOS and previous palliative care visit were adjusted for survival outcome, number of procedures during hospitalization, number of previous chronic conditions, and number of the diagnosis during hospitalization. The model for TOTCHG and previous palliative care visit were adjusted for survival outcome, number of procedures and length of stay. We found that previous palliative care encounter was associated with both lower total hospital charge (P < 0.0001) and shorter length of stay in patients with metastatic cancer (P < 0.0001).

Conclusions

Prior palliative care visit has been associated with decreased length of stay and total hospital charges. Future studies are needed to determine if early outpatient palliative care encounter will especially benefit patients with certain tumor types.

Legal entity responsible for the study

Yuzhou Liu

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1395P - Specialized ambulatory palliative care: (SAPV) 5-year results of a multi-professional care model by HomeCare linker Niederrhein gGmbH (HC) in the Lower Rhine region

U. Grabenhorst (Viersen, Germany)

Background

In recent times, German legislation has given terminally ill patients the right to receive SAPV, a multi-professional palliative care model which is aimed at prevention of hospital admission and enabling patients to die at home despite severe symptoms and a high need
for palliative care. This new type of care raises the question about the best implementation and impact of SAPV. HC provides SAPV to 560,000 inhabitants of the city of Mönchengladbach and the district of Viersen.

Methods
Data collected during daily care from 2012 to 2016 are summarized and analysed in order to describe the implementation and results of SAPV.

Results
1798 patients were treated in 5 years. The first contact with SAPV was initiated by a GP in 30% of patients and by a specialist in 4.5%; in 26% through a hospital, in 6% by a palliative care unit and in at least 30% by non-medical participants, such as relatives, nursing services, counseling centers etc. 20% of all patients were treated only temporarily by SAPV. 6% were admitted to a hospice, 14% were transferred to regular care after counseling or crisis intervention. Of the remaining patients, only 3.3% had to be hospitalized at the end and 96.7% were able to remain in their chosen home environment. That was at home for 80%, at a relative's home for 3%, in a nursing home for 14%, and miscellaneous for the remaining 3% of patients. Sonography, thoracic and abdominal paracentesis, patient-controlled analgesia etc. were performed in the patient's home by the SAPV team. Of all 1798 patients, 112 had to be hospitalized; 64 were subsequently retreated with SAPV and 48 were not. The main reasons for hospitalization were palliative interventions due to ileus and urinary retention in the upper tract, radiation of a fracture, psychosocial decompensation of the supporting relatives and confirmation of the palliative concept. The average treatment duration was 19 days, the median was under 10 days. In detail, 112 patients were treated for less than 24 hours, 271 patients for less than 48 hours, 57 patients were treated for more than 90 days and 4 patients for over 200 days.

Conclusions
The wish of patients to die at home and to avoid unnecessary hospitalization can be achieved with this model of specialized care. Further comparative investigations are necessary to identify the optimal implementation and impact of SAPV.

Clinical trial identification
not applicable

Legal entity responsible for the study
Ulrich Grabenhorst

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1396P - Increasing palliative interventions at the end of life: patterns in metastatic colorectal cancer (mCRC)

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Background
Advances in chemotherapy for mCRC have improved median survival to more than 24 months. This has resulted in increased opportunity to undergo more frequent interventions
for symptom relief at the end of life. We explored patterns of palliative interventions (surgery, endoscopy, interventional radiology (IR), drainage procedures, radiotherapy) in mCRC patients over a time of evolving chemotherapy regimens.

Methods
A retrospective review was undertaken of all mCRC patients referred to palliative care at a tertiary cancer center in Toronto, Canada. Patients treated 2000-2004 (early cohort) were compared to 2006-2010 (later cohort) as more effective palliative chemotherapy was available in the later time period. Descriptive statistics, t-tests, and chi-squared tests were employed.

Results
A total of 542 (212 early and 330 later cohort) patients were included. Compared to the early cohort, the later cohort was significantly younger (62 vs 65 years, p = 0.012), had more Stage 4 disease (47 vs 42%, p = 0.029), fewer curative surgeries (58 vs 70%, p = 0.005) and fewer had adjuvant chemotherapy (26 vs 38%, p = 0.002). Palliative care referral was delayed for the later cohort with longer times between diagnosis of unresectability and referral (13 vs 8 mths, p = 0.0019) and shorter times between referral and death (6 vs 8 mths, p = 0.019). More patients in the later cohort had palliative surgery (31 vs 22%, p = 0.015), palliative IR procedures (15 vs 4%, p < 0.0001) and did not receive any chemotherapy (44 vs 29%, p < 0.0001). The later cohort underwent more interventions in the last months of life with more chemotherapy and drainage procedures closer to death (7 vs 12 mths, p = 0.002 and 2 vs 9 mths, p = 0.006 respectively). There was no difference in survival (calculated from date of diagnosis to death) between the cohorts (median survival 35 months).

Conclusions
In their final months of life, palliative mCRC patients are undergoing more interventions requiring multi-disciplinary input with the aim of improving quality of life than previously. Increasing use of interventions in the last months of life has significant ramifications for patients, service provision, staffing and funding.

Funding
PSI Foundation

Disclosure
All authors have declared no conflicts of interest.

1397P - Chronic pleural effusion in malignancy: A single center’s ten years expertise with indwelling pleural catheters

N. Frost (Berlin, Germany) M. Brünger (Berlin, Germany) B. Temmesfeld-Wollbrück (Berlin, Germany) D. Schüermann (Berlin, Germany) N. Suttorp (Berlin, Germany)

Background
Chronic and recurrent pleural effusion (PE) in malignant diseases is a common cause of dyspnea, cough and chest pain. The vast majority is malignant pleural effusion (MPE), nevertheless disease-associated but not directly disease-caused paramalignant pleural effusions (PPE) have also been described. Talc pleurodesis had been the only treatment option for decades, while for 20 years indwelling pleural catheters (IPC) have emerged as an alternative leading to spontaneous pleurodesis without any chemical agent in 40-50%.

Methods
Our aim is to explore patient characteristics, procedural variables and outcomes in a large population of patients with IPC due to PE in malignancy. Further, our objective is to identify factors associated with outcome.

Results
From 2006 until 2016 448 IPC were inserted in 395 patients, 52 received bilateral drainages (12.7%). 77.0% of the effusions were malignant (n = 304), 14.9% paramalignant (n = 59), in 8.1% the etiology could not be clarified (n = 32). The most common underlying diseases were ovarian cancer (30.6%, 121 patients), lung cancer (23.0%, 91 patients) and breast cancer (11.4%, 45 patients). The median length of insertion was 1.2 months (0.03-23.6), the median survival time after insertion 2.4 months (lung cancer 1.6 months, ovarian cancer 2.8 months, breast cancer 4.0 months). Spontaneous pleurodesis was observed in 28.6% (128/448 catheters) and was significantly associated with overall survival (HR 0.54, 95%-CI 0.39-0.75, p < 0.001). Complications occurred in 12.3% of all procedures (55/448 catheters), in 6.5% the catheter had to be removed (29/448 catheters). The most common complications were superficial infections (n = 14), empyema (n = 11; 1 grade 5 complication) and mechanical obstruction of the catheter (n = 13).

Conclusions
In conclusion, our retrospective series is the largest to date to report on IPC in malignancy and showed a manageable safety profile. Spontaneous pleurodesis was significantly associated with survival.

Clinical trial identification
Not applicable

Legal entity responsible for the study
Charité Universitätsmedizin Berlin

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1398P - Aggressiveness of care at the end of life in children with cancer: A nationwide cohort study

A. Cardoso (Penafiel, Portugal) D. Martins Branco (Lisbon, Portugal) A. Lacerda (Lisbon, Portugal)
B. Gomes (London, United Kingdom) S. Lopes (Lisbon, Portugal)

Background
Cancer remains the leading medical cause of death in children. Ensuring quality of life should be a priority, but it may be difficult to stop treatments, particularly in settings where palliative care is scarce. Little is known about how many children dying from cancer experience aggressive care near the end of life (ACCEoL) in such settings (the most common worldwide). Our study aims to determine time trends in the prevalence of ACCEoL in this population.

Methods
Cohort study of children (0-17yo) who died with ICD-9-CM diagnosis of cancer in public hospitals in mainland Portugal (Jan’10 to Dec’15), identified from the Hospital Morbidity database. Based on previous studies and clinical experience, measures of ACCEoL comprised: in last 14 days of life: a) intravenous chemo/immunotherapy; in last 30 days of
life: b) >14 days spent in hospital, c) >1 hospitalization, d) intensive care unit (ICU)
admission, e) advanced life support (e.g. cardiopulmonary resuscitation), f) insertion of
devices (e.g. central vascular access, CVA), g) total parenteral nutrition (TPN). We
calculated prevalences and tested for time trends using chi2 for trend.

Results
The study included 300 patients (median age 9 yo, IQR 4-14, 58.7% male). The
prevalence of ACCEoL was stable over time, with 87.8% of the children experiencing at
least one ACCEoL measure (85.2% in 2010, 88.4% in 2015; p = 0.816)). The most
prevalent individual ACCEoL measures were >14 days spent in hospital (51.0%) and >1
hospitalization (43.3%). Most measures showed no statistically significant time trend.

Conclusions
In a setting in early stages of pediatric palliative care development, we found that eight in
ten children dying from cancer experience ACcEoL in their last month of life. This estimate
is higher than those found in countries in more advanced developmental stages and may
indicate a need to increase paediatric palliative care availability. The findings also prompt
healthcare professionals to reflect on their current practice, balancing treatments and
hospitalisations with patients’ quality of life in the days they have to live.

Legal entity responsible for the study
N/A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

PREVENTION AND SCREENING

M. J. Ijzerman (Enschede, Netherlands)

1403P - Community-based lung cancer screening of high-risk population with
low-dose computed tomography in China

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R. Shi (Shanghai, China) L. Jiang (Shanghai, China) A. Gu (Shanghai, China) Y. Zhao (Shanghai, China)
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Background
Low-dose computed tomography (LDCT) screening for lung cancer has been
recommended for high-risk individuals meeting the National Lung Screening Trial (NLST)
criteria. However, there still is a debate concerning respective recommendations for Asian
countries. Meanwhile, the proper duration and interval for lung cancer screening remains
uncertain.

Methods
From November 2013 to July 2016, participants from Xuhui district of Shanghai were aged
45-70 years, and with either of the following risk factors: 1) smoking history ≥20
pack-years, and, if a former smoker, had quit within the past 15 years; 2) cancer history in
immediate family members; 3) personal cancer history; 4) professional exposure to
carcinogens; 5) long term exposure to second-hand smoke; 6) long term exposure to cooking oil fumes. The eligible participants were randomly assigned to a screening arm with two rounds of alternate years LDCT screens and a control arm.

**Results**

A total of 6659 eligible participants were enrolled, 3147 participants were randomly assigned to control arm, 3512 were assigned to LDCT prevalence screening (S1), of which 1516 participants underwent the second round of LDCT screening (S2) in the alternate year. Positive screening results were observed in 849 (24.2%) participants in S1 and 380 (28.0%) in S2. 80 (2.3%) cases were highly suspected of lung cancer in S1 and 31 (2.0%) in S2 according to the suggestions from multiple disciplinary team. By April 2017, lung cancer was diagnosed in 44 participants (1.3%) after S1, 12 (0.8%) after S2, and 10 (0.3%) in the control group (stage 0 to I: 97.7%, 91.7% vs 20%; stage II to IV: 2.3%, 8.3% vs 80%). Only 18 (32%) of these 56 lung cancer patients detected by LDCT would have qualified as NLST high-risk patients. There were 2 lung cancer-specific deaths in control group, whereas 0 in the screening arm participants.

**Conclusions**

LDCT screening increased the detection of early-stage lung cancer and reduced lung cancer-specific mortality. In China, lung cancer CT screening may also benefit patients outside the NLST criteria with great efficiency. Screening done at biennial intervals could be taken into consideration due to few advanced-stage diseases.

**Legal entity responsible for the study**

Shanghai Chest Hospital

**Funding**

Shanghai Municipal Commission of Health and Family Planning

**Disclosure**

All authors have declared no conflicts of interest.

**1404P - Colon cancer screening by fecal immunochemical testing in Iran**

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S. Merat (Tehran, Iran) A. Delavari (Tehran, Iran) R. Malekzadeh (Tehran, Iran)

**Background**

Colorectal cancer (CRC) is the third-most common cancer in Iran. We aimed to measure the uptake and feasibility of a pilot CRC screening programme based on fecal immunochemical test (FIT) in population aged between 45 and 75 years and the implications for scaling-up at the national level.

**Methods**

This pilot study was conducted in Tehran and individuals aged between 45 and 75 years in rural and urban areas were enrolled in the screening programme. The FIT was offered by health navigators in primary health centers by collecting one single sample directly into buffer kits by each participant. Health navigators aimed at increasing uptake and handled the whole screening programme from invitation to the referrals and provided the participants with information regarding the nature and importance of the CRC screening and details as to how to collect stool samples and send them back to the laboratory for analysis. If the first kit was not returned within 48 hours, a reminder call was sent. Those participants who had a positive FIT were referred to undergo a colonoscopy.
Results
A total of 1044 asymptomatic average-risk individuals were enrolled. The age mean was 54.1 and nearly 63.0% (n = 657) were female. Only small fraction of participants had awareness about CRC (13.7%) or polyps (8.3%) or screening tests (9.2%). Likewise their prior screening practice was extremely weak (2.2%). In multivariate regression analysis, awareness about CRC and screening tests significantly varied according to the ethnic groups, years of schooling, and family history of cancers (P < 0.05). In sum, 1002 returned the FIT kit, of which stool sample in six participants (0.6%) was deemed unsatisfactory for testing. The FIT uptake was 96.0%, the positivity rate was 9.1% and the detection rates were 11.9% for adenomas and 7.1% for advanced adenomas. No cancer was detected.

Conclusions
This is the first study on minimal quality metrics within a CRC screening process for the pilot phase and indicates that FIT modality as a test of choice is a safe and highly acceptable method of CRC screening in average-risk asymptomatic people. We suggest FIT as an initial CRC screening tool along with other preventive services in primary health care system in the nation.

Clinical trial identification
NA

Legal entity responsible for the study
Prof. Reza Malekzadeh

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1405P - Diagnostic analysis of patients referred from general practitioner with serious non-organ-specific symptoms and signs of cancer: A retrospective cohort study

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Background
Recently, a diagnostic fast track for patients with serious non-organ-specific symptoms and signs of cancer was established in Denmark. For patients without cancer diagnosed within the first month, the prognosis is currently unclear.

Methods
A retrospective cohort study of 926 patients referred to Diagnostic Outpatient Clinic (DOC) at Herlev Hospital from April 2012 to December 2013. Baseline clinical parameters were collected from patient records. Time to cancer, death, cancer specific mortality (CSM), and death due to other causes were recorded until May, 2016. 724 patients were identified without cancer one month after examination and divided into 2 sub-cohorts based on the initial assessment: true negatives (TNs; patients diagnosed without cancer at DOC and after 1 month) and false positives (FPs; patients referred from DOC with suspicion of cancer, but without cancer the 1. month). Cumulative incidence of cancer, death, CSM, and death from other causes were estimated by the Aalen-Johansen estimator using 31 days after initial assessment as baseline. Hazard ratios (HR) and 95% confidence
intervals (CIs) for the initial evaluation were estimated in Cox models with cancer and mortality, respectively, as outcomes.

Results
Clinical characteristics of the 724 patients: median age 65 years (range 17-92); 44% were men; 70% were referred from their general practitioner; 43% were former/current smokers; 18% were former/current alcohol abusers. The median age (p < 0.01) and comorbidity score (p < 0.01) were highest among the FPs. TNs vs. FPs had a lower risk of subsequent cancer (HR: 0.08; 95% CI: 0.05-0.13; p < 0.01), mortality (HR: 0.26; 95% CI: 0.16-0.41; p < 0.01) and CSM (HR: 0.07; 95% CI: 0.03-0.16; p < 0.01). Mortality from other causes was similar in the two groups (HR: 0.58; 95% CI: 0.29-1.19; p = 0.14). The negative predictive value (NPV) was 0.94 and the positive predictive value was 0.46. However, around 40% of the FPs was diagnosed with cancer within the first year.

Conclusions
Ruling out cancer by investigation at DOC was associated with low risk of subsequent cancer and the NPV was high. The FPs had higher risk of cancer, mortality, and CSM compared to the TNs.

Clinical trial identification
This is not a clinical trial, but a retrospective cohort study.
The project have been approved by the Danish Data Protection Agency (local j.nr.: HGH-2016-052, I-Suite nr.: 04524) and by the Danish Health and Medicine Authority (nr. 3-3013-1588/1/)

Legal entity responsible for the study
Claus Larsen Feltoft

Funding
Department of Internal Medicine, Herlev and Gentofte Hospital (no specific grant number); Danish Cancer Society (grant number: R152-A9695-16-S7).

Disclosure
All authors have declared no conflicts of interest.

1406P - Increased mutation burden in high-risk lung tissues: Toward precision cancer risk diagnosis

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Background
Mutations are believed to accumulate in normal tissues at extremely low levels as a result of exposure to various carcinogenic factors. The degree of accumulation, namely mutation burden, is likely to be associated with cancer risk. However, owing to the limits of current detection methods for such extremely low frequency mutations, the mutation burden present in normal human lung tissues has been unclear. To overcome this limitation, we established a novel method for the quantification of extremely low frequency mutations in DNA samples. Using this method, we aimed to reveal the presence of mutation burden in normal lung tissues and its association with cancer risk.

Methods
Somatic mutations were quantified in normal lung tissues without smoking history (n = 11) (“entirely normal lung tissues”:G1), normal lung tissues with smoking history (n = 11)
(“smoking-exposed normal tissues”:G2), and non-cancerous lung tissues of patients with lung cancer and smoking history (n = 11) (“smoking-exposed non-cancerous tissues”:G3). A sequence library (15,724 bases of 291 regions of 55 cancer-related genes) was prepared by multiplex PCR using 100 DNA molecules. Libraries were sequenced using a next generation sequencer.

Results
The mutation burden in G3 (2.7 ± 0.8 × 10⁻⁵ mutations/base) was significantly higher than that in G1 (1.8 ± 0.5 × 10⁻⁵ mutations/base) (p = 0.0189). Accumulation of somatic mutations tended to be associated with increased cancer risk (OR = 3.75; 95% CI = 0.54–26.046). C>T mutations were significantly more frequent in G2 and G3 than in G1, which is in accordance with reported mutation signatures in cancer tissues [Alexandrov et al., Science, 354:2016]. GCC>GTC and CCC>CTC mutations, signatures of exposure to the nitrosamines contained in tobacco smoke, were significantly enriched in G2 and G3.

Conclusions
To the best of our knowledge, this is the first study showing that mutations accumulate in high-risk lung tissues due to exposure to tobacco smoking. This will lead to a novel approach to precision cancer risk diagnosis.

Legal entity responsible for the study
Toshikazu Ushijima

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1407P - Change of natural history of hereditary diffuse gastric cancer after identification of a novel CDH1 mutation
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Background
CDH1 germline mutations are the major cause of hereditary diffuse gastric cancer (DGC). Carriers of CDH1 mutations can present multiple signet ring cell carcinoma foci at early age. Therefore, prophylactic total gastrectomy (PTG) is widely recommended. We report a family with a novel CHD1 mutation and analyze endoscopic and PTG findings among the mutation carriers.

Methods
Genetic CDH1 testing by Sanger was performed in a three-generation family with multiple relatives with DGC. Direct sequencing was offered to individuals at risk >18 years. Unaffected carriers were recommended PTG and preoperative esophagogastroduodenoscopy with random gastric biopsies (RGB). Each PTG specimen was wholly sectioned (median # cassettes: 203) to look for occult cancer and histopathology was compared to RGB findings.
Results
A novel pathogenic variant in CDH1 c.48G>A (p.Q16Q) was identified in 28 family members, 16 male/12 female. Prior to variant identification, 6 obligate carriers were diagnosed with an advanced DGC, median age 56 (53-62) years and all died of the disease. After genetic testing, 8 asymptomatic carriers were found early-stage DGC in the PTG specimen, median age 25 (19-59) years. Age-specific frequency of DGC in carriers according to PTG is shown in the Table.

<table>
<thead>
<tr>
<th>Age</th>
<th>No PTG</th>
<th>PTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 8</td>
<td>n = 20</td>
</tr>
<tr>
<td>10-20</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>21-30</td>
<td>3</td>
<td>20%</td>
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<tr>
<td>31-40</td>
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<td>25%</td>
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<td>1</td>
<td>30%</td>
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<tr>
<td>51-60</td>
<td>5</td>
<td>62%</td>
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<tr>
<td>61-70</td>
<td>1</td>
<td>75%</td>
</tr>
</tbody>
</table>

Histopathological RGB and PTG correlation was performed in 17 carriers attended at our institution (May 2013-Sept 2015). Median age at PTG was 34 (19-63) years. All preoperative RGB were negative, but one, which identified a single milimetric DGC foci. PTG specimens revealed one Tis and six T1a DGC, conferring RGB a predictive negative value (PNV) of 66% for DGC. Stage IA DGC had a median of 2.8 foci/gastrectomy, localized in the body (83%) and atrium (17%), with average diameter 0.73 mm and e-cadherin expression in 100% of the foci. No severe postoperative morbidity was recorded after a median follow-up of 29 (16-44) months.

Conclusions
PTG has changed the natural disease history in c.48G>A CDH1 carriers. Endoscopic RGB showed a low PNV for DGC and PTG is still highly recommended. More reliable screening methods are required in order to delay PTG in CDH1-mutation carriers.

Legal entity responsible for the study
Vall d’Hebron Hospital

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1408P_PR - A study of body fat composition, derived from DXA-scans, in association with cancer incidence in postmenopausal women

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Background
Cervical cancer (CC) is the fourth most common cancer in women in France. Human papillomavirus vaccination and screening are complementary secondary prevention measures against CC. Screening by conventional Pap smear is recommended every three years for women aged 25-65y.

Methods
The EDIFICE nationwide observational surveys assess population attitudes to cancer screening in general. Representative samples of the French population aged 50-75 years are interviewed by phone using the quota method. Although the French CC screening program covers all women aged 26-65y, the present analysis pertains to a subpopulation aged 50-65y (N = 356 in 2014 and N = 460 in 2016). Interviewees, with no personal history of cancer, were asked if they had ever had a smear test during a gynecological exam. The date of the last test was noted. Data analysis focused on age group, socioprofessional categories (SPC) and social vulnerability (defined by the EPICE score).

Results
In 2016, 94% of interviewees reported at least one lifetime smear test vs. 99% in 2014 (P<0.01). In line with current interval recommendations, 74% in 2016 and 75% in 2014 (P=0.81) had had the latest test done in the past three years. Younger age groups were significantly more likely to be compliant with the recommendations in 2014 (P<0.01) though not in 2016 (P=0.18). SPC also had a significant impact on compliance rates in 2016 (P=0.01) but not in 2014. Vulnerable women were less likely to be screened at least once in their lifetime; this trend was non-significant in 2014 (98% vs 100% in non-vulnerable, P=0.14) but significant in 2016 (89% vs. 97%, P<0.01). Vulnerable women were also significantly less likely to be compliant with the recommendations (64% vs 81%, P<0.01 in 2014; 63% vs.79%, P=0.01 in 2016).

Conclusions
Between 2014 and 2016, participation in CC screening decreased and compliance rates stagnated. Compliance with screening recommendations was negatively affected by the following: unemployment, low SPC or classification among vulnerable populations. Additional analysis will further investigate these findings, which highlight the need for generalized population-based screening programs and targeted actions for non-participants, as advocated earlier this year by the French National Cancer Institute (INCa).

Legal entity responsible for the study
Kantar Health

Funding
Roche

Disclosure
T. de la Motte Rouge: Consultancy work AstraZeneca, Roche, MSD, Eisai, Sanofi Travel Grants/meeting support Roche, Novartis, Pfizer. Corporate-sponsored research Novartis. J-F. Morere, J-Y. Blay, F. Eisinger: Honorarium fees from Roche Edifice surveys were
Background
Tumour markers are molecules which may be present in higher than usual concentrations in the tissue, serum or other bodily fluids of patients with cancer. Roughly 15 million are requested in the UK each year. They are used to aid diagnosis, guide treatment choice, monitor progress both during and after treatment and guide prognosis. Inappropriate use for diagnosis can cause anxiety, delay correct diagnosis and have an economical implication to the health service. NICE (National Institute for Health and Care Excellence) indicate only four situations where a tumour marker is used for diagnostic purposes, none of these are the use of multiple requests.

Methods
We identified all tumour marker requests within Abertawe Bro Morgannwg University Health Board (ABMU) in Wales between June and December 2015 from both primary and secondary care. We did not include requests from Oncology or Urology. This gave us information about location of request and clinical details for the request. We used patient demographics to see whether there were multiple requests for individual patients. We split the multiple requests from the individual requests and compared these demographics with our local cancer registry. We analysed the clinical notes for those patients who had a positive cancer diagnosis to assess if the tumour marker was of clinical benefit in the diagnostic phase.

Results
In primary care alone there were 12,405 single requests and 985 multiple requests. Of the multiple requests, cancer was only diagnosed in 5% of patients, with the tumour marker being useful in 0.5% of diagnoses. In secondary care there were 4,953 single requests and 762 multiple requests. Of the multiple requests cancer was only diagnosed in 32.4% with the tumour marker being useful in 10% of diagnoses. When extrapolated over a 12-month period there was a cost of nearly £100,000 for the health board.

Conclusions
Inappropriate requesting has economic implications but also increases anxiety and distress for the patient. Unnecessary additional investigations may delay the correct diagnosis and treatment. As a result of the findings we have now provided education through bulletins, presentations and laboratory comments to encourage more appropriate tumour marker requesting consistent with NICE guidelines.

Clinical trial identification
Not Applicable

Legal entity responsible for the study
South West Wales Cancer Centre

Funding
None

Disclosure
Background
Worldwide practices of genetic counseling remain variable. We present genetic counseling, mammography and MRI screening & risk-reducing surgeries on patients with BRCA mutations & VUS of our BRCA mutations study (El Saghir et al, Oncologist 2015).

Methods
Chart review & phone calls for collection of information were done on 45 pts out of the 250 pts tested. IRB approval obtained. 14 pts (5.6% of total) with deleterious mutations & 31 pts (12.4% of total) with VUS were included. 7 pts had metastatic breast cancer. 4 pts were not reachable. We present results on 33 pts for whom we collected information about genetic counseling, screening, Contralateral Prophylactic Mastectomy (CPM) & Risk Reducing Salpingo-oophorectomy (RRSO).

Results
14 pts with deleterious mutations (7 BRCA1 & 7 BRCA2 positive pts) & 19 pts with 20 VUS mutations (4 BRCA1 & 16 BRCA2; 1 pt had both BRCA1 & BRCA2) were examined. Of the 14 pts with BRCA deleterious mutations, 57.14% (8/14 pts) said they received some genetic counseling from their own oncologist and not a specialized genetic counselor. 85.71% (12/14) are undergoing regular screening mammography, 35.71% (5/14) are undergoing regular screening breast MRI. 50% (7/14) underwent CPM & 57.14% (8/14) underwent RRSO. Also, 57.14% (8/14) advised their family members, namely sisters & daughters, to undergo BRCA mutation testing. Of the 19 pts with VUS mutations, only 10.5% (2/19 pts) of the pts said they received some genetic counseling. 78.9% (15/19) are undergoing regular screening mammogram, 31.5% (6/19) are undergoing regular screening MRI breasts. 1 pt underwent CPM & 2 pts RRSO. Also, only 21.0% (4/19) advised their family members to undergo BRCA mutation testing.

Conclusions
The majority of pts with BRCA mutations continue to undergo screening mammography & breast MRI. Only 50% of pts with BRCA deleterious mutations underwent CPM & 60% RRSO, while a few pts with VUS mutations underwent CPM & RRSO. Genetic counseling is mostly done by medical oncologists. Our data supports recommendations to include genetic counseling in the training and Continuing Medical Education CME of Oncologists, and to improve patient education. More importantly, there is an urgent need for more certified professional genetic counselors in Lebanon & worldwide.

Legal entity responsible for the study
Nagi El Saghir

Funding
None

Disclosure
All authors have declared no conflicts of interest.
Background
Ischemic Stroke (IS) has been related to cancer in postmortem studies of oncologic patients and as being the first expression of an occult neoplasm, probably because of hypercoagulability attributed to cancer. The aim of the study was to detect an association between cancer and IS, and possible predictors of cancer among these patients.

Methods
Nine hundred seventeen patients with IS were retrospectively collected from January 2012 to December 2014 in our hospital with a following time of 18 months. Patients with active or previous cancer within 5 years, TIA or cerebral hemorrhage, inability to follow-up or absence of complementary study of IS were excluded. Detection of cancer divided the patients in two cohorts. Demographical, clinical, analytical and prognostic characteristics were collected and subsequently compared between patients with development of tumor (Cancer Patients -CP-) and those free of malignancy (No Cancer Patients -NCP-).

Results
Cancer were detected in 29 out of 381 IS patients who finally met criteria (7.61%), instead of the 17 patients expected, according to cancer incidence in general population. The mean time from IS onset to cancer diagnosis was 6 months, with 44.83% of the diagnoses within the first 6 months after IS. The most frequent locations were colon (24%), lung and prostate (14%). 62% of CP presented metastatic or locally advanced diseas. Older age (p = 0.003), previous cancer >5 years (p = 0.042), higher fibrinogen (p = 0.019) and lower hemoglobin (Hb) values (p = 0.004) were predictors of occult neoplasm. No differences were found in other analytical parameters, thromboembolic risk factors, nor with the etiology and clinical manifestations of the stroke.

Conclusions
In our study IS is associated with cancer, based on the fact that the incidence is almost twice that of general population. The diagnosis of cancer was mainly in advanced stages and within 6 months from IS. It suggests the presence of cancer at the diagnosis of IS due to prothrombotic effect of cancer, without being atributted, therefore, to a greater medical control than general population. Older age, previous cancer, fibrinogen and Hb values were related to the diagnosis of cancer after IS, being potential predictors in this group of patients.

Legal entity responsible for the study
Servicio de Oncología Médica, Hospital Universitario de La Princesa. Instituto de Investigación Sanitaria Princesa

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1413P - Gastric cancer detected after Helicobacter pylori eradication at one private
Background

Helicobacter pylori eradication (Hp-er) has become widespread in Japan since Japanese public insurance started covering that treatment.

Methods

The data of the esophagogastroduodenoscopy (EGD) screening program from June 2012 through February 2017 at Ota Memorial Hospital (OMH) in Japan was reviewed. All cases of gastric cancer (GC) with Hp-er history (Hp-er Hx) detected in the EGD screening program were analyzed to reveal their characteristics.

Results

21,817 individuals were enrolled in EGD screening program of OMH during the above period. 5,563 of them (25.5%) have Hp-er Hx. Fifty cases of GC were found in that program (detection rate 0.23%) and 27 of them (54%) have Hp-er Hx (detection rate 0.49% in participants with Hp-er Hx). The intervals between Hp-er and GC detection were ascertained in 19 cases. Median duration is 3 years and the longest interval is 20 years. Anti-Hp IgG antibody (Hp-Ab) was measured in 26 GC cases with Hp-er Hx. Although 6 cases still had 10 or more than 10 U/ml (Hp-Ab “positive”), other 20 showed less than 10 U/ml (Hp-Ab “negative”) and 5 of them revealed less than 3 U/ml. Seventeen cases (63%) of GC with Hp-er Hx were the current or former smoker. The median of their Brinkman index is 690. Other 10 cases were non-smoker and 8 of them (80%) had family history of GC although only 23.5% had such a family history among current or former smokers with Hp-er Hx. All 27 cases of GC with Hp-er Hx suffered from chronic atrophic gastritis (CAG). Twenty-five of them were diagnosed as the open type (or advanced type) CAG. Other two had the closed type CAG but C-3 (nearly advanced atrophy) in Kimura-Takemoto’s CAG classification. Although GC lesions were localized at any part of the stomach, all of them were found in atrophic gastric mucosa by EGD. Five of them were diffuse type and other 22 were intestinal type on Lauren’s classification in their histopathologic findings.

Conclusions

It is important for individuals with Hp-er Hx to take periodic or annual EGD screening to search for GC because more than half cases of GC had Hp-er Hx in EGD screening program of OMH. Among them, ones with smoking or family history of GC have high risk. It is necessary for such individuals to have meticulous EGD inspection of the whole stomach, especially the area of atrophic gastric mucosae.

Legal entity responsible for the study

Ota Memorial Hospital

Funding

None

Disclosure

All authors have declared no conflicts of interest.

Knowledge of cervical cancer preventive strategies among market women in
Nigeria
Y. C. Adetule (Ibadan, Nigeria)

Background
Cervical cancer is the fourth most common cancer worldwide for females and the seventh most common cancer overall. Nigeria, a developing country, ranked tenth globally and fifth in Africa, has a mortality rate of 22.9 deaths per 100,000 with 14,000 new cases being diagnosed annually. In an effort to reduce this mortality rate, this research was undertaken to assess the level of awareness, attitude and practice of common cancer preventive strategies such as screening and the treatment precancerous lesion using LEEP as a case study among women.

Methods
A descriptive design using simple random sampling methods with self-administered questionnaires or interview methods (for illiterates) were used to collect data from the sample population. Market women were used (4 major markets in Ibadan) because they provided a sample population of women both in their reproductive and menopausal groups, with various level of literacy. Data was analyzed using the SPSS version 15.

Results
Of the total 100 respondents, only 55% had heard about cervical cancer while just 35% had heard about cervical screening test. 26% cited schools while 16% of the 35% cited mass media as their sources of awareness about the disease. 96% agreed that it was important to be screened for early diagnosis, 90% of all acknowledged the importance of this screening test in reducing deaths from cervical cancer. However, only 4% had ever been screened in their lifetime. Despite this, 74% of total respondents had a positive attitude to being screened while an additional 16% would have loved to be screened if the test was made free. On the role of treatment of precancerous lesions as a means of reducing mortality rate, 26% were aware about the Loop Electrosurgical Excision Procedure (LEEP) while only 40% of that agreed that it was curative. 84% agreed that women should be aware about the procedure, 85% agreed that it could reduce maternal mortality rates from cervical cancer.

Conclusions
Despite limitations in funding, it is suggested that more research work can be done to assess possible ethical beliefs towards contraceptives, HPV vaccine and sexual practices and how they affect cervical cancer incidence and mortality rates.

1415P - NGS and Sanger screening for BRCA1/BRCA2, CHEK2 and TP53 in Argentinian high-risk breast/ovarian cancer families and bioinformatic studies: Initial results
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Background
In this study, we aimed at reporting the frequency of BRCA, CHEK2 and TP53 mutations in our high risk breast/ovarian cancer population, in order to determine the role of these genes testing in breast cancer risk assessment.

**Methods**

Total DNA of 484 unrelated cases and 180 relatives were sequence using either Sanger (564) or NGS (100) for BRCA1/BRCA2, CHEK2 and TP53 mutations. While 64.5% (312/484) of the population studied belong to jewish ethnicity, the remaining patients were european-amerindians.

**Results**

Of the 484 probands analyzed, 15.9% were BRCA1/BRCA2 mutation carriers, 9.7% in BRCA1, 6% in BRCA2 and one patient was double heterozygous. Overall, 18.9% of the jewish patients presented ashkenazi founder mutations and 9.9% of european-amerindian population was positive for BRCA mutations. The c.66_67delAG was the most frequent alteration, representing 34.2% of all mutations identified. Pathogenic variants in CHEK2 and TP53 genes were present in 4% and 1.1% of our european-amerindian cases. Eighteen pathogenic variants different from ashkenazi panel were identified in BRCA, three were novel and twelve not previously reported in argentinian population. Twenty-seven variants of uncertain significance were found.

**Conclusions**

An association between genetic ancestry and mutational profile was observed only in the Jewish population. The 66.7% of the pathogenic variants found in our non-jewish cohort were in BRCA2. Our results confirm the high level of admixture present in argentinian population, and highlight the detection of novel variants that could be typical of our region. The knowledge of them is relevant to improve patient risk assessment.

**Legal entity responsible for the study**

Centro Nacional de Genética Médica, ANLIS, Malbrán, Ministerio de Salud de la Nación

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

### 1416P - The change in self-perceived characteristics of health and lifestyle due to colorectal cancer screening invitation and attendance

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#### Background

Previous research implies that colorectal cancer (CRC) screening may have an effect on lifestyle. The aim of the current study was to evaluate the effect of CRC screening on self-perceived health and lifestyle among men and women within a randomized health-services study in Finland.

#### Methods

A random sample of 31951 Finnish men and women born in 1951 were randomized 1:1 for CRC screening for the first time in 2011. A random third received a questionnaire on lifestyle before and after screening in 2010 and 2012 (n = 10271). The current study population responded to the questionnaire on both years (n = 4895). Self-rated health
(SRH), perceived healthiness of diet and perceived physical fitness were assessed with logistic and ordered logistic models using calendar time (2010, 2012), screening randomization and demographic characteristics as covariates.

**Results**

SRH, healthiness of diet and physical fitness improved over time (OR 1.32, CI 1.17–1.48, OR 1.23, CI 1.08–1.41 and OR 1.44, CI 1.28–1.60, respectively). CRC screening invitation had no effect on these measures compared to controls (OR 0.91, CI 0.74–1.12, OR 0.95, CI 0.75–1.20 and OR 1.09, CI 0.87–1.37, respectively). Women reported better health than men. However, further analysis showed that the attender women reported weaker and the attender men better health than the corresponding control groups.

**Conclusions**

CRC screening did not have an effect on self-perceived health and lifestyle. However, the difference between men and women both in controls and in CRC screening attendees needs further research. The randomized setting enables us to generalize of the results to the whole screening target population.

**Legal entity responsible for the study**

Nea Malila

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1417P - Multi-gene panels: new clinical experience in hereditary breast and ovarian cancer**

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**Background**

Mutations in BRCA1 and BRCA2 genes explain about 22% of families meeting testing criteria for hereditary breast/ovary cancer (HBOC). Next-generation sequencing based multi-gene panels allow the analysis of a high number of genes simultaneously with a high sensitivity and are currently integrated into clinical practice.

**Methods**

A total of 177 women/families with clinical criteria for HBOC underwent genetic testing with a 26-gene commercial panel related to hereditary cancer. The analysis included 150 women with a personal diagnosis of BC/OC meeting national consensus for testing except 7 patients that did not comply these criteria, 6 healthy women at high-risk with ≥1 BC/OC affected first-degree relative and 21 patients with a previous BRCA1/2 negative result by other techniques.

**Results**

A total of 11 BRCA1/2 mutations were identified three of which were previously
undetected by other techniques. Mutations in other high or moderate BC/OC risk genes were found: one new mutation in RAD51D gene, two mutations in CHEK2 gene, one mutation in ATM gene, one mutation in PALB2 gene and two probably pathogenic variants in PALB2 and CHEK2 genes (according to predictors in silico). In addition, 8 variants of uncertain significance were detected. Subsequently, members of any of these 18 HBOC families started presymptomatic genetic diagnosis and prevention strategies.

Conclusions
In contrast to traditional sequential testing, the incorporation of multi-gene panels in our clinical practice has allowed us to obtain a more efficient genetic diagnosis on a greater number of families. Detecting actionable mutations in either previous BRCA1/2 negative or other HBOC associated families will optimize candidate identification for changes in medical management. The determination of the pathogenicity of frequent variants of uncertain significance in high or moderate penetrance genes remains the main challenge for cancer geneticists.

Legal entity responsible for the study
Hospital Santa Creu i Sant Pau

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1418P - Clinical features and outcomes of reversible posterior encephalopathy syndrome following bevacizumab treatment
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Background
Reversible posterior leukoencephalopathy syndrome (RPLS), also known as Posterior reversible encephalopathy syndrome (PRES) is a distinct clinicoradiological entity characterized by a constellation of clinical features, and a potentially devastating complication of bevacizumab treatment.

Methods
Patients were identified from the published literature using ‘PubMed’ databases using the terms ‘bevacizumab’ or ‘RPLS’ and ‘RPES’ from January 2006 to December 2016, who developed RPLS (RPES) features within 3 weeks of bevacizumab treatment, who had brain imaging findings of focal vasogenic edema and radiologic proof of reversibility.

Results
To date, a total of 22 cases of RPLS (PRES) following the administration of bevacizumab have been reported in the literature. The mean age at presentation of these patients was 50 years (range 34–74 years), 6 of whom were male and 14 female. Headaches (n = 11), seizures (n = 10), visual disturbances (n = 9) and nausea and vomiting (n = 8) were the common presenting symptoms. In a majority of patients, an increase in blood pressure from their baseline values was observed during their hospitalization. RPLS occurred in 3 patients who received bevacizumab as monotherapy and the rest had received bevacizumab in combination with other chemotherapeutic agents (oxaliplatin, n = 8; fluorouracil, n = 6; leucovorin, n = 5; gemcitabine, n = 3; paclitaxel, n = 3; capecitabine,
n = 3; doxorubicin, n = 2; carboplatin, n = 2; and irinotecan, n = 1). In 20 out of 22 patients, PRES resolved following withdrawal of bevacizumab and strict control of blood pressure. 3 patients also received prednisolone and mannitol as part of their treatment for RPLS. However, 2 out of 22 patients could not recover from severe coma, and died.

Conclusions
A high level of suspicion for RPLS is advisable in patients who develop headache, seizures, visual disturbances, during bevacizumab treatment, either as monotherapy or in combination with other chemotherapeutic agents. These data support the need for close vigilance of neurological features and blood pressure monitoring of patients undergoing bevacizumab treatment. Prompt withdrawal of bevacizumab and blood pressure control appear to portend favorable outcomes in these patients.

Legal entity responsible for the study
OMC-BC

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1419P - Deliberative democracy and cancer screening. The use of citizens’ s juries in health policy decision-making

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Background
Participants in breast cancer screening programmes may benefit from early detection but may also be exposed to the risks of overdiagnosis and false positives. It is argued that citizens’s juries offer important insights into how democratic deliberation could be institutionalised in contemporary political decision making processes. The aim of this deliberative democracy study was to know if Andalucia’s Public Health System should offer screening mammography for women aged 50 and 69 years. We selected a citizens’s jury to evaluate the reasons for their decision and to know the recommendations for politicians.

Methods
Thirteen women aged 50 and 69 years, who regularly participate in the breast cancer screening programme, agreed to participate as a jury to deliberate of the harms and benefits of this controversial topic. The participants were assembled on three consecutive days. On the first day a neutral expert trained the jury to understand the exposures during the second day of two expert witnesses positioned in favor of and against screening mammography, respectively. The third the jury deliberated, extracted its conclusions, cast its vote and exposed its recommendations for politicians. Transcription of the text and the qualitative analysis of the information was done with the support of the ATLAS.ti software.

Results
We observed an improvement in the knowledge using analysis quantitative design. The Citizen’s Jury voted 11-2. Eleven women voted yes and two did not. Women thanks for it, but there are still ignorance and confusion about breast cancer screening. There are three
reasons for voting yes, for their health, for the nature of the test and for their individual freedom. There are women who argue the lack of effectiveness and the cost to justify their negative vote to mammography, at least with a universal character. Women make proposals to policymakers related to improving information, psychological care and research.

Conclusions
Spanish women have a very positive attitude to breast cancer screening although the information transmitted changes the opinion of some women, who want an informed decision making. They bet to maintain or increase the medicalization of their lives.

Legal entity responsible for the study
Dr. José Manuel Baena Cañada

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Disclosure
All authors have declared no conflicts of interest.

1420P - Genetic landscape in HBOC families from Brazil: A mutational analysis

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M. F. Sa Ribeiro (Sao Paulo, Brazil) N. F. Vaz (Sao Paulo, Brazil) B. Garicochea (Sao Paulo, Brazil)

Background
Even if 10% of breast cancers are diagnosed in the context of hereditary predisposition, for a great proportion of families the molecular mechanism of cancer predisposition remains unclear. Founder mutations with increased risk for breast and other cancers have been described in some Latin American countries, but the hereditary breast and ovarian cancer (HBOC) mutational landscape remains understudied in this population of highly mixed genetic contributions. Our study aims to evaluate the contribution of germline BRCA1/2 and moderated penetrance genes mutations in the incidence of HBOC brazilian families.

Methods
This is a retrospective analysis of a series of 666 consecutive patients with HBOC syndrome who underwent genetic test between March 2007 and March 2017 in Sirio-Libanes Hospital. Clinical, pathological and sequencing available data on mutations and unclassified variants in high, moderate and low penetrance genes was analysed.

Results
The majority of the patients were tested in the context of multigene NGS pannels (69%), 205 of the patients had only access to BRCA1/2 full gene screening. A pathogenic mutation was identified in 227 index cases (34%). Unclassified variants (UV) were present in 139 tests (19%). BRCA1/2 mutations could explain the molecular mechanism of cancer predisposition of 133 cases (20%) while TP53 gene was the second most commonly mutated gene in our cohort (46 patients, 7%). 83% of TP53 mutation corresponded to the brazilian TP53 founder mutation R337H (c.1010G>A). Intermediate penetrance genes mutations were present in 22 cases (3,3%): 11 for PALB2, 6 for ATM, 4 for CHEK1, 1 for BRIP1. Mismatch repair genes were mutated in 3% of the patients. The index cases were in majority women (98%) diagnosed with breast cancer under 50 years (34%), 68 (10%) of them with bilateral breast tumors.

Table:
Gene Pathogenic mutations (n) UV
BRCA1 90 17
BRCA2 43 39
TP53 46 6
PTEN 0 1
CDH1 0 6
STK11 0 0
PALB2 11 5
ATM 6 13
BRIP1 2 5
CHEK2 4 10
RAD51C 1 3
BARD1 2 3
BAP1 0 3
MLH1 8 7
MSH2 7 6
PMS2 5 6
MSH6 0 11
EPCAM 0 0
BMPR1 0 0

Conclusions
For the majority of the patients the mechanism of predisposition remains unknown. All together BRCA1, BRCA2 and TP53 mutations could explain the predisposition of 27% of the index cases in our cohort.

Legal entity responsible for the study
Registro de Câncer Hereditário Brasileiro

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1421P - Recommended cancer screening and vulnerable populations: results from the EDIFICE 5 survey
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Background
Based on data from the 2011, 2014 and 2016 EDIFICE surveys, we sought to identify potential links between impoverished living conditions and participation in screening in the context of organized programs (colorectal [CRC], breast [BC] and cervical cancers [CC]).

Methods
The EDIFICE observational phone surveys were conducted among representative population samples (age 40-75 yrs in 2011 [N = 1603] and 2014 [N = 1602]; age 50-75 years in 2016 [N = 1501]) using the quota method. Attitudes regarding screening were assessed in subgroups of individuals within the target age-groups for each screening program. Participation in screening and follow-up rates were assessed by asking if respondents had undergone at least one screening examination in their lifetime and within the recommended time frame (2 yrs for CRC and BC, 3 yrs for CC). Data were analyzed according to the validated EPICES vulnerability score.

Results

For CRC, over the period 2011/2014/2016, participation increased in non-vulnerable subgroups (60% vs. 63%, NS and 63% vs. 68%, P = 0.05) as did follow-up rates (34% vs 33%, NS and 33% vs 40%, P = 0.01). Participation (60%/54%/53%) and follow-up (31%/30%/31%) were stable among vulnerable individuals. Participation was lower in vulnerable vs. non-vulnerable individuals in 2014 (P = 0.02) and 2016 (P < 0.01). For BC, participation rates were stable over 2011/2014/2016, in non-vulnerable (97%/98%/98%) and vulnerable individuals (94%/96%/93%), but follow-up rates decreased (87%/85%/79% and 81%/76%/65%, respectively). In 2016, participation and follow-up rates were lower in vulnerable vs. non-vulnerable groups (P = 0.01, P < 0.01). For CC, participation rates decreased significantly from 2014 to 2016, in non-vulnerable (100%/97%, P = 0.02) and vulnerable individuals (98%/89%, P = 0.02), and follow-up stabilized (81%/79% and 64%/63%). Participation and follow-up were lower in vulnerable vs. non-vulnerable groups in 2016 (P < 0.01, P = 0.01).

Conclusions

The 2016 EDIFICE survey confirms the increasing impact of social vulnerability on recommended screening programs, particularly for CRC.

Legal entity responsible for the study
Kantar Health

Funding
Roche

Disclosure
J-F. Morere, F. Eisinger, J-Y. Blay, S. Couraud, A. Cortot, L. Greillier: Honorarium fees from Roche Edifice surveys were funded by Roche S.A. C. Lhomel: Employee of Roche Edifice surveys were funded by Roche S.A. All other authors have declared no conflicts of interest.

PSYCHO-ONCOLOGY

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1423P - Loneliness and cognitive dysfunction in elderly cancer patients

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S. Aras (Ankara, Turkey)M. Varlı (Ankara, Turkey)F. Çay Şenler (Ankara, Turkey)

Background

The number of geriatric cancer patients is progressively increasing. The evaluation of cognitive functions is important. Loneliness is an emotional experience that results from unmet personal or social requirements. The association between loneliness and cognitive
dysfunction has been well documented in elderly patients. However, there is no data in elderly cancer patients. The purpose of this study is to evaluate the association between loneliness and cognitive dysfunction in geriatric cancer patients.

Methods
Patients, more than 65 years of age, in departments of medical oncology and geriatrics were included. Patients were evaluated with structured questionnaires to define sociodemographic and clinical characteristics. In addition, patients were tested with multidimensional Scale of Perceived Social Support (PSC), UCLA loneliness Scale (ULS), standardized mini mental state examination (SMMSE), Clock drawing test and geriatric depression scale (GDS).

Results
314 elderly patients (214 with a diagnosis of cancer and 120 without cancer) were evaluated. Scores of PSC, ULS, SMMSE were higher in patients without cancer. Median score of GDS in cancer patients was higher than non-cancer patients (4 vs 2, p < 0.001). The analysis of ULS and SMMSE showed a negative correlation between loneliness and cognitive functions ($r = -0.185$, $p = <0.001$). The negative correlation was observed both in cancer patients ($r = -0.206$, $p = 0.001$) and non-cancer patients ($r = -0.262$, $p = 0.002$). In multivariate analysis; presence of depression, low PSC scores and low educational status were associated with high ULS scores. In the multivariate analysis of factors associated with cognitive dysfunction concluded that depression was associated with increased risk of cognitive dysfunction. (RR: 2.64 (1.3-5.1), 95% CI), $p = 0.004$) (Table).

Table: 1423P

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>High Loneliness Score</th>
<th>Cognitive Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR(95%CI)</td>
<td>p</td>
</tr>
<tr>
<td>Presence of depression</td>
<td>1.98 (1.0-3.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Low social support</td>
<td>2.01 (1.1-3.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Educational status- low</td>
<td>3.0 (1.3-6.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;75 years old</td>
<td>1.46 (0.8-2.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Female</td>
<td>1.24 (0.5-2.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>High income</td>
<td>1.36 (0.7-2.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Retired</td>
<td>0.64 (0.2-1.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cancer diagnosis</td>
<td>0.93 (0.5-1.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Live in Rural</td>
<td>1.61 (0.7-3.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Loneliness score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions
In elderly cancer patients, cognitive functions are negatively affected by increased loneliness. However, the association between cancer diagnosis, loneliness and cognitive dysfunction couldn’t be demonstrated in multivariate analysis.

Legal entity responsible for the study
Ali Alkan

Funding
None
Disclosure
All authors have declared no conflicts of interest.

1424P - The study of emotional distress in oncology patients

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Background
A study of the levels of emotional distress in patients during diagnostics and hospitalization was conducted at Petrov Oncology Scientific Research Institute in 2016. The work presented analyzes the results of the study of emotional distress in oncology patients. Groups of oncology patients, who most acutely require professional psychological aid, have been allocated.

Methods
The study is based on the modified distress self-evaluation method of International Psycho-Oncology Society (IPOS).

Results
4,113 patients have been studied in total, of them 2,113 at the stage of diagnosis and 2,000 during hospitalization. The percentage of outpatients who report an abnormal anxiety level on the self-evaluation scale is distributed among nosology as follows: breast – 22%, gynecology – 18%, urology – 16%, unspecified diagnosis – 13%, digestive tract – 11%, lungs – 7%, soft tissue and skin tumors – 5%, and bones – 3%. The analysis of the data distribution between in-patient departments has shown that, among the patients reporting abnormal anxiety levels, 21% are hospitalized in the breast tumors department, 16% in the gynecology department, 10% in the head and neck tumors department, 9% in the radiology department, while the chemotherapy, thoracal surgery and urology departments admit 8% each, 6% are in the oncohematological department, and 5% are in the general oncology department during hospitalization.

Conclusions
More than 40% of oncology patients experience abnormal anxiety levels related to the disease, the treatment and related changes in lifestyle. The majority of patients who describe their anxiety as abnormal have breast cancer.

Clinical trial identification
None

Legal entity responsible for the study
Kristina Kondrateva

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1425P - Risk of mood disorders in long-term cancer survivors: A population-based cohort study

W. Huang (Taoyuan, Taiwan)
Background
Evidence regarding whether long term survivors (≥ 5 years) of adult cancers (LSAC) have a higher risk of mood disorders than the general population is not consistent. We aimed to compare the mood disorder rates between the two cohorts and to identify potential risk factors.

Methods
We conducted a retrospective population-based cohort study using the Taiwan National Health Insurance Research Database. We identified LSAC who were newly diagnosed between January 1, 2000 and December 31, 2007. One control was matched per patient for age, sex, index date, and the Charlson comorbidity index (CCI). The primary outcome was diagnosis of mood disorders during the follow-up period. Cumulative incidences and sub-hazard ratios (SHR) were calculated and multivariate analyses were conducted after adjusting for mortality.

Results
We identified 190,748 LSAC and 190,748 controls. The mood disorder risk was significantly higher in the LSAC cohort than in the control cohort (adjusted SHR = 1.16, 95% confidence interval [CI] = 1.13–1.18, P < 0.0001). Patients with certain cancer types were at increased risk, particularly in the first 2 years after diagnosis. However, patients with head and neck cancers or esophageal cancers had a higher risk after the 5-year follow-up period (incidence rate ratio = 1.40, 95% CI = 1.18–1.67; 2.46, 95% CI = 1.29–4.69, respectively). Multivariate analysis indicated that being female, aged 40–59 years, with more than two primary cancers, receiving two or more treatment modalities, having CCI scores higher than 3, a higher urbanization level, and lower monthly income were independently associated with an increased risk of mood disorders.

Conclusions
Long-term cancer survivors have an increased risk of mood disorders and therefore should be followed-up for depression especially in those with certain site-specific cancer types.

Legal entity responsible for the study
Wen-Kuan Huang

Funding
Chang Gung Medical Foundation, Chang Gung Memorial Hospital at Linkou

Disclosure
All authors have declared no conflicts of interest.

1426P - What oncologists should know about the screening of psychological distress: One example of pilot study in Ancona

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Background
Screening for psychological distress is one of the most important steps in Psycho-Oncology research and clinical assistance. In our Institution, before the present study, four studies have been carried out in this area from 2013 to 2016: 441 people were screened and 881 questionnaires were administered.

Methods
The study has been carried out using the following tools: Needs Evaluation Questionnaire (investigates five areas: informative needs, needs related to assistance and care, relational needs, needs for psycho-emotional support, material needs); Beck Depression Inventory II (BDI II), both for caregivers and for patients; Mini Mental Adjustment to Cancer (MiniMac, for the copying style); State-Trait Anger Expression Inventory–2 (for the expression of anger).

Results
From February to April 2017, 78 people have been screened (44 patients and 34 caregivers; Male/female ratio was 29/49; median age was 54 years (range 21-84); 32% of patients showed informative needs, 48% indicated a psychological need, 18% assistance needs. Depression was more present in patients (30%) than in the caregivers (22%) and problems concerning sleep (65%) and fatigue (60%) were more common; only 61% of patients had a fighting spirit while 24% of caregivers showed a high expression of anger. Fischer test showed a correlation between anxious preoccupation (MiniMac) and symptomatic depression (P = 0.000432860); moreover, Helpless-Hopeless copying style was also related (P = 0.00539636) to depression; caregiver’s expression of aggressiveness (P = 0.114394682) to patients’ anxious preoccupation. The relationship between patients’ depression to caregivers’ aggressiveness requires further investigation (P = 0.247399740).

Conclusions
Psychological screening can fulfill the following aims: discover expressed needs, coping styles, depression, familiar distress, burden. The results and the correlations underline the importance of managing the patients’ anxiety and the expression of the caregivers’ aggressiveness and the relationship of such issues with depression. Moreover, informative needs are associated to the most diffused psychological needs.

Legal entity responsible for the study
Clinica Oncologica Ancona

Funding
Fondazione Rossetti-Fedecostante Ancona

Disclosure
All authors have declared no conflicts of interest.

1427P - Biopsychosocial factors underlying older patients treated for an incurable cancer in a two-tiered health care system in Brazil

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W. Dale (Duarte, United States of America)

Background
Patients with advanced cancer experience symptoms that include pain, fatigue, and depression. We sought to describe prevalence and identify factors associated with biopsychosocial distress in older patients (65+) diagnosed with cancer stage IV.

Methods
Participants were recruited from two different types of health care facilities, public [PUB] and private [PRI] institutions, in Brazil. A cross-sectional analysis of common
biopsychosocial symptoms (anxiety, depression, pain, and fatigue), and quality of life
reported by older patients undergoing chemotherapy treatment was performed.

Results
Older patients (n = 167) were enrolled (Mean age=73; SD = 5.6); 59.3% from PUB.
Majority were female (56.3%; 38.9% PUB), white (68.9%; 35.7% PRI, p<.01), married
(59.3%; 32.1% PUB, p<.01); and diagnosed with GI (29.9%; 15.8% PUB), GU (16.2%;
4.9% PUB), and hematologic (13.8%; 7.5% PRI) cancers. Almost 16% of patients reported
depression symptoms (9.6% PUB) and 12% of anxiety (8.4% PUB). PUB patients also
reported associated lower QOL, which is at 50th percentile of the US norm (PRI is at 75th
percentile). PUB patients reported significantly more biopsychosocial problems including
distress (21.6% vs 7.2%), pain (28.1% vs 12.0%), fatigue (34.7% vs 16.8%), sleep (22.8%
vs 15%), neuropathy (22.8% vs 8.4%), and financial toxicity (16.2% vs 5.4%), compared
to patients treated at PRI (all p < 0.05). Mostly pain (B = 1.8; B=-6.6), fatigue (B = 0.8;
B=-6.5) and sleep (B = 1.2; B=-8.3) were associated with moderate to severe distress and
worst QOL (all p<.01).
Conclusions
Older patients with late-stage cancer in Brazil suffer substantial unrecognized morbidity
which impacts their distress and QOL. Biopsychosocial screening for older patients should
be included in quality cancer care. Moreover, patients treated within PUB show worse
outcomes than PRI counterparts, and they are at higher risk for multiple physical,
psychological, and financial morbidity. Earlier initiation of biopsychosocial screening with
appropriate supportive care may improve their QOL.

Legal entity responsible for the study
Cristiane Decat Bergerot

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1428P - Family-associated factors influence the postoperative prognosis in patients
with non-small cell lung cancer

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T. Akamine (Fukuoka, Japan)
F. Hirai (Fukuoka, Japan)
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T. Okamoto (Fukuoka, Japan)
Y. Maehara (Fukuoka, Japan)

Background
The relationship between family-associated factors and the postoperative prognosis is
unknown in patients with non-small cell lung cancer (NSCLC). We hypothesized that
family-associated support was associated with postoperative prognosis via nutritional
pathway. The aim of this study is to elucidate the relationship between family-associated
factors and postoperative prognosis in patients with NSCLC.

Methods
We selected 195 patients with NSCLC who underwent curative surgery between 2005 and
2010 whose computed tomography images within 1 month preoperatively and after 1 year
postoperatively were available. The nutritional indices such as prognostic nutritional index
PNI), controlling nutritional status (CONUT), modified Glasgow prognostic score (mGPS) and skeletal muscle area (SMA) were used to estimate the change in nutritional condition after 1 year postoperatively. Paravertebral muscle area at the 12th thoracic vertebra level was used to analyze the SMA.

Results
One hundred and forty-four patients (73.8%) had both children and a partner. Twenty-seven (13.8%) only had children and 14 (7.2%) only had a partner. Childless patients showed a significantly shorter overall survival (OS) and disease-free survival (DFS) than those with children (p<0.05 and p<0.05, respectively). The postoperative exacerbation of PNI, CONUT, mGPS and SMA were found to be significantly correlated with childless patients compared with those with children (p=0.002, p=0.001, p<0.001 and p=0.029, respectively). Childless patients with a partner showed a particularly shorter OS and DFS than those with children (p<0.001 and p<0.001, respectively). The childless patients with a partner showed significant postoperative exacerbation of PNI, CONUT, mGPS and SMA compared with those with children (p=0.037, p<0.001, p<0.001 and p=0.039, respectively).

Conclusions
The patients without any children had a significantly poorer postoperative prognosis than those with children. The childless partner-present patients showed a particularly shorter OS and DFS than those with children. It was suggested that the childless patients were significantly associated with postoperative exacerbation of the nutritional status.

Legal entity responsible for the study
Shinkichi Takamori

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1430P - Sexual functioning and quality of life in Egyptian premenopausal patients receiving treatment for breast cancer

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Background
In Egypt, due to cultural reasons, breast cancer patients may suffer in silence struggling with their sexual problems. This is the first study to explore the sexual functioning of Egyptian breast cancer patients receiving anti-cancer treatment.

Methods
The study included 105 married premenopausal patients aged ≤55 years, who underwent surgery and were receiving adjuvant treatment. We used the Arabic validated versions of the EORTC quality of life questionnaire (EORTC QLQ-C30, v 3.0) and the breast cancer module (EORTC QLQ-BR23) to assess quality of life and the female sexual function index (FSFI) to assess sexual functioning.

Results
The median age of patients was 43 years, 11% of them were employed, 81% were literate and 98% were circumcised. The average FSFI score was 16 (±9). The FSFI differed
significantly according to systemic treatment \( (p = 0.007) \). Patients receiving chemotherapy had the lowest score \((12 \pm 8.5)\) and those receiving tamoxifen had the highest \((18 \pm 8.5)\). The FSFI score did not differ according to the type of surgery \( (p = 0.892) \). However, the body image scale of EORTC QLQ-BR23 was significantly better among patients who underwent breast conservative surgery compared to modified radical mastectomy \( (p = 0.004) \). There was a significant positive correlation between the FSFI score and the scores of global health status \( (p < 0.001) \), physical functioning \( (p = 0.002) \), role functioning \( (p < 0.001) \), emotional functioning \( (p = 0.004) \), social functioning \( (p = 0.041) \) scales of EORTC QLQ-C30 and body image \( (p < 0.001) \) and future prospective \( (p < 0.001) \) scales of EORTC QLQ-BR23. There was a significant negative correlation between the FSFI score and scores of fatigue \( (p = 0.001) \), pain \( (p = 0.006) \) and appetite loss \( (p = 0.028) \) scales/items of EORTC QLQ-C30 and systemic therapy side effects \( (p = 0.003) \) scale of EORTC QLQ-BR23.

Conclusions
The current results suggest that Egyptian breast cancer patients receiving chemotherapy experience significant sexual dysfunction. The type of surgery has no direct effect on sexual functioning, but may affect it indirectly through its impact on body image satisfaction. Overall, sexual dysfunction is strongly related to the quality of life in this group of patients.

Clinical trial identification
Legal entity responsible for the study
Ain Shams University, Cairo, Egypt

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1431P - Primary results of a study to evaluate a decision aid for women offered neoadjuvant systemic therapy for breast cancer

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Background
Women diagnosed with large or highly proliferative operable breast cancer may be offered neoadjuvant systemic therapy (NAST) for reasons including downstaging, prognostication or expanding surgical options. We aimed to systematically develop, and evaluate a DA for women who had been offered NAST.

Methods
Eligible women who were considered candidates for NAST, from four Australian recruiting centres were enrolled in a single arm longitudinal study. Participants completed online questionnaires prior to accessing the DA, and on three occasions post-DA. Primary outcomes were feasibility of use, and acceptability to patients and clinicians. Secondary outcomes were patient reported measures relevant to patient decision-making.

Results
Seventy-nine women were offered study participation and 59 enrolled. Patients were
typically well educated, married, had health insurance and were information seekers (mean information needs: 7.5/10; SD 1.84). 59/79 (74.7%) patients who were offered study participation accessed the DA and 49 (79.7%) of those 59 participants reported having read it. 41/51 (80.4%) participants who completed the post-DA assessment reported that the DA helped them with their decision about NAST. 51/59 (86%) participants elected to receive NAST. 16/18 (88.9%) investigators would continue to use the DA in routine practice. Post-DA, decisional conflict decreased significantly across all subscales (p < 0.01); anxiety and distress decreased significantly; 86.3% achieved at least as much decisional control as they desired; a high level of knowledge was demonstrated; and 39/51 (76.5%) patients had a high (≥24) Satisfaction with Decision score (mean 25.5, SD 3.6). 84.4% reported that they shared responsibility for the decision about NAST. Investigators reported that the DA was able to be integrated into patient care.

Conclusions
Study primary outcomes were positive, showing the DA was feasible and acceptable to patients and clinicians. Improvements in decision-related outcomes were demonstrated, and the DA could be included in routine workflow. This DA can be implemented into routine clinical practice for women with operable breast cancer who are candidates for NAST.

Clinical trial identification
Registration: Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au): ACTRN12614001267640

Legal entity responsible for the study
Australia and New Zealand Breast Cancer Trials Group

Funding
HCF Research Foundation Australia and New Zealand Breast Cancer Trials Group

Disclosure
All authors have declared no conflicts of interest.

1433P - Burnout syndrome: What impact on clinical research?
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Background
Burnout is a job-related psychological syndrome causing depersonalization, emotional exhaustion and lack of personal accomplishment. Albeit studies mainly focus on professionals who have a direct contact with patients, physicians and nurses, little is known about burnout among other professionals employed in clinical research, that requires stressful efforts to maintain quality standards. We decided to evaluate perceived and actual burnout levels experienced by professionals who are at the “bottleneck” of research: Clinical Research Coordinators (CRCs).

Methods
The Gruppo Italiano Data Manager spread an anonymous questionnaire among about 130 CRCs. The survey consisted of 8 items on workload and perceived stress levels and a specific burnout test developed by a group of Italian psychologists.

Results
The survey was completed by 36% of subjects. On average, interviewed CRCs work 42 hours/week and follow 25 studies; 89% feel stressed and 64% believe that this affects negatively the quality of their work. Moreover, 57% of CRCs declare that this condition may soon cause a job change. The major sources of stress are: contract type (43%); workload (17%); lack of skills recognition (11%). Interestingly, the factor that most frequently has been identified among the first 3 causes of stress is the contract type (81%), followed by lack of skills recognition (32%). Based on the psychological test, the average stress level of the sample is 68 points out of overall 225; the highest levels pertain the emotional (average: 17.0/45) and physical spheres (16.3/45), while the social area is the least affected (9.7/45). Stress levels show only a very weak correlation with workload (Pearson coefficient = 0.062) and hours worked (0.095).

Conclusions
Albeit almost all CRCs perceive high levels of stress, psychological testing shows a medium-low degree of burnout. An explanation could be that CRCs are settled into distressing work conditions, so this no longer results in burnout. Burnout was substantially uncorrelated to quantitative estimates of workload, rather depending on other, qualitative, factors, such as lack of skills recognition and contractual instability. Lastly, our data suggest that current workload evaluation methods, mainly based on the number of followed studies, are no longer appropriate.

Clinical trial identification
na

Legal entity responsible for the study
Gruppo Italiano Data Manager (GIDM)

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1434TiP - Effectiveness of the HuCare Quality Improvement Strategy on health-related quality of life in patients with cancer: Study protocol of a stepped wedge cluster randomized controlled trial (HuCare2 study)
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Background
Our group previously demonstrated the feasibility of the Hucare Quality Improvement Strategy – HQIS, aimed at integrating into practice 6 psychosocial interventions recommended by international guidelines. This trial will assess whether the introduction of the strategy in oncology wards improves patient Health-related quality of life (HRQoL).

Trial design
Multicenter, incomplete stepped-wedge cluster randomized controlled trial, conducted in three clusters of 5 centers each, in three equally spaced time epochs. The study also includes an initial epoch when none of the centers is exposed to the intervention, and a final epoch when all centers will have implemented the strategy. The intervention is applied at a cluster level, and assessed at an individual level with cross-sectional model. 720 patients who received a cancer diagnosis in the previous 2 months and about to start medical treatment will be enrolled. Primary aim is to evaluate the effectiveness of the
HQIS vs standard care in terms of improvement of at least one of two domains (emotional and social functions) of HRQoL using the EORTC QLQ-C30 questionnaire, at baseline and at 3 months. This outcome was chosen because cancer patients generally exhibit low HRQoL, particularly at certain stages of care, and because it allows to assess the strategy's impact as perceived by patients themselves. The HQIS comprises three phases: 1) clinician training - to improve communication-relational skills and instruct on the project; 2) center support – 4 on site visits by experts of the project team, aimed to boost motivation, help with context analysis and identification of solutions; 3) implementation of EBM recommendations at the center.

Clinical trial identification
NCT03008993

Legal entity responsible for the study
Italian Association of Medical Oncology (AIOM)

Funding
Association of Medical Oncology (AIOM); MEDeA (non-profit volunteer association)

Disclosure
All authors have declared no conflicts of interest.

PUBLIC HEALTH

J. Martin-Moreno (Valencia, Spain)

1445P - Inclusion of older patients with colorectal cancer in clinical trials: the SAGE prospective multicenter cohort study

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F. Brunetti (Créteil, France) T. Aparicio (Paris, France) R. Coriat (PARIS, France) K. Maley (Paris, France)
O. Colussi (Paris, France) C. Tournigand (Creteil, France) E. Paillaud (Créteil, France)
S. Bastuji-Garin (Créteil, France)

Background
Whereas older patients represent the major part of new cancer cases, their underrepresentation in clinical trials leads to weak external validity. The main objective was to assess the proportions of older patients for whom there is an ongoing clinical trial available, eligible to at least one trial, invited to participate and finally included. Secondary objective was to investigate associated factors.

Methods
The SAGE multicenter prospective cohort study settled up in 7 centers in Paris Area between 2013 and 2016. All patients aged 65 years or more with a colorectal cancer were included. The endpoints were 1) the presence of at least one ongoing clinical trial available regarding stage and tumor location 2) the patient's eligibility 3) invitation and 4) inclusion.

Results
577 patients (mean age: 75.6 years +/-7; 56% of men; 74% of colon tumor; 40.9% with metastasis) were included; 37 trials were ongoing (9 trials in median per center; academic sponsors: 62.2%; phaseI/II: 59.5%; chemotherapy: 75.7%). Overall, 12.3% of patients were included in a trial (65-69 yrs class: 19.1%; 70-75 yrs: 14.9%; 75-79 yrs: 12.8%; 80
18% (103/577) had none available trial for his/her stage and tumor location; among patients with available trial, 73% (347/577) were non-eligible; from the remaining, 34% (43/127) were not invited; from the remaining, 19% (17/88) refused to participate. Non-eligibility was, by order of frequency, related to tumor characteristics (31%), requested para-clinical exams (19%), history of anti-cancer treatment (15%), comorbidities (13.5%), functional status (10%) and age (5%). Among eligible patients, increased age, Performance Status and decreased Body Mass Index were independently associated with non-inclusion (Table). Among patients invited to participate, patient’s refusal was not associated with age.

### Table:

**1445P Factors independently associated with non-invitation to clinical trials in older eligible patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted Odds Ratio (95%CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years 65-60</td>
<td>Reference (1.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>70-75</td>
<td>0.26 (0.07-0.90)</td>
<td></td>
</tr>
<tr>
<td>75-80</td>
<td>0.23 (0.06-0.96)</td>
<td></td>
</tr>
<tr>
<td>&gt; 80</td>
<td>0.05 (0.01-0.29)</td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>Reference (1.00)</td>
<td>0.02</td>
</tr>
<tr>
<td>1</td>
<td>0.19 (0.06-0.62)</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>0.50 (0.09-2.75)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>21-24.9 Reference (1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>&lt; 21</td>
<td>0.25 (0.07-0.90)</td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>0.76 (0.24-2.42)</td>
<td></td>
</tr>
</tbody>
</table>

*Hierarchical multivariate logistic regression with the patient at the level 1 and the center at the level 2 and adjustment for all variables listed in the table, the number of trials in the center and the number of chemotherapy trials.

### Conclusions

Inclusion of older cancer patients decreased dramatically after 80 years. Non-eligibility was the main reason for non-inclusion but rarely related to chronological age. Moreover, one-third are non-invited to participate and one-fifth refused.

### Clinical trial identification

NCT01754636

### Legal entity responsible for the study

AP-HP (Assistance Publique - Hôpitaux de Paris)

### Funding

French Ministry of Health - PHRC

### Disclosure

All authors have declared no conflicts of interest.

1446P - Risk of second primary cancers and competing mortality in survivors of adult-onset cancer: changing pattern over three decades

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Background
Survivors of first adult-onset cancers are at risk of developing second primary cancers (SPCs) and are at risk of death from their subsequent cancers and other competing causes. Here we investigated patterns of incident SPC risk and cause-specific mortality in survivors of adult-onset cancer during the past three decades.

Methods
Data were extracted from the population-based Tasmanian Cancer Registry in Australia. Patients diagnosed with a first primary cancer between 1980 and 2009 were followed for incident SPCs to December 31, 2013 and for deaths to December 31, 2014. SPC risks were quantified by using standardised incidence ratios (SIRs). Trends in SPC risk over time were assessed in multivariable Poisson models. The cumulative incidence and subdistribution hazard ratios (SHR) of cause-specific deaths were estimated using competing risk models.

Results
5,339 SPCs were observed from 51,802 cancer survivors. The SIRs for any SPC increased from 0.98 with a first cancer diagnosis in 1980-1984 to 1.12 in 2005-2009. The increase in SIRs was significant in multivariable Poisson models (P<0.001). Deaths were identified in 39,976 (69.8%) of 57,288 patients. The 5-year cumulative incidence of death due to first primary cancer gradually decreased from 57.2% for a first cancer diagnosis in 1980-1984 to 30.7% in 2005-2009. However, the 5-year cumulative incidence of deaths due to subsequent cancers varied across periods of first cancer diagnosis, with an increase from 1.0% in 1980-1984 to 1.7% in 1995-1999, and a decrease to 1.4% in 2005-2009. The SHR of deaths due to first primary gradually decreased over time in multivariable competing risk models, but varied over time for deaths due to subsequent cancers: the SHR increased from 1.00 (reference) in 1980-1984 to 1.19 (95%CI 1.03-1.36) in 1995-1999, then decreased to 0.80 (95%CI 0.69-0.94) in 2005-2009.

Conclusions
The risk of SPC has increased in Tasmania over the last three decades. While the risk of death due to first primary cancer decreased over time, the risk of death due to subsequent cancers did not. The increased risk of deaths from subsequent cancers might be an outcome of overdiagnosis of first primary cancer in the 1990s.

Legal entity responsible for the study
Menzies Institute for Medical Research, University of Tasmania

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1447P - Reporting of results of randomized trials in common cancers in the lay media
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Background
Limited data exist about the role of the lay media (including the financial press) in the dissemination of results of randomized controlled trials (RCTs) in common cancers.
Methods
We searched clinicaltrials.gov to identify phase III RCTs evaluating new drugs in breast, colorectal, lung and prostate cancer. We included all completed and active trials that have completed accrual between 1 January 2005 and 31 October 2016. Reporting of trials in the lay media was identified by a systematic search of Lexis-Nexis Academic using the name of the drug and trial. Scientific reporting was defined as presentation at a conference or publication in full in the scientific literature. Associations between reporting in the lay media before scientific reporting and study design, results and sponsorship were evaluated using logistic regression.

Results
Of the 180 RCTs identified, 55% were positive, 79% were performed with palliative intent and 79% evaluated targeted therapies (including endocrine and immunotherapy). We identified 93 (52%) reports in the lay media (66% of positive trials and 38% of negative trials). In 49 cases (27%) reporting in the lay media occurred before scientific reporting with an increasing trend over time (p = 0.009). Among these, 53% presented quantitative data. The median time between lay media reporting and scientific reporting was 16 weeks (range 1-220 weeks). Reporting in the lay media before scientific reporting was associated with positive results (OR 3.12, p < 0.001), industry compared to academic sponsorship (OR 3.20, p = 0.04), palliative intent (OR 2.84, p = 0.04), journal impact factor of full publication (OR 1.02, p = 0.03), evaluation of targeted therapy compared to chemotherapy (OR 3.70, p = 0.05) and prostate cancer compared to breast cancer (OR 4.86, p = 0.003). There was no association between early reporting in the lay media and study endpoint, or quantitative reporting.

Conclusions
Over a quarter of all RCTs in common cancers are reported in the lay media before they are reported scientifically. Positive trials, industry sponsorship, palliative intent, journal impact factor and evaluation of new targeted therapy, especially in prostate cancer are associated with early reporting in the lay media.

Legal entity responsible for the study
Eitan Amir

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1448P - Effect of rural residence (RD) and distance travel to the cancer center (DTC) on neoadjuvant chemoradiation (NCRT) in localized rectal cancer
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Background
Neoadjuvant chemoradiation therapy (NCRT) has been associated with a lower rate of local recurrence and represents an accepted standard of care. Yet, access to treatment or decisions about treatment can be affected by contextual factors such as rural residence (RD) and distance travel to cancer center (DTC). In the current study, we evaluated relationship between RD and DTC and NCRT.
Methods
A cohort of patients diagnosed with localized rectal cancer during 2009-2013 in the province of Saskatchewan was studied. The logistic regression analyses were performed to assess relationship between RD and DTC and lack of NCRT.

Results
Total 279 patients were identified with median age of 66 yrs (IQR:59-76) and M:F of 1:0.71. 94 (33.6) had a major comorbid illness. 183 (65%) were rural resident. The median DTC was 141 km (IQR 7-233). Of 279 patients, 116 (41%) were referred for NCRT, 161 (58%) underwent upfront surgery, and 2 declined surgery. The mean DTC for group treated with NCRT was 111.5 ±122km compared with 169.0±176km if they did not receive NCRT (p = 0.001). Of urban resident, 52/96 (54%) were referred for NCRT compared with 64/183 (35%) of rural resident (p = 0.002). After excluding 33 (12%) patients who had clinical stage I disease and underwent upfront surgery, a univariate regression analysis revealed that both DTC (OR 1.92, 95% CI: 1.15-3.20) and RD (OR 2.51, 95%CI: 1.46-4.32) were significantly correlated with lack of NCRT. On multivariate analysis following relationships were noted with lack of NCRT. Age ≥ 70 yrs (OR 1.45, 95%CI: 0.84-2.45), comorbid illness (OR 1.52, 0.86-2.67), ECOG performance status of > 1 (OR 1.25, 0.49-3.17), DTC (OR 1.07, 0.51-2.23), and RD (OR 2.56, 1.17-5.57).

Conclusions
Our results revealed that RD but not DTC is associated with a lower rate of NCRT in patients with localized rectal cancer. Future studies are required to explore the underlying cause of differential referral.

Clinical trial identification
Not applicable

Legal entity responsible for the study
Saskatchewan Cancer Agency

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1450P - European survey of 907 people with cancer about the importance of nutrition

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Background
Nutritional and metabolic disorders are highly prevalent among cancer patients. We aimed to analyse the dimension of nutritional alterations among cancer patients and survivors in Europe by using a structured questionnaire encompassing the perspectives of patients and their physicians on nutritional issues.

Methods
A structured questionnaire was designed to analyse the importance of nutrition for people with cancer. The questionnaire was subdivided in specific areas of interest, such as the presence of feeding problems, perception of nutrition importance, role of food supplements, and their view of their physician’s approach to nutrition. All cancer patients
and survivors were eligible to answer the questionnaire, except for people diagnosed with brain and breast cancer. The study was conducted by the European Cancer Patient Coalition (ECPC), Sapienza University of Rome, and Healthware International. ECPC ensured the dissemination of questionnaire to its Members in 10 countries, who translated and disseminated the questionnaire.

**Results**
The survey was answered by 907 cancer patients and survivors. 59.2% (n = 537) of respondents were diagnosed with cancer less than 3 years ago, and 46.2% (n = 419) were treated for cancer for 1 year or less (46.2%; n = 419). 82.4% of respondents (n = 689) believed it was important to maintain physical activity during cancer treatment, although only 53.8% (n = 450) of the respondents reported that their physicians advised them to do so. 72.9% (n = 603) of the respondents didn’t know the meaning of the term “cachexia”, and 92.4% (n = 764) did not receive any information about cachexia from their health professionals. 69.7% (n = 586) of respondents reported that they lost weight after the cancer diagnosis, and for 36.7% (n = 309) of respondents this loss was moderate to severe.

**Conclusions**
Most people with cancer surveyed reported that they would like to receive more information about how to improve their nutrition during and after treatment. There is a need to empower individual patients and patient associations by producing more information on cancer patients’ nutritional needs. Such information material should be produced by patients in close collaboration with medical oncologists and other healthcare professionals.

**Legal entity responsible for the study**
European Cancer Patient Coalition

**Funding**
Baxter and Helsinn

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

1451P - Breast cancer specific survival (BCSS) in young women <40 years with node negative luminal breast cancer (BC) treated based on tumor gene expression

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**D. Miller** (Redwood City, United States of America) **A. Kurian** (Stanford, United States of America) **V. Petkov** (Bethesda, United States of America)

**Background**
BC at a young age is generally associated with poor prognosis, more aggressive treatment, long-term toxicities, and unique psychosocial concerns. Little data is available on outcomes defined by molecular profiles. We characterized BCSS in female patients (pts) <40 y with node negative (N0), hormone receptor positive (HR+), HER2 negative disease who were treated based on 21-gene assay Recurrence Score (RS) result.

**Methods**
RS results were provided electronically to SEER (US population based cancer registries) per their linkage methods (Petkov et al, npj Breast Cancer, 2016). Eligible pts were diagnosed (Jan 2004 - Dec 2012) with N0 HR+ BC, and had no prior malignancy or
multiple tumors. BCSS was analyzed for female pts <40 and ≥40 y with RS results, excluding HER2+ disease. Survival was compared using a log-rank test.

Results
1,761 of 7,186 pts <40 y (24.5%) had RS results. The proportion of pts <40 with RS < 18, RS 18-30, and RS ≥ 31 was 47%, 42%, and 11%, respectively. 47,644 of 203,033 pts ≥40 y (23.5%) had RS results. The proportion of pts ≥40 y with RS < 18, RS 18-30, and RS ≥ 31 was 56%, 37%, and 8%, respectively. The distribution of tumor size and tumor grade was similar in younger and older pts. Reported CT use increased with increasing RS, and was higher for pts <40 y (p < 0.001). Continuous RS result was associated with BCSS for both <40 and ≥40 y (p < 0.001). 5-y BCSS with RS < 18 was excellent for 820 younger pts <40 y, even in those without reported CT use (Table). Similar results were observed for ages <30 y (n = 120), 30-34 y (n = 411), and 35-39 y (n = 1,230).

Table: 1451P

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<tr>
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<th>RS &lt; 18</th>
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<th>RS 18-30</th>
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<th></th>
<th>RS ≥ 31</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>CT (%)</td>
<td>5-y BCSS (95% CI)</td>
<td>N</td>
<td>CT (%)</td>
<td>5-y BCSS (95% CI)</td>
<td>N</td>
<td>CT (%)</td>
<td>5-y BCSS (95% CI)</td>
</tr>
<tr>
<td>All Pts (N = 49405)</td>
<td>27308</td>
<td>7% (99.4%,99.7%)</td>
<td>18268</td>
<td>35% (98.5%,98.9%)</td>
<td>3829</td>
<td>70% (94.4%,96)</td>
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<tr>
<td>&lt;40 y (N = 1761)</td>
<td>820</td>
<td>17% (100.0%,100.0%)</td>
<td>744</td>
<td>56% (98.8%,100.0%)</td>
<td>197</td>
<td>80% (85.9%,97)</td>
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<tr>
<td>≥40 y (N = 47644)</td>
<td>26488</td>
<td>6% (99.5% (99.4%, 99.6%)</td>
<td>17524</td>
<td>34% (98.7%, (98.4%, 98.9%)</td>
<td>3632</td>
<td>70% (95.5%, (94.4%,96)</td>
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</tbody>
</table>

Conclusions
This large population-based study of N0 HR+ HER2- BC indicates not all young women have aggressive tumor biology and poor prognosis. Nearly half (47%) of women <40 y have RS < 18 and favorable 5-y BCSS with limited CT use. An important minority (11%) with high RS have worse outcomes despite CT. Longer term follow-up is planned.

Legal entity responsible for the study
National Cancer Institute

Funding
National Cancer Institute

Disclosure
S. Shak: Full-time employee of Genomic Health and a shareholder of Genomic Health. D. Miller: Employee of Genomic Health. All other authors have declared no conflicts of interest.

1452P - Risk of malignant mesothelioma in Spain from environmental asbestos exposure
J. S. Torres-Roman (Ica, Peru)G. Lopez-Abente (-, Spain)J. M. Sanz-Anquela (-, Spain)

Background
The link between malignant mesothelioma (MM), and asbestos exposure (AE), is very high. AE may have occupational or environmental non-occupational source. The highest levels of AE occur in the workplace and mainly affect men. However, environmental AE,
affect men and women equally. As the occupational AE prevails over the environmental non-occupational, a sex-ratio < 2 alert of possible environmental AE. The objective of this study is to evaluate the spatio-temporal distribution of the sex-ratio, in order to identify those areas with possibly higher environmental AE.

Methods
We conducted an analysis of the 6,143,124 deaths in Spain during the period 2000–2015, looking for those deaths caused by MM. Information regarding sex, year of death, age at death, province, and cause of death (ICD-10) was extracted from the deceased registry of the National Institute of Statistics. We calculated the sex-ratio between the deceased by MM according to its distribution by provinces and years, and the ratio of mortality rates adjusted for age (European standard population). We also obtained the proportion of MM among the total deceased (MM per 10,000 deaths).

Results
MM deaths were 5,345. Men 4,025 and women 1,329 (sex-ratio: 3.31). During the 2000-2015 period the sex-ratio remained relatively stable, ranging from 2.21 in 2007 to 4.31 in 2005. In the years 2000 and 2015 the sex-ratio was 3.34 and 3.07, respectively. Likewise, in the years 2000 y 2015 the men/women age-adjusted rates was 2.83 and 3.93, respectively. The variations by provinces were more pronounced. The lowest sex-ratio (1.5) corresponded to the 140 deaths of Navarre and the highest (12.67), to the 41 deaths of Vitoria. Other low sex-ratio values were detected for Almeria (2,07), Donostia (2,02), Huesca (2) and Tarragona (1,97). Among these provinces with a possible higher environmental AE risk (sex-ratio equal to or < 2.07), Donostia and Navarra have a high MM mortality (more of 13/10,000 deaths), but the other have a low or medium mortality.

Conclusions
The high provincial variability in Spain of the proportion of women who died of MM, makes necessary the carry out of new research focused in the provinces detected as with a possible greater risk of environmental asbestos exposure in the general population.

Legal entity responsible for the study
Jose Miguel Sanz-Anquela; Junior Smith Torres-Roman

Funding
None

Disclosure
J.M. Sanz-Anquela: Occasionally has served as a consultant to the court, always at the request of plaintiff asbestos victims. All other authors have declared no conflicts of interest.

1453P - Tobacco exposure and adverse pathological features in oral cancer: Does age impact survival?

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Background
The role of tobacco in oral cancer is well established, however there is a wide variation in the incidence of tobacco-related oral cancer in the literature, ranging between 70-90%. Our data shows that only half of the patients with oral cancer have any history of tobacco
exposure (smoking, chewing or others). Younger patients with oral cancer (<50 years) are being shown to be a distinct subset of patients, with more aggressive disease, possibly due to an underlying immunological basis. No previous literature has shown if the effect of tobacco exposure is similar in all age groups.

**Methods**

From a prospectively maintained database of patients treated for oral cancer in our institution, we extracted details for 643 patients of oral cavity squamous cell carcinoma. We divided these patients into four groups, younger patients (<55 years) with or without tobacco exposure and older patients (≥55 years) with or without tobacco exposure and compared the effect of any tobacco exposure on prognostically relevant variables (like diameter, depth of invasion, extranodal extension). We also compared the progression free survival (PFS) and overall survival (OS) between those with and without tobacco exposure in each age group separately.

**Results**

The percentage of those with tobacco exposure was comparable in both age groups. Tobacco exposure correlated with tumour thickness (p = 0.001), perineural invasion (p = 0.002), lymphovascular invasion (p = 0.004) and local recurrence (p = 0.006) in the younger patients but not in the older patients. In younger patients, those with tobacco exposure also had a positive trend for poorer differentiation (p = 0.07) and extranodal extension (p = 0.06). Patients <55 years who had a history of tobacco exposure, had a significantly worse PFS and OS (p = 0.03). In patients ≥55 years, the PFS and OS between the cohorts with and without tobacco exposure was comparable (p = 0.10).

**Conclusions**

Younger patients with exposure to tobacco have worse clinical outcome, possibly as a result of adverse pathological features like perineural invasion and lymphovascular invasion. Whether this relationship is due to an underlying immune mechanism requires further study. Younger tobacco users with oral cancer are more likely to have a poor prognosis.

**Clinical trial identification**

This is not a clinical trial

**Legal entity responsible for the study**

Amrita Institute of Medical Sciences, Kochi, India

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1455P - Initiation of systemic anti-cancer treatment in the inpatient setting in a tertiary hospital in London**

J. Lam (London, United Kingdom)K. Ng (London, United Kingdom)T. Emms (London, United Kingdom)R. Gillmore (London, United Kingdom)

**Background**

The landscape of adult medical oncology care has shifted across the past three decades from the hospital to the outpatient setting, reflecting factors such as patient preference, technological advancements in the delivery of therapeutics, and cost-effectiveness. There
are no recent guidelines to indicate when systemic treatment should be initiated as an inpatient. This clearly presents difficulties, particularly since inpatients are associated with a poorer performance status.

**Methods**

We retrospectively generated data of patients at the Royal Free Hospital commencing cycle 1 of chemotherapy as an inpatient, with a particular focus on 30-day mortality, overall survival, performance status recorded prior to initiation, treatment dose and line of therapy. Data was collected over a period of 24 months from January 2015 to December 2016.

**Results**

We identified 34 patients across a range of tumour types and with varying performance status who fulfilled our criteria. The median age of patients treated was 54.5 years. Of these, the 76% (26/34) were administered full dose therapy, with 17.6% given a 25% dose reduction, and 5.8% given with a 50% dose reduction. Of the 34 cases, 76% (26/34) were first line therapy. The treatment intent in all cases was palliative, except one case where the intent was neoadjuvant. There was a positive correlation between performance status, full-dose therapy, and first line therapy with survival (Table 1). The outcomes of inpatients were significantly worse than outpatients. 7 of 34 in our cohort died with 30 days (20.5%), while only 38.3% of them were alive at 6 months. This is compared to the overall 30-day mortality rate of our department at 2.9%. Table:

**Table:**

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<thead>
<tr>
<th>Performance Status</th>
<th>Median Survival (Days)</th>
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<tr>
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<td>1</td>
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<tr>
<td>2</td>
<td>61</td>
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<td>64</td>
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<table>
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<th>Line of Therapy</th>
<th>Median Survival (Days)</th>
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</thead>
<tbody>
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<td>1st line</td>
<td>107.5</td>
</tr>
<tr>
<td>2nd line</td>
<td>68</td>
</tr>
<tr>
<td>3rd line</td>
<td>12</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of Therapy</th>
<th>Median Survival (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Dose</td>
<td>110</td>
</tr>
<tr>
<td>80%</td>
<td>46</td>
</tr>
<tr>
<td>75%</td>
<td>24</td>
</tr>
<tr>
<td>50%</td>
<td>38</td>
</tr>
</tbody>
</table>

**Conclusions**

1) Inpatients commenced on systemic treatment are associated with poorer overall survival compared with outpatients. 2) We would suggest adherence to the new ‘2016 UK CQUIN: Optimising Palliative Chemotherapy Decision Making’, which recommends peer discussion within the MDT when chemotherapy is commenced or continued when PS is greater or equal to 2, or decisions regarding commencement of 2nd line treatment or beyond are required, when there is outright progression through the first cycle of chemotherapy.
Background
Recent studies suggest an increase in the incidence of colorectal cancer (CRC) in young-age patients. Data concerning clinical behavior, pathologic findings and prognosis are still poorly understood for this age group. The aim of this study is to analyze clinical features and survival of the young-onset CRC population in our institution.

Methods
We retrospectively reviewed records of 5,806 patients diagnosed with CRC between January/2011 and November/2016 in Instituto do Câncer do Estado de São Paulo and identified 781 patients aged 50 years or younger Kaplan-Meier method was used to estimate overall survival (OS) and uni/multivariate analysis were carried out to identify factors associated with OS.

Results
We found an absolute increase in the incidence of CRC in patients < 50 years by 1.88% to 2.23% annually (2011-2012: 11.6%; 2013-2014: 13.5%; 2015-2016: 15.7%) with a relative increase of 35.3% between 2011 and 2016. Median age was 42 years (17-49), 57.4% were female and 20.9% reported family history (FH) of CRC. Mismatch repair (MMR) protein immunohistochemical analysis were performed in 466 patients and 78 (16.7%) had MMR deficient CRC. Left-sided tumors were more frequent (left colon 8.2%, sigmoid 33.7% and rectum 31.5%), whereas the incidence of right-sided tumors was 19.4%. Almost all of patients were symptomatic (93.9%) and abdominal pain (39.6%) and rectal bleeding (28.7%) were common. MMR deficiency was associated with better OS (p = 0.029). The stage distribution was stage I 2.6%, II 25.8%, III 34.1% and IV 37.5%. The median OS of stage IV was 25 months (CI95% 20.7-29.3) and not reached for I-III (p < 0.001). FH of CCR (p = 0.021) and adjuvant chemotherapy (p < 0.001) were independently associated with better OS in stage IV. For stages I-III, wild-type KRAS (p = 0.003), FH of CCR (p = 0.024) and absence of lymphovascular invasion (p < 0.001) were associated with better OS.

Conclusions
In our experience, the incidence of early-onset CRC is increasing. Young patients were more likely to be diagnosed with metastatic disease, left-sided/rectum site and symptoms at presentation. These findings highlight the emerging importance of young-age onset colorectal cancer.
CRC and the need to discuss strategies to early diagnosis.

Legal entity responsible for the study
Instituto do Câncer do Estado de São Paulo

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1457P - Improved provision of written information on metastatic spinal cord compression to at-risk cancer patients at a tertiary referral centre

P. Mahaligam (London, United Kingdom) K. Ng (London, United Kingdom) A. McLaren (London, United Kingdom) K. Fordham (London, United Kingdom) J. King (London, United Kingdom)

Background
Metastatic spinal cord compression (MSCC) affects up to 10% of patients with disseminated malignancies, and early diagnosis correlates with improved clinical outcomes. Up to 85% of patients who present with MSCC already have motor deficit by the time of presentation. We investigated our Trust’s compliance with national guidelines on providing at-risk patients with written information on the signs and symptoms of MSCC. Following a period of educational intervention we re-audited our practice.

Methods
All Oncology doctors and Specialist Nurses at the Royal Free Hospital were completed an online survey on their knowledge of national guidelines and their clinical practice. We delivered an educational intervention (including formal teaching and presentation at Departmental meetings, case discussions and providing patient information leaflets to clinicians) and re-audited our practice after 3 months.

Results
There were 29 and 20 respondents to the baseline and repeat surveys respectively. 57% vs 84% reported being moderately or very familiar with the MSCC guidelines; 32% vs 47% reported knowing where the information leaflets were kept; 3% vs 15% reported providing written information on MSCC to at risk patients at least every month. (baseline and repeat surveys, respectively)

There was a consensus amongst the clinicians that patients with spinal metastases should be considered at “highest risk”, and verbal information about the risks of MSCC was most commonly given to this group. There was a 42% increase in the proportion of respondents who provided written information on the risk of MSCC to patients with spinal metastases (19 vs 61%) following the intervention.

Conclusions
1) Provision of written patient information leaflets, formal education sessions and case discussions with clinicians resulted in increased knowledge of guidelines on MSCC at 3 months, and positive changes in clinical practice. 2) There was a significant increase in the provision of written information to the highest risk patient groups (19 to 61%). 3) By increasing patient awareness, we can increase the proportion of early self-presentations and diagnosis. This will lead to prompt intervention and improvement of neurological outcomes.

Clinical trial identification
Background
The impact of mastectomy on social well-being (SWB) and family dynamics (FD) may involve the individual, social role and perception of the usefulness of social and family support affects. The purpose of the current study is to identify that impact and its related implications on SWB and FD.

Methods
This was a cross-sectional study in which a total of 173 female patients who had mastectomy in GS hospitals completed a face-to-face questionnaire designed by the researchers; which contains 3 sections including: socio-demographic data, SWB and FD. All measures utilized a five-point Likert-type scale ranging from 1 (worst outcome) to 5 (best outcome). The study was conducted at European Gaza Hospital (n = 60) and Alshifaa Hospital (n = 113) in the GS from August 2015 to September 2016. The data was analyzed using SPSS software.

Results
Among 173 female patients, the mean age was 51 years ± 10. About 91% were unemployed, 52% had low income and 73% were of low educational level. The overall SWB score was negatively affected by 44.2% (mean score= 2.21 ± 1.33). Seventy percent of patients had a financial impact and decreased home activities. Interestingly, 57.8% claimed that involvement in family activities was not affected after mastectomy. Shockingly, 95.4% of women worried of getting divorced due to their illness. The overall impact on FD is estimated to be by 49.2% (mean score= 2.46 ± 1.64). Surprisingly, the diagnosis of BC had an impact on sexual performance in 27.1% compared to 19.1% after mastectomy.

Conclusions
Improving patients’ quality of life should be one of the primary goals of BC treatment. Involving patient’s family in the process of medical care may promote their SWB and FD. However, the great fear of divorce found in this study, demonstrates the insecurity of women within the society of Gaza and is possibly an expression of the lack of security in
the Gaza-Strip. Assessing and addressing the SWB and FD among BC patients may enhance providing a holistic medical care and further research in the future can help in implementing this.

**Legal entity responsible for the study**
Faculty of Medicine at the Islamic University of Gaza, Gaza-Strip, Palestine.

**Funding**
None

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

### 1459P - Cancer incidence and mortality trends in Crete, Greece during the last two decades (1992-2013): Results from the cancer registry of Crete

**V. Chatzea (Heraklion, Greece)**
D. Sifaki-Pistolla (Heraklion, Greece)
F. Koinis (Heraklion, Greece)
E. Saloustros (Heraklion, Greece)
L. Vamvakas (Heraklion, Greece)
G. Pitsoulis (Heraklion, Greece)
N. Tzanakis (Heraklion, Greece)
D. Mavroudis (Heraklion, Greece)
V. Georgoulis (Heraklion, Greece)
C. Lionis (Heraklion, Greece)

**Background**
Cancer registration is the systematic collection of data about cancer and tumor diseases and is a valuable tool for understanding what causes cancer and how best to diagnose and treat it. In Greece, this data collection is managed only in the island of Crete, by the Cancer Registry of Crete (CRC). In this study, we present data on the cancer incidence and mortality for all neoplasms in Crete, during 1992-2013. Secondary objectives were to map the longitudinal trends of all MN and per type.

**Methods**
Data were obtained from the Cancer Registry of Crete which is the only population-based registry in Greece since 1992 (permanent residents=623,000). Data were coded according to the ICD-10 and included several parameters on demographics, medical history, and lifestyle factors. Age-standardized incidence/mortality/100,000/year (ASIR, ASMR) were estimated, while Bayesian models were performed to assess any longitudinal variations (a = 0.05).

**Results**
ASIR and ASMR for all cancers in Crete were 302.8 and 150.5 respectively. Cancer of the lung and bronchus is the most common invasive cancer and cause of cancer mortality in males and females (40.2 new cases/100,000/year and 36.5 deaths/100,000/year). Colorectal cancer accounted for 25.1 new cases/100,000/year and 14.7 deaths/100,000/year, and breast cancer for 28.6 new cases/100,000/year and 11.1 deaths/100,000/year. The invasive neoplasms that presented the greatest statistically significant increasing trends during the past 22 years were: lung and bronchus (in women), colorectal cancer (in both sexes), cervical cancer, leukemia (in men) and thyroid cancer (in both sexes).

**Conclusions**
Although the Cretan cancer rates are still lower than the mean European ones, significant increasing trends were identified; indicating the urgency for clinical and public health
measures. Since the cancers that account the most in this increase are preventable by smoking cessation, screening, and vaccination. High priority should be given to the development of population-based interventions.

**Legal entity responsible for the study**
University of Crete

**Funding**
Region of Crete

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

**1460P - Robotic anticancer drug compounding assist system for the preparation of injectable antineoplastic drugs**

**S. Masuda (FUKUOKA, Japan)**H. Watanabe (FUKUOKA, Japan)T. Irisa (FUKUOKA, Japan)
K. Hata (FUKUOKA, Japan)A. Kumagai (FUKUOKA, Japan)C. Tanaka (FUKUOKA, Japan)
N. Ozawa (FUKUOKA, Japan)K. Nakashima (FUKUOKA, Japan)

**Background**
Many antineoplastic drugs are known to be mutagenic or teratogenic. Medical personnel handling antineoplastic drugs are at a high risk of occupational exposure. Therefore, in collaboration with Yaskawa Electric Corporation and Nikka Micron Co., Ltd, we developed the Cancer Drug Compounding Assist System (CDCAS). The CDCAS is an automated robotic system designed to efficiently facilitate the accurate preparation of drugs based on dose. In this study, we evaluated the CDCAS for accuracy, site contamination, and washing performance in the preparation of antineoplastic drugs.

**Methods**
5-Fluorouracil (5-FU; 600, 800, or 1200 mg) was added to 100 mL of saline; 5 samples of each formulation were prepared. The weight of the mixed drugs prepared using the CDCAS was compared to those prepared by a pharmacist, and the accuracy of each preparation was calculated in terms of percentage relative error. The acceptable variance was set at ±5%. To test for contamination, cyclophosphamide (800 mg) was continuously added to 50 bags of 100 mL saline solution. Then, 25 locations inside the isolator were identified for measurement. Cyclophosphamide was collected from those sites by using a sampling sheet method. Twenty of those samples revealed adherence of 5-FU (300 µL) to the infusion bag surface. Ozonated water was used to wash 5-FU from the surface of the infusion bags. After the washing process, any 5-FU remaining on the infusion bag surface was recovered via a wiping method.

**Results**
The average weight error ratio for the CDCAS and the pharmacist was −0.62% and 2.69%, respectively. Contamination of cyclophosphamide was confirmed at eight sites. Pollution of 5-FU was confirmed for two samples, and the removal rate was ≥ 99.9%.

**Conclusions**
Our study demonstrated that the CDCAS’s preparation accuracy and cleaning performance are within acceptable limits. Thus, the CDCAS could be used to potentially reduce occupational exposure to antineoplastic drugs.

**Legal entity responsible for the study**
Satohiro Masuda
Funding
None

Disclosure
All authors have declared no conflicts of interest.

1461P - Monitoring of contamination with cytostatics in pharmacies and hospitals in the Czech Republic
S. Kozakova (Brno, Czech Republic)

Background
Monitoring of contamination with cytostatics was introduced in practice in the Czech Republic by CYTO project managed by the pharmacy of Masaryk Memorial Cancer Institute (MMI) in years 2006-2010. The number of prescriptions of cytostatic drugs increased within the Czech Republic from 23000 bags and syringes in 2010 up to 38000 in 2015. So as to set up standards for the protection of healthcare professionals, it is necessary to monitor contamination regularly at all work sites engaged in compounding or administration - both in the pharmacy (Pharm) and at the hospital departments (HD)/stationaries (S). We have introduced the monitoring of cyclophosphamide (CP) and Pt cytostatics (Pt) to routine practice in 2007. In 2015, there was also implemented monitoring of 5-fluorouracil (FU). These drugs belong to the most frequently used cytostatics in MMI (49.0% of compounded units).

Methods
The samples for detection of contamination of surfaces were collected with a nonwoven swab. CP and FU were assessed with HPLC with TQ-S MS, with limits of detection 1.1 pg.cm$^{-2}$ for CP und 7 pg.cm$^{-2}$ for FU. Pt cytostatics were analyzed by MS with inductively coupled plasma proving LOD 0.7 pg.cm$^{-2}$.

Results
Maximal levels of FU detected on floors were: 775 pg.cm$^{-2}$ at HD, 564 pg.cm$^{-2}$ in P, at compounding units and 25 pg.cm$^{-2}$ in P, in storage rooms. Similarly, maximal detected levels of CP on floors were found at the HD: 3244 pg.cm$^{-2}$, 638 pg.cm$^{-2}$ in the P, compounding units and 235 pg.cm$^{-2}$ in P, in the storage rooms. Maximal detected levels of Pt on floors was again found in the HD, with levels of 5390 pg.cm$^{-2}$, then 84 pg.cm$^{-2}$ in P, compounding units, and 57 pg.cm$^{-2}$ in P, in the storage rooms.

Conclusions
According to our findings, hospital pharmacists are able to decrease the contamination on their workplaces. On the other hand, improvement is needed at the hospital departments and stationaries, where hospital pharmacists may co-operate on setting the safety standards.

Legal entity responsible for the study
Masaryk Memorial Cancer Institute

Funding
Masaryk Memorial Cancer Institute

Disclosure
All authors have declared no conflicts of interest.
1462P - New treatments in Oncology: Clinical practice regarding the management of Adverse Events (AEs). Results from a survey conducted by the Hellenic Group of Young Oncologists (HeGYO)


**Background**

Targeted therapies with distinct toxicities have revolutionized treatment of advanced cancer. Aim of this study was to assess patterns of practice for the management of these AEs, which can impair patient's quality of life and hamper compliance, potentially leading to treatment failure.

**Methods**

Between March 2017 and May 2017, an online questionnaire was distributed by HeGYO to oncologists to provide their answers anonymously.

**Results**

79 oncologists participated in the survey. The majority were medical oncologists (80%), 18% were clinical/radiation oncologists and 2% haematologists oncologists. Of them, 30% were in specialty training and 72% were ESMO members. Although 64.6% stated that they are very familiar with the new treatments in oncology, the majority (67.1%) spend less than 30% of their treatment initiation visit to inform pts on AEs. Only a minority (29.1%) gives diaries to pts for self reporting of AEs, but 59.4% offers educational material and 89.8% reaches proactively to pts. 53.2% do not make follow up phone calls between scheduled visits, while 58.2% report that there is not a call center service available in their institution for the pts to report AEs. More than 80% of oncologists described their practice to treat toxicities as more guideline-based than empiric and 92.4% of them were keen to refer pts to other medical specialties to optimize management of toxicities. 60.8% reported that a dose reduction or discontinuation was necessary in 10-30% of their pts and 59.5% reported that at least 1 of their pts discontinued treatment without informing them. Time constraints and the chaotic nature of web information were the predominant barriers interfering with doctor's education.

**Conclusions**

This survey emphasizes the unmet need for continuous education among health professionals and pts and effective multidisciplinary collaboration for the optimization of AEs management. The majority of participants acknowledged the importance of informing their pts and treating their side effects according to guidelines. However, they describe significant obstacles in their daily practice.

**Legal entity responsible for the study**

Hellenic Group of Young Oncologists (HeGYO), under the auspices of the Hellenic Society of Medical Oncology (HeSMO)

**Funding**

None

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

1463P - Oncologists’ perspectives on biologic substitution
M. Reilly (Washington DC, United States of America) A. Spiegel (Bala Cynwyd, United States of America)

Background
Biosimilars are similar but not identical to originator biologics. As more biosimilars are approved, pharmacy or hospital-level substitution of biologics is becoming more common, potentially excluding physicians from decisions regarding the treatment of their patients.

Methods
The Alliance for Safe Biologic Medicines (ASBM) conducted regional, 15-minute web-based surveys among biologics prescribers around the world to determine their opinions on biologic substitution. Prescribers were asked to rate: (1) the importance of authority to decide the most suitable biologic for their patients, (2) the importance of designating a biologic as “dispense as written” (DAW, or equivalent), (3) the acceptability of biologic substitution, and (4) the importance of notification of biologic substitution.

Results
A total of 1,856 responses were received: 470 (25%) Europe, 427 (23%) Canada, 400 (22%) US, 399 (21%) Latin America, and 160 (8.6%) Australia. Across regions, most prescribers were from the hospital setting, and most had ≥ 11 years in practice. Between 10% and 25% of prescribers were oncologists (16% Europe, 10% Canada, 16% US, 18% Latin America, and 25% Australia). Across regions, most oncologists (75%) feel that it is critically/very important to have sole decision-making authority regarding the suitability of a biologic, and 71% that it is critically/very important to have DAW authority. Only 6% of oncologists feel that pharmacy-level substitution is totally acceptable; 58% consider switching to a biosimilar unacceptable, and 36% consider switching acceptable provided it has been agreed to in advance. Most (76%) also feel that it is critically/very important to be notified of pharmacy-level substitution. Responses were mostly aligned across regions; however, one notable difference was the relatively low percentage of Australian oncologists (23% vs 58% overall) who feel that substitution is unacceptable.

Conclusions
Our survey indicates that most oncologists believe it is important for them to be able to control which biologic—original product vs biosimilar—they prescribe for their patients. This is likely to become increasingly important with the availability of biosimilars used for curative intent.

Legal entity responsible for the study
Alliance for Safe Biologic Medicines

Funding
Amgen and AbbVie

Disclosure
M. Reilly: Funding from Amgen and AbbVie Inc.
A. Spiegel: Funding from BIO, PhRMA, Amgen, Roche, EMD Serano.

1464P - Ukrainian Association for helping patients with lymphoproliferative diseases: Patients support care program
I. Kryachok (Kiev, Ukraine) O. Novosad (Kiev, Ukraine) T. Skrypets (Kiev, Ukraine) T. Kadnikova (Kiev, Ukraine) I. Titorenko (Kiev, Ukraine) O. Aleksik (Kiev, Ukraine) K. Filonenko (Kiev, Ukraine) A. Martynchyk (Kiev, Ukraine)
Background
Treatment patients with cancer, including chronic lymphoproliferative diseases (CLPD), includes not only special therapy, such as surgery, chemo- and radiation therapy, as well as psychological and social support to this group of patients. With this goal, the first Ukrainian Association for helping Patients with Lymphoproliferative Diseases (UAPLPD) was founded in 2006.

Methods
1) To cooperate with various institutions and doctors who treat patients with CLPD. 2) To create programs which promote social assistance and protection for patients with CLPD 3) To create an appropriate financial framework for solving diagnosis and treatment difficulties.

Results
Currently, there are 18 centers in 24 regions of Ukraine and 1000 members (25% of health professionals and researchers and 75% of patients and their family members) in UAPLPD. Each year, the number of association members is growing rapidly. Since 2006, the association has been carrying out a lot of activities aimed to support patients, their relatives and of course, doctors. Nowadays, we have 6 ongoing projects: “Lymphoma day”, “Psychological help for patients and relatives”, social project with Ukrainian pop-stars “I will survive…”, program which help to reduce prices for expensive drugs “Support patient”, “Art against cancer” and “Survivors day”. Within the framework of all projects, the association provides a lot of charity concerts, art exhibitions, shoot video for promo-actions, provide art-therapy, therapeutic horse riding. There are also many educational events for patients and doctors. The UAPLPD pays attention to the assistance for diagnosing and treating patients and partially allocates money for reagents purchasing, perform PET/CT scans for free to over 40 patients annually and could cover cost-effective treatment. The Association has printed out a lot of informational material such as patient brochures on nutrition, physical therapy with our patients' stories and examples. We update and edit this information annually, including the scientific editions as well. The latter one include guidelines for diagnostic and treatment multiple myeloma, anemia, the evaluation of response after treatment in patients with lymphoma. Since 2015, a psychologist has been working for a full time at the oncohematology department.

Conclusions
The work of the Association for helping patients is very important and necessary for effective treatment and patient rehabilitation.

Legal entity responsible for the study
I. Kryachok

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1465P_PR - Do oncology patients understand clinical trials? A nationwide study by Cancer Trials Ireland
Background
Clinical trials are critical to improve cancer outcomes. We conducted a nationwide survey to assess oncology patients (pts) understanding of some fundamental concepts in clinical trial methodology.

Methods
Patients with a diagnosis of malignancy, ≥18 years, able to provide informed consent and complete a questionnaire independently were eligible. Questionnaires were administered to pts attending 14 cancer centres across Ireland. Collection began 22nd April 2016 and ended Nov 23rd 2016.

Results
The median age of the 1,090 pts completing the survey was 60 years (IQR 50-69), comprising 386 (35.6%) men and 697 (64.4%) women. 303 pts (27.8%) stated they had previously participated in a cancer clinical trial. Most were diagnosed between 2014-2016 (694, 66%). Breast (31.4%), colorectal (15.6%), haematological (12.6%), genitourinary (11.6%) and lung (6.8%) were the most commonly reported cancer types. Almost all pts (n = 1048, 98.3%) considered it important to have clinical trials available in Ireland. Most pts (n = 841, 82.3%) reported understanding the term medical/cancer clinical trials. Pts were given statements about clinical trials and asked to indicate whether they were ‘True’ or ‘False’ or to mark as ‘Don’t know’ if they were unsure. When asked ‘In a randomised trial the treatment you get is decided by chance’ 334 (33.5%) pts answered ‘True’, 425 (41.4%) answered ‘False’ and 257 (25%) answered ‘Don’t know’. When asked ‘Clinical trials are only used when standard treatments have not worked’ 226 (22%) pts answered ‘True’ and 273 (26.6%) answered ‘Don’t know’. When asked ‘My doctor would know which treatment in a clinical trial was better’ 581 (56.5%) pts answered ‘True’, and 238 (23.2%) answered ‘Don’t know’. When asked ‘My doctor would make sure I get (got) the better treatment in a clinical trial’ 633 (60.9%) answered ‘True’. Of the 303 pts who had taken part in a cancer clinical trial 185 (63.6%) answered ‘True’.

Conclusions
Although oncology pts consider it important to have clinical trials available to them, many do not understand key concepts such as randomisation, chance and equipoise. The data collected from this study will be used to address this and develop customised interventions to improve understanding and informed trial participation.

Legal entity responsible for the study
Catherine M. Kelly

Funding
Funding provided to Cancer Trials Ireland by Amgen, Abbvie, Bayor and Inveva

Disclosure
C.M. Kelly: Funding was provided by the following companies; Bayer, Amgen, Abbvie, Inveva to Cancer Trials Ireland (formerly ICORG) our National Clinical Trials group. The research conducted was totally independent of these funders. All other authors have declared no conflicts of interest.

1466P - Feasibility and barriers to optimal oncological treatment in solid organ transplant patients with de novo cancer

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Background
Transplanted patients (tpts) display higher cancer incidence rates compared to general population. Anti-tumor treatment after transplantation remains scarcely described. This study aimed to report oncological therapy feasibility and outcome in tpts with de novo cancers.

Methods
We retrospectively analyzed all consecutive cases of de novo cancer in renal and liver tpts treated in our center. Pts were identified based on systematic research in tpts databases from 2000 to 2016. Pts presenting with non-melanic cutaneous tumors only were excluded. Clinical features, treatments, toxicity and survival data were collected. Active optimal treatment was assessed by comparing treatment that was actually administered with guidelines.

Results
Among 4637 tpts, 209 cases of de novo cancer were identified in 176 (3.8%) pts. Mean age was 52.5 +/- 11.3 at transplantation and 59 +/- 10.6 at cancer diagnosis; 122 (69%) were men; 96 (55%) were renal tpts and 80 (45%) liver tpts. At cancer diagnosis, performance status (PS) was 0-1 in 89% (n = 142/160). Tumor type was mainly epithelial (75%, n = 150/200); tumor stage was localized in 80% (n = 163/205) and advanced in 20% (n = 42/205). Among pts with initially localized tumors, 13% (n = 22/163) had cancer recurrence. Median overall survivals of pts with localized and advanced cancer were of 166 (CI95%: 100.3-ND) and 8.8 (CI95%: 5.0-47.2) months, respectively. Among pts with initially localized tumors, 13% (n = 22/163) had cancer recurrence. Median overall survivals of pts with localized and advanced cancer were of 166 (CI95%: 100.3-ND) and 8.8 (CI95%: 5.0-47.2) months, respectively. Among pts with localized tumors, 80% (n = 134/156) received optimal treatment. Reasons for non-optimal treatment were comorbidities in 36% (n = 8/22), risks for the transplant in 36% (n = 8/22), and/or toxicity in 36% (n = 8/22). In contrast, at advanced/recurrent stage, only 36% (n = 19/53) of pts received optimal treatment, and 28% (n = 15/53) best supportive care only. Barriers to optimal treatment were comorbidities in 19% (n = 6/32), risks for the transplant in 22% (n = 7/32), toxicities in 19% (n = 6/32), and poor PS in 33% (n = 17/32).

Conclusions
Oncological treatments are feasible in tpts and survival seems similar to general population. Concerns about the risk of toxicity for the transplanted organ and comorbidities were the main reasons for non-optimal treatment. These observations warrant confirmation in a prospective multicenter study.

Clinical trial identification
1467P - Generating patient reported outcome norms for an EU cancer population using real world data (FACT-G)

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B. Bennett (Bollington, United Kingdom)  K. Byrne (Bollington, United Kingdom)  P. Hallworth (Bollington, United Kingdom)
T. Desai (Bollington, United Kingdom)  K. Cocks (Bollington, United Kingdom)

Background
The main aim of this analysis was to generate population norms from an EU sample of cancer patients for the FACT-G instrument using real world data. Comparisons were made between existing norms based on a US population and the newly developed EU norms.

Methods
Data was collected through the Adelphi Real World Disease-Specific Programmes (DSPs) across breast, gastric, melanoma, non-small cell lung and prostate cancers. Cross-sectional surveys were administered to physicians and patients between January 2015 and March 2017, resulting in a total sample of 4899 patients. The US population norms outlined by Brucker et al. (Evaluation & the Health Professions. 2005;28(2):192-211) are commonly used to aid interpretation of FACT-G scores but there are no large sample norms specifically derived for the EU population. Analysis included checking internal reliability of the FACT-G sub-scales in the EU sample and comparisons between the EU and existing US population norms using minimum important differences (MIDs) of 3 points for FACT-G sub-scales and 7 points for total FACT-G score (Yost et al. Evaluation & the Health Professions. 2005;28(2):172-191).

Results
The EU sample had similar population characteristics to the US sample with respect to age, gender and ECOG status but consisted of a wider sample of cancer types (including haematological cancers). Internal consistency was met (α > 0.7) for all sub-scales within the FACT-G for the EU population. Comparisons between the population norms indicate differences in FACT-G scores between the EU and US samples based on MIDs. Differences exceeding MIDs were noted across social well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and overall FACT-G, but not for physical well-being (PWB). Further analysis was undertaken to explore differences by gender.

Table:

<table>
<thead>
<tr>
<th>SWB</th>
<th>EWB</th>
<th>FWB</th>
<th>PWB</th>
<th>FACT-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU mean score</td>
<td>17.4</td>
<td>13.3</td>
<td>12.3</td>
<td>18.5</td>
</tr>
<tr>
<td>US mean score</td>
<td>22.1</td>
<td>18.7</td>
<td>18.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Population difference</td>
<td>4.7*</td>
<td>5.4*</td>
<td>6.6*</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Indicates MID exceeded.

**Conclusions**
Differences highlighted between FACT-G scores for the EU and US cancer populations indicate that population norms may be region-specific or specific to cancer type. The resulting EU population norms can be used to aid interpretation of FACT-G scores across a range of cancer types.

**Legal entity responsible for the study**
Adelphi Real World

**Funding**
None

**Disclosure**

**1468P - Development of a web-based application using machine learning algorithms to facilitate systematic literature reviews**

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H. H. Samawi (Vancouver, Canada) J. Lavoie (Vancouver, Canada) A. Spreafico (Toronto, Canada)
A. R. Hansen (Toronto, Canada) S. Sahebjam (Tampa, United States of America) L. L. Siu (Toronto, Canada)
S. P. Ivy (Bethesda, United States of America) C. Paller (Baltimore, United States of America)
D. Renouf (Vancouver, Canada)

**Background**
Systematic review is an important element of medical research but rapid proliferation of published literature presents challenges to manual review. Computer science advances can improve workload by using algorithms to automatically select and extract data from articles. We initiated a systematic review of phase I immunotherapy clinical trials and used natural language processing to aid article screening.

**Methods**
A literature search was performed across MEDLINE, Embase and CENTRAL in September 2016 using 100+ search terms in the categories “neoplasm”, “immunotherapy” and “phase I clinical trial”. Only English language studies published since 1990 were included. We developed a web-based interface that allowed human reviewers to apply inclusion/exclusion labels based on title and abstract screening. Articles were screened by two independent reviewers who were blinded to results. An article similarity based algorithm using weighted logistic regression to predict “include” and “exclude” labels is being trained and herein we report interim results.

**Results**
28,235 articles were identified from the literature search; 19,000 remained after duplicates and conference abstracts were excluded. 4,034 (21.2%) were screened, of which 532 (13.2%) were labeled “include” by at least one reviewer. 1,944 (10.2%) were screened by two reviewers with concordance of 93.7%. The prediction algorithm was weighted to improve the detection of “include” labels, and achieved 80.6% sensitivity and 78.2%...
specificity when compared to manual review results. The positive and negative predictive values were 34.4% and 96.6%, respectively.

**Conclusions**
A machine learning algorithm trained on manual reviews was able to predict systematic review article inclusion with approximately 80% accuracy. Algorithm performance was affected by the low rate of included articles, but irrelevant articles were able to be excluded with high confidence. Further development is ongoing to optimize the algorithm to improve sensitivity. Once optimized, this innovative machine learning process could transform the conduct of systematic reviews.

**Clinical trial identification**
N/A

**Legal entity responsible for the study**
N/A

**Funding**
None

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

**1469P - Survival patterns for different types of cancers in the United States (1973-2012)**

**M. A. Gouda (Shebin El Kom, Egypt)**

**Background**
Most studies addressing survival patterns focus on 5-years survival data due to difficulties in long-term patients’ follow up. The aim of this study was to explore data on survival making use of the main advantage of SEER (National Cancer Institute Surveillance, Epidemiology, and End Results) program; that is long-term follow up of patients’ records. This enabled reporting 5-years relative survival, 10-years relative survival, and 20-years relative survival for different types of cancers. Survival trends as a function of time and tumor types were also provided.

**Methods**
SEER*Stat version 8.3.4 was used for data acquisition and analysis, where (SEER 18 Regs Nov 2015 Submission) database was used as the data source. Only cases diagnosed between 1973-2012 with malignant behavior, known age, and microscopic confirmation were included. Relative survival was calculated using Ederer II method. Tumors were classified according to ICD-O-3 into either solid malignancies (8000/3-9581/3) or hematological malignancies (9590/3+).

**Results**
Cancer cases diagnosed between 1973 and 2012 showed a 5-years relative survival of 64.6% (CI: 64.5%-64.6%), a 10-year relative survival of 58.7% (CI: 58.6%-58.7%), and a 20-years relative survival of 51.4% (CI:51.3%-51.5%). All of these percentages were much higher with solid malignancies than hematological ones [Table].

**Table:**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions
Long-term follow up data were suggestive of 20-years relative survival of 51.4% for all cancers. Data were also suggestive of improved relative survival over time. Unexpectedly, hematological malignancies, despite most of them being thought of as curable ones, appeared to have lower relative survival than solid tumors.

Clinical trial identification
N/A

Legal entity responsible for the study
Mohamed Alaa Gouda

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1470P - Decisions and supports around clinical trial participation: A national study by Cancer Trials Ireland

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Background
We conducted a national survey of cancer patients (pts) to determine what factors influence their decision to participate in a cancer clinical trial (CCT) and what supports they use(d).

Methods
Pts with a diagnosis of malignancy, ≥ 18 years, able to provide informed consent and complete a questionnaire independently were eligible. Questionnaires were administered to pts attending 14 cancer centres from 22nd April to Nov 23rd 2016.

Results
1,090 pts completed the questionnaire (386 (35.6%) men and 697(64.4%) women).
Median age was 60 years (IQR 50-69). 311 (29.5%) had previously been offered a CCT and 303 pts had participated. Factors most frequently ranked as important regarding decisions about CCT participation included; chance to advance research (n = 846, 81.0%); living longer/feeling better (n = 851, 81.5%); recommendation by cancer doctor (n = 797, 76.3%); closer monitoring (n = 528, 50.5%); fear of more side-effects (381,36.5%) or death (n = 337,32.3%); concerns about the treatment not working (n = 446,42.7%); increased hospital visits (n = 292, 28.0%); age (n = 355, 34.0%). Only 83 pts (9.3%) independently asked about participating in a CCT. Pts were asked about hypothetical participation in a CCT of a new drug that appeared safe but which could be better than/similar to/or worse than standard treatment (ST). 687 (65%) pts reported they would consider participation but more than half 336 (51.1%) of those reconsidered when a subsequent question re-stated the possibility the study drug could be worse than ST. Of those previously offered a CCT most (n = 214, 68.8%) had decided without help. When making decisions about CCT participation; family (n = 175, 56.2%), internet (n = 67, 21.5%) and GP (n = 48, 15.4%) were frequent sources of support. Most sources encouraged (n = 169, 54.3%) or were neutral about participation (n = 72, 23.2%). Cancer doctors and specialist nurses scored highest in terms of pts’ trust about CCT information; 250 (69.8%) and 196 (59.4%) pts gave them full scores respectively.

Conclusions
Decisions about CCT’s are complex, based on personal and altruistic factors and may be influenced by the type and detail of information given and by who provides it. Few pts we surveyed asked about a CCT, but most who had been offered a CCT had participated.

Legal entity responsible for the study
Catherine M. Kelly

Funding
Cancer Trials Ireland with funding from Abbvie, Bayor, Amgen and Inveva for this project

Disclosure
All authors have declared no conflicts of interest.

1471P - Academic clinical research: Enough players to get out there?

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Background
The European Regulation 536/2014 definitively establishes the equality between pharma-sponsored and academic clinical research, raising the bar of standards for no profit trials. Italy has always been known for the quality of its studies: our researchers have produced the 3.9% of world scientific papers in 2015-16 and 44 were among the 2016 world’s most influential scientific minds. However, the new compelling rules imposed by law make these great minds lacking in the absence of well-arranged staff, with dedicated professionals as clinical research coordinators (CRCs). Unfortunately, the national collective health contracts allow the employment of these experts only through atypical contracts that, due to new government requirements, will soon be banned. We have decided to map how much the problem was widespread among Italian CRCs.

Methods
In November 2016 a web survey, focused on the imminent contracts’ expiration problem, has been sent to about 300 CRCs.
Results
Our survey was completed by 231 CRCs (77%). The majority of respondents (78%) work thanks to atypical contracts, while few can count on more stable ones (7.4% fixed term and 14.6% open-ended). Public hospitals have the more difficulties to ensure stable employment: only 25% of permanent contracts come from this type of structures and purely thanks to loopholes; indeed, despite their educational background, CRCs are employed almost exclusively as non-qualified administrative personnel. The 67.5% of respondents will be affected by the contract problem, with multiple expiration timing: 32% Jan-Apr 17; 23% May-Aug 17; 23% Sep-Dec 17; 17.3% from Jan 18. Interestingly, about 50 CRCs were unwilling to participate, demoralized from the age-issue of the lack of professional recognition.

Conclusions
The need for clinical trials units officially and contractually recognized by competent authorities is a priority. The new government dispositions about atypical contracts could create a vacuum of skilled work force, which can hardly be covered by physicians. Since data are understated and the problem also affects another “big ghost” of clinical research (study nurse), in the absence of a permanent solution, Italy is unlikely to meet the required standards with a loss of appealing, but mostly with a slump of therapeutic options.

Legal entity responsible for the study
Gruppo Italiano Data Manager (GiDM)

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1472P_PR - Change of patient perceptions of chemotherapy side effects in breast and ovarian cancer patients
B. Ataseven (Essen, Germany) J. Frindte (Essen, Germany) P. Harter (Essen, Germany) G. Göke (Essen, Germany) J. Holtschmidt (Essen, Germany) C. Vogt (Essen, Germany) A. Traut (Essen, Germany) B. Vincenzo (Essen, Germany) M. Vincent (Essen, Germany) H. Florian (Essen, Germany) S. Kuemmel (Essen, Germany) S. Prader (Essen, Germany) M. Sporkmann (Essen, Germany) S. Schneider (Essen, Germany) A. Du Bois (Essen, Germany)

Background
Previous studies demonstrated changes of patient perceptions (PP) and individual ranking of chemotherapy side effects (CSE) between 1983-2002. We updated this survey and evaluated changes in PP in comparison to previous studies and as longitudinal observation.

Methods
Patients with breast (BC) and ovarian cancer (OC) planned for chemotherapy were recruited in this prospective study. At three different visits (before (T1), week 12+/−3 (T2), and at the end of chemotherapy (T3)) patients were asked to identify out of 72 cards, displaying potential physical and non-physical CSE, the ten most burdensome and rank them finally to top five by severity.

Results
In total, 141 patients (95 BC and 45 OC) were recruited. All three interviews were
completed in 113 patients. The most severe CSE reported was “difficulty sleeping” compared to “vomiting” in 1983, “nausea” in 1993, and “affects my family/partner” in 2002 (Table 1a). “Loss of hair” remained a top concern over all studies. Over the complete observation period “affects my family/partner” and “difficulty sleeping” were among the top five severe side effects. “Feeling of not coping” and “nausea” were ranked only at T1, but not at T2/T3. “Loss of hair” was ranked at T1/T2, but no longer at T3. In contrast, “numbness in limbs” became relevant in T2/T3 (Table 1b).

Conclusions
Patient perceptions of CSE have changed markedly compared with previous studies. However, “loss of hair” has remained an unsolved problem over decades. Furthermore, we demonstrated that PP of CSE changes over the treatment period. However, social concerns like “affecting family/partner” remain long-lasting problems.

Legal entity responsible for the study
Beyhan Ataseven

Funding
None

Disclosure
All authors have declared no conflicts of interest.

Table 1a
Rating of side effects

<table>
<thead>
<tr>
<th>Year</th>
<th>Vomiting</th>
<th>Nausea</th>
<th>Affects my family or partner</th>
<th>Difficulty sleeping</th>
<th>Loss of hair</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983 (Coates et al.)</td>
<td>Vomiting</td>
<td>Nausea</td>
<td>Affects my family or partner</td>
<td>Difficulty sleeping</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>1993 (Griffin et al.)</td>
<td>Nausea</td>
<td>Constantly tired</td>
<td>Affects my family or partner</td>
<td>Difficulty sleeping</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>2002 (Carelle et al.)</td>
<td>Loss of hair</td>
<td>Loss of hair</td>
<td>Constantly tired</td>
<td>Difficulty sleeping</td>
<td>Loss of hair</td>
</tr>
<tr>
<td>2016 Current study</td>
<td>Thought of coming treatment</td>
<td>Thought of coming for treatment</td>
<td>Affects my work, home duties</td>
<td>Numbness in limbs</td>
<td>Numbness in limbs</td>
</tr>
<tr>
<td>2016 Current study</td>
<td>Length of time treatment takes at clinic</td>
<td>Vomiting</td>
<td>Affects my social activities</td>
<td>Difficulty sleeping</td>
<td>Difficulty sleeping</td>
</tr>
</tbody>
</table>

Table 1b
Ranking

<table>
<thead>
<tr>
<th>Year</th>
<th>Affects my family or partner</th>
<th>Difficulty sleeping</th>
<th>Difficulty sleeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (before initiation of chemotderapy)</td>
<td>Affects my family or partner</td>
<td>Difficulty sleeping</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td>T2 (after 12+/3 w weeks of chemotderapy start)</td>
<td>Feeling of not coping with treatment</td>
<td>Affects my family or partner</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td>T3 (end of chemotderapy +/- 2 weeks)</td>
<td>Loss of hair</td>
<td>Numbness in limbs</td>
<td>Affects my work,</td>
</tr>
</tbody>
</table>
SUPPORTIVE CARE

F. Scotté (Paris, France)

1550P - Primary prevention of nausea and vomiting induced by moderately emetogenic chemotherapies: findings from the French CONVINCE-ME survey

F. Scotté (Suresnes, France) R. Chevrier (Clermont-Ferrand, France) H. Bertucat (Vichy, France)

Background

Despite the considerable progress achieved in the last 30 years vomiting and especially nausea continue to be two of the most distressing side-effects of cancer chemotherapy. The objective of this survey was to assess the compliance of anti-emesis prescriptions with the ESMO 2016 and French AFSOS 2013 guidelines (French speaking association for supportive care in cancer), in primary prophylaxis of moderately emetogenic chemotherapies (MEC) as defined by ESMO guidelines.

Methods

Between February and November 2016, 35 pharmacists and 41 nurses from 35 French centers specialized in cancer treatment completed a 13-item questionnaire drawn up by a scientific committee about their anti-emesis practices. Concurrently, the nurses at each center recorded prospectively treatments prescribed to 10 to 20 patients starting the first cycle of MEC.

Results

Data were gathered on 448 patients with gastrointestinal cancers and 166 with lung cancers; 29% and 47% of all patients were treated with carboplatin or oxaliplatin respectively. The most frequent CINV preventive treatments for the acute phase were the combination of 5HT3 antagonist + corticoid (52% of patients) and the combination of 5HT3 antagonist + corticoid + anti-NK1 (33%). For the delayed phase, 5HT3 antagonist only (23%), anti-NK1 only (17%) and the combination of 5HT3 antagonist + anti-NK1 (17%) were the most prescribed treatment. Overall, 49% and 33% of patients in the acute phase and 10% and 17% in the delayed phase were treated in compliance the ESMO and AFSOS guidelines respectively.

Conclusions

The CONVINCE-ME survey shows inadequate use of existing recommendations at specialized centers and highlights the need for improved understanding and guideline application.

Legal entity responsible for the study

Florian Scotté

Funding

MSD

Disclosure

F. Scotté: Roche, Vifor, MSD, Teva, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, Sanofi, Amgen, Pierre Fabre Oncologie, Tesaro. H. Bertucat: MSD. All other
Background

Current antiemetic guidelines recommend antiemetic triplet regimen for cisplatin-based chemotherapy. Although several prior studies have identified risk factors for chemotherapy-induced nausea and vomiting (CINV), only a few have evaluated antiemetic triplet regimen, particularly with palonosetron. Therefore, the purpose of the present study was to confirm and compare the risk factors for CINV when using palonosetron or granisetron.

Methods

A total of 825 patients in the phase III clinical trial on cisplatin regimen were evaluated. The primary endpoint was complete response (CR) rate in the overall period (0–120 h). All patients were evaluated for CINV risk factors. Using a post-hoc analysis, the impact of antiemetic treatment on CR was assessed, and odds ratio (OR) with 95% confidence intervals (CIs) for antiemetic treatment failure were evaluated by using multivariate logistic regression models. CINV risk factors were also evaluated separately in each treatment group.

Results

The multivariate analysis revealed that female (OR: 2.572; 95% CI: 1.855–3.566), less than 60 years old (OR: 1.717; 95% CI: 1.252–2.355), the cisplatin dosage (OR: 1.017; 95% CI: 1.001–1.033), and granisetron use (OR: 1.357; 95% CI: 1.013–1.817) were all significantly associated with antiemetic treatment failure in the entire study group. Similarly, female and age were also identified as the risk factors associated with treatment failure in both groups (P < 0.0001). Kaplan–Meier plots of time to event classified each treatment group and revealed no significant difference between the groups for patients with zero risk factors (P = 0.353). For patients with one or more risk factors, those treated with palonosetron experienced significantly higher CR rates than those treated with granisetron (P = 0.049).

Conclusions

This analysis revealed risk factors of CINV when using triplet antiemetic regimen including palonosetron or granisetron for cisplatin. Palonosetron might be preferred for patients with one or more risk factors.

Clinical trial identification

Clinical trial information: UMIN 000004863 *UMIN: University Medical Information Network

Legal entity responsible for the study

Pharma Valley Center, Shizuoka Organization for Creation of Industries

Funding

Pharma Valley Center, Shizuoka Organization for Creation of Industries

Disclosure

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Background
Preventing CINV in most patients is possible when guideline-recommended prophylactic antiemetics are utilized. Because oncology nurses play a critical role in risk assessment and management of CINV, a survey of European nurses was conducted to evaluate antiemetic practices, determine awareness of and adherence to current guideline recommendations, and explore barriers to adherence.

Methods
Between March 2016 and March 2017, 212 oncology nurses in 16 European countries completed a 20-question online survey.

Results
Respondents had 15 years (median) experience as an oncology nurse and most were able to suggest or prescribe antiemetics. Most (n = 169, 80%) worked in the public not-for-profit hospital setting, seeing both in- and outpatients (n = 107, 50%). While nurses were most familiar with ASCO (n = 97, 46%) and MASCC/ESMO (n = 84, 40%) guidelines, individual institution guidelines were used most (n = 99, 47%). Key discrepancies between antiemetic use and guideline recommendations were: i) underutilization of NK₁RAs, 5-HT₃ RAs and a steroid on Day 1 in the HEC setting and ii) high use of 5-HT₃ RAs during days 2-5 when guidelines recommend a steroid (Table 1). Metoclopramide use (not guideline recommended) was also high, with 30% and 50% of nurses reporting usage for acute and delayed phases, respectively, for both HEC and MEC settings. The most common barrier to the use of guideline-recommended agents was reported as physician preference (n = 84, 40%). Product cost and formulary inclusion also played a role. The 2 most common challenges in managing CINV were “controlling nausea and vomiting in the delayed phase” (n = 135, 64%) and “reducing the impact of CINV on patients’ quality-of-life” (n = 130, 61%).

Table: 1552P Antiemetic Utilization - European Nurse Survey

<table>
<thead>
<tr>
<th>Setting</th>
<th>Antiemetic Class</th>
<th>Antiemetics Utilized n (% respondents)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acute Phase (0-24 h)</td>
</tr>
<tr>
<td>HEC</td>
<td>5-HT₃ RA NK₁ RA NEPA</td>
<td>171 (81%) 130 (61%)</td>
</tr>
<tr>
<td></td>
<td>Steroid (eg, DEX)</td>
<td>48 (23%) 173 (82%) 1</td>
</tr>
<tr>
<td></td>
<td>Phenothiazine Benzodiazepine</td>
<td>(0%) 35 (17%) 10 (5%)</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic Metoclopramide</td>
<td>63 (30%)</td>
</tr>
</tbody>
</table>
HEC: highly emetogenic, MEC: moderately emetogenic, DEX: dexamethasone, NEPA: fixed combination of netupitant/palonosetron

Conclusions
This survey highlights many opportunities to improve utilization of guideline-recommended antiemetics, thereby optimizing prevention of CINV and quality-of-life for patients receiving emetogenic chemotherapy.

Legal entity responsible for the study
Helsinn Healthcare SA

Funding
Helsinn Healthcare, SA

Disclosure
P. Dielenseger: Member of advisory boards of Helsinn, Bayer Healthcare, Pfizer, Shire, Tesaro, Janssen, and BMS A. Young: Received honorarium from MSD (advisory board and presentations given), Helsinn (advisory boards) and Chugai (presentation given). P. Jahn: Support includes travel support: Helsinn (2014); Current consulting or advisory role: Bristol-Myers Squibb, Chugai, Norgine, and Clinigen; Clinical Research Fund by Chugai. All other authors have declared no conflicts of interest.

1553P - A pooled analysis evaluating the combination antiemetic therapy on chemotherapy-induced nausea and vomiting in patients with colorectal cancer receiving oxaliplatin-based chemotherapy of moderate emetic risk

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Background
The incidence and risk factor of delayed chemotherapy-induced nausea and vomiting (CINV) for colorectal cancer (CRC) patients receiving oxaliplatin-based chemotherapy has not been clearly controlled. To evaluate the efficacy and risk factor of combination antiemetic treatment for delayed CINV in CRC patients receiving oxaliplatin-based chemotherapy.

Methods
Aggregated data were pooled from the two prospective observational studies and one clinical trial; A nationwide survey of CINV study group, the other prospective observational study in Japan and SENRI Trial in Japan. We assessed whether delayed CINV were controlled with 3 antiemetic treatment. We also evaluated risk factors by logistic regression analysis.

Results
A total of 661 patients were evaluable in this study. The median age was 64 (range:19-85) with 391 males and 270 females. Three antiemetics were used in 220 (33.3%) patients.
Delayed CINV were experienced more commonly in women than in men. Delayed nausea was well controlled with 3 antiemetics than with 2 antiemetics for women (38.3% vs. 52.8%; \(P=0.0295\)). Delayed vomiting was well controlled with 3 antiemetics than with 2 antiemetics for overall (4.1% vs. 15.9%; \(P<0.0001\)) and for women (5.3% vs. 24.4%; \(P<0.0001\)). We identified several risk factors; women (odds ratio [OR], 1.853; 95% confidence interval [CI], 1.326 to 2.591; \(P=0.0003\)), motion sickness (OR, 1.947; 95%CI, 1.230 to 3.082; \(P=0.0044\)) and age (OR, 0.976; 95%CI, 0.961 to 0.991; \(P=0.0020\)) for delayed nausea, and women (OR, 2.447; 95%CI, 1.475 to 4.059; \(P=0.0005\)), motion sickness (OR, 1.892; 95%CI, 1.024 to 3.494; \(P=0.0417\)), 2 antiemetics (OR, 4.890; 95%CI, 2.362 to 10.122; \(P<0.0001\)) and FOLFOX regimen (OR, 1.680; 95%CI, 1.028 to 2.747; \(P=0.0384\)) for delayed vomiting.

**Conclusions**

Three antiemetics combination are encouraged for CRC female patients treated with oxaliplatin-based chemotherapy to alleviate delayed CINV. Identification of individual risk factors will assist in the development of personalized treatments for delayed CINV.

**Legal entity responsible for the study**

N/A

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1554P - Efficacy of neurokinin-1 receptor antagonists in the prevention of Chemotherapy-Induced Nausea and Vomiting in patients receiving carboplatin-based chemotherapy: a systematic review and meta-analysis**

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**Background**

According to current ESMO – MASCC guidelines, a combination of a neurokinin-1 receptor antagonist (NK1RA), dexamethasone and a 5-HT3 receptor antagonist (5-HT3RA) is recommended to prevent carboplatin-induced emesis, with moderate level of confidence and not unanimous consensus. Our aim was to perform a meta-analysis of all randomized trials (RCTs) evaluating the role of a NK1RA in the prevention of emesis for patients receiving carboplatin.

**Methods**

A systematic review was performed in January 2017, including RCTs comparing NK1RA + dexamethasone + 5-HT3RA vs. dexamethasone + 5-HT3RA in patients receiving first cycle of carboplatin-based chemotherapy. Primary outcome was complete response (CR), defined as no emesis and no use of rescue medication. CR was measured in day 1 (acute phase), days 2-5 (delayed phase) and days 1-5 (overall period). A random effects model was applied.

**Results**

9 trials were potentially eligible (7 aprepitant, 1 fosaprepitant, 1 rolapitant): 6 were RCTs including only patients receiving carboplatin, and 3 were subgroup analyses of patients receiving carboplatin within RCTs including various moderately emetogenic regimens.
Data of CR were available in 8 trials (1598 patients). Addition of NK1RA improves CR in all phases: acute phase, 94.5% vs. 90.1% (Odds Ratio 1.75, 95%CI 1.19-2.59, p = 0.005); delayed phase, 76.4% vs. 61.7% (Odds Ratio 2.04, 95%CI 1.64-2.55, p < 0.0001); overall period, 75.3% vs. 60.4% (Odds Ratio 2.04, 95%CI 1.64-2.54, p < 0.0001). There was no significant heterogeneity among trials. Sensitivity analyses, performed excluding subgroup analyses and excluding open-label trials, produced similar results.

**Conclusions**

In patients receiving carboplatin-based chemotherapy, triple antiemetic therapy with NK1RA, dexamethasone and 5-HT3RA is associated with a statistically significant and clinically relevant improvement in CR, compared to 5-HT3RA plus dexamethasone. Individual patient data meta-analysis could help to identify patients who are likely to obtain the highest improvement from the addition of NK1RA.

**Clinical trial identification**

- **Legal entity responsible for the study**
  Massimo Di Maio

**Funding**

None

**Disclosure**

M. Di Maio: Roles as advisor, and speaker’s fee for Merck Sharp & Dohme, AstraZeneca, Bayer, Janssen, Bristol Myers Squibb, and Eli Lilly. E. Bria: Roles as advisor, and speakers’ fee for Merck Sharp & Dohme, AstraZeneca, Celgene, Pfizer, Eli-Lilly, Bristol Myers Squibb, and Novartis. All other authors have declared no conflicts of interest.

**1555P - Pharmacokinetic (PK) study of a single oral dose of NEPA in Chinese healthy volunteers (HV)**

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A. Bernareggi (Lugano, Switzerland)P. Hu (Beijing, China)

**Background**

NEPA, a combined neurokinin-1 receptor antagonist (RA) netupitant (NETU; 300 mg) and 5-HT\(_3\)RA palonosetron (PALO; 0.50 mg), is the first approved oral combination antiemetic. NEPA has shown superior efficacy over PALO in preventing chemotherapy-induced nausea and vomiting (CINV), in cisplatin and AC-chemotherapy settings, leading to its approval in the US and Europe (with 85% of patients Caucasian in the clinical trials). A recent phase 3 registration trial in Asian patients demonstrated non-inferiority of a single oral dose of NEPA in preventing CINV compared with a 3-day oral aprepitant/granisetron regimen. The present study was undertaken to assess the PK profile of NETU and PALO in Chinese HVs.

**Methods**

Eligible HVs received a single oral dose of NEPA administered as a hard gelatin capsule on day 1, after 10-h fasting. Blood samples for PK analysis were collected pre-dose and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, and 240 h post-dose. The plasma concentration of NETU and PALO was determined by liquid
chromatography-tandem mass spectrometry (LC-MS/MS). PK parameters were estimated via non-compartmental analysis using the WinNonlin 6.3 software (Certara Inc., Princeton, NJ, USA).

Results
A total of 18 subjects were enrolled (16 male; median body weight 62.7 kg [52.6–75.2 kg]; median age 27 y [21–37 y]). After a single oral dose of NEPA, mean (±SD) values of peak plasma concentration (C\text{max}) for NETU were 698±217 ng/mL at a median of 4.5 h (T\text{max}; 3–6 h), with mean (±SD) overall exposure up to the last measurable concentration (AUC\text{0-t}) of 20.2±3.93 h*mg/L. PALO plasma concentrations reached mean (±SD) C\text{max} of 1800±252 ng/mL at 3 h (2–6 h) with mean (±SD) AUC\text{0-t} of 77.6±13.3 h*µg/L. NEPA was well tolerated in all HVs.

Conclusions
In Chinese HVs the PK profile of NETU was comparable to that previously observed in Caucasians. For PALO, C\text{max} and AUC\text{0-t} were higher in these Chinese HVs compared to Caucasians, which may be explained by CYP2D6 (involved in the metabolism of PALO) polymorphism. However, the similar efficacy and safety for PALO and NEPA in pivotal studies in both populations suggests that the higher exposure to PALO in Chinese HVs is unlikely to be clinically relevant.

Legal entity responsible for the study
Helsinn Healthcare SA

Funding
Helsinn Healthcare SA

Disclosure
S. Chessari, C. Lanzarotti, A. Bernareggi: Helsinn Healthcare SA employee

All other authors have declared no conflicts of interest.

1556P - Iron deficiency anaemia in oncology: an epidemiological prospective study
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Background
Anaemia in oncology is frequent, decreasing quality of life and prognosis. Its causes are multiples and still largely unknown, among them, iron deficiency (ID) is seldom studied. Associated with inflammatory syndrome, ID leads to the sequestration of iron in macrophage, making it unavailable for erythropoiesis. Prevalence of ID needs to be specified in oncology as it could be easily corrected by intravenous iron, avoiding use of EPO or blood transfusion and their side effects.

Methods
In this prospective, multicentre cohort study (NCT01968304), anaemia and ID were evaluated in patients with locally advanced or metastatic solid tumour and lymphoma newly diagnosed before starting a chemotherapy regimen. Blood samples were collected at the inclusion (week 0 - W0), 6 weeks (W6) and 12 weeks (W12) after. Prevalence was
evaluated for both functional ID (FID) and absolute ID (AID) in the general population and according to the tumours location. ID was correlated with tumour response (RECIST criteria).

**Results**

129 patients were enrolled between 2013 and 2015. 119 had solid tumours (breast 36, colorectal 27, lung 28, prostate 12, others 16) and 10 had lymphomas (not shown).

**Table:**

<table>
<thead>
<tr>
<th>Location</th>
<th>N (%)</th>
<th>Location</th>
<th>Anaemia N (%)</th>
<th>Functional iron deficiency N (%)</th>
<th>Absolute iron deficiency N (%)</th>
<th>Functional ID associated with Anaemia N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W0</td>
<td>W6</td>
<td>W12</td>
<td>W0</td>
<td>W6</td>
<td>W12</td>
</tr>
<tr>
<td>Breast 36</td>
<td>13</td>
<td>20</td>
<td>17</td>
<td>15</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>(30)</td>
<td>(36.1)</td>
<td>(64.5)</td>
<td>(63.0)</td>
<td>(41.7)</td>
<td>(64.5)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>20</td>
<td>16</td>
<td>11</td>
<td>14</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>27 (23)</td>
<td>(74.1)</td>
<td>(72.7)</td>
<td>(68.8)</td>
<td>(51.9)</td>
<td>(36.4)</td>
<td>(18.5)</td>
</tr>
<tr>
<td>Lung 28</td>
<td>16</td>
<td>22</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>(24)</td>
<td>(57.1)</td>
<td>(88.0)</td>
<td>(93.3)</td>
<td>(48.1)</td>
<td>(32.0)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Prostate 12</td>
<td>9</td>
<td>11</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>(10)</td>
<td>(75.0)</td>
<td>(91.7)</td>
<td>(81.8)</td>
<td>(50.0)</td>
<td>(25.0)</td>
<td>(0.0)</td>
</tr>
<tr>
<td>All solid</td>
<td>63</td>
<td>75</td>
<td>56</td>
<td>62</td>
<td>49</td>
<td>9</td>
</tr>
<tr>
<td>tumours 119</td>
<td>(52.9)</td>
<td>(72.8)</td>
<td>(71.8)</td>
<td>(48.0)</td>
<td>(43.0)</td>
<td>(7.0)</td>
</tr>
</tbody>
</table>

At W0, 62 patients (48%) had FID, 32 (26.9%) had FID associated with anaemia and 9 (7%) had AID. FID prevalence remains constant from W0 to W12, so as FID anaemia and AID. Also, ID incidence remains constant between W6, 17 (15.2%) and W12 10 (11.6%). Localization was not correlated with FID or FID anaemia but prevalence of AID is higher for colorectal tumours. ID (evaluated at W12) was significantly correlated (p = 0.04) with tumour response at W12, 51.2% of responders among patients with no ID versus only 33.3% among patients with ID.

**Conclusions**

Our data confirm the high prevalence of ID in cancer patients. Localization is not correlated with the prevalence of ID whereas absolute ID is of higher rate in colorectal cancer. Also, ID at W12 without supplementation seems to be predictive of chemotherapy response.

**Clinical trial identification**

NCT01968304. Release date: October 1, 2013

**Legal entity responsible for the study**

Centre Antoine Lacassagne

**Funding**
1557P - Nutritional risk as a predictor of short-term outcomes in a prospective cohort of elderly patients with cancer

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M. G. Mello (Recife, Brazil) M. Rebello (Recife, Brazil) Z. Cavalcanti (Recife, Brazil) D. Sales (Recife, Brazil)
N. Cruz (Recife, Brazil) L. S. Thuler (RIO DE JANEIRO, Brazil)

**Background**
To determine if the nutritional risk identified by the Mini Nutritional Assessment Short-Form (MNA®-SF) is an independent predictor of short-term outcomes (infection, hospitalization and premature death).

**Methods**
A prospective cohort study of elderly patients (≥60 years) with a recent diagnosis of cancer admitted to an outpatient oncology unit was performed. Sociodemographic and clinical variables and MNA®-SF were collected at baseline. The outcomes were healthcare-associated infection, hospitalization and death. Data were analysed using the multivariate Cox proportional hazards models. Overall survival was estimated using the Kaplan–Meier method and survival curves were compared using the Log rank test.

**Results**
The cohort consisted of 608 elderly patients followed for 180 days. The mean age was 71.9 years (range: 60–96) and 50.2% participants were at risk of malnutrition as measured by the MNA®-SF. During follow-up, 35.5% of participants were hospitalized, 29.4% had healthcare-associated infections and 16.4% died. After adjustment for age, site and stage of cancer, the multivariate regression Cox model showed that being undernourished was an independent predictor of infection (adjusted Hazard Ratio [aHR] = 1.88, 95% CI 1.32–2.67, p < 0.001) hospitalization (HR = 1.5, 95% CI: 1.10–2.06, p = 0.012) and death (HR = 3.12, 95% CI: 1.74–5.78, p < 0.001).

**Conclusions**
Nutritional risk at admission was identified as a significant predictor of risk for premature death, infection, and need for hospitalization in elderly cancer patients. The use of MNA®-SF should be incorporated into regular geriatric assessment of older patients with cancer.

**Clinical trial identification**
NO APPLICABLE

**Legal entity responsible for the study**
Jurema Telles De Oliveira Lima

**Funding**
FACEPE CNPQ

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

1558P - A patient-centered approach to the re-development of supportive care services for oncology adolescent and young adult (AYA) patients (pt(s)) across
Background
Most AYA pts (age 18-44) across the RCN are seen in adult oncology settings tailored to
the medical and supportive care needs of the general cancer population. The purpose of
this study is to conceptually re-develop the delivery of supportive care services to this pt
population and create a care model that could be used as a framework for AYA clinics in
Canada and abroad.

Methods
An analysis of the Ambulatory Oncology Patient Satisfaction Survey (AOPSS) 2012-2015
was conducted to better understand AYAs’ satisfaction with the current level of care in
RCN. A Chi-square test was employed to investigate differences between AYAs (ages
18-34 vs 35-44) and pts age 45 and over (n = 2,438).

A Delphi study, composed of two panels (pts vs. health care professionals), was
conducted. Panelists were asked to select a set of strategies proposed by Zebrack et al.
(2010) to address the service gaps identified through AOPSS. Selection was made by
rank ordering strategies based on scores of importance (7 point Likert scale). Analysis of
variance (ANOVA) was used to examine study results.

Results
The analysis of the AOPSS results revealed important differences related to i) the overall
satisfaction and perception of quality of care; ii) access to services and iii) satisfaction with
specific aspects of care such as emotional support, communication, access to information
and physical comfort.

Both Delphi panels have identified access to 1) age-appropriate education programs; 2)
standardized symptom management, pain control, palliative care; and 3) fertility
preservation as important strategies to enhance delivery of supportive care services to
AYAs (Table).

<table>
<thead>
<tr>
<th>Patient Panel (n = 31)</th>
<th>Health Care Professionals Panel (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank Order (round 1)</td>
<td>Importance Score (0-7 Likert scale)</td>
</tr>
<tr>
<td>Patient education programs that provide quality care</td>
<td>1</td>
</tr>
</tbody>
</table>
AYAs with knowledge regarding treatment options and the potential physical and QOL implications of cancer therapy

Inform reproductive-age patients of cancer-related fertility risks as early in the treatment planning as possible (as per ASCO guideline) and refer as needed to an appropriate fertility preservation specialist

Provide access to a systematic and standardized symptom management, pain control, and palliative care program

Conclusions
Evidence gathered through the AOPSS and Delphi studies will be used to inform health administrators of strategies needed to better respond to the unique supportive care needs of oncology AYAs.

Legal entity responsible for the study
Petr Kavan

Funding
Rossy Cancer Network

Disclosure
All authors have declared no conflicts of interest.

1559P - Multidimensional telemonitoring of cancer patients (pts) receiving chronomodulated (chrono) Irinotecan (I), 5-fluorouracil (F), leucovorin (L) and oxaliplatin (O; chronolFLO4) combination at home

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Background
FOLFIRINOX is an active yet toxic regimen against intestinal cancers. Improving its tolerability could widen its use in routine clinical practice. Circadian-based chrono administration of this triplet can be performed using a multichannel programmable-in-time pump. Here, we show the safety of chronolFLO4 at home, through real-time multidimensional telemonitoring of circadian rest-activity rhythm (CircAct), sleep, patient-reported outcome measures (PROM) and body weight changes (BWC) using 1st generation e-Health platform inCASA.

Methods
Pts received Day (D) 1 chrono I (180 mg/m2, over 6-h; peak rate at 5:00), and D 2-4 chrono O (25 mg/m2/d, over 11.5-h; peak rate at 16:00) and F-L (800 mg/m2/d and 400 mg/m2/d, respectively, over 11.5-h; peak rate at 04:00), q2 weeks at home. Pts completed the 19-item MD Anderson Symptom Inventory (MDASI) on an interactive electronic screen, weighed themselves on a dedicated scale, and continuously wore a
watch-sized wrist-accelerometer for CircAct and sleep monitoring. Daily data were securely teletransmitted via Internet to a specific server accessible by the hospital team. The validated and clinically-relevant CircAct parameter I

Results
Eleven patients (48-72 years; 45% males; 27% PS = 0) received 26 cycles (cy) of chronoIFLO4, and provided 5,891 data points/8,736 expected (67.4%). No grade 3-4 clinical toxicity occurred. The most severe MDASI scores remained low: interference with work (mean: 5.1/10) or general activity (4.9); fatigue (4.9); distress (4.2) and appetite loss (3.6). Mean BWC was -0.9% and mean SE remained above 82%. CircAct disruption (I

Conclusions
ChronoIFLO4 represents a safe therapeutic option at home, and the pt-centered multidimensional telemonitoring solution allows the design of innovative management approaches, ultimately improving pt experience with chemotherapy, safety and outcomes.

Legal entity responsible for the study
INSERM and European Commission

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1560P - A pilot study to evaluate the feasibility, usability, and perceived satisfaction with eCO (eCediranib-Olaparib), a mobile application for side effect monitoring and reporting, in women with recurrent ovarian cancer

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S. Morrissey (Boston, United States of America)E. Komatsu (Boston, United States of America)
J. Lee (Bethesda, United States of America)N. Houston (Bethesda, United States of America)
R. M. Wenham (Tampa, United States of America)D. M. O'Malley (Columbus, United States of America)
E. Strock (Boston, United States of America)R. Phillips (Cambridge, United States of America)K. Mari (Lyon, France)
S. P. Ivy (Bethesda, United States of America)B. Killam (Ashburn, United States of America)

Background
Cediranib inhibits VEGFR1-3 with significant but treatable side effects of hypertension and diarrhea. High frequency of these events occurred in a trial of cediranib with olaparib (C+O). Effective control of these side effects is therefore important for C+O therapy. eCO, a cloud-based mobile medical device, was developed to provide secure capture, storage, and transmission of accurate BP and diarrhea data to aid in remote monitoring. Pts receive automated reminders and instructions for self-management based on severity. HCPs monitor pt status via a secure web portal and email alerts.

Methods
Pts enrolled in a Ph 2 study of C+O (NCT02345265) could opt to participate in this pilot study. Pts received eCO-based prompts, used eCO to record BP via a Bluetooth-linked BP cuff and to enter diarrheal events, and received eCO-based reminders and recommendations. Pts completed a 17-item usability and satisfaction questionnaire after 4 weeks of eCO use. The primary objective was to evaluate the feasibility, usability, and satisfaction of eCO use. Data were analyzed by Wilcoxon Rank Sum Analysis.

Results
15 pts completed the pilot study. Pts indicated they felt closely monitored, connected with the healthcare team, involved in their own care, and satisfied with ease of learning and use of many eCO functions (alpha < .01). Pts were satisfied with diarrhea entry and finding past recommendations (alpha < .05) and were not satisfied with reporting diarrhea side effects. eCO captured 98.1% of expected BP values (94.2% direct upload; 5.8% manual entry). BP events (≥2 consecutive BP > 140/90 mmHg) occurred in 11 pts (6 with 1 event, 2 with 2 events, 3 with 3 events) with median duration 5 days (range 3-28 days). 12 pts reported 20 diarrhea events (range 1-4 events); median duration was 1.4 days (range 1.0-2.7 days); 31 entries were made (28 Gr 1, 3 Gr 2).

Conclusions
In this initial pilot, eCO captured accurate BP and diarrhea events from pts for remote monitoring. Pts reported overall usability and satisfaction with eCO, especially feeling closely monitored, more connected, involved in self-care and ease-of-use. Use of eCO in other studies is planned.

Clinical trial identification
NCT02345265

Legal entity responsible for the study
National Cancer Institute

Funding
National Cancer Institute

Disclosure

1561P - Study of the satisfaction level of an education program for cancer patients

Y. Kim (Busan, Korea, Republic of) H. Lee (Busan, Korea, Republic of) B. Seo (Busan, Korea, Republic of) Y. Choi (Busan, Korea, Republic of) K. Kwon (Busan, Korea, Republic of) E. Son (Busan, Korea, Republic of)

Background
As the demand for cancer patient education has increased lately, the administrative body of the universal health insurance in South Korea has decided to include the cost for cancer patient education to its insurance coverage. Dongnam Institute of Radiological Medical Sciences (DIRAMS) in Busan, South Korea, created its cancer patient education program in 2016 and has educated cancer patients about their treatments according to the program since then. This paper will discuss the study conducted at the hospital in order to estimate the level of satisfaction among the patients who participated in the education program.

Methods
The program consists of an 80-minute long education session led by a doctor, a nurse, and a clinical dietitian before each cancer patient receives his or her chemotherapy, radiation therapy, or a surgery. questionnaire survey was conducted on patients who participated in the education program from July 2016 to March 2017.

Results
Among the patients who participated in the survey, the number of patients who had chemotherapy education is 663. Stomach cancer was the most prevalent cancer type in this group, followed by cholangiocarcinoma. 75.3% of the patients in this group received palliative chemotherapy, and the rest received adjuvant chemotherapy. The satisfaction level of the chemotherapy education was 4.98 on a five-point Likert scale. The number of patients who had the radiotherapy education was 195. Breast cancer represents the largest portion in this group. The satisfaction level of the radiotherapy education was 4.3. The number of patients who received the surgery education was 70. The satisfaction level of the surgery education was 4.6.

**Conclusions**
The total 928 patients who participated in the education program rate their level of satisfaction as 4.8 in average on a scale of 1 to 5. This high rating can be seen as an indication of high satisfaction in the quality of the education about their treatments. To enhance the education program further, it will be worthwhile to investigate improvements in each part of the program and in the perspective of patients. Subsequently, it is also worthwhile to investigate how the education program affects cancer patients.

**Legal entity responsible for the study**
Ha Young Lee

**Funding**
None

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

1562P - Factors influencing the use of thromboprophylaxis in cancer outpatients: CAT AXIS, a case-vignette study on clinical practice

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**Background**
Data on long-term venous thromboembolism (VTE) prophylaxis in cancer outpatients remain scarce. In the absence of consistent treatment guidelines, our objective was to describe clinical practice and to identify factors influencing the use of thromboprophylaxis.

**Methods**
CAT AXIS was a multicenter cross-sectional study based on the completion of physician-profile questionnaires and the assessment of 10 e-mailed credible clinical scenarios of lung, colon and breast cancer by each of participants using the case-vignettes validated method.

**Results**
A total of 224 physicians participated allowing the completion and the analysis of 2,085 case vignettes corresponding to 765, 703 and 617 fictive clinical scenarios on lung, colon and breast cancers, respectively. The overall rate of thromboprophylaxis was 680/2085 (32.6%) among participants with a comparable proportion for the three types of cancer. Low-molecular-weight heparin (LMWH) was the most frequently used, by 92.7%, 93.8% and 83.9% of participants for lung, colon and breast cancer, respectively; treatment duration of ≥ 3 months was prescribed by 74.4% of participants. Multivariate analysis of factors influencing thromboprophylaxis based on patient’s characteristics is summarized in Table.

Table:
1562P Factors influencing the prescription of thromboprophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Lung cancer</th>
<th>Colon cancer</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR [95% CI]</td>
<td>OR [95% CI]</td>
<td>OR [95% CI]</td>
</tr>
<tr>
<td>ECOG index score: 3 vs 0-2</td>
<td>3.3 [2.4; 4.6]</td>
<td>2.4 [1.7; 3.6]</td>
<td>2.2 [1.5; 3.1]</td>
</tr>
<tr>
<td>Antineoplastic treatment</td>
<td>2.1 [1.3; 3.6]</td>
<td>2.2 [1.2; 3.6]</td>
<td>0.012 [0.8; 1.7]</td>
</tr>
<tr>
<td>Chemotherapy+targeted therapy (TT) vs TT only</td>
<td>3.6 [1.5; 5.2]</td>
<td>3.9 [2.1; 5.2]</td>
<td>0.015 [3.2; 0.84]</td>
</tr>
<tr>
<td>Chemotherapy only vs TT only</td>
<td>2.8 [1.2; 1.9]</td>
<td>2.1 [1.2; 1.9]</td>
<td>1.1 [0.6; 1.9]</td>
</tr>
<tr>
<td>History of VTE: Yes vs no</td>
<td>1.9 [1.3; 2.5]</td>
<td>1.7 [1.2; 2.4]</td>
<td>1.3 [0.9; 1.9]</td>
</tr>
<tr>
<td>Cancer stage: Metastatic vs local</td>
<td>1.6 [0.9; 2.7]</td>
<td>0.088 NI</td>
<td>2.3 [1.5; 3.5]</td>
</tr>
</tbody>
</table>

NI: not included in the analysis.

**Conclusions**

In the absence of clear guidance, the use of thromboprophylaxis remains low and rather empiric even though the selection of LMWH by the majority of participants and treatment duration seems appropriate based on available data to date. ECOG index, metastatic malignancy, chemotherapy and history of thrombosis were significantly associated with the decision to use thromboprophylaxis in most situations.

**Legal entity responsible for the study**

Guy Meyer

**Funding**

Leo Pharma

**Disclosure**

F. Scotté: Roche, Vifor, MSD, TEVA, Norgine, Prostrakan, Leo pharma, Janssen, Hospira, Boehringer, Sanofi, AMGEN, Pierre Fabre Oncologie, TESARO D. Mayeur: Leo Pharma, Pfizer G. Meyer: Investigator (uncompensated) in clinical trials for: Daiichi Sankyo; Bayer; Sanofi Aventis; Leo Pharm; BMS-Pfizer, Daiichi Sankyo; Boehringer-Ingelheim, Bayer All other authors have declared no conflicts of interest.

1563P - Literature review of TPOR agonists for CIT

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**J. K. Park** (Thousand Oaks, United States of America)

**Background**

Chemotherapy-induced thrombocytopenia (CIT) can lead to dose delay/reduction.
Currently there are no specific treatment recommendations beyond transfusion. We performed a systematic literature search on the use of thrombopoietin receptor (TPOR) agonists for CIT.

**Methods**

We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, PubMed, EMBASE, clinicaltrials.gov, and Health Technology Assessments from 1995-2017 for studies of TPOR agonists [eg, romiplostim, eltrombopag, TPO, and megakaryocyte growth and development factor (MGDF)] for CIT. Each publication was independently reviewed by two people and data extracted into Excel.

**Results**

We screened 892 titles/abstracts, assessed 52 articles, and abstracted data from 14 articles and 15 abstracts/posters from 1997-2016 (10 TPO, 7 MGDF, 8 romiplostim, and 4 eltrombopag), which included 18 randomized trials. TPOR agonist regimens varied widely. Common cancers included leukemia/lymphoma (n = 8 studies) and non-small cell lung cancer (n = 4), and common chemotherapies were platinum-based (n = 15) or included cytarabine (n = 5). Median or mean baseline platelet counts were \(56 \times 10^9/L-324 \times 10^9/L\) in studies to treat CIT (N = 7) and \(109 \times 10^9/L-597 \times 10^9/L\) in studies to prevent CIT (N = 22). The 16 placebo-controlled or crossover studies (MGDF n = 6 studies, TPO n = 5, romiplostim n = 3, eltrombopag n = 2) generally found that TPOR agonists increased platelet counts and reduced transfusions and dose delays/reductions (Table). Safety measures included thromboses (n = 19 studies) and bleeding (n = 8).

Table: 1563P Study Design and Endpoints TPOR Agonist vs. Control (Range study incidences)

<table>
<thead>
<tr>
<th>CIT Prevention: Vs. Placebo/Observation or Crossover (n = 16 studies)</th>
<th>TPOR Agonist (N = 625)</th>
<th>Control (N = 428)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy dose delay/reduction</td>
<td>3% - 40%</td>
<td>58% - 75%</td>
</tr>
<tr>
<td>Grade 3-4 thrombocytopenia</td>
<td>0% - 100%</td>
<td>0% - 42%</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>6% - 58%</td>
<td>8% - 83%</td>
</tr>
<tr>
<td><strong>Safety Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0% - 29%</td>
<td>0% - 33%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0% - 100%</td>
<td>0% - 50%</td>
</tr>
<tr>
<td><strong>CIT Treatment: Vs. rhIL-11 (n = 2 studies)</strong></td>
<td>TPOR Agonist (N = 63)</td>
<td>Control (N = 71)</td>
</tr>
<tr>
<td><strong>Efficacy Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy dose delay/reduction</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade 3-4 thrombocytopenia</td>
<td>Grade 3: 54%</td>
<td>Grade 3: 85%</td>
</tr>
<tr>
<td></td>
<td>Grade 4: 14%</td>
<td>Grade 4: 41%</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>11%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Safety Endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Bleeding</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
CIT Treatment: Vs. PBO/Observation or Crossover (n = 2 studies)  
TPOR Agonist (N = 172)  
Control (N = 65)

Efficacy Endpoint
Chemotherapy dose delay/reduction: N/A  N/A
Grade 3-4 thrombocytopenia: N/A  N/A
Platelet transfusions: N/A  N/A

Safety Endpoint
Thrombosis: 5% - 13%  7% - 21%
Bleeding: 2% - 9%  9%

Conclusions
While TPOR agonists have not been approved for use in CIT, this literature review suggests that TPOR agonists may increase platelet counts and decrease chemotherapy dose delay/reduction. Further study with well-characterized bleeding and platelet thresholds is needed to explore the possible benefits of TPOR agonists for CIT compared with current care options (eg, transfusions, dose reduction).

Clinical trial identification
As this was a literature search, there were no trial protocol numbers.

Legal entity responsible for the study
Amgen Inc.

Funding
Amgen Inc.

Disclosure
G.A. Soff: Research support from Amgen. J. Fryzek: Employee of EpidStat, which serves as a consultant with Amgen. M. Mullins: Consultant for EpidStat, which itself consults for Amgen. L.C. Bylsma: Employee of EpidStat, which consults for Amgen. J.K. Park: Amgen employee. All other authors have declared no conflicts of interest.

1564P - Random optimization interactive system based on Kernel learning (RISK) for venous thromboembolism risk assessment in chemotherapy-treated cancer patients

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Background
Using a combined approach of Kernel machine-learning (ML) and random optimization (RO) techniques we recently developed a set of predictors (ML-ROs) for VTE risk assessment. Aim of this study was to validate a model incorporating the two best ML-ROs to devise a web-based graphical interface for VTE risk stratification.

Methods
Pre-chemotherapy age, sex, tumor site and stage, hematological attributes, fasting blood lipids, glycemic indexes, liver and kidney function, BMI, ECOG, supportive and anti-cancer drugs of 608 cancer outpatients were entered in the model, with numerical attributes analyzed as continuous values. Variables were clustered into groups according to clinical significance, and RO was used to devise their relative weight in final prediction.
Results
VTE occurred in 7.1% of patients. Overall, 6% were at high-risk for VTE, as per current guidelines (Khorana Score (KS) ≥3), 11% of which had VTE during treatment. 42% and 52% were at intermediate (KS 1/2) or low-risk (KS = 0), with VTE rates of 9% and 5%, respectively. Accordingly, the performance of KS, despite a 94% specificity, was characterized by a 9% sensitivity with an area under the ROC curve (AUROC) of 0.589, translating into non-significant positive (+LR) [1.58 (0.48-4.30)] or negative likelihood ratio (-LR) [0.96 (0.83-1.04)]. Conversely, the VTE risk prediction performance of the combined ML model showed a 0.716 AUROC, which was significantly higher than that observed with KS (difference between areas: 0.127, p = 0.0044). At a criterion >1 (risk estimate achieved by both predictors) this combined approach showed significant +LR [2.30 (1.70-2.82)] and -LR [0.46 (0.28-0.69)] and a 4.9 Hazard Ratio (95%CI: 2.5-9.4) with a 6-month VTE rate of 3.4% in the low-risk, compared with 14.9% in the high-risk category.

Conclusions
These results demonstrate that a ML approach, optimizing the relative weight (by RO) of groups of clinical attributes, is of clinical value for VTE risk prediction, performing better than KS. We are now finalizing the architecture of a web service with a graphical interface helping oncologists in the critical phase of decision making.

Clinical trial identification
Not applicable

Legal entity responsible for the study
RISK Research Group

Funding
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Disclosure
All authors have declared no conflicts of interest.

1565P - Association between systemic inflammation and symptoms in advanced cancer patients

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Background
There is growing evidence relating inflammation as a prognostic factor in cancer patients. Previous reports have found a small but significant association between systemic inflammation and symptoms in advanced cancer patients. The aim of this study was to analyse the relationship between systemic inflammatory response markers with the symptoms and performance status of advanced cancer patients that have been admitted to an Acute Palliative Care Unit (PCU).

Methods
We conducted an observational study including all cancer patients admitted in the PCU between January 2012 and April 2015. We performed a correlation analysis (spearman’s rho) between serum C-reactive-protein (CRP), the modified Glasgow Prognostic Score (mGPS) and Neutrophil-to Lymphocyte Ratio (NLR) with patients symptoms recorded as the Edmonton Symptom Assessment Sytem (ESAS) and performance status recorded as
Results
Data of 951 patients were available. The median survival was 17 days. CRP was significantly correlated with ECOG (ρ:0.180, P:0.000), dyspnoea (ρ:0.079, p:0.019), fatigue (ρ:0.162, p < 0.001), anorexia (ρ: 0.103, p:0.002), somnolence (ρ:0.096, p.0.009), wellbeing (ρ:0.012, p < 0.001), Barthel (ρ:-0.178, p < 0.001) and PPS (ρ:0.173, p < 0.001). In relation to mGPS, a significant correlation was found with ECOG (0.116, p:0.001), fatigue (ρ:0.184, p < 0.001), anorexia (ρ:0.107, p.0.003), somnolence (ρ:0.080, p.037), Barthel (ρ:-0.127, p < 0.001) and PPS (ρ:-0.125, p < 0.001). Finally, NLR was significantly correlated with ECOG (ρ:0.112, p0.001), dyspnoea (ρ:0.117, p < 0.001), fatigue (ρ:0.107, p:0.002), Barthel (ρ:-0.115, p < 0.001) and PPS (ρ:-0.100, p:0.002).

Conclusions
There is a small but significant correlation between systemic inflammation and symptoms. Further studies are needed to confirm the results and to test this relation in earlier phases of the disease.

Legal entity responsible for the study
Hospital Universitario La Paz

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1566P - Outcomes of patients with malignancy admitted to the intensive care units (ICU): A prospective study

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Background
Decisions regarding whether advanced cancer patients should be admitted to the intensive care units (ICU) is based on a complex suite of considerations, including short and long term prognosis, quality of life, and options to treat cancer. We set to describe demographic, clinical, and survival data and to identify factors associated with short and long term mortality in critically ill advanced cancer patients with non-elective admissions to general ICUs.

Methods
Critically ill adult cancer patients non-electively admitted to the ICUs at the American University of Beirut Medical Center (AUBMC) between August 2015 and 2016 were included. Demographic, clinical, and laboratory data was prospectively collected from first day of ICU admission up to 30 days after discharge. This study was observational and clinical decisions were left to the ICU team and attending physician.

Results
91 patients were enrolled between August 2015 and 2016, with 41 patients (46%) dying in the ICU, and 12 patients (13.5%) within 30-days post-discharge. 7 patients were lost to
follow-up. Mean OS was 137 days, and median OS was 31 days since date of admission to the ICU. Most common reasons for ICU admission were sepsis (68.5%) and respiratory failure (19%). Cox regression showed direct admission from the ED (2.4 times more likely to die), those with uncontrolled malignancies (1.8 times), chemotherapy within the last 30 days prior to ICU admission (2.3 times), and development of multi-organ failure (MOF) (2.5 times) in the ICU are major predictors of poor prognosis.

Conclusions
Our study showed receiving chemotherapy within thirty days prior to admission as a predictor of poor outcome in univariate and multivariate analyses. This has not been reported in a study population of this kind before. Also, many studies state that developing MOF, whether in the ICU or prior to admission negative prognostic factor. Finally, our study found that direct admission from the ED is a negative prognostic factor, which has only been reported for hematological malignancies in other studies. Thus, there is a need for the development of proper admission criteria for this population.

Legal entity responsible for the study
American University of Beirut Medical Center

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1568P - Management of thrombosis in cancer patients in Greece

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G. Papatsimpas (Athens, Greece) I. Sgouros (Athens, Greece) E. Stergiou (Athens, Greece)
P. Thalassinou (Athens, Greece) I. Boukovinas (Athens, Greece) P. Papakotoulas (Athens, Greece)
I. Varthalitis (Athens, Greece)

Background
Venous thromboembolism (VTE) is a common cause of adverse outcomes in patients with cancer. The risk of VTE varies with cancer type, stage, grade, therapy and other patient characteristics. Low-molecular-weight heparin (LMWH) remains the standard therapy for VTE in cancer patients.

Methods
This is an observational study conducted by the Hellenic Society of Medical Oncologists (HeSMO) that aims to record and highlight the current clinical practice and management of VTE in patients with cancer in 18 Greek centers, with nationwide dispersion.

Results
The participating centers reported a total of approximately 4300 cancer patients managed on a monthly basis, where the vast majority (80%) were treated in an outpatient setting. For this study, 340 patients with active cancer were enrolled, with the following characteristics: 53.2% male; mean age 64.3; 62.1% of patients had PS of 0-1; tumor types: lung 22.3%, pancreas 16.3%, colon 13.6%, breast 11%, stomach 8.3%, ovarian 6.5% and other tumors 21.7%. The majority of patients (95.3%) received anticancer treatment; 21.3% were inpatients and 78.6% outpatients. Among these 340 patients, 86
were diagnosed with VTE: 81.4% had symptomatic VTE while 18.6% had incidental VTE. Regarding patients with VTE, 94.2% received anticancer treatment and the majority of these (65.1%) were treated in an outpatient setting. Of the patients diagnosed with VTE, 76.9% had performance status 0-1 and 74.4% had metastatic disease. In the metastatic stage there was no differences in the incidence of symptomatic or incidental VTE, 75% vs 74.3% respectively (p = 0.99). Highest percentage of incidental VTE observed was in patients with lung cancer (43.8%), followed by pancreatic (18.8%) and colon cancer (12.5%). All patients with VTE received antithrombotic treatment with LMWH according to the current clinical guidelines.

**Conclusions**

The majority of patients who developed VTE were outpatients undergoing anticancer treatment with metastases. Incidental VTE was more frequent in patients with lung cancer. Our findings of 18.6% incidental VTE further confirm the previously described results in similar studies.

**Legal entity responsible for the study**

Hellenic Society of Medical Oncology (HeSMO)

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1569P - Incidence and outcome of Incidental Pulmonary Embolism (IPE) in oncology patients with current macroscopic disease**

**M. Moe (Yeovil, United Kingdom)**

**Background**

IPE is defined as a PE detected on a CT scan (not a pulmonary angiogram) done for reasons other than suspected PE. This study is to evaluate the incidence of IPE in oncology patients with current macroscopic disease, and the outcome that could potentially be affected by a delay in starting anticoagulation therapy due to delayed reporting of these routine (non-urgent) scans.

**Methods**

CT thorax with iv contrast done on oncology patients between 01.01.15 – 31.12.15 in two district general hospitals in a cancer network were identified from the database. The scan reports and clinic letters were reviewed for data on cancer diagnosis, macroscopic disease, PE, treatments and survivals.

**Results**

2147 scans were identified. 543 scans were excluded due to absence of macroscopic disease (No IPE was reported in any of these scans.) leaving 1604 scans eligible for this study. Incidence for different tumour is shown in the table 1. 26 IPE patients are female = 15; median age = 66 (range 32 – 90); main artery = 9; lobar artery = 5; average time from CT scan to anticoagulation (LMWH) therapy is 9.7 days (median = 5 days; range = 0 – 61 days; no treatment in 3 patients) mainly due to the delay in reporting (median = 1 day; range = 0 – 60 days). The median survival from the scan date is 7 months (range = 1 – 22) with 9 patients still alive and 2 lost to follow up. None of the patients whose anticoagulation started 5 or more days after the CT scan died within 3 months. IPE was
absent in all subsequent CT scans. This happened without any anticoagulation therapy in one patient who had a segmental IPE. Table 1. Incidence of IPE for different tumour types.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Scans</th>
<th>Scans with IPE (% of total scans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>235</td>
<td>587 9 (1.5%)</td>
</tr>
<tr>
<td>Breast</td>
<td>148</td>
<td>267 5 (1.9%)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>142</td>
<td>310 5 (1.6%)</td>
</tr>
<tr>
<td>Oeso/gastric</td>
<td>72</td>
<td>163 2 (1.2%)</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>8</td>
<td>19 1 (5.3%)</td>
</tr>
<tr>
<td>CUP</td>
<td>15</td>
<td>30 1 (3.3%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>15</td>
<td>31 1 (3.2%)</td>
</tr>
<tr>
<td>NET</td>
<td>1</td>
<td>1 1 (100%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>41</td>
<td>87 1 (1.2%)</td>
</tr>
<tr>
<td>Anal</td>
<td>1</td>
<td>2 0</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>1 0</td>
</tr>
<tr>
<td>H &amp; N</td>
<td>8</td>
<td>18 0</td>
</tr>
<tr>
<td>Heptaobiliary</td>
<td>10</td>
<td>20 0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>4 0</td>
</tr>
<tr>
<td>Ovary</td>
<td>3</td>
<td>4 0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>26</td>
<td>58 0</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>0 0</td>
</tr>
<tr>
<td>Total</td>
<td>731</td>
<td>1604 26 (1.6%)</td>
</tr>
</tbody>
</table>

Conclusions

Incidence of IPE in oncology patients with current macroscopic disease is low (1.6%) in daily practice. Most patients are likely to have lung, breast and colorectal cancers. This is probably due to the fact that these are common tumours, and the frequency of scanning in their management. No sudden death or mortality within 30 days was noted among patients who had anticoagulation therapy started 5 or more days after the CT scan. Spontaneous resolution of PE happened in one patient with segmental PE. More research is needed to select patients who may not get any meaningful benefit from anticoagulation in the presence of advanced malignant disease.

Clinical trial identification
NA

Legal entity responsible for the study
Maung Maung Myat Moe

Funding
None

Disclosure
All authors have declared no conflicts of interest.
Background
Immune related adverse events (IrAEs) are unique and completely different from what we have seen previously. There is no prospective data on these toxicities and guidelines are based on symptomatic management from the ongoing clinical trials. Ipilimumab and nivolumab induce irAEs to the skin, gastrointestinal, liver, endocrine and other systems.

Methods
A retrospective review of data from 45 patient records were used to describe the IrAE’s associated with 19 patients treated with Ipilimumab and 25 patients treated with Nivolumab and 1 patient with combination of ipilimumab and nivolumab. This is a single centre review in an expanded access programme/clinical trial setting.

Results
A total of 45 patients (28 males, 17 females) were analyzed. The median age was 63 years. Three patients with metastatic melanoma, 18 with non-small cell lung cancer (NSCLC), 2 with renal cell carcinoma and 2 with Hodgkin’s disease were treated with nivolumab and 19 with metastatic melanoma received ipilimumab. One patient with combination of ipilimumab and nivolumab. In total 167 cycles of nivolumab (median = 4, range 1-16) and 60 cycles of ipilimumab (median = 4 cycles, range 1-4) were administered. The patient receiving combination of ipilimumab and nivolumab received 1 cycle. Seven IrAEs are described in 15 ipilimumab treated patients. These include endocrinopathy in 3 patients (hypophysitis in patient and hypothyroidism in 2 patients), colitis in 3 patients (1 required infliximab) and hepatitis in 1 patient. Among the patients treated with nivolumab, 7 IrAEs were documented. These included pneumonitis in 2 patients, skin rash in 3 patients, mild diarrhea in 1 patient and mild uveitis in 1 patient. One patient developed autoimmune thrombocytopenia, and nephritis. Three chest infections were documented including pulmonary tuberculosis in a NSCLC patient. The patient receiving combination ipilimumab and nivolumab had grade 4 skin toxicity requiring treatment discontinuation. No IrAE related deaths were document.

Conclusions
A plethora of irAEs are described with anti-PD1 and anti-CTLA4 antibodies. Colitis was more common with ipilimumab while pneumonitis more common with nivolumab. Prompt IrAE’s diagnosis will result in decreased morbidity and mortality.

Clinical trial identification
NA

Legal entity responsible for the study
BL Rapoport

Funding
None

Disclosure
B. Rapoport: MSD, BMS and Roche Speaker Engagements, Advisory Board and Contract Research All other authors have declared no conflicts of interest.
Background
Febrile Neutropenia (FN) is a potentially life-threatening and dose-limiting complication of myelosuppressive chemotherapy (CT) that often requires hospital admission (HA). Patients (pts) with FN must initiate antibiotic (atb) therapy promptly and delay in diagnosis and subsequent treatment are associated with higher mobility and mortality.

Methods
Retrospective single institution review of all FN episodes that occurred in the years 2012 to 2016 in pts with solid tumors with an absolute neutrophil count (ANC) <1.000/µl and blood cultures (BC) collected within 30 days of an IV CT treatment. With a population base of 278.000 individuals, and 550 new solid tumor pts in Medical Oncology per year, we reviewed all BC collected during the first 5 years of Hospital Beatriz Angelo (2012-2016) and crossed with the registry of pts treated with IV CT. FN was defined as a tympanic temperature > 38 °C and ANC <1.000/µl and expected to decrease to < 500/µl in the following 7 days. Pts with hematologic malignancies were excluded.

Results
Among 1.947 eligible pts, 152 had a NF (8%) with a total of 173 NF episodes. Median age was 67yo; 90 were males (59%). Median initial ANC was 310/µl, range 20-990 (<500/µl in 69% and <100/µl in 17%). In the emergency room, median time from hospital nurse triage to medical observation (MO) was 38 min (range 4min-6h11m), MO to blood count specimen withdrawal 55min (range 10min-6h43m) and MO to arrival of BC to the lab 5h51min (range 24min-23h41m). 33 NF episodes were associated with positive BC (19%, 6 with two agents), 11 BC with Gram positive and 28 with Gram negative bacteria. 157 episodes led to HA (90%), 15 were treated as outpatients and in 1 NF episode the pt died at presentation from E. coli pneumonia. Median days of hospitalization was 8 (range 0-36). Median time on atb was 9 days (range 1-31), with first-line regimen including piperacilin/tazobactam in 110, amoxicilin/clavulanic acid + ciprofloxacin in 17, meropenem in 9, other agents in 11 and 1 with no treatment. Mortality during the NF episode was 20% (n = 34) from 173 NF episodes.

Conclusions
FN is a serious and common complication of CT treatment which must be diagnosed and treated rapidly. Delays in the evaluation of febrile cancer pts on systemic treatment may compromise the outcome of these pts.

Legal entity responsible for the study
João Moreira Pinto

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1572P - G-CSF and G-CSF biosimilars: a meta-analysis of randomized clinical trials in breast cancer patients
E. Botteri (Oslo, Norway) A. Krendyukov (Holzkirchen, Germany) G. Curigliano (Milan, Italy)

**Background**

The granulocyte colony-stimulating factors (G-CSFs) filgrastim and pegfilgrastim are widely used to prevent neutropenia in cancer patients undergoing myelosuppressive chemotherapy. Several G-CSF biosimilars are available, their development involving a step-wise approach including analytical comparison with the reference and iterative process development. Randomized clinical trials (RCTs) have confirmed that the reference product and its biosimilar provide the same clinical efficacy and safety and play pivotal role in the totality of evidence concept. However some heterogeneity exists among the studies. For G-CSF biosimilars, patients with breast cancer (BC) are the most sensitive population in which to confirm similarity. The aim of this meta-analysis was to compare the clinical efficacy of approved or proposed G-CSF biosimilars (filgrastim or pegfilgrastim) with reference G-CSF in patients with BC.

**Methods**

A Medline literature search up to March 2017 identified randomized clinical trials (RCTs) comparing biosimilar G-CSF to reference in BC patients. Primary efficacy endpoint was mean difference in duration of severe neutropenia (DSN). Secondary efficacy measures were differences in depth of absolute neutrophil count (ANC) nadir and time to ANC recovery. Random effect models were fitted to obtain pooled estimates of the mean difference and their corresponding 95% confidence intervals (CIs).

**Results**

Eight eligible RCTs were included. Overall difference in DSN between reference and biosimilar medicines was not statistically significant (0.06 days [95% CI -0.05, 0.17]) (Table). The secondary efficacy endpoints also showed no significant differences between reference and biosimilars.

### Table: 1572P Mean and mean difference on duration of severe neutropenia* during chemotherapy Cycle 1

<table>
<thead>
<tr>
<th>Study and year of publication</th>
<th>Reference G-CSF</th>
<th>Biosimilar G-CSF</th>
<th>Mean No. of patients</th>
<th>Mean No. of patients</th>
<th>Weight IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackwell 2015</td>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>1.17</td>
<td>1.2</td>
<td>14.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>107</td>
<td>107</td>
<td>-0.03 [-0.32, 0.26]</td>
</tr>
<tr>
<td>Blackwell 2016</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>1.36</td>
<td>1.19</td>
<td>20.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>155</td>
<td>153</td>
<td>0.17 [-0.07, 0.41]</td>
</tr>
<tr>
<td>Del Giglio 2008</td>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>1.1</td>
<td>1.1</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140</td>
<td>136</td>
<td>0.00 [-0.43, 0.43]</td>
</tr>
<tr>
<td>Harbeck</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>0.75</td>
<td>0.83</td>
<td>28.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>155</td>
<td>155</td>
<td>-0.08</td>
</tr>
</tbody>
</table>
### Results

**Pooled estimate (95% CI)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug</th>
<th>AUC[^2^]</th>
<th>Maximum</th>
<th>Days with absolute neutrophil count less than 0.5 x 10^9/L (&lt;500/μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>Filgrastim</td>
<td>Pegfilgrastim</td>
<td>2.28</td>
<td>36</td>
<td>2.08</td>
</tr>
<tr>
<td>Waller 2010</td>
<td>Filgrastim</td>
<td>Filgrastim</td>
<td>1.6</td>
<td>165</td>
<td>1.3 85</td>
</tr>
<tr>
<td>Waller 2016</td>
<td>Pegfilgrastim</td>
<td>Pegfilgrastim</td>
<td>1.2</td>
<td>127</td>
<td>1.2 67</td>
</tr>
<tr>
<td>Pooled estimate (95% CI)</td>
<td>885</td>
<td>741</td>
<td>100%</td>
<td>0.06</td>
<td>[-0.05, 0.17]</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi[^2^] = 6.27 (P = 0.39); I[^2^] = 4% *Days with absolute neutrophil count less than 0.5 x 10^9/L (<500/μL)

### Conclusions

This meta-analysis showed no differences in clinical efficacy between biosimilar and reference G-CSF in breast cancer patients.

### Legal entity responsible for the study

n/a

### Funding

None

### Disclosure

A. Krendykou: Employee of Hexal AG G. Curigliano: Honoraria from Pfizer, Roche, Sandoz. All other authors have declared no conflicts of interest.

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### 1573P - Pharmacokinetic and pharmacodynamic comparability of B12019: A proposed pegfilgrastim biosimilar

**K. Roth** (Munich, Germany) H. Wessels (Munich, Germany) J. Hoefler (Munich, Germany) R. Jankowsky (Munich, Germany)

#### Background

B12019 is being developed as a biosimilar to Neulasta® (INN pegfilgrastim), a pegylated, long-acting form of recombinant human granulocyte-colony stimulating factor (G-CSF) for the prevention of chemotherapy-induced neutropenia. A clinical development program was conducted with B12019 in comparison to EU-authorised Neulasta to confirm the biosimilarity as established by analytical, functional and preclinical data.

#### Methods

The clinical development program for B12019 consisted of two clinical studies. Study B12019-101 investigated pharmacokinetics (PK) and pharmacodynamics (PD) comparability of B12019 to Neulasta. The 6mg single-dose, randomised, double-blind, two-way crossover study enrolled 172 healthy volunteers. The primary PK endpoints were the area under the plasma concentration-time curve (AUC[^0^]-[^last^]) and the maximum
concentration ($C_{max}$) as well as the area under the effect curve ($AUEC_{0-last}$) for absolute neutrophil count (ANC) for PD. In study B12019-102 immunogenicity and PD comparability of B12019 and Neulasta were investigated in a 3mg multiple-dose, randomised, double-blind, three-period, two-sequences crossover study in 96 healthy volunteers. Primary endpoints were $AUEC_{0-last}$ for PD and anti-drug antibody rate (ADA) for immunogenicity.

**Results**

Study B12019-101, using 6 mg, confirmed PK and PD comparability (compare also Roth et al, Blood, Dec 2016). In study B12019-102, 82 subjects were included in the model-based PD comparison. PD comparability was demonstrated, with the $AUEC_{0-last}$ geometric mean ratio with a CI of 99.6; 103.6 being within the pre-specified acceptance range. In both studies, no imbalance of ADA-positive samples after single or repeated dosing were observed. Neither anti-G-CSF nor neutralising antibodies were detected for B12019 or Neulasta.

**Conclusions**

· The clinical program confirmed the biosimilarity of B12019 and Neulasta in highly sensitive clinical study settings. · PK comparability of B12019 and Neulasta was demonstrated at the clinical dose of 6 mg. · PD comparability of B12019 and Neulasta was shown at the clinical dose of 6 mg and the reduced dose of 3 mg. · The safety and immunogenicity profile of B12019 did not show any clinically meaningful differences to Neulasta.

**Clinical trial identification**

NCT02912377 NCT02629562

**Legal entity responsible for the study**

Cinfa Biotech S.L., Olloki, Spain

**Funding**

Cinfa Biotech S.L., Olloki, Spain

**Disclosure**

K. Roth, H. Wessels, R. Jankowsky: Employee of Cinfa Biotech J. Hoefler: Employee of Staburo GmbH, statistical consultancy

**1574P - Efficacy and safety of RGB-02, a proposed biosimilar pegfilgrastim to prevent chemotherapy-induced neutropenia: Results of a randomized, double-blind, phase III clinical study vs. reference pegfilgrastim in patients with breast cancer receiving docetaxel/doxorubicin**


**Background**

Treatment with recombinant human granulocyte-colony stimulating factor (G-CSF) is accepted standard for prevention of chemotherapy-induced neutropenia. RGB-02, a pegylated G-CSF (pegfilgrastim) developed by Gedeon Richter is a proposed biosimilar to the reference pegfilgrastim product Neulasta®. Here we are presenting the results of a
randomized, comparative, double-blind, multicenter study to evaluate efficacy and safety of RGB-02 in breast cancer patients receiving cytotoxic regimen (EudraCT nr: 2013-003166-14).

Methods
239 women presenting with breast cancer were randomized to RGB-02 (n = 121) and to the reference pegfilgrastim, Neulasta® (n = 118). All patients received up to 6 cycles of docetaxel/doxorubicin and a once-per-cycle injection of a fixed 6 mg dose of pegfilgrastim. Primary endpoint was the duration of severe neutropenia (ANC < 0.5 x10^9/L) in Cycle 1 (2-sided CI interval 95%). Secondary endpoints included incidence and duration of severe neutropenia, incidence of febrile neutropenia, time to ANC recovery, depth of ANC nadir, and safety outcomes.

Results
The mean duration of severe neutropenia in Cycle 1 was 1.7 (RGB-02) and 1.6 days (reference), with a difference (LS Mean) of 0.1 days (95% CI -0.2, 0.4). Therapeutic equivalence could be established as the CI for the difference in LS Mean lay entirely within the pre-defined range of ± 1 day. The incidence of severe neutropenia decreased from cycle 1 to 2 in both groups with no statistical significant differences, for RGB-02 from 84.6% (99 patients) to 54.1% (60 patients) and from 77.0% (87 patients) to 43.7% (45 patients) in the comparator group. Both groups were similar regarding mean time to ANC recovery with 3.4 ± 1.84 days (RGB-02) and 3.7 ± 1.88 days (reference) during Cycle 1. Safety profiles were comparable between groups.

Conclusions
Therapeutic equivalence and similar safety profiles between RGB-02 and Neulasta® as once-per-cycle administration could be demonstrated. RGB-02 can provide a biosimilar alternative for the prevention of neutropenia.

Clinical trial identification
EudraCT nr: 2013-003166-14

Legal entity responsible for the study
Gedeon Richter Plc.

Funding
Gedeon Richter Plc.

Disclosure
K. Horvat-Karajz, A. Illes: Employee of Gedeon Richter Plc. All other authors have declared no conflicts of interest.

1575P - Impact of resistance exercise on metabolic syndrome (MetS) parameters in men receiving androgen deprivation therapy (ADT) for prostate cancer

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D. I. Quinn (Los Angeles, United States of America) J. Pinski (Los Angeles, United States of America)
T. Schroeder (Los Angeles, United States of America) S. Groshen (Los Angeles, United States of America)
C. Dieli-Conwright (Los Angeles, United States of America) J. Kiwata (Los Angeles, United States of America)

Background
Cardiovascular disease is the leading cause of death in men with prostate cancer. ADT is effective treatment, but can adversely impact MetS components, which may contribute to excess cardiac risk. We tested whether a resistance exercise program, designed to
increase skeletal muscle mass during ADT, could offset adverse changes.

**Methods**

Prostate cancer patients on ADT were randomized to exercise (EX) or no exercise (noEX). EX was supervised, periodized resistance training followed by stretching 3x/week for 12 weeks, 45 min/session. noEX did home-based stretching 3x/week. Baseline and post-intervention measurements included weight, waist circumference (wCirc), lean body mass, lipids, insulin, glucose. Mean differences in changes were compared with intent-to-treat linear regression models adjusted for baseline values. Cohen’s D effect sizes were calculated for these pilot data to estimate effects for a fully powered trial.

**Results**

Thirty-two men (EX n = 13, noEX n = 19) completed the protocol. Age (mean± SD) was 67.3 ± 8.7 yr (range 52 - 84). Mean duration ADT was 14.4 ± 13.4 months (range 3 – 57). EX patients had higher baseline BMI with 63% >25 kg/m2 compared to 25% in the NoEX group, p = 0.024. wCirc decreased significantly (p = 0.032) in EX (-1.18 cm 95%CI [-3.3, -1.0] cm) compared to NoEX (+1.97 cm [0.2, 3.7]). Lean mass increased and body fat decreased in EX compared to NoEX. Moderate effect sizes (D = 0.2-0.5) were seen between groups for other parameters (see Table).

**Table:**

<table>
<thead>
<tr>
<th>Baseline mean</th>
<th>Week 12 mean</th>
<th>Mean change [95% CI]</th>
<th>p</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>wCirc (cm) EX</td>
<td>106.8 97.9</td>
<td>105.9 99.6</td>
<td>-1.18 [-3.3, -1.0]</td>
<td>0.032</td>
</tr>
<tr>
<td>NoEX</td>
<td></td>
<td></td>
<td>1.97 [0.2, 3.7]</td>
<td></td>
</tr>
<tr>
<td>Lean Body Mass (kg) EX</td>
<td>48.5 kg</td>
<td>43.2 kg</td>
<td>0.17 [0.35, 1.79]</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>51.5 kg</td>
<td>48.6 kg</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Body Fat EX</td>
<td>36.8%</td>
<td>35.9%</td>
<td>-0.9 [-1.78, -0.01]</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>33.9%</td>
<td>34.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg) EX</td>
<td>76.9 79.0</td>
<td>75.4 79</td>
<td>-1.91 [-6.3, 2.5]</td>
<td>0.437</td>
</tr>
<tr>
<td></td>
<td>79.0</td>
<td>75.4</td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>HDL-C (mg/dL) EX</td>
<td>46.5 61.3</td>
<td>49.0 61.5</td>
<td>3.83 [-1.9, 9.6]</td>
<td>0.270</td>
</tr>
<tr>
<td></td>
<td>41.3</td>
<td>49.0</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>HOMA-IR EX</td>
<td>2.56 1.34</td>
<td>1.42 1.82</td>
<td>-0.63 [-1.9, 0.6]</td>
<td>0.433</td>
</tr>
<tr>
<td></td>
<td>1.34</td>
<td>1.42</td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Conclusions**

Supervised resistance exercise for 12 weeks improves wCirc and body composition in men receiving ADT for prostate cancer with moderate effect on other MetS parameters.

**Clinical trial identification**

NCT01909440

**Legal entity responsible for the study**

University of Southern California, Keck School of Medicine

**Funding**

National Strength and Conditioning Association, California State University Chancellor's Doctoral Incentive Program
Disclosure
All authors have declared no conflicts of interest.

1576P - Body mass index (BMI), lifestyle behaviors, and perceptions in cancer survivors
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Background
Obesity is associated with poorer outcomes across multiple cancer types. Lifestyle behaviours (smoking, physical activity (PA) and alcohol) can improve outcomes among cancer survivors.

Methods
Cancer patients of all subtypes were cross-sectionally surveyed on their smoking, alcohol and PA levels, and their perceptions of these behaviours on quality of life (QoL), fatigue and survival (OS). Multivariable logistic regression models evaluated the association of BMI 1 year prior to diagnosis with behaviour changes and perceptions.

Results
Of 1269 patients, 205 smoked at diagnosis and 44% quit at 1 year; 350 (at diagnosis) and 238 (at follow-up) met PA guidelines; 661 drank alcohol at diagnosis while 50% reduced consumption after. Median BMI was 25.8 (22% obese); 75%+ patients perceived PA as improving QoL and OS, while 70%+ described smoking and 55%+ described alcohol as worsening QoL and OS. At diagnosis, increased BMI was associated with ex-smoking (vs current smoking; P = 0.003), never using alcohol (vs former use; P = 0.05) and not meeting PA guidelines (P = 0.01). Among smokers at diagnosis, increased BMI was associated with smoking cessation (aOR = 1.08 per 1 unit BMI, P = 0.03) and perceptions that smoking worsens OS (aOR = 1.10, P = 0.04) and fatigue (aOR = 1.08, P = 0.08). Among those not meeting PA guidelines at diagnosis, increased BMI was associated with perceptions that PA worsens fatigue (OR = 1.02, P = 0.06) and is unsafe (OR = 1.04, P = 0.06), but were not associated with PA levels changes after diagnosis. Among drinkers at diagnosis, increased BMI was associated with perceiving alcohol to be less harmful (aOR = 0.93, P = 0.002) and less likely to worsen OS (aOR = 0.96, P = 0.04) and fatigue (aOR = 0.97, P = 0.09), but not with alcohol use changes after diagnosis. BMI was not associated with counselling rates; however, 66% of current smokers received cessation counselling while only 14% of current drinkers and 13% of those not meeting PA guidelines received counselling on their respective behaviours.

Conclusions
Obese patients were more likely to quit smoking and perceive it to be harmful but less likely to perceive alcohol as harmful. Survivorship programs should consider focusing on PA and alcohol counselling in obese patients.

Legal entity responsible for the study
Princess Margaret Cancer Centre

Funding
None
Disclosure
All authors have declared no conflicts of interest.

1577P - Barriers to improving awareness of the importance on exercise and dietary intervention, impact of it on lung cancer survivors’ behavior

J. Sim (Seoul, Korea, Republic of) Y. Yun (Seoul, Korea, Republic of) S. Yoo (Seoul, Korea, Republic of)

Background
Awareness of the importance on exercise and dietary intervention can provide significant benefits for lung cancer patients and survivors. This study first aimed to identify the barriers and preferences to improving awareness of the importance on exercise and dietary education. In addition, the study also explored the impact of patients’ awareness of the importance on exercise and diet education toward the stage of behavior change, intention of actual participation to the programs.

Methods
Total 830 lung cancer survivors from two hospitals in South Korea participated in this postal questionnaire–survey. Standardized measures including patients’ socio-demographic variables, preferences for appropriate education time and place were identified as the barriers for their awareness of the importance of exercise and diet counseling program. In addition, the impacts of it on each intention of actual participation to both programs and maintaining regular exercise and balanced diet were analyzed in order.

Results
Patients who recognized exercise education program very important had more intention of actual participation to the program (adjusted Odds Ratio [aOR], 2.11; 95% Confidential Interval [CI], 1.57-2.83). In addition, subjects who recognized diet counseling programs very important maintained their behavior of balanced diet more than 6 months (aOR, 2.57; 95% CI, 1.92-3.61). However, significant differences based on the socio-demographic variables and program preferences (i.e., lower education and income, preferred time and place etc.) were identified as main barriers for survivors’ awareness of the importance of the exercise and diet counseling program.

Conclusions
Identification of main barriers provides valuable information regarding improving survivors’ awareness of the importance on exercise and dietary intervention, which should be targeted in maintaining future physical activity and balanced diet, and encouraging the intention of actual engagement to the programs.

Clinical trial identification
None

Legal entity responsible for the study
Ministry of Health & Welfare, Republic of Korea

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1578P - Current perspectives of healthcare providers on weight loss and supportive
nutritional care in cancer patients

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N. Georgiou (Schiphol Airport, Netherlands) R. Audisio (St. Helens, United Kingdom) M. Sawyer (Edmonton, Canada)
S. Kaasa (Oslo, Norway)

**Background**
Malnutrition and cachexia occur in most cancer patients (pts) impacting quality of life (QoL) and anticancer treatment (Tx) outcomes. Nutritional care can help reverse weight loss and improve pt outcomes; however, previous surveys at ESMO (2014, 2015) suggest nutritional care/assessment is insufficiently implemented in clinical practice, despite educational and academic efforts.

**Methods**
This survey created by the authors, including questions from prior surveys, was completed by ESMO 2016 delegates visiting the Nutricia booth.

**Results**
Of 2,011 respondents, 78% were medical oncologists, 56% were Europe based; 61% always discuss nutritional aspects during multidisciplinary tumor boards. To assess malnutrition, 44% measure weight, 30% evaluate systemic inflammation, and 14% assess muscle loss. Eligibility of pts to receive nutritional support is assessed before (48% [44% in 2015; 47% in 2014]) or during (54%) initiation of anticancer Tx, at primary diagnosis (28%), if weight loss is visible during outpatient visits (42%), and when anticancer Tx ends (26%). Main impacts of malnutrition are increased anticancer Tx toxicity (58%; 2015: 53%; 2014: 53%), surgery/radiotherapy complications (40%; 37%; 36%), anticancer Tx discontinuation/decreased effectivity (54%; 40%; 40%), decreased QoL (58%; 56%; 54%), impaired physical function (47%; 44%; 45%), or distress of family members (35%; 32%; 32%). Main goals of nutritional support include QoL (65%; 69%; 64%), completion of anticancer Tx (54%; 52%; 45%), or stabilizing weight (48%; 44%; 47%). Popular approaches to minimize weight loss are antiemetics (48%; 56%), appetite stimulants (41%; 48%), more-effective anticancer Tx (39%; 47%), anticachexia drugs (38%; 43%), and timely and individually tailored dietary advice (36%). During systemic Tx, 85% apply physical exercise programs (either alone or in combination with nutritional care).

**Conclusions**
Compared with our previous surveys, awareness and assessment of malnutrition in cancer pts seems slightly increased. HCPs recognize impacts of malnutrition but may need better guidance on how to improve nutritional care in the supportive and palliative setting.

**Legal entity responsible for the study**
Nutricia Advanced Medical Nutrition

**Funding**
Nutricia Advanced Medical Nutrition

**Disclosure**
F. Strasser: Funds from: Acacia ACRAF Amgen Baxter Celgene Danone Fresenius GSK Grunenthal Helsinn IsisGlobal Millennium/Takeda Mundipharma Novartis Novelpharm Nycomed Obexia Ono Otsuka Pfizer Pharm-Olam PsiOxus PrlME Santhera Sunstone Teva Vifor A. Laviano: Other substantive relationships: independent talks at industry sponsored educational/scientific events N. Georgiou: Corporate-sponsored research;
1579P - A survey of patient acceptance of skin toxicities from cetuximab-based therapy

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M. E. Lacouture (New York, United States of America)

Background
Inhibition of the epidermal growth factor receptor (EGFR) extends patient survival in multiple tumor types. However, EGFR inhibition is associated with skin toxicities such as mild to moderate acneiform rash, which can be severe in up to 18% of patients. A previously performed structured literature search revealed an unmet need for research regarding the influence of dermatologic adverse events (dAEs) on patients’ quality of life (QoL), patient acceptance of cancer treatments, and therapeutic risk/benefit tradeoff from the patients’ perspective. This survey reports on these topics in patients who received the anti-EGFR monoclonal antibody cetuximab.

Methods
Using a multinational survey that included 195 patients, we conducted a subanalysis of 66 patients who previously received cetuximab-based cancer therapy (44 with metastatic colorectal cancer [mCRC] and 22 with squamous cell carcinoma of the head and neck [SCCHN]) to gauge attitudes regarding skin toxicities.

Results
64/66 patients (43/44 with mCRC and 21/22 with SCCHN) experienced dAEs. Skin toxicities were cited as causing pain and physical discomfort as well as impairing QoL. Despite the negative social, physical, and functional impacts of dAEs, 70% of patients with mCRC and 64% of patients with SCCHN who received cetuximab stated that they would prefer a more efficacious cancer therapy that induced more severe skin reactions over a less efficacious therapy associated with less severe skin reactions. Furthermore, in an efficacy-safety tradeoff exercise, nearly two-thirds of patients (65%) stated that they would accept a new therapy with improved efficacy, even if 1 out of every 2 patients experienced a severe skin rash on this therapy.

Conclusions
Patients with mCRC or SCCHN who previously received the anti-EGFR antibody cetuximab as part of their cancer therapy were willing to accept skin toxicities as an AE if these toxicities were the anticipated byproduct of a more effective therapeutic regimen.

Clinical trial identification
N/A

Legal entity responsible for the study
Merck KGaA, Darmstadt, Germany

Funding
Merck KGaA, Darmstadt, Germany Disclosure: P. Ronga: Employee of Merck KGaA M.E. Lacouture: Consulting:AZ, BI, Dignitana, Foamix, Genentech, Janssen R&D, Merck S-D, EMD Serono, Michaels Mission, NVS, Oncology Training International, Quintiles, RP
Background
Proton pump inhibitors (PPIs) may interact with several orally administered drugs, possibly by raising gastric pH levels, leading to altered dissolution and absorption. In a previous study, we found that co-administration of PPIs with cetuximab was associated with increased skin toxicity. To confirm this preliminary observation, we tested this observation retrospectively. Since both these drugs can induce hypomagnesemia, the possibility of synergism between them was also tested.

Methods
The files of patients with metastatic colorectal carcinoma (mCRC) or head and neck (H&N) carcinoma treated at our center with cetuximab as a single agent or in combination with chemotherapy or radiotherapy were reviewed. All eligible patients treated with cetuximab during 2015 and 2016 were included in the study. The concomitant use of PPIs was defined if a drug belonging to that class was included in the patient’s chronic medications list.

Results
One hundred eighteen patients (61 with H&N carcinoma, 57 with mCRC) were included in the study. Median follow-up from onset of cetuximab was 12.6 months [range, 0.5-63.2 months]. Fifty-eight patients received PPIs concomitantly with cetuximab. Skin toxicity of any grade was reported in 33/58 (56.9%) patients on PPIs compared with 22/60 (36.7%) patients not on PPIs (p = 0.08). Grade 3-4 skin toxicity was reported in 19/58 (32.8%) patients on PPIs compared to 2/60 (3.3%) not on PPIs (p = 0.001). Median time to detection of severe skin toxicity was 0.7 months [range, 0.2-11.0 months].

Hypomagnesemia (Mg serum level <1.2 mg/dL) was reported in 14/58 (25.9%) PPIs treated patients compared with 5/60 (10.4%) patients not on PPIs as a chronic medication (p = 0.08). Median time to detection of hypomagnesemia was three months [range, 0.4-52.8 months]. Complications of all grade skin toxicity or hypomagnesemia were reported in 40/58 (69%) patients on PPI compared to 23/60 (38.3%) patients not on PPIs (p = 0.04). Grade 3-4 skin toxicity or hypomagnesemia (Mg < 0.9 mg/dL) were reported in 23/58 (39.7%) patients on concomitant treatment with PPIs compared with 3/60 (5%) patients not on PPIs (p = 0.001).

Conclusions
Both the rate and the severity of cetuximab-induced skin toxicity and hypomagnesemia were increased by chronic concomitant administration of PPIs. A prospective study is needed to confirm the possible interaction between cetuximab and PPIs.

Legal entity responsible for the study
Mahmoud Abu Amna

Funding
None
Disclosure
All authors have declared no conflicts of interest.

The potential protective effect of exogenous antioxidant “L-Carnosine” on Oxaliplatin-Induced Peripheral Neuropathy in colorectal cancer patients; A perspective on targeting Nrf 2 and NF-κB pathway.

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Background
Chemotherapy-induced peripheral neuropathy is a common side effect afflicting patients with cancer treated with neurotoxic chemotherapeutic agents, as oxalipatin. Aim: The study aims at investigating the use of anti-oxidant L-carnosine for prevention of acute oxalipatin neurotoxicity in colorectal cancer patients by assessing its effect on Nuclear factor-2 erythroid related factor-2 (Nrf2) induced oxidative stress pathways by assessment of serum levels of Malondialdehyde (MDA), Nuclear factor-kappa light chain enhancer of B cells (NF-κB) anti-inflammatory pathway and pro-apoptotic signals Caspase-3 (Casp-3).

Methods
In this pilot study 65 patients were recruited using prospective randomized controlled study design and enrolled randomly into to two arms; Arm A (31 patients) received FOLFOX-6 regimen (oxaliplatin, 5FU & leucovorin) and Arm B (34 patients) received FOLFOX-6 regimen and oral L-carnosine 500 mg daily all along the treatment. All recruited patients were followed up for three months, then both arms were analyzed for neuropathy incidence/grade and any additional toxicities according to NCI-CTC version 4.

Results
In both arms the correlation analysis was significantly positive between NF-κ B and either Nrf2 and caspase 3.
Concerning the improving impact of L-Carnosine added to oxalipatin, represented in Arm B, on inflammatory markers, it caused a significant decrease in the levels of NFkB (27%) compared to Arm A. Intriguingly, this ameliorative anti-inflammatory effect of L-Carnosine was also reflected on its anti-apoptotic and anti-oxidative effects, by reducing caspase activity (49%), MDA level (51.8%) as well as significant elevation of Nrf2 (38.7%), compared to Arm A.

Conclusions
Dietary supplementation with L-Carnosine proved to improve Oxalipaltin induced peripheral neuropathy by amelioration of the pathophysiologic triad of inflammation, oxidative stress and apoptosis. These results led to the recommendation of safe add-on therapy of Carnosine to chemotherapeutic agents, and opens thereby, a new supportive strategy in oncologic diseases.

Clinical trial identification
NCT02808624

1582P - NeuroCog-FX study: A multicenter cohort study on cognitive dysfunction in patients with early breast cancer

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Background

Many breast cancer patients complain about cognitive dysfunction (CD) with mnestic and attentional deficits. These complaints persist even after completion of therapy in approximately one third of the patients and affects both social life and working capacity. The exact nature and genesis of CD in breast cancer patients is still not fully understood and risk factors are not yet described.

Methods

To determine CD and risk factors, we used the computer-based neuropsychological test NeuroCog-FX during a three weeks oncological rehabilitation in breast cancer patients. Eight subtests addressed attention, working memory, verbal and figural memory, and language. Test duration was <30 minutes. A cognitive deficit was diagnosed if at least one subtest was clearly below average (score < M - 1.5 SD) of the normative age group. The data on cognitive function were correlated with the level of depression (PHQ-9 test), QoL (EORTC QLQ-30) and clinical parameters (nodal status, chemo-/radiotherapy and endocrine therapy).

Results

From February 2013 to December 2014 a total of 476 patients were recruited in 9 oncological rehabilitation centers in Germany. NeuroCog-FX was used to examine 439 patients. Median age was 50 years (range: 24-62 years); 93% of patients had early tumor stage (T0-T2) and 67% were node-negative. Sixty-one percent of the patients received chemotherapy while 84% of the subjects underwent radiotherapy. CD was found in 59% and a moderate to severe depression in 38% of the patients. The severity of depression was correlated with slower reaction times and reduced verbal memory performance. These two cognitive parameters were also associated with a reduced global health status and a reduced physical function score on the EORTC-QLQ30 questionnaire suggesting an impact of cognitive deficits on quality of life. Cognitive function was not associated with type of treatment or node status.

Conclusions

In this large and homogeneous cohort of breast cancer patients, CD has been shown in most of the subjects using a valid test method. CD was associated with depression and reduced quality of life. Neither tumor therapy nor other clinical parameters had a significant impact on development of CD.

Legal entity responsible for the study

Frankfurt

Funding

None

Disclosure

All authors have declared no conflicts of interest.

1583P - Autonomic neuropathy in geriatric patients with gynecologic cancer receiving taxanes and platinum chemotherapy

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A. Vora (New Delhi, India)G. Biswas (Bhubaneshwar, India)H. Malhotra (Jaipur, India)
**Background**

The standard of care for ovarian cancer in elderly is using paclitaxel and carboplatin, an effective and efficient combination, but has serious toxicities. Peripheral neurotoxicity is one of the commonest toxicities which are seen occurring in 60% to 90% of patients. It is debilitating and vexing. Unfortunately, there is very little or no data regarding autonomic neuropathy in this setting. This study is an attempt to highlight this problem.

**Methods**

Single center cohort study of patients for the period 2013-2015. All patients were above the age of 65 years. 88 patients were tested for. All patients were screened for neuropathy using standard forms and methods including positional sense and stereognostic sense for neuropathy. NCI scales of grading peripheral neuropathy were followed. Autonomic neuropathy assessments were done by cardio vascular autonomic reflex test and gastro-intestinal autonomic neuropathy by using gastric phase emptying test. Genito-urinary autonomic neuropathy was tested for erectile dysfunction and bladder dysfunction. The tests were administered at baseline after 2nd, 4th and 6th cycle or if the patient complained of suggestive symptoms.

**Results**

37% of patients developed grade 3/4 peripheral neuropathy. 59% of patients developed symptomatic autonomic neuropathy. Cardio vascular autonomic neuropathy occurred in 30% while gastric neuropathy was seen in 19%. Combined was seen in 10%. Constipation, diarrhoea and reeling of head were the most common complaints. Autonomic neuropathy was more common in diabetics 60% vs 48% (p > 0.05). Attempts to intervene using pharmacotherapy methods and non-pharmacotherapy methods were attempted.

**Conclusions**

Autonomic neuropathy seems to be common in geriatric population treated by this drug combination although there is not much mention either in real life or in clinical trials or if available as data attributed to other causes. Caution must be exerted in patients in diabetics and proper screening should be done in this patient population for autonomic neuropathy and peripheral neuropathy.

**Legal entity responsible for the study**
G S Bhattacharyya

**Funding**
None

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

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**1586P - Potential drug interactions in older patients with cancer: Updated data from the ELCAPA cohort survey**

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P. Caillet (Créteil, France)

**Background**

Because of polypharmacy, older cancer patients are at risk of adverse events related to
potential drug interactions (PDI). We aim to identify PDI in daily medications, between daily medications and chemotherapy (CT), and related potential clinical outcomes (PCO).

**Methods**

All cancer patients aged ≥70 years, referred for geriatric assessment at Henri Mondor Hospital (Paris’ area, Créteil, France), included in the prospective ELCAPA cohort survey (2007–2014), and who received CT were included. PDI were identified using Lexicomp® (LexiComp, Hudson, USA) software and the Theriaque® website. PDI were classified as: A, no interactions; B, no action needed; C, monitor therapy; D, consider therapy modification; X, avoid combination. Factors associated with grade C or D/X PDI were analyzed using ordered multivariate logistic regression.

**Results**

We analyzed 442 patients (median age: 78 years; 49% women). Main tumor sites were upper digestive tract (23%), colorectal (21%), urological tract (19%), lymphoid malignancies (15%), and breast (12%); 23% had metastasis. Median number of drugs/patients/day was 3 (Q1-Q3 [1-6]). We identified 1742 PDI: 87% in daily medications (183 patients had grade C PDI (41%), 128 grade D/X (29%)), and 13% between daily medications and CT (66 patients had grade C PDI (15%), 56 grade D/X PDI (13%)). Main PCO involving daily medications were hypotension risk (33%), psychotropic effects (17%), glycemic (12%) and hemostasis (9%) dysregulations. Main PCO related to PDI involving CT were risk of CT over-exposure (34%), hypotension risk (20%), and hemostasis dysregulation (11%). In multivariable analysis, adjusted for number of drugs, factors associated with grade D/X PDI, both with or without CT were: ≥2 metastatic sites (p = 0.01) and lymphoid malignancies (p = 0.01). Patients living alone had less grade D/X PDI in daily medications (p = 0.003), while breast cancer (p = 0.04) was associated with more grade D/X PDI in daily medications. Higher body mass index was associated with grade D/X PDI involving CT (p = 0.03).

**Conclusions**

The high prevalence of PDI in older cancer patients highlights the need to assess precisely the iatrogenic risk before anti-cancer treatment.

**Legal entity responsible for the study**

Assistance Publique - Hopitaux de Paris

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1587P - How do Spanish medical oncologists manage breakthrough pain? A national study**

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**Background**

Many cancer patients experience transient exacerbations of severe pain, known as
breakthrough cancer pain (BTcP), a complex pain state that negatively impacts patients’ quality of life. We evaluated the knowledge of BTcP management according to the Spanish Society of Medical Oncology (SEOM) clinical practice guideline.

**Methods**

Fundación ECO (Foundation for Excellence and Quality in Oncology) conducted a survey regarding knowledge of managing BTcP focusing on: awareness of SEOM guidelines, agreement with recommendations, and implementation in clinical practice.

**Results**

A total of 83 oncologists responded: 65% were female, mean age was 40-year-old and mean time in practice was 13 years. Overall, 82% were aware of guidelines and the agreement with recommendations ranged from 99-100%. Regarding implementation, 87.6% declared full compliance, nonetheless adherence in clinical practice ranged from 30.1% to 86.7% for documentation of BTcP episodes in medical records, and 75.9% to 91.6% for therapeutic management. 100% of oncologists agreed on the prescription of specific medication for BTcP and most of them (91.6%) that rapid onset fentanyl formulations should be considered the first line of treatment.

Table:

<table>
<thead>
<tr>
<th>CPG</th>
<th>AGREEMENT</th>
<th>IMPLEMENTATION (in medical records)</th>
<th>IMPLEMENTATION (ranked drug of choice characteristics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWARENESS</td>
<td>81.93% (68/83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEOM</td>
<td>97.1%</td>
<td>100% documentation</td>
<td>Rapid onset</td>
</tr>
<tr>
<td>ESMO</td>
<td>63.2%</td>
<td>99% best evidence</td>
<td>High potency</td>
</tr>
<tr>
<td>NCCN</td>
<td>58.8%</td>
<td>99% specific medication</td>
<td>Short duration</td>
</tr>
<tr>
<td>Instit</td>
<td>19.1%</td>
<td>99% fentanyl 1st choice</td>
<td>Route of administration</td>
</tr>
<tr>
<td>Other</td>
<td>7.3%</td>
<td>75.9% triggers</td>
<td>Ease of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73.5% relief strategies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.1% time to peak</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>86.7% etiopathogenesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>66.3% pain intensity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.8% duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.1% time to peak</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>73.5% relief strategies</td>
<td>Minimum side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>86.7% etiopathogenesis</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

Our results support efforts and targeted education of medical oncologists in BTcP management. However, our study raises concerns about guidelines dissemination deficiencies as well as vague statements that underscore a need for more effective dissemination policy and more effective detailed recommendations.

**Legal entity responsible for the study**

Fundación ECO (Foundation for Excellence and Quality in Oncology)

**Funding**

Kyowa Kirin Farmacéutica, S.L.U.
Background
Enhanced Supportive Care (ESC) is a fresh approach to supporting patients through cancer treatment and recognised nationally by NHS England. The Supportive Care Team (SCT) and Experimental Cancer Medicine Team (ECMT) at the Christie Hospital applied the validated ‘Integrated Palliative care Outcome Scale’ (IPOS; http://pos-pal.org/) in a pilot study examining the impact of ESC for patients (pts) entering early phase clinical trials. The main aims of this study were to maximise patient recruitment and retention and enhance the patient experience within the context of experimental cancer medicine clinical trials.

Methods
The IPOS tool was used to assess the effect of ESC on patient outcomes in pts on an ECMT trial. It was administered by the SCT healthcare professionals to any pts with baseline symptoms thought to be related to their underlying cancer diagnosis and at all pt visits as per trial protocol. Analysis is based on patient data where both an initial and subsequent form had been completed. Three aspects of the IPOS tool were reviewed; the overall IPOS score, the score for all symptoms as a whole and individual pain score.

Results
Data was collected from 24 pts within ECMT trials during a four-month period in 2016. The mean age was 56 years (31 to 79); 10 male and 14 female. Performance status at initial assessment was 0 (3 pts); 1 (18 pts); 2 (1 pt); unknown (2 pts). 16 pts had no previous contact with SCT services. The commonest reason for referral to the SCT was for optimisation of pain control (24/24 pts) followed by general symptom control (8/24) and psychological issues (2/24). 21 pts were seen on the day of referral, 3 pts seen ≤ 8 days of referral. 16/24 pts (67%) reported improvement in pain (and IPOS scores) within 4 weeks and 17/24 pts (71%) reported improvement in overall symptom control within 4 weeks.

Conclusions
This study has demonstrated the effectiveness of ESC on the outcomes of patients being reviewed by the SCT on ECMT clinical trials. There were considerable reductions in the overall IPOS scores and in pain score specifically. ESC has now been adopted into
routine practice by our ECMT, and we are the first unit to do so in the UK. We next plan to measure the impact of ESC on patient experience, adverse events on trials, hospital admissions and treatment duration.

**Legal entity responsible for the study**
Experimental Cancer Medicine and Enhanced Supportive Care Team

**Funding**
None

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

1589P - Cancer patient interest and perceptions of lifestyle behavior programs

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**Background**
Lifestyle behaviors including smoking cessation, physical activity (PA) and alcohol moderation are important aspects of a cancer survivorship program. We assessed cancer patient (pt) interest and perceptions of programs for these behaviors.

**Methods**
501 cancer pts from all subtypes were surveyed on their smoking, PA and alcohol consumption patterns along with their interest and perceptions for programs for these behaviors. Multivariable logistic regression models identified factors associated with pt interest and perceptions.

**Results**
At diagnosis, 115 pts smoked; 41% had second hand smoke (SHS) exposure; 238 were drinking alcohol; 313 did not meet PA guidelines. At risk individuals’ (e.g. smokers for smoking cessation, exposed to SHS for household smoking cessation) survey results are shown in the table. Perceptions of how these behaviors impact quality of life, survival and fatigue was not associated with program interest (P > 0.05). However, pts perceiving that alcohol worsened and PA improved these outcomes were more likely to believe associated programs are beneficial (alcohol aORs = 2.1-2.2 P < 0.03; PA aORs = 1.9-3.2 P < 0.02) and should be routine care (alcohol aORs = 1.9-3.5 P < 0.03; PA aORs = 1.7-2.4 P < 0.1). Pts with more pack-yrs less likely perceived benefit in a household cessation program (aOR = 1.02 P < 0.007) or in a routine care program (aOR = 1.01 P < 0.02). Pts preferred discussing programs with doctors (35%+) or counsellors (42%+).

<table>
<thead>
<tr>
<th>Program</th>
<th>% at risk interested in program</th>
<th>Believe Program is Beneficial</th>
<th>Believe in Routine Care Program</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Agree aOR of being interested (95% CI)</td>
<td>P</td>
</tr>
</tbody>
</table>

Table: 1589P

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## Conclusions

About half of pts feel that lifestyle behavior programs would be beneficial and should be part of routine care. These factors were more important than perception of the behaviors on outcomes in influencing pt interest. Initial discussions with pts should focus on discussing benefits of these programs.

### Legal entity responsible for the study

Princess Margaret Cancer Centre

### Funding

None

### Disclosure

All authors have declared no conflicts of interest.

1590P - The investigate relationship between severe neutropenia and ABCB1 and ABCG2 gene polymorphisms with esophageal cancer patients receiving docetaxel, cisplatin and 5-fluorouracil chemotherapy

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### Background

The combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is a newly developed chemotherapy for esophageal cancer (EC) patients (pts). Severe neutropenia is one of the major adverse events that necessitate chemotherapy dose reduction. This study aimed to investigate relationship between grade 3 and 4 neutropenia and genetic polymorphisms in EC pts received DCF.

### Methods

EC pts who had undergone DCF chemotherapy at National Cancer Center Hospital East from August 2011 to December 2016 were enrolled in this study. Prophylactic administration of granulocyte-colony stimulating factor was not conducted for the all EC pts during the above chemotherapy. Seven polymorphisms in the genes encoding docetaxel-metabolizing enzymes and transporters were genotyped, and then relationship between these genotypes and the grade 3 and 4 neutropenia was then investigated. Risk factors that enable to predict grade 3 and 4 neutropenia after first cycle of chemotherapy were explored using multivariate logistic regression analysis.

### Results

A total of 170 pts treated with DCF were enrolled in this study period. The median age

<table>
<thead>
<tr>
<th>Lifestyle Behavior</th>
<th>Baseline</th>
<th>Change</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking Cessation</td>
<td>53%</td>
<td>57%</td>
<td>2.85 (1.0-7.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Household Smoking Cessation</td>
<td>37%</td>
<td>55%</td>
<td>2.73 (1.1-6.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>PA</td>
<td>53%</td>
<td>70%</td>
<td>4.73 (2.5-9.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol Moderation</td>
<td>25%</td>
<td>55%</td>
<td>2.54 (1.3-5.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
was 64 years, median body mass index was 22.0 (15.3 - 31.0), median serum hemoglobin level was 13.5 (8.7 - 17.1) g/dL, median prognostic nutritional index was 50.1 (36.7 - 68.7) and baseline absolute neutrophil count (ANC) was 4305 (1660 - 11020)/mm$^3$. The proportion of pts with grade 3 and 4 neutropenia was 56 (32.9%) and 34 (21.2%), respectively. Multivariate logistic regression analysis adjusted for potential risk factors revealed ABCB1 3435C > T ($p = 0.015$), ABCG2 34G > A ($p=0.044$), age (60<) ($p < 0.001$) and baseline ANC (< 4305) ($p = 0.001$) were independent and significant risk factors for grade 3 and 4 neutropenia.

Conclusions
We identified that genetic polymorphisms in ABCB1 3435 C > T and ABCG2 34 G > A was a significant predictor for grade 3 and 4 neutropenia of EC pts receiving DCF.

Legal entity responsible for the study
National Cancer Center Hospital East

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1591P - Hepatitis B and C reactivation rates due to cytotoxic chemotherapy in patients with solid tumors
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Background
We tried to determine the incidence of the reactivation rates of chronic HBV and HCV infections in cancer patients who received different types of chemotherapy or immunosuppressive therapy. Also we tried to identify the chemotherapy regimens though to be associated with this reactivation of chronic HBV and HCV infections.

Methods
Between 2000 and 2014, 8322 cancer patients who were admitted to oncology departments were evaluated retrospectively and 3890 patients in whom hepatitis serology were available were included in this study. Their mortality rates, chemotherapy regimens, cancer types, number of positive hepatitis serology and reactivation rates were also obtained.

Results
In all 8322 cancer patients, only 3890 (47%) patients had hepatitis serology results and 355 patients had positive hepatitis serology results (HBsAg, anti-HBcAg, anti-HCV). Of them, 4.24% had anti-HBcAg positivity, 3.65%had HBsAg positivity, and 1.23% had anti-HCV positivity. Nineteen patients with HBsAg positive (13.38%), 4 patients with anti-HBcAg positive (2.42%), and 2 patients with anti-HCV positive (4.16%) had reactivation. hepatitis reactivation was seen significantly higher in lymphoma patients ($p = 0.032$). Reactivation rate of hepatitis B in those patients (HBsAg positive) was detected as 57.14%. In patients with hepatitis reactivation, the rates of usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine were determined as significantly higher than patients with positive hepatitis serology results but without hepatitis reactivation ($p > 0.05$ for all).
Conclusions
An association between hepatitis reactivation and the usage of 5-FU, cisplatin, cyclophosphamide, doxorubicin, steroid, rituximab, and vincristine was detected. Thus physicians should consider antiviral prophylaxis before initiating these chemotherapeutics.

Legal entity responsible for the study
Individuals: Ahmet Ozet, Deniz Tural

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1592P - Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab

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Background
Ramucirumab, a human IgG1 monoclonal antibody receptor antagonist of vascular endothelial growth factor receptor 2 (VEGFR-2), has been approved for treatment in gastric/gastroesophageal junction, non-small cell lung, and metastatic colorectal cancers. A total of 6 global, randomized, double-blind, placebo-controlled, phase 3 trials across multiple tumor types and a large patient population have currently been completed. To further establish the safety profiles of ramucirumab, a meta-analysis has been performed based on the data from these 6 trials and the results are presented here.

Methods
Fixed-effects or mixed-effects models were used to conduct an individual patient meta-analysis across the 6 completed phase 3 trials and derive the relative risk (RR) and associated 95% confidence intervals (CIs) for all-grade and high-grade (Grade ≥3) adverse events (AEs) possibly related to VEGF pathway inhibition.

Results
This meta-analysis included a total of 4996 treated patients (2748 patients in ramucirumab arms, 2248 in control arms). Proteinuria, gastrointestinal (GI) perforation, hypertension, wound-healing complications, infusion-related reactions, and low-grade (Grade 1-2) bleeding were observed at a higher percentage in the ramucirumab arms compared to control. However, our data did not demonstrate a definite increased risk with ramucirumab in high-grade bleeding (RR: 1.1, 95% CI 0.8-1.5), high-grade GI bleeding (RR: 1.1, 95% CI 0.7-1.7), venous thromboembolic events (VTE, all-grade, RR: 0.7, 95% CI 0.5-1.1; high-grade, RR: 0.7, 95% CI 0.4-1.2), or arterial thromboembolic events (ATE, all-grade, RR: 0.8, 95% CI 0.5-1.3; high-grade, RR: 0.9, 95% CI 0.5-1.7).
Conclusions
The risk of developing certain AEs with ramucirumab is consistent with other antiangiogenic agents; and, the safety profile is consistent with the ramucirumab labels. Our results showed no clear evidence for an increased risk of high-grade bleeding, high-grade GI bleeding, VTE, or ATE in this large and patient level meta-analysis.

Clinical trial identification
REGARD = NCT00917384, RAINBOW = NCT01170663, REVEL = NCT01168973, RAISE = NCT01183780, REACH = NCT01140347, ROSE = NCT00703326

Legal entity responsible for the study
Eli Lilly and Company

Funding

1593P - The preventive role of intravenous L-alanyl L-glutamine in reducing the incidence of oral mucositis in head and neck cancer patients receiving radiotherapy with or without chemotherapy
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Background
The current prospective comparative phase 2 study aimed to assess the role of intravenous L-alanyl L-Glutamine in reducing the rate of oral mucositis for squamous head and neck cancer patients receiving radiotherapy with or without concurrent chemotherapy.

Methods
From September 2014 to September 2016, 100 head and neck cancer patients were treated with radiotherapy or combined chemo-radiation at the Clinical Oncology Department, Tanta University Hospitals. Patients were randomized in 1:1 ratio into Group...
A (n = 50 patients) treated by radiotherapy or concurrent chemo-radiotherapy and Group B (n = 50 patients) to receive same treatment in addition to intravenous Glutamine. The investigational drug was infused daily at dose of 0.3-0.4 g/kg diluted in NS and administered at rate of 0.1g/Kg/hr. All patients received total dose of 65-70 Gy using Linac 6MV photon beam supplemented with electron beam when needed. For concurrent chemotherapy, Cisplatin (40mg/m2) was administered weekly.

Results
Mucositis was assessed by WHO grading system. A significantly higher incidence of mucositis was reported in 45% of Group A patients compared with patients in group B who received glutamine 10% P < 0.001). Group B patients had significantly longer period free from mucositis in comparison to group A with median time (12 weeks vs 8 weeks) P < 0.001. A significant lower rate of radiotherapy interruption was reported in group B compared to group A (50% vs 15%) P < 0.001. More Patients needed hospitalization in group A (20%) vs (5%) in group B P = 0.059. No adverse effects were observed in relation to glutamine.

Conclusions
Intravenous L-alanyl L-Glutamine may be an effective measure to lower incidence or prevention of oral mucositis in head and neck cancer patients treated by radiotherapy or combined chemo-radiation.

Legal entity responsible for the study
Tanta University Hospital

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1594P - Biosimilar epoetin alfa (HX575) for the treatment of chemotherapy-induced anaemia: Development, approval and 10 years’ clinical experience

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Background
Patent expirations for biological products have prompted the development of biosimilars, which have comparable quality, safety and efficacy to a licensed biological medicine (the ‘reference’ medicine). HX575 (Binocrit®, epoetin alfa biosimilar) was approved in Europe in 2007 for the treatment of chemotherapy-induced anaemia (CIA).

Methods
The development and approval of HX575 included extensive analytical characterisation and comparison with the reference epoetin alfa, followed by a clinical development programme; this included phase I pharmacokinetic/pharmacodynamic studies to show bioequivalence to the reference medicine, and a confirmatory phase III study to confirm therapeutic effectiveness in CIA. Since approval, HX575 has been extensively used in real-world clinical practice.

Results
An array of analytical methods confirmed the similarity of HX575 and the reference epoetin alfa in terms of primary protein structure, higher-order protein structure, isoform
pattern, post-translational modifications, receptor binding and biological activity. Phase I studies showed that HX575 and the reference medicine were bioequivalent following intravenous and subcutaneous administration. In a confirmatory phase III study (n = 114), HX575 was effective in treating CIA in cancer patients, and had a safety profile consistent with the therapeutic class and as expected for the therapeutic area. Post-approval data are also available for a range of cancer types; positive results have been reported from a multi-centre retrospective clinical study, single-centre experiences from several countries, and a large-scale prospective observational study. No additional/unexpected safety issues have emerged after 10 years of pharmacovigilance. A pilot study has suggested that HX575 may also be effective for the treatment of anaemia in low-/intermediate-1 risk myelodysplastic syndromes.

Conclusions
As of Feb 2017, HX575 has generated >252,000 patient years’ experience in CIA worldwide. Accumulated data and experience over a decade are reassuring that HX575 is effective and well tolerated for the treatment of CIA in patients with different cancer types.

Clinical trial identification
N/A

Legal entity responsible for the study
N/A

Funding
None

Disclosure
M.S. Aapro: Consulting or Advisory Role: Sandoz Speakers’ Bureau; Sandoz Research funding: Sandoz A. Krendyukov, N. Höbel, A. Seidl: Employee of Hexal AG P. Gascón: Lectureship in Sandoz International GmbH sponsored events

1595P - Experience with the implant of vascular access devices by medical oncologist in a non-surgical scenery

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L. Fáez García (Oviedo, Spain) S. Fernández Arrojo (Oviedo, Spain) C. Iglesias Gómez (Oviedo, Spain)
N. Villanueva Palicio (Oviedo, Spain) P. Jimenez Fonseca (Oviedo, Spain) M. Luque Cabal (Oviedo, Spain)
C. Álvarez Fernández (Oviedo, Spain) M. Izquierdo (Gijón, Spain) J. Viéitez (Oviedo, Spain)
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Background
Totally implantable central venous catheters are widely used in the management of patients (pts) with malignant diseases in order to facilitate drug delivery for the new therapeutic protocols. These are based on continuous administration and higher doses of chemotherapeutic agents with relative phlebitis problems and supportive treatment. Staff of our department, specially trained on the routinely implant of central venous accesses were in charge of the procedure. The technique was carried out under local anesthesia in a special suite of day hospital, under strict aseptic measures without fluoroscopic control.

Methods
From Sep 94 to January 2017, 1665 devices (port-a-cath systems [PS]) were implanted in 1627 pts, with a median age of 50.5 yr (range 14-81), and median K.I. 70% (50-100),
female 982/male 683. Venous access: right interior jugular 983, left subclavian 316, right subclavian 333, left interior jugular 33. A thorax X-ray was performed after each procedure and in 216 pts prophylactic antibiotics were given.

Results
The venous access remained implanted a median of 438 days (1-+2210). Complications occurred in 266 placements (16%): Infections 116 (7%); deep venous thrombosis 66 (4%) obstruction 10 (0.6%); malpositioned 16 (2%); fractures/migration 28 (1.7%); pneumothorax 6 (0.32%); local skin necrosis 7 (0.6%). Five hundred and twenty devices were removed, three hundred and forty-seven (66%) after completing planned therapy and 173 (34%) due to complications [Infections (92), migration (22), malposition (12), venous thrombosis (26), obstruction (11) and skin necrosis (10)]. Cost-effectiveness of venous catheters in a non-surgical scenery compared to devices implanted by interventional vascular radiologists in operating room turned out to be 1000 euro cheaper for each device.

Conclusions
Our experience suggests that implant of vascular access devices by medical oncologist in a non-surgical scenery has similar or even less complications and is more cost effective with regard to radiology suite and operating room placement procedures.

Legal entity responsible for the study
Emilio Esteban, Oncología Médica, Hospital Universitario Central de Asturias.

Disclosure
All authors have declared no conflicts of interest.

1596P - Management of chemotherapy-related side effects- do patients know where to get help?
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Background
Timely access to oncology healthcare providers for advice about chemotherapy-related symptom management is a provincial priority in Ontario, Canada. The aim is for all chemotherapy patients to have access to an oncology care provider for urgent advice thereby reducing unscheduled visits such as emergency room (ER) attendance and hospitalizations which are common during chemotherapy. Here, we explore patients’ knowledge about how to access urgent advice for side effects.

Methods
Between September and November 2016, 4 hospitals providing systemic therapy in Toronto, Canada (one academic & three community centers) performed a program evaluation for quality improvement purposes. A paper survey was developed. Patients with breast, lung, gastrointestinal, hematological cancers and sarcoma ≤4 weeks after their first chemotherapy cycle were questioned in chemotherapy day units. The survey
explored patients’ knowledge about where to get help for chemotherapy related side effects at different time points (weekdays 9am-5pm, weekdays 5pm-9am, weekends). Descriptive statistics and Chi square were used to describe results.

**Results**

A total of 140 surveys were administered to 32 lung, 38 breast, 39 GI, 22 hematology and 9 sarcoma patients. Overall, 81% of patients stated they knew where to go to get help for side effects; 56% of patients were told where to get help by a staff member, usually a nurse (44%) or oncologist (23%), while 19% reported they were not told where to get help by anyone. Across all time points the majority of patients stated they would present to ER for side effect management (41, 76 & 81% respectively). The only exception was the academic hospital where 69% of patients reported calling the clinic/nursing telephone line on weekdays 9am-5pm (comparison between academic and community centers p < 0.001). Qualitative analysis of comments revealed that patients want more resources and education in easily accessible formats and prefer to speak to a person rather than leaving voice messages.

**Conclusions**

Significant gaps in patient care and education are highlighted by these results. Site specific quality improvement projects are currently underway to address these findings prior to re-administering the survey.

**Legal entity responsible for the study**

Regional Systemic therapy program

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

**1597P - The effects of nurses’ empathy skills on attitudes towards patients with cancer**

**A. Alkan (Osmaniye, Turkey)**

**Background**

Empathy is sine qua non-ability of nurses and the positive effects of empathy on clinical management have been documented. In addition, its positive effects have also been reported in oncology practice. The purpose of this study is to evaluate the predictors of empathy skills and attitude towards cancer patients and association between nurses’ empathy skills on attitudes towards patients with cancer.

**Methods**

A structured questionnaire was used to evaluate the nurses’ empathy skills and their attitudes towards patients with cancer. Jefferson Scale of Empathy (JSE) and Attitudes Towards Cancer Scale (ATCS) were used. The predictors of JSE/ATCS scores and correlation between JSE and ATCS were analyzed.

**Results**

305 nurses participated in the study (84.2% of all nurses). The median age was 33 (20-52) and most of the nurses were female (82.6%). Most of the participants were married (188, 61.6%) and 40.3% of nurses had an job experience more than 10 years. Female sex, being married, having job experience more than 10 years or caring more cancer patients
were associated with higher JSE scores. Nurses caring more cancer patients weekly, experience with cancer patients, participation in educational activities about cancer care or presence of relative with a diagnosis of cancer were found to have more positive attitudes towards cancer patients. Spearman correlation analysis showed a positive, weak correlation between JSE and ATCS (r = 0.017, p = 0.38)

Conclusions
Empathy skills are important while caring patients, especially in oncology practice. Although a direct correlation between empathy skills and attitudes towards cancer patients couldn’t be demonstrated, health care workers caring cancer patients should be both evaluated for empathy skills and educated.

Legal entity responsible for the study
N/A

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1598P - Can postponement of death be used in shared decision making in patients treated with adjuvant chemotherapy?

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Background
Standard adjuvant treatment to patients with stage III colon cancer is six months of adjuvant combination chemotherapy with a 5-fluorouracil derivate (5-FU) and oxaliplatin. In some cases, 5-FU monotherapy may be an option. The aim is to develop a different way of explaining the benefit of different treatment options by using the concept of “postponement of death”.

Methods
We identified pivotal phase III publications about adjuvant treatment for stage III colon cancer. Data regarding overall survival was extracted for observation versus 5-FU monotherapy and combination chemotherapy versus 5-FU. Data about the impact of N1 and N2 category was extracted if available. Data was used for restricted mean survival analysis. Postponement of death was defined as the mean difference in survival time between the two randomized treatment arms. Survival curves was plotted into the tool WebPlotDigitizer and the area under the curve (AUC) was calculated for each treatment.

Results
AUC for patients receiving 5-FU was 69.1 months and for combination chemotherapy 71.9 months. The mean survival difference at 10 years was 2.8 months. For the subgroup of patients with N1 category, the postponement of death was 0.5 months if treated with combination chemotherapy instead of 5-FU. For patients with N2 category the difference was 11.6 months when treated with combination chemotherapy compared to monotherapy. In the trial comparing 5-FU with observation, the AUC was 73.7 months and 63.3 months, respectively, at 8.5 years. The overall postponement of death between 5-FU and observation was 10.4 months not adjusted for N status.

Conclusions
Postponement of death can be calculated using restricted mean survival analysis and published survival curves. Patients with colon cancer stage III can be advised that up to 6 months of 5-FU will postpone death on average 10 months compared to observation alone. Adding oxaliplatin will postpone death an additional 3 months with no adjustment for N status. Oxaliplatin has minor effect in N1 category (2 weeks) and major effect in N2 category (12 months). Future studies should investigate how the concept of postponement of death can be implemented in daily clinical practice.

**Legal entity responsible for the study**
Natacha Dencker Trabjerg

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

**1599P - Cancer patient attitudes and preferences towards smoking status assessment**

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W. Xu (Toronto, Canada) D. P. Goldstein (Toronto, Canada) J. M. Jones (Toronto, Canada) P. Selby (Toronto, Canada)
M. E. Giuliani (Toronto, Canada) G. Liu (Toronto, Canada)

**Background**
Continued smoking after a cancer diagnosis is associated with poorer outcomes. As smoking cessation is an important part of cancer care, understanding cancer patient (pt) attitudes towards smoking status assessment will help with integrating smoking cessation programs into cancer care.

**Methods**
Cancer pts from all subtypes were surveyed on their smoking history, assessment rates and attitudes/preferences towards smoking status assessment. Multivariate logistic regression models helped assess for factors associated with screening preferences.

**Results**
Among 501 pts, 115 smoked at diagnosis and 60% quit after; 53% had a tobacco related (lung/head and neck) cancer (TRC); 64% were treated curatively; 40% reported that their smoking status was assessed only on their first clinic visit, while 32% were assessed at a few visits and 12% all visits. Most felt that smoking status should be assessed at the first visit (95%), while half (58%) felt it should be assessed every visit. Most felt comfortable with being assessed (96%), felt it was important for clinicians to be aware of smoking status (98%) and that smoking cessation discussions should occur at the first visit (87%). Most preferred being assessed by their oncologist (88%); less than half preferred being asked by another healthcare provider (44%), on paper (29%) or electronic surveys (32%).

When compared to ex/never smokers, current smokers were assessed more often at every/most visits (36% vs 20% P = 0.001); fewer felt assessment should occur at the first visit (89% vs 97% P = 0.008) and were less comfortable with being assessed (88% vs 98% P < 0.001). Among current smokers, lung cancer pts were more agreeable (54%) to being assessed every visit compared to head and neck (aOR = 2.45 95% CI [0.9-6.5] P = 0.06) and non TRCs (aOR = 2.63 [1.0-6.8] P = 0.05). Among all, pts who are older
(aOR = 1.03 [1.0-1.1]), curative (aOR = 1.92 [1.1-3.2]) and smoked less (aOR = 0.98 per pkyr [0.97-0.99]) were more agreeable to assessment at each visit.

**Conclusions**
Most cancer pts felt that assessment of smoking status was important, were comfortable with being assessed and preferred being assessed directly by their oncologist. Routine screening of those currently smoking is recommended to help with cessation.

**Legal entity responsible for the study**
Princess Margaret Cancer Centre

**Funding**
None

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

1600P - Optimizing Physician Surveys in Pharmacovigilance Using ecancer Online Community

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R. A. Gleave (Bristol, United Kingdom) C. Hartley (Bristol, United Kingdom) D. Niepel (Vienna, Austria)
A. Liede (South San Francisco, United States of America)

**Background**
Physician knowledge surveys have increasingly been requested of drug manufacturers in the post-authorization setting as part of risk minimization plans. Surveys in pharmacovigilance require considerable time and resource, and result in low response rates and questionable representativeness. After EMA consultation, an educational programme was initiated with ecancer to evaluate the potential of online communities in measuring knowledge of drug safety risks. Here, we describe the baseline survey used to measure basic knowledge of osteonecrosis of the jaw (ONJ) risks among prescribers of bone targeting agents (BTAs).

**Methods**
Clinical experts developed 8 multiple choice questions on BTAs and ONJ risk as described in the summary of product characteristics. BTAs included denosumab, zoledronate, or pamidronate. Invitations were sent out to ecancer and ECCO members. Eligible were physicians who treated ≥5 new/continuing adult patients with bone metastases from solid tumours in the last 3 months (mos), currently practicing as an oncology specialist in the European Union, Switzerland or Norway, and prescribed a BTA in the last 12 mos. Responses for eligible and ineligible were compared.

**Results**
Among visits to the online survey, 87% completed the questions: 336 eligible/ineligible respondents from 52 countries, 292 from 26 European countries. Ineligibility was driven by the criterion of treating ≥5 patients in last 3 mos. Eligible respondents (n = 182) had higher level of correct responses than those who did not meet eligibility: mean 81% vs. 73% (p < 0.01) (Table). Question 3 yielded lowest correct responses on the topic of ONJ incidence as reported in BTA clinical trials.

**Table:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Correct Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>73%</td>
</tr>
<tr>
<td>Other</td>
<td>81%</td>
</tr>
<tr>
<td>Question</td>
<td>Eligible (n=182)</td>
</tr>
<tr>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>Number</td>
<td>Correct Responses</td>
</tr>
<tr>
<td>1</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>93%</td>
</tr>
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<td>3</td>
<td>52%</td>
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<td>85%</td>
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<td>91%</td>
</tr>
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<td>6</td>
<td>80%</td>
</tr>
<tr>
<td>7</td>
<td>81%</td>
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<tr>
<td>8</td>
<td>85%</td>
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</tbody>
</table>

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Conclusions
Online professional communities offer a pragmatic and efficient approach for recruitment of physicians for knowledge assessments. Basic knowledge of ONJ risks was high overall in this ecancer proof of concept. The strategy can achieve responses representative of today's physicians who seek information online. These findings may be compared with knowledge among physicians who may not seek information online.

Legal entity responsible for the study
ecancer

Funding
Amgen

Disclosure
J-J. Body: Consultant for Amgen Inc. O. Nicolatou-Galitis: Consultant for Amgen J.M. Sprafka, A. Liede: Amgen Inc. Employee, including stock ownership D. Niepel: Amgen GmbH employee, including stock ownership All other authors have declared no conflicts of interest.

1601P - Ideal cardiovascular health (ICVH) in patients with a recent diagnosis of colorectal cancer (CRC)

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F. Hidalgo (Madrid, Spain) A. Leon (Madrid, Spain) M. Mendez (Madrid, Spain) C. González (Madrid, Spain)
A. Sanchez (Madrid, Spain) S. Martinez (Madrid, Spain) L. Pagola (Madrid, Spain) L. Brea (Madrid, Spain)
C. Fiuza-Luces (Madrid, Spain) A. Lucia (Madrid, Spain) A. Ruiz-Casado (Madrid, Spain)

Background
Cardiovascular events are an important cause of mortality in patients cured of colorectal cancer and are also potential complications of new therapies for metastatic CRC. The American Heart Association’s “Simple 7” offers a practical public health conceptualization of cardiovascular health. They include healthy behaviours: non-smoking, active physical activity (MVPA > 150 min/w), healthy diet and low body mass index (BMI); and health factors: no hypertension, no diabetes, no hypercholesterolemia. Whereas factors are non-modifiable, behaviours can be changed. Studies have shown that prevalence of ideal cardiovascular health in the US is only 0.1%.

Methods
Patients with a recent diagnosis of CRC who accepted to participate were prospectively evaluated. BMI, blood pressure, glucose and cholesterol were measured at the hospital. Physical activity was objectively evaluated with accelerometers. Adherence to a healthy diet was evaluated through the PREDIMED (adherence to Mediterranean diet) questionnaire. Information about smoking and past cardiovascular disease or risk factors was obtained from the clinical record.

**Results**

91 patients were recruited between March 15 and March 17. 36% were metastatic. Age 65 (25-81), 69% male 31% female, BMI 26.2 ±3.6, Waist 95.6 ±12 cm, mean MVPA 350±248 min/wk, mean sedentarism 3394±1123. 9% had a history of CV disease (ischemic, cerebrovascular, heart failure). 34% were classified as high CV risk. Only one patient showed an ICVH.

**Table:**

<table>
<thead>
<tr>
<th>Healthy behaviours</th>
<th>Health Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICVH No CV history</td>
<td>Nonsmoking BMI &lt;25 Healthy Diet MVPA No HTA No DM No DL</td>
</tr>
<tr>
<td>1.1% 91%</td>
<td>90.5% 36% 67% 96% 51% 84.3% 66%</td>
</tr>
</tbody>
</table>

**Conclusions**

The prevalence of ICVH in a population of Spanish CRC patients was 1%. This population was overall compliant with PA recommendations, adhered to a healthy diet and less than 10% smoke in the last year. Hypertension was the most prevalent risk factor. Overweight was the most prevalent unhealthy behaviour. Interventions should be aimed at reducing BMI. Interventions exploring programs with vigorous physical activity and diet modifications in CRC survivors are warranted.

**Legal entity responsible for the study**

Ana Ruiz-Casado

**Disclosure**

All authors have declared no conflicts of interest.

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**1602P - Additive effect of vinca alkaloids as the risk factor for hearing impairments in the childhood cancer survivors**

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**Background**

The survival rate of childhood cancer is approaching to over 80%, and survivorship is gathering more attention. The survivors receive chemotherapy, radiotherapy and surgery in their early life stages, and the risk of ototoxicity is increased. We evaluated the degree of risk of the clinical factors causing the ototoxicity, in childhood cancer survivors.

**Methods**

We established survivorship program for late effects in Yonsei Cancer Center, Seoul, Korea. In all 531 enrolled survivors in the clinic, 105 patients were invited to evaluate
otoxocitity in their bi-annual visits and the clinical risk factors were reviewed retrospectively.

**Results**
The median age at diagnosis was 6.0 (026). Most common diagnosis was leukemia/lymphoma (N = 30, 30%), and brain tumor was the next (N = 29, 29%). Platinum agents were used in 64%, alkylating agents was in 83% and vinca alkaloid was in 78%. Severe hearing impairments defined as over than 60 dB loss were observed in 37% of left ears and 39% of right ears. The proportion of the survivors who had 20 dB loss in any side of ears was 28%. The 69% of abdomen tumor survivors and 56% of brain tumors had any of hearing impairments, but only 28% of leukemia/lymphoma survivors showed hearing loss (P < 0.001). The class of platinum agents use, vinca alkoids were adverse factors, however, the class of antimetabolites use or antibiotics use were all protective factors for hearing impairments (P < 0.001, <0.001, 0.006, <0.001, respectively). Both use of platinum and vinca alkaloids showed significantly higher risk of hearing impairments compared with use of none or one class of two classes of agents (P < 0.001 for right ear and P < 0.001 for left ear). Young age at diagnosis (<7.5 years old) showed higher risk of hearing loss in abdomen tumor and brain tumor group (P = 0.006 for right, P = 0.051 for left). Total 5000 cGy or more of head and neck region radiation showed increased risk (P = 0.001 for right, P = 0.007 for left). In multivariate analysis, both use of platinum and vinca alkaloids was independent risk factor (O.R.=8.1, P = 0.004 for right; O.R.= 8.7, P = 0.004 for left).

**Conclusions**
Hearing impairments were common late effects in childhood cancer survivors, and vinca alkaloids had additive adverse effects on the platinum use for the hearing loss.

**Legal entity responsible for the study**
Jung Woo Han

**Funding**
None

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

**1603P - Development and validation of chewing swallowing inventory (CSI) in head and neck cancer patients**

Y. Lai (Taipei, Taiwan)

**Background**
Chewing and swallowing dysfunction are the common problems in head and neck cancer patients. They may interfere patients’ eating and lead to malnutrition. An easily used tool to assess the problems is needed. The purposes of the study were to (1) develop the Chewing Swallowing Inventory (CSI) and (2) examine the psychometric properties of CSI.

**Methods**
This is an instrument development and testing study. We recruited adult patients with head and neck cancers in the head and neck cancer outpatient clinics in the medical center in northern Taiwan. The items of CSI was developed based our previous research results, clinical observation, literature review and preliminarily validated by experts panel.
Psychometric testing includes content validity, internal consistency reliability, construct validity by examining of its factor structures (exploratory factor analysis), theoretical supported correlation and discriminated constructs by groups.

**Results**

The CIS was a 21-item 0 to 4 Likert’s typed scale with 0 representing “no problem/difficulty at all” and 4 representing “having extremely severe difficulty”. We recruited 175 patients. The results showed that (1) CSI has good internal consistency reliability with Cronbach’s 𝛼 value as 0.93. (2) The factor analysis suggest that CSI contains four clear factors which are chewing, swallowing, tongue moving/stirring and taste and saliva changes which explained 70.32% of variances. (3) CSI has good construct supported correlation with nutrition. (4) CSI had good discriminate validity to differentiate patients with different diagnosis, surgical modalities, treatments, and disease stages.

**Conclusions**

CSI is a simple, easily used, reliable and validated tool to assess patients’ eating difficulties. It will better support health care professionals to detect HNC patients’ eating related chewing and swallowing problems and provide personalized intervention to prevent malnutrition.

**Legal entity responsible for the study**

National Taiwan University Hospital

**Funding**

None

**Disclosure**

All authors have declared no conflicts of interest.

1604P - The Relationship between Oral Supportive Care and Oral Complications in Cancer Patients Receiving Chemotherapy: A Retrospective Study

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**Background**

Oral supportive care for cancer patients received medical insurance coverage in 2012 in Japan. Management includes not only prevention of wound infection and perioperative pneumonia but also treatment of oral complications during chemotherapy and radiotherapy in cancer patients. We conducted a retrospective study to analyze the efficacy of oral supportive care for cancer patients receiving chemotherapy.

**Methods**

We retrospectively analyzed consecutive 1,142 cases received anticancer chemotherapy in our hospital from April 2013 to March 2017.

**Results**

Patients were 633 males and 509 females aged 23-92 years (median 66). Primary sites were lung in 246, esophagus in 193, breast in 137, head and neck in 112, and others in 454. Treatment was chemotherapy in 752, and concurrent chemoradiotherapy in 390. Before beginning chemotherapy, all patients received a dental check and acquired tooth brushing techniques. We compared the oral hygiene status in 752 patients before the beginning of therapy and at the 1-month check. Rates of improved, stable and regression status were 56.9%, 23.5%, and 19.6%. Regression appeared due to worsening of general condition, and also to oral mucositis among head and neck cancer patients. Oral
supportive care was continued to maintain good oral hygiene, detect oral complications early and manage them with dental treatment, dental extraction, mechanical cleaning, medicine, mouthwash and topical ointment and analgesics. Oral complications of ≥ Grade 3 (NCI-CTC AE ver. 3.0) were antiresorptive agents-related osteonecrosis of the jaw, teeth infections, and oral mucositis occurred during treatment. There was a significant difference in the incidence of oral complications between more and less than 3 months from the latest dental visit at the start of chemotherapy (p < 0.02).

Conclusions
Oral supportive care for cancer patients receiving chemotherapy should begin before the start of treatment and continue until the successful completion of treatment, especially for the deteriorated patients, head and neck cancer patients, and patients who did not receive dental checkups and cleaning for more than 3 months.

Legal entity responsible for the study
Kobe Minimally Invasive Cancer Center

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1605P - Safety and effectiveness of sensor-controlled scalp cooling in women receiving chemotherapy for primary breast cancer

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Background
Sensor-controlled scalp cooling (SCSC) to prevent chemotherapy-induced alopecia (CIA) in patients (pts) with primary breast cancer (PBC) is approved by the FDA. However, SCSC is infrequently used in many countries due to concerns regarding both safety and feasibility. This retrospective analysis sought to obtain more detailed information about the effectiveness and safety of SCSC using the Paxman system (Paxman, Huddersfield, UK) in PBC pts exposed to neoadjuvant (NACT) or adjuvant Ctx (ACT) in the clinical routine.

Methods
79 pts were identified from our database: NACT, 41 (51.9%); ACT, 38 (48.1%); dose-dense (dd) Ctx, 56 (70.9%); non-dd Ctx 23 (29.1%); premenopausal, 44 (55.7%); postmenopausal, 35 (44.3%). The following Ctx regimens were used: anthracycline-based (A), 1 (1.3%); taxane-based (T), 21 (26.6%); AT-based, 55 (69.6%); non AT-based, 2 (2.5%). Pts were subjected to SCSC during each Ctx cycle. CIA was quantified using the Dean score (DS) determined 3 wks after the last Ctx cycle. Data were analyzed regarding the SCSC completion rate, quality of hair preservation (success: DS 0-2, failure: DS 3-4), reasons of SCSC discontinuation, and toxicity. Moreover, the following parameters were investigated in regard to the success of SCSC: menopausal status, NACT vs ACT, dd Ctx vs non-dd Ctx, AT-based Ctx vs A-/T- or non-AT-based Ctx.

Results
55 pts (69.6%) completed SCSC with 36 (45.6%) showing complete (DS 0), and 19 (22.8%) showing partial success (DS 1-2). 24 pts (30.4%) discontinued SCSC with CIA
seen in 18 pts (22.8%). Headache and local discomfort (“feeling cold”) were reported in 4 pts (5.1%) each. Side effects were all not severe and resolved quickly after cessation of SCSC. SCSC was equally effective in all analyzed subgroups. The relative risk (RR) to experience CIA was 1.11 (CI: 0.82-1.54) for post- vs premenopausal pts; 1.11 (CI: 0.83-1.53) for ACT vs NACT; 1.31 (CI: 0.96-1.72) for AT vs other Ctx protocols, and 0.99 (CI 0.72-1.43) for dd Ctx vs non-dd Ctx.

Conclusions
In our study, SCSC was safe and effective to prevent CIA in PBC pts. The success rate in our study is in good agreement to previous randomized trials of SCSC in PBC arguing in favor that SCSC is a valuable supportive treatment in the clinical routine.

Legal entity responsible for the study
Christian M. Kurbacher

Funding
None

Disclosure
All authors have declared no conflicts of interest.

1606P - Pharmacokinetics and safety of FOLFOX therapy in patients undergoing hemodialysis
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Background
Due to a lack of information, there is no guideline regarding the dosage and timing of chemotherapy in cancer patients undergoing hemodialysis (HD). Therefore, we studied the pharmacokinetics of 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) in cancer patients undergoing HD.

Methods
HD patients (HD group) and patients with normal renal function (control group) who had received either modified FOLFOX6 therapy or modified FOLFOX7 therapy were prospectively enrolled. The blood concentrations of 5-FU and 5-FU metabolites, including α-fluoro-β-alanine (FBAL), fluoroacetic acid, and ammonia were measured using inductively coupled plasma-mass spectrometry. The blood concentrations of total and ultrafilterable platinum were measured in the HD group. To estimate the amount of L-OHP removal by dialysis, we also measured the platinum concentration in dialysate.

Results
There were six patients in the HD group and eight patients in the control group. In the HD group, L-OHP was administered just before the HD session in four patients, and on a non-dialysis day in two patients. The amount of L-OHP removal by dialysis was 10% or less of the administered dose, and did not depend on the timing of L-OHP administration. Regarding the 5-FU metabolites, the blood concentration of FBAL was significantly higher in the HD group than in the control group (p < 0.01). We observed hyperammonemia in two patients in the HD group, which was accompanied by elevated blood levels of FBAL and fluoroacetic acid, and was therefore considered to be related to 5-FU administration. Conscious level deterioration was observed in one patient with hyperammonemia.
Conclusions
The amount of L-OHP removal by dialysis was up to 10% regardless of the timing of L-OHP administration. Hyperammonemia should be monitored during FOLFOX therapy among HD patients.

Legal entity responsible for the study
Onco-nephrology Consortium

Funding
None

Disclosure
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1607TiP - J-FORCE study: A randomized, double-blind, placebo-controlled phase III study evaluating olanzapine (5 mg) combined with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based, highly emetogenic chemotherapy

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Background
In the Alliance A221301 study, olanzapine (OLZ; 10 mg) significantly improved the prevention of nausea in patients who were receiving highly emetogenic chemotherapy (HEC). However, growing concerns exist concerning somnolence and sedation. We previously reported on the efficacy and safety of two doses (5 mg and 10 mg) of OLZ in combination with aprepitant (APR), palonosetron (PALO), and dexamethasone (DEX) in patients receiving HEC. OLZ (5 mg) seemed to lead to lower somnolence than OLZ (10 mg) and was equally effective in preventing nausea. The aim of this phase III study is to evaluate the efficacy and safety of 5 mg OLZ doses as compared with placebo, in combination with APR, PALO, and DEX, for the control of nausea in patients receiving HEC.

Trial design
Eligibility criteria for patients include those who are aged 20–75 years, have an Eastern Cooperative Oncology Group (ECOG) performance status between 0–2, and have malignant disease who will be scheduled to receive HEC with cisplatin at a dose ≥ 50 mg/m². Having diabetes mellitus or being treated with antipsychotic agents within 48 hours before enrollment make patients ineligible for the study. Patients are randomly assigned to receive either a 5 mg OLZ dose or placebo orally after supper on days 1–4, in combination with APR (125 mg p.o. on day 1, 80 mg p.o. on days 2–3), PALO (0.75 mg i.v. on day 1) and DEX (9.9 mg i.v. on day 1 and 6.6 mg i.v. on days 2–4). The primary endpoint is a complete response (CR), defined as no emetic episodes and without the use of rescue medications in the delayed phase (24 to 120 hours). Secondary endpoints include a CR during acute (0 to 24 hours) and overall phases (0 to 120 hours), complete and total control rates, and the level of nausea, appetite and somnolence. A total of 690
patients are required to achieve 80% power for a one-sided significance level of 0.025. We expect the CR rate of the placebo and olanzapine arms to be 65% and 75%, respectively.

Clinical trial identification
UMIN000024676

Legal entity responsible for the study
Japan Supportive, Palliative and Psycho Social Oncology Group

Funding
Japan Agency for Medical Research and Development

Disclosure
All authors have declared no conflicts of interest.

1608TiP - Heath related quality of life (HRQOL) assessment for patients with advanced renal cell carcinoma (mRCC) treated with tyrosine kinase inhibitor (TKI) using electronic patient reported outcome (PRO) in daily clinical practice

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Background
In mRCC, two therapies are mainly used in first line setting: pazopanib and sunitinib. These two TKI are equally effective in terms of survival however they are responsible for frequent adverse events. Physician mainly use RECIST progression-free survival (PFS) and NCI CTCAE safety as a guide to evaluate treatment efficiency and tolerance. In contrast HRQOL assessment is often restricted to clinical trial. It could be of particular interest to evaluate HRQOL in daily clinical practice in order to adequately choose and manage therapy. Currently the development of Information and Communication Technology may allow HRQOL monitoring in routine practice. The objective of the QUANARIE Study is to evaluate the feasibility of HRQOL assessment in daily clinical practice for patients with mRCC treated with TKI using electronic PRO.

Trial design
QUANARIE study (NCT03062410) is an interventional, prospective, multicenter trial involving 9 french oncological centers. Patients diagnosed with mRCC initiating TKI anti-VEGF treatment (Sunitinib or Pazopanib) will be invited to complete the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 cancer specific questionnaire and the EQ-5D before each visit with the physician. Questionnaires completion will be done by patients on tablets and/or computer terminals via the CHES software (Computer-based Health Evaluation System) at hospital before consultation or at home via secured portal. Physician will immediately have access to a visual summary of HRQOL evaluation. Primary objective is to assess the feasibility of routine assessment of HRQOL evaluated by the rate of filled questionnaires at 12-months. Key secondary objectives are: exhaustiveness, acceptability and effectiveness. Physician’s satisfaction with electronic HRQOL evaluation will be assessed. We hypothesized that 80% of filled
questionnaires at 12-months would be meaningful. A sample size of 56 patients would be needed. Enrollment is expected to last for 6 mo. Study started in April 2017. Update will be display on poster during ESMO congress.

Clinical trial identification
NCT03062410

Legal entity responsible for the study
University Hospital Jean Minjoz

Funding
Novartis

Disclosure
All authors have declared no conflicts of interest.

1609TiP - Impact of a cancer care coordination program based on health information technologies for patients treated by oral anticancer therapy: The CAPRI randomized trial

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Background
The emergence of oral delivery in cancer therapeutics results in an increased need for better coordination between all treatment stakeholders, mainly to ensure adequate treatment delivery to the patient. There is a significant interest in cancer care coordination programs, especially those combining Nurse Navigators (NN) and the use of new technologies. However, the potential impact of these combined strategies is limited by a lack of rigorous evidence.

Trial design
A monocentric randomized trial (1,000 patients, 1:1) is designed to assess the impact of a cancer care coordination program namely CAPRI. This program is based on two NN and a web application. NN ensure remote patient monitoring, via phone calls and email. They also provide a link between hospital professionals, patients and primary care professionals (GP, private nurse, pharmacist, etc.) by giving them access to the web application with the patient’s authorization. Patients can enter data related to their health. Alerts are sent to the NN in case of abnormal data. NN evaluate the alert level on the basis of algorithms and determine the necessary action. The study will evaluate CAPRI’s efficacy in comparison with regular care during a 6-month period for adult patients with metastatic cancer. Hypothesis is that with a closer monitoring of the patient, the management of toxicities is more efficient and results in fewer dose adjustments of oral cancer therapeutics and avoids unnecessary hospital visits. The primary research aim is to assess the impact of the CAPRI program on treatment delivery for cancer patients who started oral cancer therapy, as measured by Relative Dose Intensity. The trial involves several secondary outcomes: patient adherence, tumor response, survival, toxicities, patient quality of life and patient experience. An economic evaluation adopting a societal perspective will be conducted, in order to estimate the use of healthcare resources. A
parallel process evaluation will be conducted to describe the implementation of the CAPRI program. Of the 1,000 patients to be recruited, 109 patients are currently enrolled since November 2016.

Clinical trial identification
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Legal entity responsible for the study
Gustave Roussy

Funding
National Research French Agency, Philanthropia Lombard Odier Foundation, Astrazeneca, Novartis

Disclosure
All authors have declared no conflicts of interest.

1610TiP - Oncological Home-Hospitalization: Prospective randomized trial to evaluate its implications for patient and society

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Background
Home-based cancer treatment offers an integrated and patient-centered approach to deal with the challenges oncological day (care) units are facing. Current cancer therapies require frequent hospital visits that are known to be stressful for the patient and generate a high workload for hospital staff. Furthermore, these hospital visits are associated with significant costs for patients and the society, this against the background of increasing attention towards more cost-effective healthcare. Consequently, the general hospital Groeninge (Belgium) has initiated a research project to assess both, the clinical and economic impact of oncological home hospitalization. The project is supported by “Kom op tegen Kanker”, a non-profit organization.

Trial design
Ambulatory treated adult cancer patients (EGOG ≤ 2 and living within a 30-minute drive of hospital) are visited at home by a clinical nurse specialist to conduct the necessary measures prior to therapy administration; that is nursing review, toxicity scoring, vital signs monitoring, blood collection, and IV line access provision. These assessments are performed one day prior to the actual therapy administration at the hospital, enabling the oncologist to prescribe and pharmacy to prepare cancer therapy before arrival of the patient. In addition, some safe experienced subcutaneous cancer therapies (i.e. bortezomib, azacitidine and trastuzumab) are administered directly at the patient’s home. This new care model will be evaluated in terms of patient’s quality of life, safety and cost-efficiency by performing a single-center randomized clinical trial allocating leastways 100 subjects to either home-hospitalization or standard ambulant hospital care. Currently, a non-randomized pilot study is launched in which the sensitivity of several validated patient reported outcome measuring tools is examined in both treatment settings (n = 50). Those instruments that show sufficient sensitivity will be included in the randomized trial. A second objective of the pilot study is to gather an extensive costs-inventory that will be used to set up an appropriate and reliable cost-analysis of home-based cancer treatment.

Legal entity responsible for the study
Background
Cancer cachexia is a multifactorial syndrome characterized by an on-going loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support alone. Cachexia has a high prevalence in cancer and a major impact on patient physical function, morbidity and mortality. Despite the consequences of cachexia, there is no licensed treatment and no standard of care. It has been argued that the multifactorial genesis of cachexia lends itself well to therapeutic targeting through a multimodal treatment. Following a successful phase II trial, a phase III trial is underway.

Trial design
MENAC is a multicentre, open, randomized phase III study comparing multimodal intervention and standard cancer care versus standard cancer care alone. Patients treated for incurable lung and pancreatic cancer will be allocated randomly to receive the multimodal intervention, either immediately, or after endpoint at six weeks. The intervention is based on evidence to date and consists of Non-steroidal Anti-inflammatory Drugs (NSAID) and an EPA containing oral nutrition supplement to reduce inflammation, a physical exercise programme consisting of both resistance and aerobic exercises to increase anabolism, as well as dietary counselling aiming to promote energy and protein balance. The overall aim is to reduce weight loss, improve food intake and maintain physical function by establish basic supportive care for cachexia. From a patient perspective, a short-term effect will be to improve physical and psychological function and reduce symptom burden. Change in body weight is primary endpoint. Secondary endpoints are change in muscle mass (CT technique) and physical activity (ActivPAL activity meter). There are several exploratory endpoints. The trial is ongoing and patients are recruited from several sites in Europa and Canada, we aim for 240 patients. If positive, the results will be practice changing for supportive treatment of patients with cancer.

Clinical trial identification
NCT02330926

Legal entity responsible for the study
NTNU through PRC is coordinating the running of the trial.

Funding
The European Union through the European Clinical Research Infrastructures Network (ECRIN) Canadian Institute for Health Research Marie Curie and Raising Tide foundation Norwegian Cancer union The Omega 3 capsules are recieved free of charge from
Background

We previously reported that S-1 chemotherapy for gastrointestinal cancer (GI cancer) induced the high incidence of eye disorders (EDs), regardless of primary cancer site, treatment regimen and administration schedule (Yagisawa M, et al. 2017 Gastrointestinal Cancers Symposium). However, because this report showed a retrospective data from single institutional small cohort by reviewing medical records, we might have underestimated the incidence of EDs. So, we have conducted this prospective cohort study to confirm the incidence of EDs induced by S-1 more precisely.

Trial design

This is a multicenter prospective cohort study to evaluate the incidence of EDs and ophthalmologic changes in GI cancer patients received S-1 chemotherapy. The key eligibility criteria are as follows: 1) Histologically confirmed carcinoma in GI cancer, including esophageal, gastric, colorectal, pancreatic, and biliary tract cancer.; 2) The patient who receives chemotherapy including S-1.; 3) No prior medication of S-1.; 4) No lachrymal duct obstruction and less than three points of corner conjunctiva epithelium disorder score. All participants receive four times of ophthalmological examinations. The primary endpoint is cumulative incidence of epiphora in periods from start of S-1 chemotherapy to 12 weeks after induction S-1. The secondary endpoints are cumulative incidence of epiphora in overall S-1 chemotherapy periods, the time of onset and severity of epiphora, the situation of ophthalmological intervention, ophthalmological changes, risk factors of epiphora, and QOL. Because we supposed that incidence of epiphora at 12 weeks after induction S-1 is 10% as already reported, we calculated the sample size as 160 based on precision of the 95% confidence interval and aimed to recruit 180 patients considering the possibility of 10% dropouts. This study is sponsored by Non Profit Organization Hokkaido Gastrointestinal Cancer Study Group.

Clinical trial identification

UMIN 000027192 24, June, 2017

Legal entity responsible for the study

Hokkaido Gastrointestinal Cancer Study Group

Funding

None

Disclosure
1613TiP - Outpatient monitoring with an eTool: self managed or with pro active intervention?

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Background
Cancer outpatients (OP) will face a maximum of potentially serious side effects (SAEI) and complications (C) at home and at distance from their caregivers (CG). This may lead to insufficient management as the care takers ignore complications and will not carry out early intervention. Worsening of quality of life (QoL) and (prolonged) hospitalisation may be the consequence. Studies have provided evidence that e-tools inquiring about the patients' well-being at home may be useful for early intervention, thus providing better quality of life and less hospitalisations. It is unclear whether these benefits could be obtained by patients' self-management or require pro active intervention (PAI) by CG. We therefore carry out a study (PRO-ELECTS= PE) using a web-based e-tool we developed based on the Edmondson Symptom Scale (ESAS). A pilot study had proved feasibility in OU of the Oncology Outpatient Unit (OOU) of the CHEM general hospital.

Trial design
This prospective randomized study compares: - I. OP documenting QoL, hospital stays/consult. during treatment intervals while under OOU visits, with: - II. P receiving daily inquiries, automated advice and alerts to contact OOU in the case of SAE, with: - III. P receiving daily inquiry superised by the OOU CG and intervention in case of alarming symptoms. All P apart from I receive daily customized questionnaires integrating an algorithm with automated answers to standard situations and alert messages inviting the P to contact the OOU tal in case of SAE. In group III, CG of the OOU will be notified of the daily response and alerted in case of SAE. They are mandated to contact the P to provide advice or convocate him to the hospital. PRO-ELECTS should be able to determine whether active electronic patient surveillance and pro active intervention is superior to patient self-management assisted by a web tool in maintaining good quality of life and limit the severity of complications. The study will also determine which strategy provides more patient adherence and satisfaction. So far 15 of a total of 120 P have been randomized. Patient acceptance is excellent. 3 serious side effects have been anticipated through active intervention. Data concerning P adherence, satisfaction, QoL and complication data will be presented.

Legal entity responsible for the study
Stefan Rauh

Funding
CHEM, Fondation Cancer Luxembourg, Integrated Biobank Luxembourg, CHEM, Janssen Cilag, Chugai

Disclosure
A. Hagemann: eHealth Consultant of the company Sananet providing the web site for the study All other authors have declared no conflicts of interest.
Background
Chemotherapy-induced alopecia (CIA) may lead to significant psychosocial and quality of life issues. Currently there are no FDA approved therapeutic agents available to prevent CIA. In murine studies, topical calcitriol reduced CIA, likely due to arrest of cell cycle in healthy hair follicles and reducing sensitivity of follicular epithelium to chemotherapy.

Trial design
A 3 + 3 dose-escalation Phase 1 study with 3 to 6 patients at each dose level (5/10/20/40/60/80 μg/mL) to determine the maximum tolerated dose (MTD) and the overall safety and tolerability of a topical compound BPM31543 (Calcitriol) in patients with a diagnosis of breast cancer, gynecologic cancer and sarcomas. Eligible patients receiving a taxane-based chemotherapy regimen applied 1mL of BPM31543 twice/daily at each cohort dose level 14 or 7 days prior to initiation of chemotherapy and then continued twice daily for 3 months or until termination of chemotherapy. In order to determine the MTD, dose escalation occurred in stepwise increments of the immediate prior dose group, in the absence of grade 3 or greater toxicities attributed to the topical calcitriol. Dose-limiting toxicity (DLT) was determined during Cycle 1 (i.e., the first 28 days of topical agent application). Patients were managed with adequate safety monitoring and pharmacokinetic (PK) analysis in order to determine levels of exposure. The potential efficacy (secondary objective) of the topical calcitriol was evaluated by photographic assessment using a Canon digital camera system (to ensure standardization and uniformity among all enrolled patients) in addition to patient self-assessments.

Clinical trial identification
NCT01588522

Legal entity responsible for the study
BERG, LLC

Funding
BERG, LLC

Disclosure