

ESMO 2017 Congress

8-12 September 2017

Madrid, Spain

Table of Contents

Summary	6
INTRODUCTION	7
BASIC SCIENCE	9
Large dataset of targetable genomic alterations created by next-generation sequencing of circulating tumour DNA	9
Comprehensive genomic profiling detects genetic alterations specific for tumour subtype	10
Subtypes of thymic carcinomas show different genomic alterations and tumour mutational burden	11
BREAST CANCER, EARLY STAGE	13
Adjuvant chemotherapy provides clinical benefit in some patients with small node negative breast cancers	13
Taselisib plus letrozole improves response in postmenopausal women with ER-positive, HER2-negative early breast cancer	14
Neratinib improves invasive disease-free survival rates over placebo following adjuvant trastuzumab for early stage HER2-positive breast cancer	15
The ExteNET study demonstrated small improvements in health-related quality of life with neratinib	16
UNICANER-NeoPal study does not show improved outcome with combined letrozole plus palbociclib over chemotherapy as neoadjuvant treatment in luminal breast cancer	17
Next generation sequencing reveals potential genomic markers of recurrence in locally advanced triple negative breast cancer	19
Strong association found between overall survival and tumour type in early breast cancer	21
BREAST CANCER, METASTATIC	23

Interim analysis shows significant clinical benefit with combined abemaciclib plus NSAID as initial treatment for patients with HR-positive/HER2-negative advanced breast cancer..	23
Promising response rates in patients with metastatic TNBC treated with nivolumab after induction treatment	24
Pembrolizumab response associates with TIL levels and PDL1 expression in metastatic TNBC	25
CNS TUMOURS	28
Combined nivolumab and radiotherapy ± temozolomide is safe in patients with newly diagnosed glioblastoma	28
PD-L1 may be prognostic of survival in patients with glioblastoma	29
DEVELOPMENTAL THERAPEUTICS.....	33
Novel mogamulizumab combined with nivolumab shows promise in patients with advanced or metastatic solid tumours	33
Patients with melanoma who progressed during anti-PD-1/PD-L1 therapy demonstrate response to BMS-986016 plus nivolumab.....	33
RXDX-105, a VEGFR-sparing potent RET inhibitor, shows promising activity in RET inhibitor-naïve patients with RET fusion-positive NSCLC	35
GASTROINTESTINAL TUMOURS, COLORECTAL	36
Location of the primary tumour, but not KRAS mutations, may indicate SIRT survival benefit in mCRC	36
GASTROINTESTINAL TUMOURS, NON-COLORECTAL	38
Updated results favour docetaxel, oxaliplatin, and fluorouracil/leucovorin in resectable oesophagogastric cancer	38
Pembrolizumab demonstrates anti-tumour activity in advanced gastric cancer as monotherapy and combined with chemotherapy.....	39
Biomarker analysis reveals lenvatinib and sorafenib upregulate different genes in unresected HCC	42
GENITOURINARY TUMOURS, PROSTATE	44
Addition of abiraterone acetate or docetaxel plus prednisone to standard of care improves response in patients with high-risk prostate cancer	44
¹⁷⁷ Lu-PSMA617 demonstrates significant clinical activity in mCRPC.....	45

Germline mutations in DNA repair genes lowers survival in mCRPC	46
GENITOURINARY CANCERS, NON-PROSTATE	49
Improved PFS with ramucirumab in patients with platinum refractory advanced urothelial carcinoma	49
Pembrolizumab continues to show greater benefit over chemotherapy in recurrent, advanced urothelial carcinoma	50
First-line nivolumab and ipilimumab therapy improves response over sunitinib in patients with advanced or metastatic RCC and intermediate to high risk	52
Progression-free rate unaffected by the sequence of cytoreductive nephrectomy and sunitinib in patients with synchronous metastatic RCC	54
GYNAECOLOGICAL CANCERS.....	56
Neoadjuvant chemotherapy followed by surgery is not superior to concurrent cisplatin and radiation therapy in patients with stage IB2 to IIB squamous carcinoma of cervix	56
Maintenance rucaparib shows clinical benefit in patients with recurrent ovarian cancer.	56
ICON8 confirms carboplatin plus paclitaxel every 3 weeks as standard of care in epithelial ovarian cancer	58
Quality of life maintained during maintenance niraparib treatment in patients with platinum sensitive ovarian cancer.....	59
Patients with ovarian cancer and TP53 disruptive mutation status demonstrate an overall survival benefit with olaparib	60
HAEMATOLOGICAL MALIGNANCIES	63
GP2013, biosimilar rituximab shows equivalent efficacy to reference rituximab in previously untreated advanced follicular lymphoma.....	63
Increased risk of AML seen in patients receiving radioactive iodine for well-differentiated thyroid cancer	64
HEAD AND NECK CANCER	66
Promising clinical benefit with durvalumab in recurrent/metastatic head and neck squamous cell carcinoma.....	66
Nivolumab demonstrates antitumour activity post-progression in recurrent/metastatic head and neck squamous cell carcinoma	67
Single agent atezolizumab shows promising efficacy in head and neck cancer	70

IMMUNOTHERAPY OF CANCER.....	72
ISA 101 vaccine plus nivolumab shows promising efficacy in HPV-positive oropharyngeal cancer	72
Rocapuldencel-T shows potential benefit in metastatic renal cell carcinoma.....	74
MELANOMA AND OTHER SKIN TUMOURS.....	76
Adjuvant dabrafenib plus trametinib significantly lowers risk of death in stage III <i>BRAF</i> V600–mutated melanoma	76
Nivolumab outperforms ipilimumab as adjuvant therapy in resected melanoma.....	77
Adjuvant vemurafenib in completely resected <i>BRAF</i> ^{V600} positive melanoma at high risk of recurrence.....	78
NETs AND ENDOCRINE TUMOURS.....	81
First report of pembrolizumab activity in patients with PD-L1-positive pNETs and carcinoid tumours	81
Immune landscape of PanNETs elucidated	82
Improved survival demonstrated with NSCLC-chemotherapy in pulmonary large cell neuroendocrine carcinoma with <i>RB1</i> wild-type	83
NSCLC, NON-METASTATIC.....	86
Durvalumab as consolidation therapy prolongs PFS in stage III patients with NSCLC without progression following platinum-based chemoradiotherapy	86
Enhanced post-surgery surveillance does not equate to prolonged OS in NSCLC.....	87
NSCLC, METASTATIC.....	88
Front-line osimertinib poised to become standard of care in <i>EGFR</i> -mutation positive NSCLC.....	88
Substantial clinical activity demonstrated in the first-line by combined dabrafenib plus trametinib in <i>BRAF V600E</i> –mutated metastatic NSCLC	89
Improved patient outcomes favour alectinib over chemotherapy in patients with previously treated ALK-positive NSCLC.....	91
First-line alectinib demonstrates improved PFS and better control of CNS disease progression over crizotinib	92
OTHER THORACIC MALIGNANCIES	94

Nivolumab plus ipilimumab slow disease progression as second or third line malignant pleural mesothelioma therapy	94
PUBLIC HEALTH AND ECONOMICS	95
Comparison of clinical trials supporting US FDA approval of orphan versus non-orphan drugs according to the ESMO Magnitude of Clinical Benefit Scale	95
Assessment of cancer therapies according to the French National Authority for Health and the ESMO Magnitude of Clinical Benefit Scale	96
Report on the ESMO/SIOPE European Landscape project key results regarding the status and needs in AYA cancer care.....	96
Survey results show the delivery of paediatric radiation therapy varies across Europe ..	97
SARCOMA	99
Adjuvant imatinib shows benefit over control only in patients with high-risk GIST: Final results of the EORTC STBSG, AGITG, UNICANCER, FSG, ISG, and GEIS trial.....	99
DCC-2618, a novel pan-KIT and PDGFR α inhibitor, shows encouraging anti-tumour activity in patients with GIST	99
SUPPORTIVE AND PALLIATIVE CARE	101
Neurokinin-1 receptor antagonist provides quality of life benefit during concomitant chemoradiotherapy for cervical cancer	101
Patients' viewpoint may not be reflected by investigator-reported clinical trial toxicity ..	102
TRANSLATIONAL RESEARCH	104
Expanding the use of approved drugs: The CPCT's Drug Rediscovery Protocol.....	104
RELATED INFORMATION	105
Save the date	106
Affiliations and Disclosure.....	107
Affiliation	107
Disclosure	107
Acknowledgment	108

Summary

The European Society for Medical Oncology (ESMO) 2017 Congress convened from 8 to 12 September 2017 in Madrid, Spain. ESMO 2017 was organised in partnership with the European Association for Cancer Research (EACR) to provide a forum where all stakeholders in the field of oncology could come together to share advances in the care of patients with cancer, including prevention, diagnosis, treatment, and healthcare policy.

The ESMO 2017 Congress offered a comprehensive scientific programme and broke all previous records. Findings from ESMO 2017 presented studies were simultaneously published in leading scientific journals including *The New England Journal of Medicine*, *Lancet Oncology*, *Annals of Oncology*, *ESMO Open*. A brief summary of some of the diverse scientific findings regarding new treatments in the curative and adjuvant setting, as well as palliative care, biomarkers, screening, public policy, basic research and myriad other topics presented at ESMO 2017 follows.

INTRODUCTION

The ESMO 2017 Congress, in partnership with the EACR, created an environment where cancer researchers and clinicians came together to collaborate and exchange ideas under the theme 'Integrating science into oncology for a better patient outcome'. This exciting partnership delivered a unique cancer congress in Europe with huge scientific reach and the true potential to improve the lives of cancer patients.

ESMO 2017 broke all previous records, with attendance increased by 15% over the 20'767 participants in the 2016 congress. This year's congress welcomed 23'916 attendees who travelled from Europe (59.78%), North America (15.63%), Asia (15.48%), Central and South America (5.40%), Africa (2.52%), and Australia and the Pacific (1.18%) to represent a total of 131 countries. Even though Europe was the region sending the most participants, the United States of America topped the five most represented individual countries at 14.25% of participants, followed by France (7.22%), Spain and the United Kingdom (6.88% each), and Germany (5.77%). Delegates represented 82.04% of congress participants with the remainder comprised of exhibitors/industry satellite (14.11%), faculty (2.19%), and press (1.66%).

The majority (59.31%) of participants who gathered to discuss the latest developments in oncology research and clinical practice were medical oncologists, but ESMO 2017 attendees also comprised 7.15% surgical oncologists, 5.49% haemato-oncologists, 2.81% internists, 1.78% clinical oncologists, and 1.72% basic researchers or scientists, with the remainder made up by haematologists, patient advocates, paediatric oncologists, immunologists, as well as many other medical professionals. This diversity was reflected in the range of interests expressed by the participants, which covered the spectrum of oncology from basic science to palliative care, with 59.31% of attendees indicating that all gastrointestinal cancers, NSCLC and chest malignancies combined (56.13%), and breast cancer (43.9%) were their primary areas of interest. Clinical research, anticancer agents, and cancer biology topped the topics of interest, with 46.2%, 41.5% and 38.5%, respectively, of survey respondents indicating these as their foremost interests.

Interestingly, over 70% of congress participants agreed or agreed strongly that ESMO 2017 would enable them to deliver better standards of care to their patients and also helped to generate new research ideas. More than 80% of respondents reported that they would definitely attend future conferences and 94% said that they would recommend the ESMO Congress to colleagues.

ESMO 2017 offered a comprehensive scientific programme designed by oncology experts to ensure widespread multidisciplinary and multi-professional appeal with a scientific programme compiling diverse aspects of basic science, translational research and medical therapy for cancer, with investigators coming from around the world to share the newest research contributing to the development of an unprecedented number of new treatments. Up to date educational symposia and state of the art teaching lectures were held that maintained the position of this congress as the largest continuing medical education accredited event in oncology in Europe.

Of the 3260 abstracts submitted, 1736 were accepted with 7% of abstracts chosen for oral presentation and 13% for poster discussion, with the bulk of abstracts presented as readily

accessible electronic posters. The abstracts represented cutting edge research and the most current treatment strategies primarily focused on the topics of gastrointestinal cancer, followed by biomarker research, and metastatic NSCLC. The abstracts detailed 101 phase I, 39 phase I/II, 177 phase II, 4 phase II/III and 161 phase III clinical trials and there were a record number of 55 late breaking abstracts. In addition, the results from 32 meta-analysis were presented. In total, 105363 patients were treated in randomised clinical trials. The oral and poster discussion sessions featured faculty that placed abstract findings into clinical perspective and discussed how the results may impact the current standard of care. Furthermore, the input from invited discussants and a well-informed audience provided lively discussion during the sessions.

This year's congress also provided a platform for the increasing number of trials testing immunotherapy and chemotherapy combination treatments, strategies for adjuvant treatment in many cancer types, and plasma-based assays for monitoring mutations in disease progression.

Over 6000 news articles were produced by media from over 30 countries.

A brief summary of some of the diverse scientific findings regarding new treatments in the curative and adjuvant setting, as well as palliative care, biomarkers, screening, public policy, basic research and myriad other topics presented at ESMO 2017 follows.

BASIC SCIENCE

Large dataset of targetable genomic alterations created by next-generation sequencing of circulating tumour DNA

Sumanta K. Pal, Medical Oncology, City of Hope, Duarte, USA, and colleagues determined the somatic genomic profiles of 35,492 plasma liquid biopsy samples obtained from 30,024 patients with various types of advanced cancer. The samples were submitted to a circulating tumour DNA (ctDNA) next generation sequencing (NGS) test that targeted up to 73 genes (Guardant360®). The positive predictive value (PPV) of ctDNA-detected driver alterations was evaluated in a comparison to available matched tissue tests including lung, colon, and other cancer types for 646 patients.

Liquid biopsies of ctDNA represent a non-invasive means of obtaining genomic information and identifying alterations that confer resistance as well as alterations that are targetable by currently approved drugs. This series comprised non-small cell lung cancer (NSCLC) samples (39%), breast (16%), colorectal cancer (CRC) (10%), and multiple other solid cancer types (35%), which had detectable ctDNA alterations in 88%, 86%, 88%, and 82%, of samples, respectively. Overall, alterations were detected in 86% of samples that revealed 19% of patients had one or more ctDNA alterations associating with an FDA-approved therapy. Resistance to approved drugs was also detected; resistance variants were found in 18% of ctDNA samples from patients with NSCLC, breast and prostate cancers, CRC, melanoma, and gastrointestinal stromal tumours.

PPV ranged from 92% to 100% across the altered genes identified; PPV was 98% for EGFR L858R/E19del/E20ins, 92% for ALK/RET/ROS1 fusions, 95% for BRAF V600E, 94% for KRAS G12/G13/Q61, and 100% for MET E14 skipping mutations.

These alterations were linked to response from already approved drugs in a pooled response rate analysis that was performed across published/in press datasets presenting response data to alterations detected by Guardant360®. The response rate for first-line EGFR tyrosine kinase inhibitors (TKIs) according to detected alterations in 43 NSCLC samples was 86% (95% confidence interval [CI] 71, 94%). The analysis also showed that the pooled response rate to osimertinib was 94% (95% CI 72) in 19 samples from patients with NSCLC, 54% (95% CI 41, 67%) to rociletinib in 63 NSCLC samples, and the response rate to crizotinib was 82% (95% CI 48, 97%) in 11 NSCLC patients. The response rate to anti-HER2 agents in 7 samples from patients with breast cancer was 86% (95% CI 49, 97%), and 80% (95% CI 37, 96%) in samples from 5 patients with gastric tumours. Pal *et al.* Abstract 1702O

Practice point and future research opportunities

Liquid biopsies are increasingly being used in clinical care since they provide a non-invasive option for obtaining genomic information. To date, few large datasets on clinical use have been published. The dataset in this study highlights the clinical impact of identifying alterations that are targetable by drugs with regulatory approval, including emergent resistance alterations and underscores that obtaining NGS of circulating tumour DNA from a liquid biopsy is feasible.

Comprehensive genomic profiling detects genetic alterations specific for tumour subtype

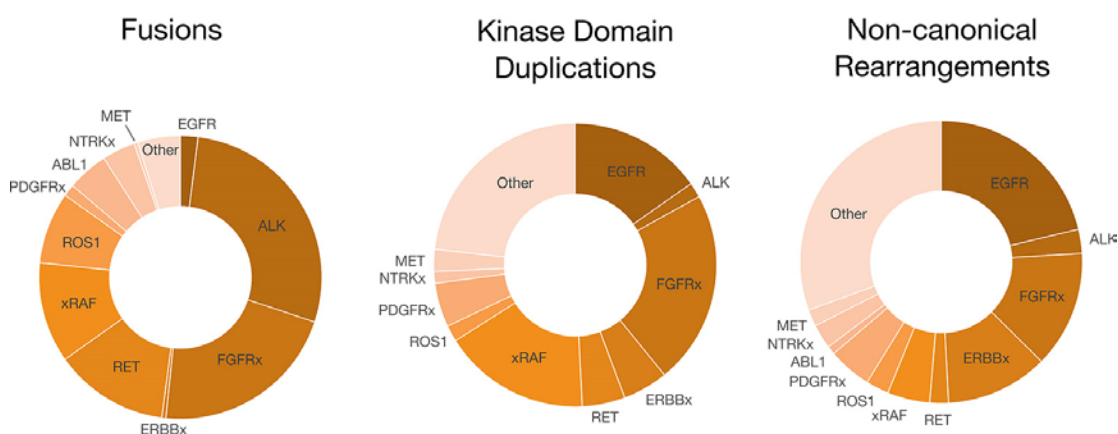
Laurie M. Gay, Senior Scientist in Pathology, Foundation Medicine, Cambridge, USA and a research team assessed the frequency of kinase-related rearrangements across hundreds of advanced cancer types to determine the landscape of oncogenic fusions, kinase domain duplications (KDD), and non-canonical rearrangements. KDD have not been characterised as extensively as fusions or other kinase-related genomic alterations seen in cancer. Kinase fusions are an important class of targetable oncogenes that are associated with both haematopoietic malignancies and solid tumours. Recently, oncogenic KDD in *BRAF* and *EGFR* were reported in the context of responses to tyrosine kinase inhibitors (TKI)^{1,2}.

The investigators performed comprehensive genomic profiling (CGP) on DNA and/or RNA from 114,200 solid tumour or haematological malignancy samples, to evaluate up to 406 cancer-related genes and selected introns from up to 31 genes that are commonly rearranged in cancer. RNA sequencing could also be done for 265 genes in some cases. CGP identified potentially actionable oncogenic rearrangements including KDD and kinase fusions that may have therapeutic implications.

KDD and fusions were detected in genes that were specific to the tumour type and/or location

Fusions, kinase domain duplications, and non-canonical rearrangements were seen in all kinases, but the relative distribution of rearrangement type varied widely by gene. For example, kinase domain duplications were common for *EGFR*, but rare for *ALK* or *ROS1*. Those two genes were far more likely to be observed as canonical fusions, like those in non-small cell lung cancer (NSCLC).

The types of rearrangements observed vary widely by kinase.



© Laurie Gay.

KDD were detected in 598 (0.62%) samples in this large series. Among the genes that were found to harbour KDD were targetable kinases, including *BRAF*, *EGFR*, *FGFR1/2/3/4*, *RET*, *ERBB2*, *MET*, *ALK*, *ROS1*, *NTRK1/2*, and the *PDGFRA/B* genes. The proportion of samples harbouring KDD differed among cancer types, with 2.7% of 6317 brain tumour samples found

to have KDD affecting genes such as *EGFR*, *BRAF*, *PDGFRA*, and *FGFR3*. Extracranial tumours were also found to harbour KDD. *RET* alterations were observed in 13 to 16% of breast, lung, and thyroid KDD-positive cases. *MET* was implicated in 15 to 20% of uterine and brain KDD-positive cases, and *ALK* was the gene most often affected in 54% of lung KDD-positive cases. KDD that were possibly related to TKI resistance were found in *BRAF* V600E-positive melanoma and *ALK*-related NSCLC.

Kinase fusions were most often detected in *ALK*, *FGFR2/3*, *RET*, and *ROS1*, with fusions in each gene found in 48 to 57 different tumour types. As previously noted, the fusion partners varied widely by tumour site. For example, *ROS1* fusions with *GOPC* predominated in gliomas and colorectal cancer, whereas *TFG-ROS1* fusions were most common in sarcomas, and *CD74-* and *EZR-ROS1* fusions in NSCLC. Targetable oncogenic drivers of several tumours were identified that may also associate with TKI response. Gay *et al.* Abstract 17000

Citations:

1. Gallant J-N, *et al.* *Cancer Discov* 2015; 5 (11):1155-63.
2. Klempner SJ, *et al.* *JAMA Oncology* 2016; 2 (2):272-4.

Practice point and future research opportunities

Although there is a clear trajectory towards eventual whole genome sequencing in cancer patients, a number of technical, computational and financial issues need to be resolved. Until then, hybrid capture technologies can resolve important gaps in our knowledge around prevalence of druggable rare genomic events across all common cancer types, driver landscape of every rare tumour, and evolution of drug resistance mutations over time in cancer patients.

These findings have clinical implication since index cases have demonstrated clinical responses to matched TKIs suggest that KDD, fusions and non-canonical rearrangements can be targeted therapeutically with currently available TKIs in many histological subtypes of cancer.

Subtypes of thymic carcinomas show different genomic alterations and tumour mutational burden

It is known that thymic gland carcinomas include a variety of histologic subtypes having variable clinical aggressiveness that respond differently to local and systemic therapies, leading Dr. Jeffrey S. Ross, Medical Director, Foundation Medicine and the Pathology Department, Albany Medical Center in Albany, USA and colleagues to investigate whether these subtypes could be further refined using comprehensive genomic profiling (CGP) to identify actionable genomic alterations for targeted therapies or immunotherapies for patients with relapsed and metastatic disease. The investigators sequenced FFPE sections obtained from 174 consecutive patients with metastatic thymic tumours using hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of >500X for up to 315 cancer-related genes plus 37 introns from 28 genes frequently rearranged in cancer. Total mutational burden (TMB) was determined on 1.1 Mb.

Although all of the patients had metastatic thymic gland tumours, twice as many men as women had thymic tumours, and the incidence of peaked in late middle age. Forty percent of samples were squamous (TSCC), 31% were non-neuroendocrine undifferentiated (TNOS), 17% neuroendocrine (TNEC), 4% adenocarcinomas (TAC), 3% basaloid (TBC), 3% lymphoepitheliomatous (TLEC), and 2% were sarcomatoid (TSRC) carcinomas.

The samples had an average of 4 genomic alterations per case. Genomic alterations were most often found in the TSRC, TSCC, TNOS, and subtypes with an average of 4.8, 4.1, 4.1, and 4.0 genomic alterations, respectively.

The investigators found an average of 0.9 clinically relevant genomic alterations (CRGA) per case, which were defined as genomic alterations (GA) that could be linked to drugs currently on the market or being evaluated in mechanism driven clinical trials. The TSCC and TSRC subtypes had the most CTGAs at an average of 1.0 each. *KIT* and *PIK3CA* genes were most commonly identified molecular targets; altered *KIT* occurred most often in the TAC, TNEC, TSCC, and TSRC subtypes, whereas *PIK3CA* was found most often in the TNOS and TSCC subtypes. Other targets included *PDGFRA*, *FGFR3*, *PTCH1*, *FBXW7*, *BRCA2*, *IDH1*, *ERBB2*, and *ERBB3*.

The more frequently occurring subtypes included TNEC, TSCC and TNOS, which also tended to have more genomic alterations, with *KIT* targets identified in approximately 10% of cases.

The metastatic thymic tumour samples demonstrated low TMB, with just 6% of cases showing more than 10 mutations/Mb and only 3% had more than 20 mutations/Mb. The TMB was highest in the TAC subtype, where 14% of samples showed TMB greater than 10 mutations per Mb. Nine percent of TSCC samples had TMB greater than 20 mutations per Mb. Ross *et al.* Abstract 1701O

Practice point and future research opportunities

The thymic gland carcinoma histologic subtypes showed varying genomic alterations and TMB status, with the TSCC, TNEC and TNOS subtypes featuring more genomic alterations. These subtypes plus the TAC subtypes had more CRGA that included *KIT* mutations and higher TMB. CGP shows promise to guide both targeted and immunotherapy selection for patients with thymic gland carcinomas.

BREAST CANCER, EARLY STAGE

Adjuvant chemotherapy provides clinical benefit in some patients with small node negative breast cancers

Konstantinos Tryfonidis, European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium and colleagues evaluated whether genomic risk, assessed per MammaPrint® or clinical risk, assessed per a modified version of Adjuvant! Online was the best indicator for the identification of patients with pT1abN0 breast cancer most likely to benefit from adjuvant chemotherapy. Five-year rates of distant metastasis-free survival (DMFS), distant metastases-free interval (DMFI) and overall survival (OS) were evaluated to determine which method yielded the most accurate estimate of the risk for developing subsequent tumours.

The tested population comprised a subgroup of 826 (12.3%) patients with pT1abN0 tumours participating in the MINDACT trial. Risk was assessed by these methods and patients characterised as low-risk by both assessments did not undergo chemotherapy, whereas patients characterised as having high risk by both genomic and clinical methods were advised to undergo adjuvant chemotherapy. Discordant cases were randomised to receive chemotherapy based upon the genomic or clinical result. The majority (37.5%) of patients was ≥ 60 years and 63.6% of patients were postmenopausal.

Nearly all patients (99.3%) were clinical low-risk; 624 (75.5%) patients were clinical low/genomic low, 196 (23.7%) were clinical low/genomic high, and 5 patients were clinical high/genomic low, with one case having missing data. No cases were high risk by both assessment methods. Of the 727 samples reviewed by central pathology 585 (80.5%) were determined invasive ductal, 662 (91.1%) were ER-positive, 46 (6.3%) were HER2-positive and 81 (11.1%) were grade 3 tumours. Immunohistochemistry subtype classification identified 426 (58.6%) as Luminal A, 193 (26.5%) were Luminal B, 38 (5.2%) Luminal B/HER2-positive, 37 (5.1%) were triple-negative tumours, and 8 (1.1%) samples were HER2-positive.

In the cohort of patients with pT1abN0 tumours and clinical low/genomic high risk, the 5-year DMFS was 97.3% (95% confidence interval [CI] 89.4, 99.3) compared to 91.4% (95% CI 82.6, 95.9) in patients without this risk determination. In the pT1abN0 cohort, patients receiving adjuvant chemotherapy demonstrated improved rates; the 5-year DMFI and OS rates were 98.8% (95% CI 91.9, 99.8) and 98.5% (95% CI 89.6, 99.8) compared to 91.4% (95% CI 82.6, 95.9) and 95.8% (89.1, 98.4%) respectively, for patients with clinical low/genomic high risk who did not receive CT. NCT00433589, EudraCT number:2005-002625-31. Tryfonidis *et al.* Abstract 150O

Practice point and future research opportunities

Biological characteristics can be used as determinants of whether to administer adjuvant chemotherapy in patients with T1abN0 tumours. An important subset (23.7%) of patients with these small tumours had clinically low but genomic high risk and derived benefit from chemotherapy.

Taselisib plus letrozole improves response in postmenopausal women with ER-positive, HER2-negative early breast cancer

The LORELEI study, conducted by Cristina Saura, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology in Barcelona, Spain and colleagues demonstrated that PI3K inhibition with taselisib increased the efficacy of neoadjuvant letrozole in women with and without tumours harbouring a *PIK3CA* mutation. Taselisib is a selective PI3-kinase (PI3K) inhibitor with enhanced activity against *PIK3CA* mutant cancer cells. Previously, confirmed partial responses had been demonstrated in *PIK3CA* mutated metastatic breast cancer with taselisib, administered either as a single agent or combined with endocrine therapy. In LORELEI, taselisib combined with letrozole improved the objective response rate (ORR) in postmenopausal women with early breast cancer overall and in a subset of women with *PIK3CA* mutant tumours.

LORELEI (NCT02273973) was a phase II randomised, double-blind study that enrolled 334 postmenopausal patients with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer from 90 sites worldwide. The women had operable early breast cancer, stages I to III, and evaluable tumour tissue for centralised *PIK3CA* genotyping. The patients were randomised to receive letrozole plus either taselisib at 4 mg in a 5 days on - 2 days off weekly cycle or placebo for 16 weeks, followed by surgery. The co-primary endpoints were ORR by centrally assessed breast MRI and pathologic complete response (pCR) defined as the rate of tumour eradication from both breast and lymph nodes (ypT0/is N0) at the date of surgery in all randomised patients and in patients with *PIK3CA* mutated tumours. The sample size was calculated to detect an absolute increase of 24% in ORR (from 40% to 64%, minimal detectable difference [MDD] 15%; 2-sided α 16%, 80% power), or 18% in pCR (from 1% to 19%; MDD 13%; 2-sided α 4%, 80% power) in patients with *PIK3CA* mutant tumours.

With the taselisib/letrozole combination, the ORR was increased from 38% to 56.2% in the *PIK3CA* mutated subset, odds ratio [OR] 2.03, 95% confidence interval [CI] 1.06, 3.88 ($p = 0.033$). The ORR was also increased from 39.3% to 50%, in the overall cohort of women with and without tumours having mutated *PIK3CA*, OR 1.55; 95%CI 1.00, 2.38 ($p = 0.049$). Neither the overall patients nor the patients in the *PIK3CA* mutated subset demonstrated significant differences in the pCR rate with the taselisib/letrozole combination compared to letrozole/placebo.

Taselisib toxicity was manageable. The most common serious (grades 3 and 4) adverse events associated with the drug included gastrointestinal disorders (7.8%), infections (4.8%), and skin / subcutaneous tissue disorders (4.8%), vascular disorders (3.6%), and metabolism and nutrition disorders (3.6%) including hyperglycaemia (1.2%). Dose reductions were made in 11.4% of patients and 10.8% of patients discontinued taselisib. One sudden death occurred in the taselisib arm that was considered unrelated to study treatment. Saura *et al.* Abstract LBA10_PR

Practice point and future research opportunities

This is possibly the first clinical proof of efficacy of a specific PI3K inhibitor, taselisib, in early breast cancer.

LORELEI demonstrated a significant increase in ORR as measured by MRI following treatment with a PI3K selective inhibitor in combination with letrozole in patients with ER-positive, HER2-negative early breast cancer. Comprehensive biomarker analyses to provide further insight into the anti-tumour responses observed with the taselisib/letrozole combination are ongoing.

Neratinib improves invasive disease-free survival rates over placebo following adjuvant trastuzumab for early stage HER2-positive breast cancer

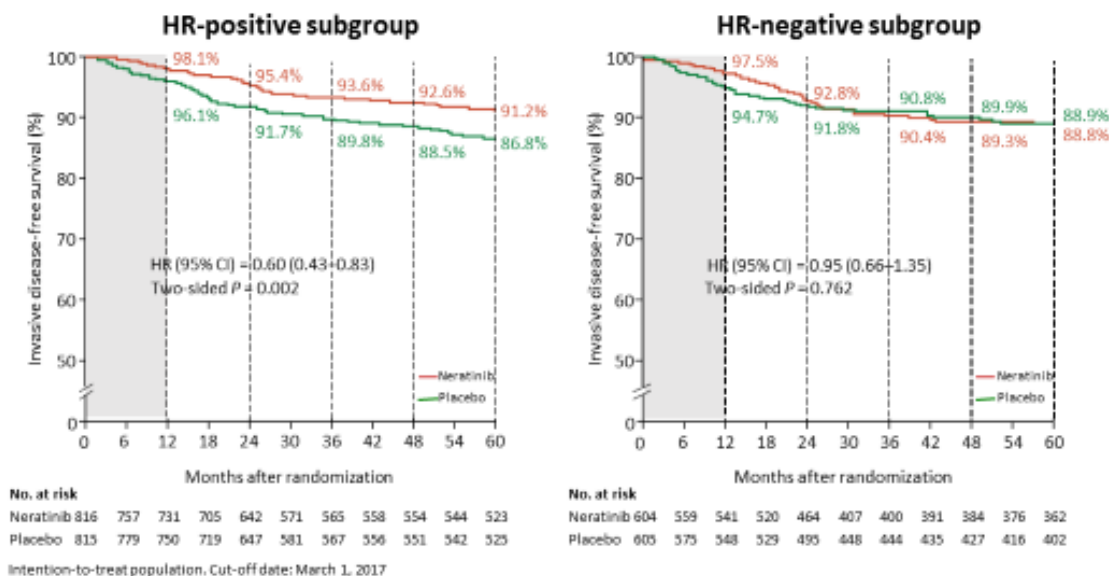
Lead author Miguel Martin, head of Medical Oncology at the Hospital General Universitario Gregorio Marañón in Madrid, Spain presented efficacy findings from a pre-planned 5-year analysis of data from the ExteNET study, which evaluated whether neratinib could improve long-term survival versus placebo after trastuzumab-based adjuvant therapy in patients with early stage HER2-positive breast cancer. The phase III international, multicentre, double-blind, placebo-controlled ExteNET trial randomised patients to oral neratinib at 240 mg daily or to placebo for one year following their initial trastuzumab treatment. At 2 years post randomisation, consenting patients allowed data collection concerning disease recurrences and survival from medical records for a further 3 years. The analysis was on the intention-to-treat (ITT) population and non-consenting patients were censored at their last physical examination.

Invasive disease-free survival (iDFS) rates were significantly better in patients treated with an one year course of sequential neratinib over placebo; neratinib showed a significant iDFS benefit at 2 years follow-up (primary endpoint) in high-risk, HER2-positive, adjuvant trastuzumab pre-treated, early breast cancer patients hazard ratio (HR) 0.67; 95% confidence interval (CI) 0.50, 0.91 ($p = 0.0091$). Fifty-three patients died during the initial 2-year follow-up and 2117 (76%) patients consented to additional follow-up.¹ These findings were confirmed by the updated 5-year efficacy results from 2840 patients in the ITT population comprising 1420 patients receiving neratinib and 1420 receiving placebo. After a median follow-up of 5.2 years, 2810 patients in the ITT population demonstrated iDFS rates of 90.2% with neratinib versus 87.7% with placebo, HR 0.73; 95% CI 0.57, 0.92 ($p = 0.008$).

HER2 was centrally confirmed in 1796 patients overall, including 90.4% of neratinib and 88.2% of placebo patients. Overall, 1209 patients were hormone receptor negative including 88.8% and 88.9% of patients in the neratinib and placebo arms, respectively ($p = 0.762$).

Findings from a protocol-specified subgroup analysis suggested hormone receptor positive breast cancer patients experienced greater benefit with neratinib.

ExteNET: iDFS by hormone receptor status



1

© Miguel Martin.

According to the authors, data from the protocol-specified subgroup analysis suggest that hormone receptor positive patients had a greater benefit from neratinib. Overall survival data are not yet mature. NCT00878709. Martin *et al.* Abstract 1490

Citation: 1. Chan *et al. Lancet Oncol* 2016; 17(3): 367-377.

Practice point and future research opportunities

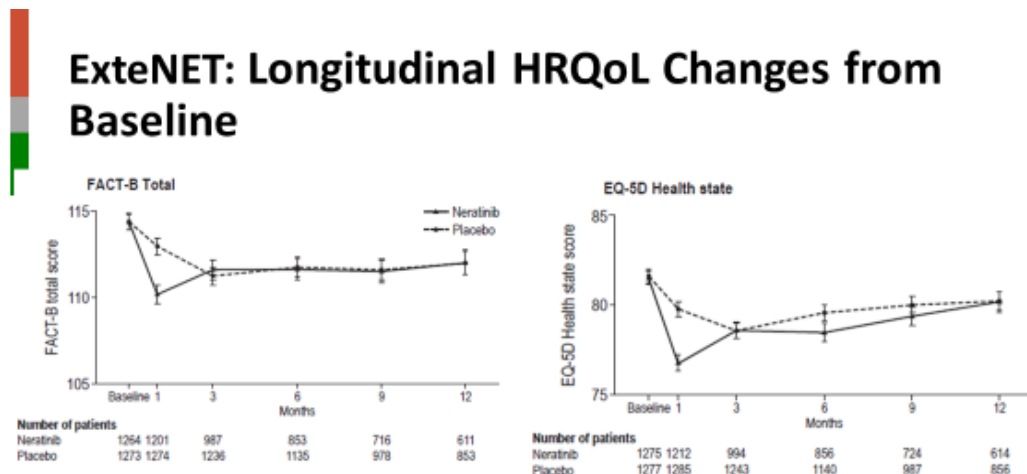
The ExteNET trial showed continued demonstration of clinically significant benefit, particularly in higher risk, hormone receptor positive disease despite limitations due to change in sponsor and initial plan for short follow-up. However, diarrhoea is a limiting factor, but it can be reduced significantly with prophylaxis, which is mandatory component of treatment. Survival data are pending and reduction in distant events is encouraging.

The ExteNET study demonstrated small improvements in health-related quality of life with neratinib

Suzette Delaloge, Associate Professor of Medical Oncology Institut Gustave Roussy, Villejuif, France and colleagues conducted a longitudinal evaluation of health-related quality of life (HRQoL), which was an exploratory endpoint of ExteNET trial. The breast cancer specific FACT-B and the general HRQoL EQ-5D questionnaires were completed at baseline and months 1, 3, 6, 9, and 12 by 2407 and 2427 patients, respectively. Patient compliance with the questionnaire was more than 85%. The FACT-B was completed by 1171 patients on neratinib and by 1236 placebo patients, whereas the EQ 5D was completed by 1186 and 1241 neratinib and placebo patients, respectively. Changes in scores from baseline using ANCOVA (with no imputation for missing values) and sensitivity analyses using alternative

methods were performed; changes in HRQoL scores were considered to be clinically meaningful if they were greater than the minimal clinically important differences (MCIDs) reported in the literature.

Neratinib was associated with a decrease in HRQoL scores at month one compared with placebo (adjusted mean differences: FACT-B total, -2.9 points; EQ-5D index, -0.02), with the between-group differences diminishing at later time-points. Except for the FACT-B physical well-being (PWB) subscale at month one (-2.4), all between-group differences were less than MCIDs. Sensitivity analyses exploring missing data did not change these results.



Mean [SE] observed scores by treatment group over time for FACT-B total and EQ-5D health state
important differences (IDs): FACT-B total, 7–8 points, and EQ health state score, 7–10 units. For both instruments, a higher score indicates a better quality of life.

- Neratinib was associated with a decrease in HRQoL scores at month 1 compared with placebo (adjusted mean differences: FACT-B total, -2.9 points; EQ-5D index, -0.02), after which the between-group differences diminished at later time-points.
- Except for the FACT-B physical well-being (PWB) subscale at month 1, all between-group differences were less than IDs.

© Suzette Delaloge.

Small improvements in the BCS scores favouring neratinib were reported; the mean difference in BCS scores was 0.3, 0.7, 0.4, 0.6, and 0.2 over the 5 time-points, all less than MCIDs. NCT00878709. Delaloge *et al.* Abstract 177P

Practice point and future research opportunities

Neratinib-related diarrhoea was possibly associated with decreased HRQoL at month one, particularly regarding physical well-being. The relatively small magnitude of differences observed over the time-points following month one in physical well-being favouring placebo and changes in the breast cancer scale favouring neratinib may not be clinically important.

UNICANER-NeoPal study does not show improved outcome with combined letrozole plus palbociclib over chemotherapy as neoadjuvant treatment in luminal breast cancer

Historically, limited benefit has been demonstrated with neoadjuvant chemotherapy in patients with luminal breast cancer (LBC). However, combined palbociclib and letrozole has demonstrated clinical benefit in postmenopausal women with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast

cancer, leading to the granting of accelerated approval for treatment in this setting by the US Food and Drug Administration, prompting Paul Cottu, Medical Oncology, Institut Curie, Paris, France and a research team to investigate letrozole plus palbociclib as neoadjuvant treatment in LBC in the randomised parallel phase II UNICANCER-NeoPAL study.

The trial enrolled postmenopausal women with stage II or III ER-positive, HER2-negative breast cancer who were not candidates for breast conserving surgery (BCS). All patients were required to have either a PAM50 luminal B or luminal A profile with proven lymph node involvement. Of 184 screened women, 106 patients with stage II-IIIa, PAM50-confirmed LBC underwent parallel 1:1 randomisation to therapy comprising six courses of third generation chemotherapy comprised of FEC100 for 3 cycles plus docetaxel 100 for 3 cycles or to 19 weeks of letrozole at 2.5 mg/day plus palbociclib at 125 mg/day for four, three-week cycles. Surgery was performed at week 20. Seventy-three percent of patients were categorised T1-2, 27% were T3, 26.5% of patients were node positive, and 89% of women had luminal B tumours. The median risk of relapse (ROR) score was 68 (range 22 to 93).

The primary endpoint was the locally assessed rate of residual cancer burden (RCB) and secondary endpoints included safety, response rate, positive and negative predictive values of PAM50 ROR-defined status, centrally reviewed RCB, and BCS rates. The protocol planned that the trial should be stopped for futility if ≤ 5 local RCB 0-I events (16.7%) were observed in the first 30 patients in the letrozole/palbociclib arm. At the interim analysis, RCB 0-I was observed in one patient in the letrozole/palbociclib arm and enrolment stopped.

At the final analysis, neither RCB nor BCS rates were improved with letrozole/palbociclib over chemotherapy; local RCB 0, I, II, and III was observed in 3.8%, 3.8%, 52%, and 40.4% of patients receiving letrozole/palbociclib compared to 5.9%, 9.8%, 37.3%, 47.1% in patients on chemotherapy, respectively. Central and local RCB assessment results were identical. The response rates with neoadjuvant letrozole/palbociclib and chemotherapy were similar; the clinical objective response rates were 74.5% versus 76%, and the BCS rates were 69.2% versus 68.6%, respectively. However, the final median Ki67 value was significantly lower in the letrozole/palbociclib arm; Ki67 was 3% (range 1 to 40) versus 8% (range 2 to 15) respectively ($p = 0.017$). Letrozole/palbociclib also demonstrated better tolerability with two serious adverse events occurring in the letrozole/palbociclib arm compared to 17 with chemotherapy ($p < 0.001$). The investigators are continuing extensive analyses of these data. Cottu *et al.* Abstract LBA9

Practice point and future research opportunities

This study is the first head to head comparison of an endocrine-based CDK4/6 inhibitor, palbociclib, versus chemotherapy. Similar trials are ongoing in metastatic breast cancer, for example PADMA. However, the challenge remains to identify patients with luminal early breast cancer for whom an endocrine-based approach will improve outcome, either replacing chemotherapy in intermediate-risk or as an add-on in high-risk disease.

Neoadjuvant letrozole/palbociclib did not improve residual cancer burden rates over chemotherapy, and the response and BCS rates were similar in both arms. However, letrozole/palbociclib was better tolerated, and significantly lowered Ki-67 levels compared to chemotherapy, suggesting that it could be an alternative to chemotherapy in some patients.

Next generation sequencing reveals potential genomic markers of recurrence in locally advanced triple negative breast cancer

Nina Radosevic-Robin, Pathology, INSERM 1240, University Clermont Auvergne, Centre Jean Perrin in Clermont-Ferrand, France and colleagues investigated the possible genomic determinants of triple negative breast cancer (TNBC) recurrence using pre-treatment samples and residual tumours at surgery obtained from participants in two neoadjuvant trials (NCT00933517 and NCT00600249). The investigators analysed tumour tissues sampled before and after administration of neoadjuvant therapy with the anti-EGFR antibodies panitumumab and cetuximab combined with chemotherapy for locally advanced TNBC. The samples were analysed by next generation sequencing (NGS) using a targeted exome panel (MSK-IMPACT) containing 410 cancer-related genes. The analysis included the data of 15 patients achieving pathological complete response (pCR) and 33 patients that did not.

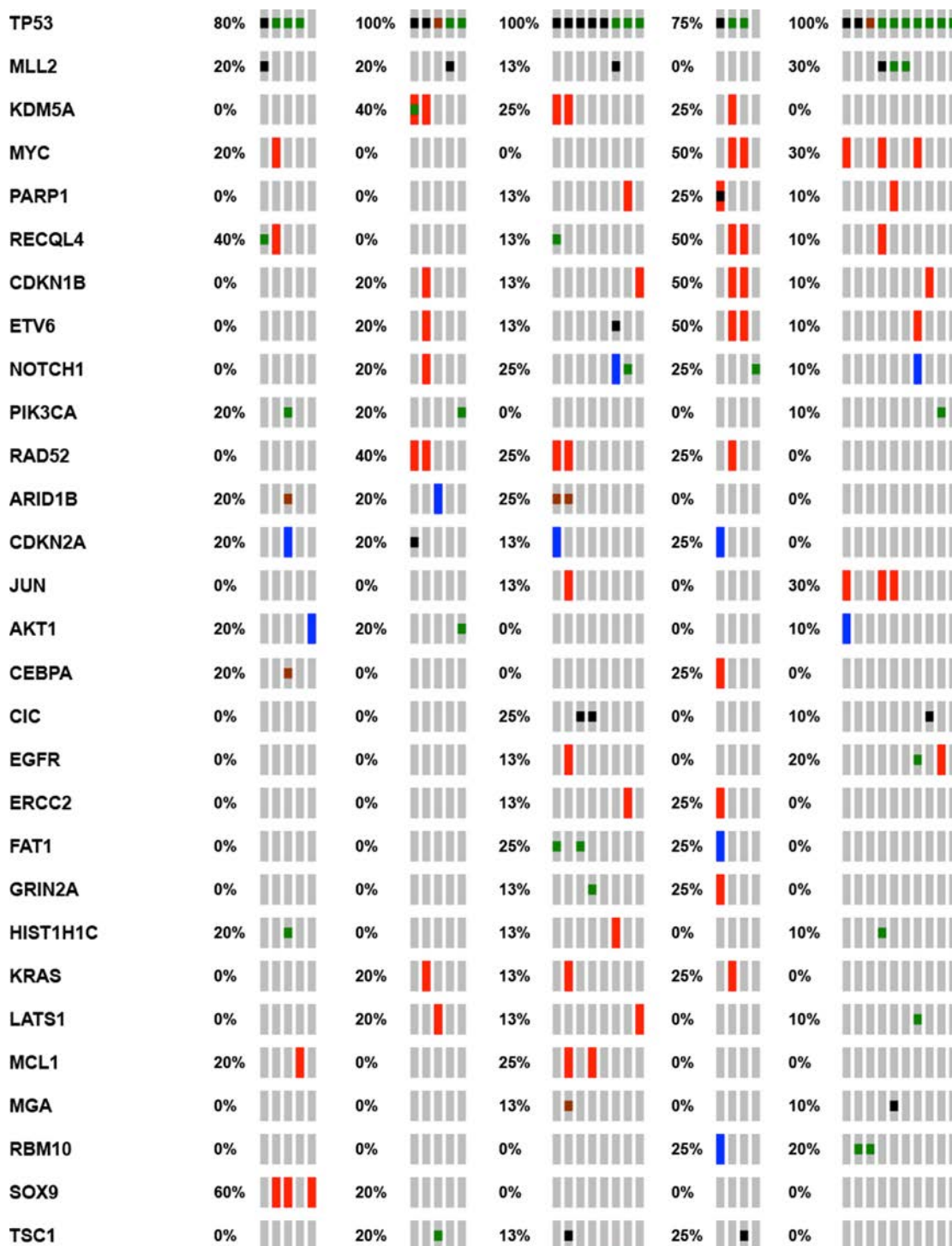
Nearly one-third of patients not achieving pathological complete response after treatment experienced recurrence within 2 years; 5 of the non-pCR patients experienced early fatal metastatic recurrences (EFMR) less than one year post surgery and an additional 5 patients demonstrated later non-fatal recurrence (LNFR) at more than one but less than 2 years post-surgery. None of the 23 patients having residual tumours experienced a recurrence within 5 years post-surgery.

Among the 15 patients achieving pCR, one patient had a LNFR consisting of a solitary brain metastasis.

Twenty-three patients having residual tumours did not experience a recurrence up to 5 years post-surgery. Among the 15 patients achieving pCR, one patient had a later non-fatal recurrence consisting of a solitary brain metastasis.

TNBC showed distinctive genomic alterations upon NGS rather than a comprehensive genomic pattern. Analysis of patients having disease recurrence yielded patient specific genomic alterations

The image below shows most frequent genomic alterations by group of recurrence.



© Nina Radosevic-Robin.

The association between disease recurrence and NGS findings was analysed in a case-by-case fashion, which yielded patient-specific genomic alterations, without obvious genomic pattern predictive of recurrence.

Interestingly, SOX9 amplification was found in tumours of 3 out of 5 patients with early fatal metastatic recurrence and nowhere else in this series.

Post-neoadjuvant residual tumours of each patient experiencing an early fatal metastatic recurrence had an individual set of genomic anomalies. For example, patient one had no mutations, but *SOX9*, *AKT1* and *TGFBR2* amplified, together with *TERT* loss. Patient two had *SOX9*, *RAD21* and *NOTCH2* amplified, as well as mutations in *PTEN*, *PIK3CA*, *ERBB3* and *ARID1B*. Patient three had *SOX9* and *MYC* amplified, *PTEN* lost and *KDM6A* mutated. Patient four had mutated *RAF1*, *FGFR2*, *MLL2*, and *GLI1*, with numerous copy number alterations of other genes. Patient five had *SETD2* mutation, *HIST2H3D*, *HIST2H3C*, *MCL1*, and *EZH2* amplification, as well as loss of *MAP3K1*.

The patient achieving complete response but later developing a single brain metastasis had *BRCA1*, *MLL2*, *CDK12*, and *PPM1D* mutation, in the pre-therapy sample.

Genomic aberrations that were detected in other non-pCR patients included 3 different activating mutations in *PIK3CA* in one single residual tumour, and the post-treatment appearance of *HRAS* G12S mutation or *PARP1* amplification. Radošević-Robin *et al.* Abstract LBA12

Practice point and future research opportunities

This hypothesis-generating study is intended to capture the intrinsic inter-tumour heterogeneity associated with response to EGFR-targeting and chemotherapy in TNBC. These genomic data should be interpreted in the context of other tumour features such as histology, protein and gene expression, immune infiltrates.

Strong association found between overall survival and tumour type in early breast cancer

David G. Cox, Cancer Research Centre of Lyon Centre Léon Bérard, Lyon, France, and colleagues are conducting a large genome wide association study in 1250 women in the SToRM study who experienced metastatic progression from March 2012 to May 2014. SToRM was planned to complement the SIGNAL/PHARE (NCT00381901/RECF1098) cohort of over 10,000 patients with early breast cancer, who are being followed by a clinical team to capture information about their treatment and survival for use in evaluating the contribution of the patient's genetic background to clinically relevant phenotypes in breast cancer metastasis. The investigators used the Illumina HumanCore Exome chip set, which is composed of over 250,000 variants and was designed to capture common variation across the genome, as well as over 200,000 variants in coding regions.

The average (standard deviation) duration between the primary diagnosis of early breast cancer and the development of metastasis was 58.5 (± 73.5) months. A total of 747 patients in SToRM had a luminal-like tumour type, 249 were HER2-positive, and 194 patients had triple negative breast cancer (TNBC). A total of 875 deaths had occurred as of April 2017, and as of July 2017, the median follow-up was 3.8 years, and 7 years in the SIGNAL and PHARE cohorts, respectively. In the combined cohorts, 1497 patients had progressed by this time, and 154 patients had died.

The investigators found that survival probability was highly associated with tumour type ($p = 2.27 \times 10^{-38}$), with patients having TNBC demonstrating the shortest median survival after metastatic diagnosis of less than 24 months, whereas median survival for luminal and HER2-positive patients exceeded 36 months. Thus far, no variants have demonstrated association with survival. However, borderline associations have emerged between a number of variants and survival among patients with TNBC and HER2-positive disease. NCT01460186. Cox *et al.* Abstract LBA15

Practice point and future research opportunities

Findings from this cohort of over 10,000 women suggest that the risk of death varies in patients diagnosed with early breast cancer depending upon the tumour type, and demonstrate that patients with triple negative disease experienced the shortest survival time from progression to metastatic disease and death.

This is probably the first study to link germline SNPs with the risk of M1 disease. Identification of DNA regions as prognostic biomarkers seems promising, with further validation in independent cohorts. Additional studies looking at the association of SNPs with specific sites of relapse, response to treatment and survival are warranted. Identification of the genes and the biology behind these observations is needed.

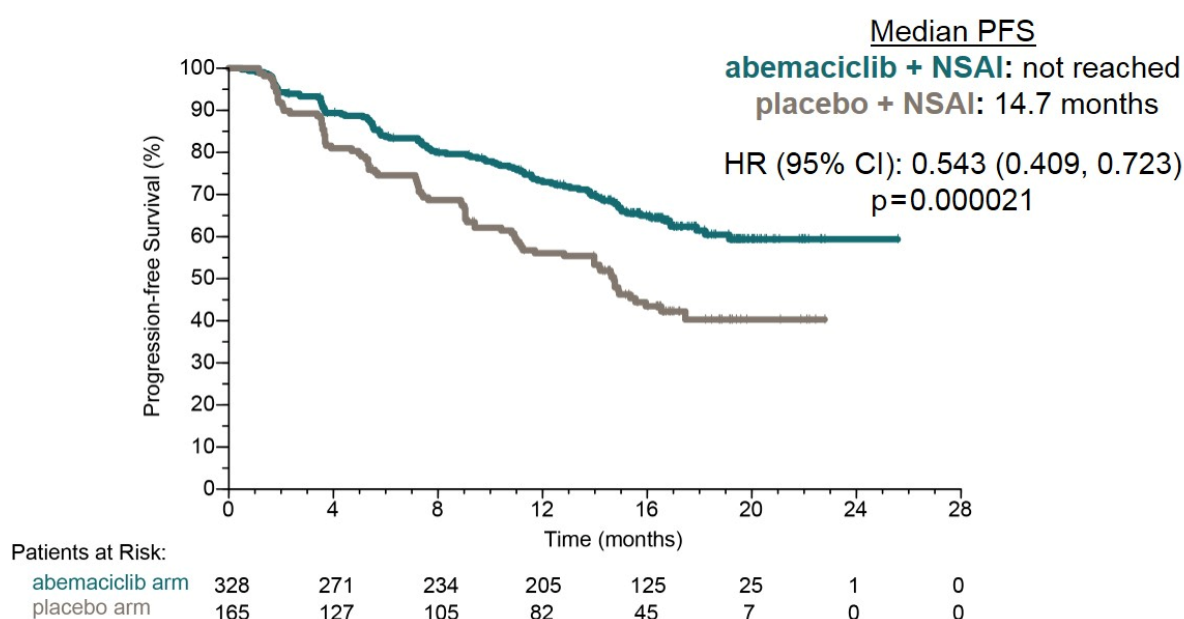
BREAST CANCER, METASTATIC

Interim analysis shows significant clinical benefit with combined abemaciclib plus NSAI as initial treatment for patients with HR-positive/HER2-negative advanced breast cancer

Angelo Di Leo, Sandro Pitigliani Medical Oncology Department, Nuovo Ospedale di Prato S. Stefano - Istituto Toscano Tumori, in Prato, Italy, presented findings from the phase III, MONARCH 3 trial of abemaciclib in combination with the non-steroidal aromatase inhibitors (NSAI), anastrozole or letrozole, in postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer (ABC). The patients had received no prior systemic therapy in the metastatic setting and were either endocrine naive or had progressed at greater than 12 months after receiving endocrine therapy. The investigators randomised 493 women, 328 in the abemaciclib arm, 165 in the placebo arm, who were also stratified according to metastatic site, including visceral, bone only, or other, and by prior endocrine therapy. Abemaciclib was administered at 150 mg orally twice daily on a continuous schedule plus either 1 mg anastrozole or 2.5 mg of letrozole, daily. The primary endpoint for the trial was investigator-assessed PFS and secondary objectives included objective response rate (ORR) and safety. The study was powered to 80% at 1-sided $\alpha = 0.025$ assuming a HR of 0.67 in favour of abemaciclib plus a NSAI, with analyses at 189 and 240 PFS events. Visceral disease was reported in 52.9% of patients, 80.5% had measurable disease, 27.4% of patients had received prior (neo)adjuvant aromatase inhibitors and 39.8% of patients had de novo ABC.

An interim analysis done at 194 PFS events showed abemaciclib plus a NSAI significantly prolonged PFS; investigator-assessed median PFS was not reached with the abemaciclib combination compared to 14.7 months with placebo plus a NSAI, hazard ratio (HR) 0.543; 95% confidence interval (CI) 0.409, 0.723 ($p = 0.000021$).

The graph below shows median PFS.



© Angelo Di Leo.

Patients having measurable disease demonstrated an ORR of 59% with abemaciclib versus 44% with placebo ($p = 0.004$).

The safety data were generally consistent with results reported in previous trials of abemaciclib. The most common adverse events (AEs) observed were diarrhoea, neutropenia, and fatigue, which occurred at rates of 81.3%, 41.3%, and 40.1% with abemaciclib compared to 29.8%, 1.9%, and 31.7% with placebo/NSAI, respectively. Grade 3 AEs included diarrhoea in 9.5%, and fatigue in 1.8% of patients on abemaciclib and 1.2% of patients on placebo had grade 3 diarrhoea. Grade 3/4 neutropenia was seen in 21.1% of abemaciclib patients versus 1.2% of placebo patients.

The CDK4/6 inhibitor, abemaciclib was granted FDA breakthrough designation in 2015 based on phase I trial data wherein single-agent abemaciclib demonstrated an ORR of 31% in 36 patients with heavily pre-treated HR-positive breast cancer¹. Other investigations of abemaciclib are ongoing; it is also being studied combined with trastuzumab in patients with HR-positive/HER2-positive locally advanced or metastatic breast cancer. The phase II monarchHER trial (NCT02675231), is assessing abemaciclib plus trastuzumab (with or without fulvestrant) in patients with HR-positive/HER2-positive locally advanced or metastatic breast cancer. NCT02246621. Di Leo *et al.* Abstract 236O_PR

Citation: 1. Patnaik A, *et al.* *Cancer Discov* 2016; 6(7):740-53.

Practice point and future research opportunities

These results, particularly from a subgroup analysis, may contribute to a change in the patients who will be treated with standard first line endocrine-based therapy. They show substantial efficacy with safety profile that is compatible with long term dosing. The consistent benefit observed across studies reflects the class effect of CDK4/6 inhibitors. There are no data yet on overall survival (OS). All CDK4/6 studies are substantially underpowered to look at OS. Median OS on letrozole alone is now approximately 50 months. Realistic power for MONARCH3 is in the range of 50%. There is a clear requirement for collaboration and meta-analysis.

It should be noted that a main conclusion from the authors, in particular that the exploratory subgroup analyses suggest that patients with indicators of poor prognosis had substantial benefit from the addition of abemaciclib, while in patients having a long treatment-free interval or bone-only disease, single agent endocrine therapy may be an appropriate initial therapy.

Promising response rates in patients with metastatic TNBC treated with nivolumab after induction treatment

Marleen Kok, Medical Oncology & Immunology, Het Nederlands Kanker Instituut Antoni van Leeuwenhoek in Amsterdam, Netherlands, and colleagues demonstrated that induction therapy is feasible and improved the response to anti-programmed death ligand-1 (PD-L1) immunotherapy with nivolumab over the historical response rates demonstrated in previous PD-1/PD-L1 blockade monotherapy studies. This adaptive phase II randomised non-comparative trial allocated 50 patients with metastatic triple negative breast cancer (TNBC)

who had received ≤ 3 lines of palliative chemotherapy to one of five 2-week induction treatments consisting of either three cycles of 8 Gy irradiation of one metastatic lesion, or two cycles of doxorubicin at 15 mg weekly, or to cyclophosphamide at 50 mg daily orally or two cycles of 40 mg/m² of cisplatin, or to receive no induction treatment. Following the 2-week induction, all patients were treated with nivolumab at 3 mg/kg until progression according to RECIST 1.1 criteria. Recruitment to treatment arms was to close after 50 evaluable patients with paired biopsies (stage I), according to a 'pick the winner' concept (Simon's two-stage design). At a median follow-up of 4 months (range 1 to 15 months), 50 patients had evaluable data and paired biopsies. Twenty percent, 52% and 28% of patients had received 0, 1 or 2+ lines of prior treatment, respectively.

Previously reported trials of single-agent anti-PD-L1 immunotherapy in unselected patients with TNBC demonstrated response rates of approximately 10%. The median response rate with nivolumab after priming the tumour microenvironment was twice that seen in prior nivolumab monotherapy trials in metastatic TNBC; the objective response rate (ORR) per RECIST 1.1 was 22%, which included 2 (4%) complete responses (CR), and 9 (18%) partial responses (PR). Additionally, stable disease (SD) lasting more than 24 weeks was achieved by 2 (4%) patients, which resulted in a 26% clinical benefit rate (CBR = CR+PR+SD>24 weeks). The median duration of response was 10.9 months (95% confidence interval [CI] 7.1, NA).

The investigators also observed changes in tumour-infiltrating lymphocytes (TIL) after irradiation or low dose chemotherapy. EudraCT number: 2015-001969-49. Kok *et al.* Abstract LBA14

Practice point and future research opportunities

The strengths of the study are that it is a very innovative trial exploring combination therapy; it provides data on the effect of chemotherapy and radiotherapy in priming the immune system, as well as a quantitative and qualitative assessment of TILs. The limits are that we are missing mutational burden before and after exposure to the induction agent, TILs before and after induction, and also useful would be another arm for ER-positive and HER2-positive breast cancer.

This is the first study in TNBC to demonstrate that nivolumab after priming the tumour microenvironment with either irradiation or chemotherapy is feasible and results in a promising response rate that appears higher than expected based on previous PD-1/PD-L1 blockade monotherapy studies in unselected TNBC. Although anti-PD-L1 therapy can provide durable responses in patients with metastatic TNBC the response rate is low, about 10%, indicating that there is an urgent clinical need to identify strategies that render the tumour microenvironment more sensitive to anti-PD-L1 agents.

Pembrolizumab response associates with TIL levels and PDL1 expression in metastatic TNBC

Sherene Loi, Lab Head and Medical Oncologist of the Peter MacCallum Cancer Center in Melbourne, Australia, and her team investigated tumour infiltrating lymphocyte (TIL) levels in tumour samples and found that patients with metastatic triple negative breast cancer (TNBC) were more likely to show a strong response to pembrolizumab if more TILs were present in

the tumour microenvironment. TILs have been observed in TNBC and may represent pre-existing antitumour immunity, and may also serve as a biomarker for response to immunotherapy in TNBC.

Data from the phase II KEYNOTE-086 study were used to determine the relationship between the quantity of stromal TILs and pembrolizumab response in patients with previously treated metastatic TNBC and any PD-L1 expression (cohort A), and patients with previously untreated, PD-L1–positive metastatic TNBC (cohort B). The response to pembrolizumab was assessed by central review according to RECIST v1.1 every 9 weeks for 12 months, then every 12 weeks. Of the first 222 patients enrolled, 193 patients had evaluable tumour samples; 147 samples were obtained from cohort A and 46 samples were from cohort B. Of these, 146 samples were newly collected and derived mostly from metastatic sites, and the 47 archival samples represented mostly primary breast tumours. Stromal TILs were quantified from tumour biopsies using haematoxylin and eosin (H&E)-stained slides by one pathologist who was blinded to the clinical data, and PD-L1 expression was assessed by immunohistochemistry (IHC) and the PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA).

Stromal TIL levels were higher in previously untreated cohort B patients with PD-L1–positive metastatic TNBC; the median stromal TIL level (interquartile range; IQR) was 17.5% (5 to 61.25%) in cohort B compared to 5% (1 to 10%) in cohort A (one-sided Wilcoxon rank sum $p < 0.001$). Stromal TIL levels were also higher in archival tumour samples versus newly collected samples at 10% (5 to 40%) versus 5% (1 to 15%; $p < 0.001$) and in lymph node versus non-lymph node samples at 10% (5 to 50%) versus 5% (2 to 16.25%; $p = 0.01$).

On logistic regression that adjusted for cohort (A versus B) and LDH concentration (continuous), a significant relationship was seen between the pembrolizumab response and stromal TIL levels. The objective response rate (ORR) in patients with stromal TIL levels \geq the median, as opposed to less than median was 6.4% versus 1.9% in cohort A, and 39.1% versus 8.7% in cohort B. The median (IQR) stromal TIL level in responders compared to non-responders was 10% (5 to 30%) versus 5% (1 to 10%), respectively, in cohort A and 50% (35 to 70%) versus 15% (5 to 40%), respectively, in cohort B. In the combined cohorts, higher stromal TIL levels associated with significantly improved ORR as a continuous variable (adjusted odds ratio 1.02; 95% confidence interval [CI] 1.00 to 1.04 [1 sided $p = 0.014$]). Area under the ROC curve was 0.784.

PD-L1 expression assessed by the combined positive score significantly correlated with TIL levels ($p = 0.496$; one sided $p < 0.001$) but did not add significantly more information to a predictive model that included stromal TILs, LDH concentration, and study cohort. NCT02447003. Loi *et al.* Abstract LBA13

Practice point and future research opportunities

TILs assessed by H&E were significantly associated with response to pembrolizumab, particularly in the first-line setting. TIL levels, LDH concentration, and cohort were independent predictors of response to pembrolizumab monotherapy. TILs and the PD-L1 combined positive score showed a significant positive correlation and it was determined that TILs can identify patients with metastatic TNBC having a greater chance of responding to pembrolizumab monotherapy.

The study strengths include a recommendation that TILs be routinely assessed in the primary tumour, in the case of triple negative or HER2-positive. TILs may serve as a stratification factor for trials using immunotherapy in breast cancer, as they reflect T cell priming, T cell attraction, and, potentially, foreignness (mutational burden). The study is limited by lack of information regarding composition and phenotype of the TILs, different immune-contexture and immune-landscape in different organs, and the need to assess tertiary lymphoid structures, principally those located in the peri-tumoural stroma.

CNS TUMOURS

Combined nivolumab and radiotherapy ± temozolomide is safe in patients with newly diagnosed glioblastoma

Michael Lim of The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, presented updated safety data from 2 exploratory cohorts of the CheckMate 143 trial. The study assessed the safety and tolerability of nivolumab combined with standard radiotherapy with and without temozolomide in patients with newly diagnosed glioblastoma. CheckMate 143 assigned patients to cohort 1c or 1d based on the methylation status of the promoter region of the *MGMT* gene; *MGMT* when methylated has been linked to improved outcomes when temozolomide is added to radiotherapy in patients with newly diagnosed glioblastoma. Cohort 1c included patients with either methylated or unmethylated *MGMT*, whereas cohort 1d included only patients with unmethylated *MGMT*. After the initial evaluation, 55 additional patients with unmethylated *MGMT* were randomised 1:1 to cohort 1c or 1d.

The safety analysis included all 113 patients receiving nivolumab. Cohort 1c included 12 patients with methylated *MGMT* and 43 patients with unmethylated *MGMT*, who received nivolumab at 3 mg/kg once every 2 weeks plus standard radiotherapy and concurrent temozolomide at 75 mg/m² daily followed by adjuvant temozolomide at 150 to 200 mg/m² for 5 days per 28-day cycle for ≥ 6 cycles. Fifty-eight patients with unmethylated *MGMT* were treated in cohort 1d with the same dose of nivolumab and standard radiotherapy, but without temozolomide. Nivolumab was continued in both cohorts until confirmed progression or unacceptable toxicity occurred.

In cohort 1c, 67% of patients with methylated *MGMT* and 93% of patients with unmethylated *MGMT* who received nivolumab, radiotherapy, and temozolomide discontinued treatment compared to 97% of patients in cohort 1d (unmethylated *MGMT*), who received nivolumab plus radiotherapy. No deaths due to study drug toxicity were reported.

In cohort 1c, treatment discontinuation due to radiographic progression occurred in 50% of patients with methylated *MGMT* and 58% of patients with unmethylated *MGMT*. In addition, discontinuation due to treatment-related toxicity and patient decision each occurred in 8% and 14% of patients with methylated and unmethylated *MGMT*, respectively.

In cohort 1d (unmethylated *MGMT*), 78% of patients discontinued treatment due to radiographic progression, and 12% of patients discontinued because of treatment-related toxicity.

The most commonly reported adverse events (AEs) of any cause were fatigue, headache, nausea, seizure, and constipation in cohorts 1c and 1d. Grade 3/4 decreases in lymphocyte counts occurred in 17% (methylated) and 12% (unmethylated) of patients in cohort 1c and 3% of patients in cohort 1d. The omission of temozolomide in cohort 1d, which was associated with a lower incidence of lymphopenia, was not associated with any significant additional immune-mediated AEs. Other commonly reported grade 3/4 AEs included increased ALT/transaminases and increased AST.

Immune-mediated AEs occurring in ≥ 15% of patients in any arm included increased ALT/transaminases, diarrhoea, rash, increased AST, and maculopapular rash. Increased

ALT/transaminases were reported in 25% (methylated) and 23% (unmethylated) of patients in cohort 1c and 16% of patients in cohort 1d. Diarrhoea was reported in 0% (methylated) and 16% (unmethylated) of patients in cohort 1c and 19% of patients in cohort 1d.

In cohorts 1c (methylated and unmethylated *MGMT*) and 1d, the most common neurological AEs were headache, which occurred in 42%, 49%, and 43% of patients, and seizure, which occurred in 25%, 19%, and 31% of patients, respectively.

The most common serious AEs included seizure, which occurred in 25% (methylated) and 9% (unmethylated) of patients in cohort 1c and 12% of patients in cohort 1d, and pneumonia, which was reported in 17% (methylated) and 5% (unmethylated) of patients in cohort 1c and 3% of patients in cohort 1d. NCT02017717. Lim *et al.* Abstract 3250

Practice point and future research opportunities

The first well-designed positive immunotherapy trial in neuro-oncology remains to be seen. The flurry of uncontrolled studies reporting very promising initial data have so far not been confirmed once rigorously tested. No unexpected toxicity of adding nivolumab to radiotherapy/temozolomide was observed. There is no signal yet for anti-PD-L1 therapy in recurrent glioblastoma but the trial in newly diagnosed patients is ongoing. PD-L1 immunohistochemistry may not be the optimal test to identify responsive patients.

However, it was demonstrated that the combination of nivolumab plus standard radiotherapy with or without temozolomide was well tolerated, with the incidence of high-grade neurological AEs being consistent with those previously reported in glioblastoma, according to the authors. In addition, the use of temozolomide in combination with nivolumab and radiotherapy was not associated with any significant additional AEs other than those that are associated with temozolomide alone.

PD-L1 may be prognostic of survival in patients with glioblastoma

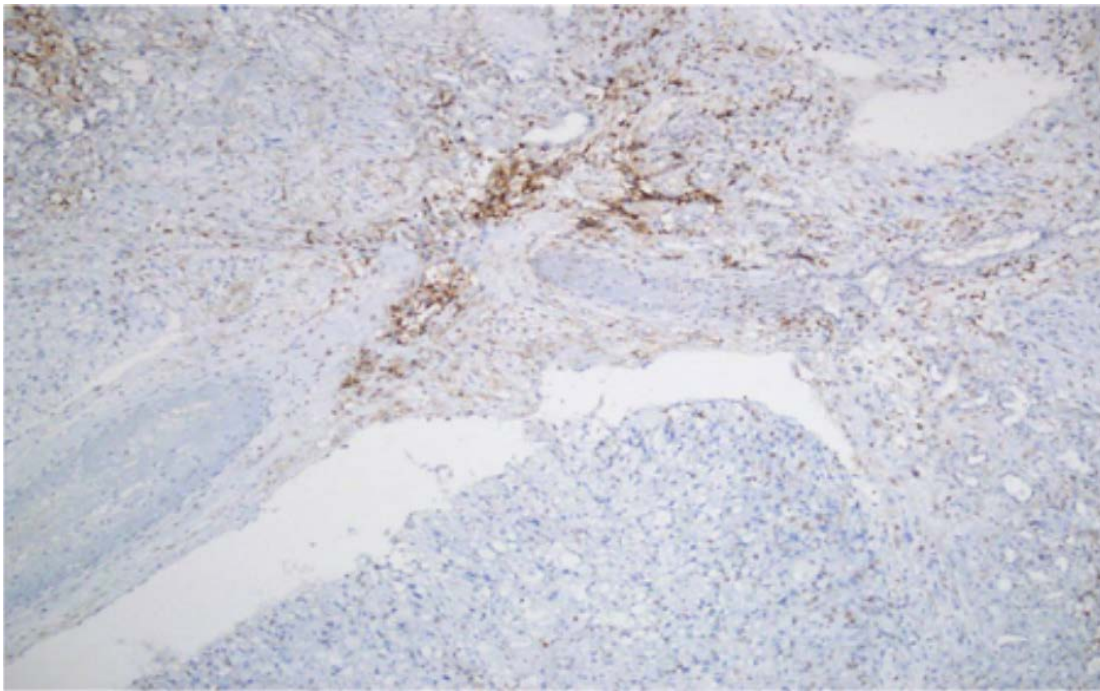
The intratumoural staining pattern of PD-L1 and the intensity of PD-1 staining in tumour infiltrating lymphocytes (TILs) emerged as potentially positive prognostic factors in patients with glioblastoma, according to Didem Şener Dede, Associate Professor in the Department of Medical Oncology, Ankara Yıldırım Beyazıt University Faculty of Medicine in Ankara, Turkey. Dede and colleagues quantitated the degree of PD-L1 and PD-1 expression, as well as CD4-positive and CD8-positive TILs, and isocitrate dehydrogenase (IDH-1) mutation to evaluate the value of expression levels as prognostic factors of response following surgery and chemoradiotherapy in patients with glioblastoma. The retrospective study included 90 patients who were newly diagnosed with glioblastoma and underwent surgery between February 2006 to February 2017 at institutions throughout Ankara.

PD-L1, PD-1 expression, CD4-positive and CD8-positive TILs, and IDH-1 mutation were assessed in the patients' tumour specimens; IDH-1 mutation analysis was done by real time PCR, and PD-L1 and PD-1 levels were assessed by immunohistochemistry using the Ventana® antibody (clon-SP263, ROCHE). TIL staining intensity in patient samples was graded as low, moderate, or dense for PD-1, PD-L1, CD4, and CD8, with the cut off value set $\geq 5\%$ staining as the threshold for PD-L1 or PD-1 positivity. The study included 90 patients with glioblastoma having a mean (standard deviation) age of 57 (± 12.3) years and 63.3% of

the patients were male. Chemoradiotherapy plus chemotherapy with temozolomide following surgery had been administered to approximately half (53.3%) of patients.

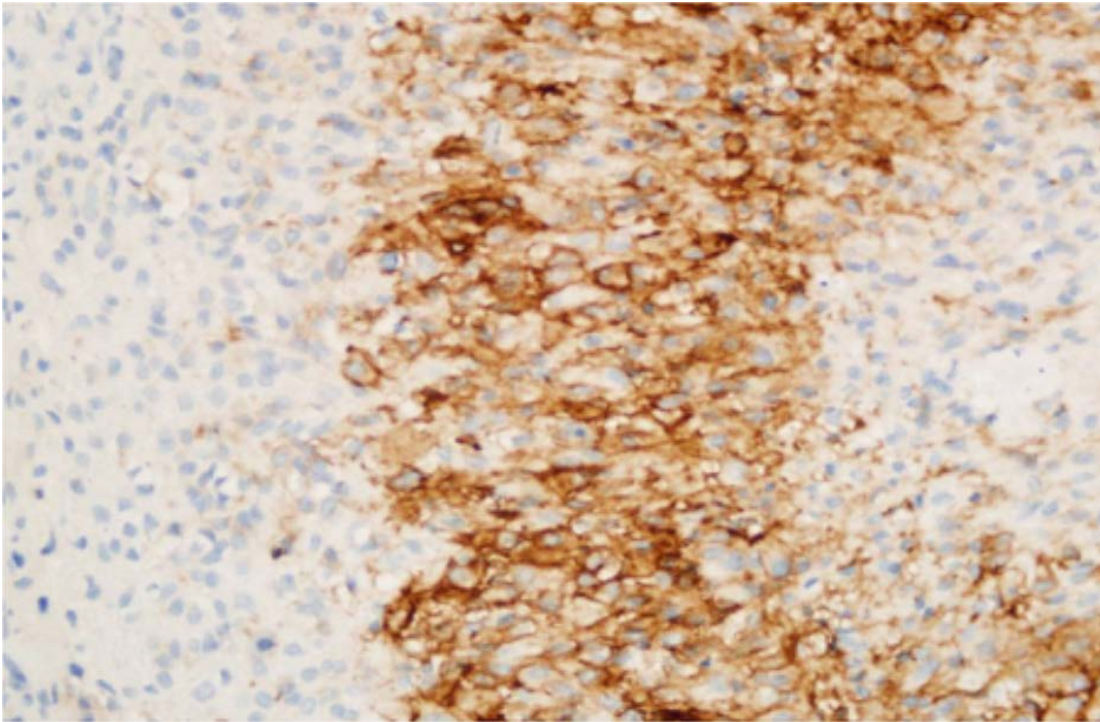
Different staining patterns of PD-L1 expression were described as diffuse fibrillary in 29 (32.2%) samples and as membranous staining in 15 (16.7%) samples. IDH-1 mutation was detected in 30 (33%) samples, and dense PD-1 staining was also seen. Intense staining of TILs in the perivascular field was observed, which the authors noted is rarely found in the intratumoral area.

The image below shows dense perivascular and moderate intratumoral staining of CD4 TILs.



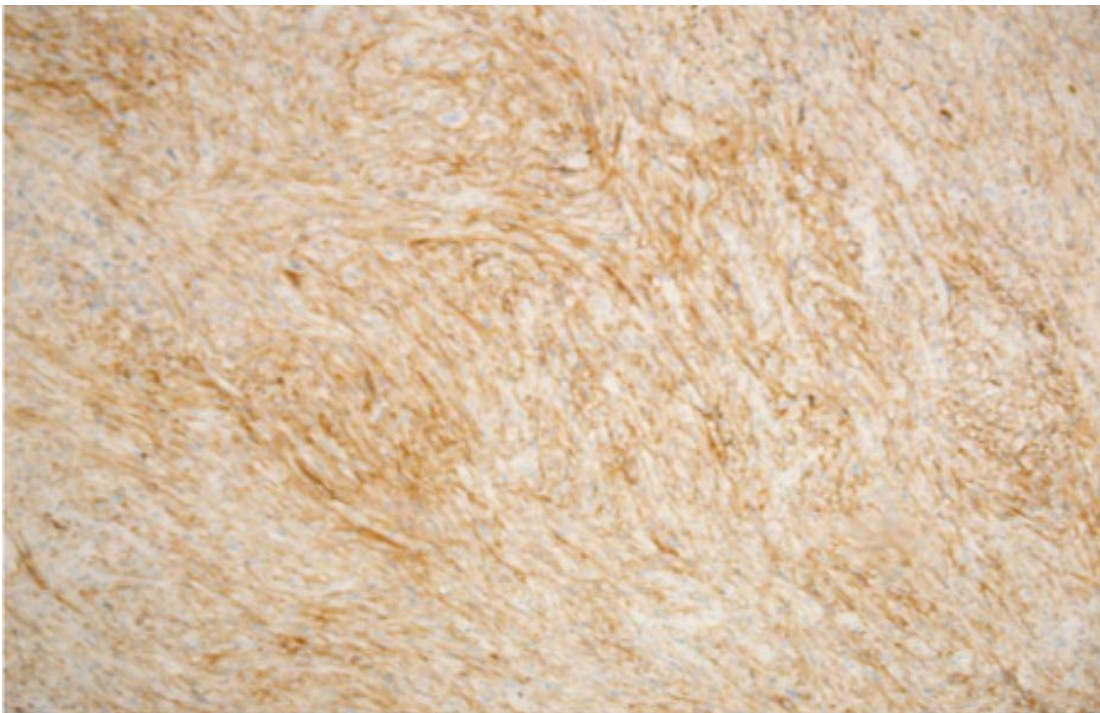
© Didem Şener Dede.

The image below shows membranous staining pattern of PD-L1.



© Didem Şener Dede.

The image below shows diffuse / fibrillary staining pattern of PD-L1.



© Didem Şener Dede.

By Kaplan Meier, Cox regression tests and SPSS 23, the density of TILs in the intratumoral/perivascular fields associated with PD-L1 positivity ($r = 0.46$; $p < 0.0001$). The intensity of TILs in perivascular areas was significantly lower in tumours that were negative for PD-L1 expression compared to PD-L1-positive tumours ($p < 0.001$). An association was not found between IDH-1, PD-L1 expression, and TILs, nor was a significant association determined between survival and sex (logrank $p = 0.78$), PD-L1 positivity (logrank $p = 0.13$), and IDH-1 mutation status (logrank $p = 0.64$). The presence of dense perivascular PD-1-positive TILs was found to be a positive prognostic factor as was dense membranous PD-L1 staining, whereas advanced age emerged as a negative independent prognostic factor by multivariate analysis. Dede *et al.* Abstract 326O

Practice point and future research opportunities

Glioblastoma is the malignancy most commonly diagnosed within the brain and carries a poor prognosis. Regarding PD-L1 expression status on different staining patterns, including cytoplasmic, membranous, and diffuse/fibrillary, it is known that PD-L1 can be expressed by both tumour and inflammatory cells within the tumour microenvironment, and the relative importance of either is currently unknown. There is no consensus to the relevance of geographic patterns of expression (e.g. proximity of PD-L1 to immune infiltrating lymphocytes, membranous versus cytoplasmic). PD-L1 positivity has been found to indicate favourable, unfavourable, or no relationship with prognosis, and variable correlations with histology and mutation status.

DEVELOPMENTAL THERAPEUTICS

Novel mogamulizumab combined with nivolumab shows promise in patients with advanced or metastatic solid tumours

Noboru Yamamoto, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan presented preliminary findings from a phase I study of mogamulizumab in combination with nivolumab in patients with advanced or metastatic solid tumours. Mogamulizumab is a humanized IgG1 monoclonal antibody targeting CCR4, which is expressed on regulatory T cells (Tregs), which is a known inhibitor of the immune responses against tumours and a putative therapeutic target. Mogamulizumab has demonstrated the ability to deplete effector Tregs and has already been approved in Japan for CCR4+ T cell lymphomas. Nivolumab, an anti-PD-1 immune checkpoint inhibitor, has demonstrated robust activity in a variety of cancer types. The combination of these agents may block multiple mechanisms involved in suppressing antitumour immunity. This study's primary endpoint was safety, with secondary endpoints of antitumour effect according to RECIST v1.1, and pharmacokinetics (PK), with the evaluation of biomarkers as an exploratory endpoint. The trial comprised a dose escalation part with 6 patients and an expansion part with 90 patients. All patients had advanced or metastatic solid tumours and were treated with a combination of nivolumab at 3 mg/kg every 2 weeks plus mogamulizumab at 0.3 to 1 mg/kg once weekly for 4 weeks and subsequently every 2 weeks until disease progression or toxicity.

No dose limiting toxicities were observed in the dose escalation phase. Drug-related adverse events (AEs) of grades 3-4 occurred in 26.0% of patients participating in both phases. No grade 5 drug-related AEs were observed. The most frequently reported drug-related AEs included rash in 38.5% of patients, maculopapular rash in 22.9%, stomatitis in 13.5%, and diarrhoea in 13.5% of patients.

Confirmed objective responses were observed in 4 (26.7%) patients with hepatocellular carcinoma; in addition, one confirmed response and 5 stable disease, including 2 unconfirmed partial responses, were reported in a subgroup of 15 patients with pancreatic adenocarcinoma. NCT02476123. Yamamoto *et al.* Abstract LBA17

Practice point and future research opportunities

The combination of mogamulizumab and nivolumab showed acceptable safety profile and encouraging antitumour activity in several advanced or metastatic solid tumours, and represents a potential new strategy in cancer immunotherapy. Further study of this combination is warranted and confirmation of these results in larger studies is needed.

Patients with melanoma who progressed during anti-PD-1/PD-L1 therapy demonstrate response to BMS-986016 plus nivolumab

Lead author Paolo Ascierto, a researcher at the Istituto Nazionale Tumori Fondazione Pascale of Naples, Italy discussed updated efficacy and safety findings from a trial of BMS-986016 administered in combination with nivolumab in patients with melanoma. BMS-986016 is an anti-lymphocyte-activation gene 3 (LAG-3), which is an immune checkpoint receptor protein found on the cell surface of effector T cells and regulatory T cells (Tregs) that functions

to control T cell response, activation and growth. Inhibiting LAG-3 may allow T cells to regain their cytotoxic function and potentially limit tumor growth, leading Dr. Ascierto and colleague to test simultaneous blockade of LAG-3 and PD-1 in this phase I/IIa study. Previously reported results showed promising antitumour activity in a cohort of melanoma patients¹.

At ESMO 2017, updated efficacy and safety findings in an expanded melanoma cohort of patients receiving prior immunotherapy that included both all-comer and biomarker-enriched populations were presented. BMS-986016 at 80 mg plus nivolumab at 240 mg was administered every 2 weeks. Primary objectives included safety and objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) per RECIST v1.1. The biomarker/efficacy association was evaluated.

As of June 15, 2017, 68 patients had been treated. Of these, 57% of patients had received prior anti-CTLA-4 and 46% of patients received ≥ 3 lines of therapy previously. Efficacy was evaluated in 61 patients, which revealed an ORR of 11.5%, including one complete response (CR), 6 partial responses (PR), and one unconfirmed response. The DCR was 49% and median DOR was not reached (0.1+, 39.3+ months).

Immunohistochemistry (IHC) was used to determine the percentage of LAG-3 positive cells among all nucleated cells within the tumour and invasive margin using mouse antibody clone 17B4. Expression $\geq 1\%$ was identified in 33 (62%) of 53 evaluable samples. In patients demonstrating LAG-3 expression $\geq 1\%$, the ORR was higher regardless of PD-L1 expression. Tumour cell PD-L1 expression was determined using the Dako PD-L1 IHC 28-8 kit. Expression $\geq 1\%$ was identified in 20 (45%) of 44 evaluable samples. In 33 patients with LAG-3 levels $\geq 1\%$ the ORR was 18% and in the subgroup of these patients that also showed PD-L1 expression $<1\%$ the ORR was 27%.

Treatment-related adverse events (AEs) occurred in 51% of patients and grade 3/4 AEs occurred in 10% of the 262 patients in all extension cohorts. In the 68 patients in the prior immunotherapy cohort, 41% of patients experienced an AE and 4.4% had a grade 3/4 AE. In the overall and prior immunotherapy cohorts, 3.8% and 1.5% of patients discontinued treatment due to an AE. NCT01968109. Ascierto *et al.* Abstract LBA18

Citation: 1. Ascierto *et al.* *J Clin Oncol.* 2017;35(suppl) [abstr 9520].

Practice point and future research opportunities

This is the largest report of outcomes in patients receiving BMS-986016 plus the nivolumab. The combination provided encouraging efficacy in heavily pre-treated patients with melanoma who had progressed on anti-PD-1/PD-L1 immunotherapy. Greater response was associated with LAG-3 expression that was irrespective of PD-L1 expression. The combination was well tolerated and demonstrated a safety profile similar to nivolumab monotherapy.

RXDX-105, a VEGFR-sparing potent RET inhibitor, shows promising activity in RET inhibitor-naïve patients with RET fusion-positive NSCLC

Alexander Drilon, Thoracic Oncology, Memorial Sloan Kettering Cancer Center in Boston, USA and a team of investigators conducted a phase I/Ib dose escalation study followed by dose expansion in patients with advanced solid tumours. During the dose escalation phase, RXDX-105 was given orally at doses ranging from 20 - 350 mg once daily. Tumour response was assessed every 8 weeks by RECIST v1.1 and adverse events (AEs) were recorded per NCI CTCAE v4.03.

RXDX-105 is a potent RET inhibitor (RETi) that leaves VEGFR signalling intact and has activity against wild-type RET, RET fusions, and RET mutations at IC50s of 0.3 nM, 0.3-0.8 nM, and 5-15 nM, respectively. RXDX-105 has demonstrated potent antitumour activity in patient derived xenograft (PDX) tumour models harbouring RET fusions, which occur predominantly in non-small cell lung cancer (NSCLC), particularly in 1 to 2% of adenocarcinomas. More than half of these involve the KIF5B gene as the fusion partner, and pooled efficacy experience with other RET-active agents suggests a lower response rate in these patients.

The study enrolled 55 patients into phase I and 89 patients into phase Ib. Of these, 73 patients were female, 71 were male and the median age was 63 years. The recommended phase II dose (RP2D) was determined to be 275 mg, daily during phase I which was taken forward to phase Ib, wherein 91 patients received RXDX-105; of these, 21 patients had NSCLC and harboured RET fusions that were confirmed by next generation sequencing, were also RET-inhibitor naïve, and evaluable for efficacy. Thirteen patients in this cohort also harboured the KIF5B-RET fusion and the other 8 patients had a variety of non-KIF5B-RET fusions.

Six of the 8 patients with non-KIF5B-RET fusions achieved a confirmed partial response (PR) yielding an objective response rate (ORR) of 75%. Median duration of response (DOR) has not yet been reached. None of the 13 patients with KIF5B-RET fusions had a RECIST response, although 4 achieved stable disease (SD) that lasted 6 or more months. Overall, time on treatment ranged from 0.5+ to 14.5+ months and 28 patients remained on treatment at data cut-off.

The most commonly reported treatment-related adverse events (AEs) were mostly grades 1 or 2 and were reversible with dose modifications. Grade 3 treatment-related AEs reported by more than 5% of patients included rash in 10% of patients, hypophosphatemia in 8%, elevated ALT in 7%, and anaemia, which was reported in 7% of patients. As previously reported, one patient experienced grade 3 rash complicated by fatal alveolar haemorrhage. No other treatment-related grade ≥ 4 AEs were observed. NCT01877811. Drilon *et al.* Abstract BA19

Practice point and future research opportunities

RXDX-105 has demonstrated antitumour activity across multiple fusion partners in patients with RET-positive NSCLC and has demonstrated a manageable safety profile. However, responses were limited to patients whose tumours did not harbour a KIF5B-RET fusion, which is consistent with previous evidence from other agents, suggesting that the KIF5B-RET fusion may be less susceptible to RET inhibition.

GASTROINTESTINAL TUMOURS, COLORECTAL

Location of the primary tumour, but not KRAS mutations, may indicate SIRT survival benefit in mCRC

Harpreet Wasan, head of the gastrointestinal clinical research programme at Hammersmith Hospital, Imperial College London, UK and colleagues in Australia conducted an analysis of 3 similarly designed, prospective randomised studies (FOXFIRE, SIRFLOX, and FOXFIRE-Global) that all evaluated first-line treatment with selective internal radiotherapy (SIRT), using yttrium-90 resin microspheres, plus chemotherapy with FOLFOX (+/- bevacizumab) in 1,103 chemotherapy-naïve patients with metastatic colorectal cancer (mCRC) and non-resectable liver metastases. The patients were randomised to receive standard oxaliplatin-based chemotherapy with or without a biologically targeted agent (control arm, n=549) or to the same chemotherapy regimen plus SIRT (test arm, n=554). Patients with ascites, cirrhosis or portal hypertension were excluded. The primary endpoint of all studies was overall survival (OS); this updated analysis assessed the influence of KRAS mutation and origin of tumour by colon location on OS.

Although adding SIRT to FOLFOX +/- bevacizumab did not improve OS or progression-free survival (PFS) overall in these patients, as expected, an unanticipated potential benefit was observed with SIRT in patients having primary tumours originating on the right side of the colon. At a median follow-up of 43.3 months, OS for the whole trial population was identical for control and SIRT patients, hazard ratio [HR] 1.04; 95% confidence interval [CI] 0.90, 1.19 (p = 0.609). No difference in PFS between the treatment arms was noted, HR 0.90; 95% CI, 0.79 – 1.02 (p = 0.108). However, the objective response rate (ORR) was higher with SIRT than control (72.2% and 63.0%, respectively, p = 0.001).

Analysis of the KRAS status of the patients showed that 182 (16.5%) patients had a KRAS mutation, 279 (25.3%) had KRAS wild-type status, and 642 (58.2%) patients currently had an unknown status. The OS did not differ between treatment arms in patients harbouring a KRAS mutation, HR 1.03; 95% CI 0.74, 1.43 (p = 0.878) or in patients with wild-type KRAS, HR 1.10; 95% CI 0.83, 1.46 (p = 0.499). Patients with currently unknown KRAS status also showed no difference in OS between treatment arms, HR 1.01; 95% CI 0.85–1.21 (p = 0.878).

However, both treatment arms demonstrated lower OS in patients with mutated KRAS than patients with wild-type, unknown, or untested KRAS status. Patients with mutated KRAS demonstrated median OS in the control versus SIRT arms of 19.1 months versus 18.7 months, whereas OS in patients with wild-type KRAS was 28.3 months versus 24.2 months, and OS in patients with unknown or currently untested KRAS status was 23.1 versus 22.6 months, respectively.

Subgroup analysis revealed that patients having a primary tumour located on the right side of the colon had significantly prolonged OS with SIRT of 22.0 months versus 17.1 months with control (p = 0.007), whereas no significant difference in OS between treatment arms was observed in patients with primary tumours located on the left side; OS was 24.6 versus 26.6 months in the respective arms (p = 0.279). These findings are consistent with emerging reports from other studies that right-sided tumours in mCRC have a worse prognosis and appear to benefit less from current cytotoxic and biological therapies¹.

SIRT was approved by the US Food and Drug Administration (FDA) in 2002 and has been authorised in several countries for patients with mCRC who are refractory to chemotherapy. The premise behind SIRT therapy, which involves injection of yttrium-90 labelled resin microspheres into the blood supply of liver tumours to deliver large but safe doses of radiation, is that it would provide control of liver metastases and lead to improved OS in patients with mCRC. ISRCTN83867919, NCT00724503, and NCT01721954. Wasan *et al.* Abstract LBA26

Note: The results from main study, excluding the KRAS analysis, were published online on 3 August in the *Lancet Oncology*. Wasan HS, *et al.* First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017; Aug 3. pii: S1470-2045(17)30457-6. doi: 10.1016/S1470-2045(17)30457-6. [Epub ahead of print].

Citation: 1. Schmoll HJ. *Lancet Oncol* 2017; Aug 3. pii: S1470-2045(17)30589-2. doi: 10.1016/S1470-2045(17)30589-2. [Epub ahead of print].

Practice point and future research opportunities

In the SIRFLOX and FOXFIRE Global study cohorts, the addition of SIRT to first-line chemotherapy was retrospectively associated with a statistically and clinically significant gain in OS for patients with right-sided primary tumours, but not for left-sided primaries. This effect is not seen for KRAS mutation status. These data suggest that the primary tumour site but not KRAS status may predict for potential treatment interaction with SIRT.

This analysis adds to the increasing literature for primary tumour location-based differences in mCRC outcomes with treatments, and may support a site-based approach to patient selection for SIRT. However, SIRT in the first-line setting cannot be recommended today.

GASTROINTESTINAL TUMOURS, NON-COLORECTAL

Updated results favour docetaxel, oxaliplatin, and fluorouracil/leucovorin in resectable oesophagogastric cancer

Salah-Eddin Al-Batran director of the Institute of Clinical Cancer Research, UCT-University Cancer Centre, Krankenhaus Nordwest in Frankfurt, Germany presented findings on behalf of the German Gastric Group from the phase III FLOT4 study. In FLOT4, 716 patients with resectable gastric or gastro-oesophageal junction adenocarcinoma of stage cT2 or higher and/or cN+ were randomly assigned to receive either 3 pre-operative and 3 post-operative 3-week cycles of epirubicin 50 mg/m² i.v., cisplatin 60 mg/m² i.v. both on day 1, and 5-FU 200 mg/m² as continuous i.v. infusion and/or capecitabine 1250 mg/m² orally on days 1 to 21 (ECF/ECX), or 4 pre-operative and 4 post-operative 2-week cycles of FLOT. The primary outcome of the study was overall survival (OS).

Patient receiving FLOT achieved greater OS compared to ECF/ECX; OS was 50 months with FLOT versus 35 months with ECF/ECX, hazard ratio [HR] 0.77 ($p = 0.012$), as well as longer progression-free survival (PFS) of 30 months versus 18 months, respectively, HR 0.75 ($p = 0.001$). A lower rate of progressive disease (PD) was observed during/after preoperative therapy with FLOT versus ECF/ECX of 1% versus 5% ($p < 0.001$). FLOT also associated with more R0-resections at 84% versus 77% ($p = 0.011$), and with a greater number of pT0/pT1 tumours at 25% versus 15% compared to ECF/ECX ($p = 0.001$). On multivariate analyses, parameters associating with favourable OS included FLOT therapy, HR 0.75 ($p = 0.006$), stomach as the primary, HR 0.74 ($p = 0.005$), and nodal negativity, HR 0.72 ($p = 0.022$). ECOG performance status of 0 showed a trend towards improved OS, HR 0.82 ($p = 0.078$); however, age and Lauren's type of histology had no impact on survival.

The patient benefit with FLOT was consistent across all subgroups and was observed in elderly (≥ 70 years) patients, and patients with tumours having a signet cell component. The FLOT advantage was numerically pronounced in Siewert type 1 oesophageal tumours (HR 0.60), Barrett tumours (HR 0.62), small tumours T1/2 (HR 0.66), and node negative tumours (HR 0.64). A post-hoc analyses of relapse-free survival that excluded patients without R0-resection still favoured FLOT, HR 0.8 ($p = 0.049$).

The most frequent sites of relapse were peritoneal in 31% of patients, followed by lymphatic in 26%, and liver in 19% of patients; 87% of all relapses were either systemic or both systemic and locoregional. NCT01216644. AL Batran *et al.* Abstract LBA27_PR

Practice point and future research opportunities

The triplet regimen used in the FLOT4 trial was developed to improve the results of ECF. It decreased toxicity by replacing epirubicin with low-dose docetaxel, and using oxaliplatin instead of cisplatin. FLOT is also more convenient to use, with one 24-hour infusion every two weeks rather than continuous infusion of fluorouracil in the ECF protocol. FLOT will be the best backbone of chemotherapy that can be used in this setting. A step forward would be to try to improve the results by adding targeted therapies or immune checkpoint inhibitors. It would also be interesting to know if the FLOT regimen shows different levels of effectiveness in the four molecular biological subgroups of gastric cancer.

This new analysis shows that the advantage of the FLOT regimen was seen across all subgroups, including those with a very poor prognosis, such as the elderly and patients with signet cell tumours. These results show that FLOT is clearly the new standard of care.

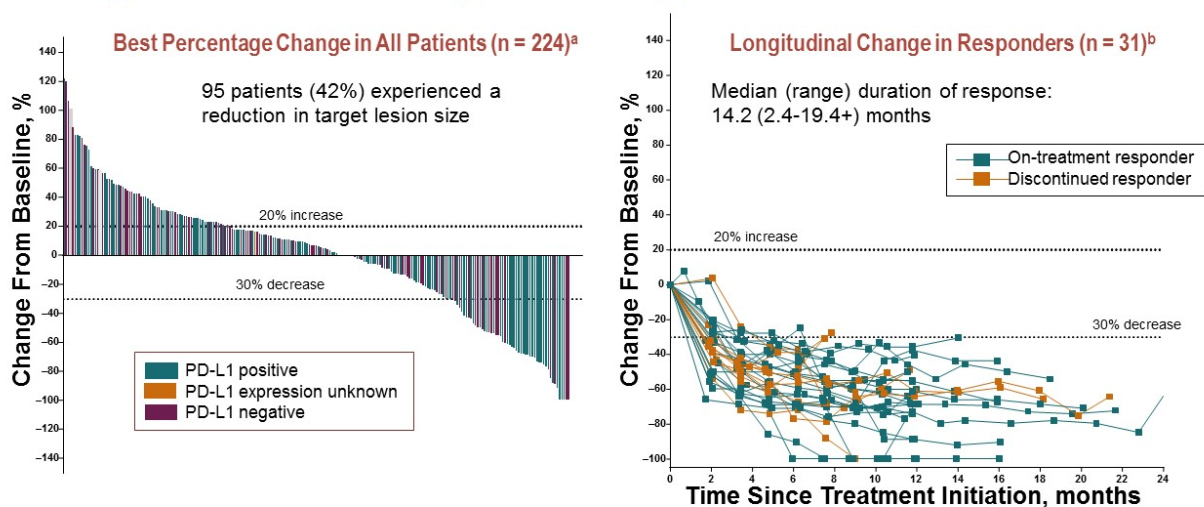
Pembrolizumab demonstrates anti-tumour activity in advanced gastric cancer as monotherapy and combined with chemotherapy

Zev A. Wainberg, Medicine Hematology and Oncology, David Geffen School of Medicine at UCLA in Los Angeles, USA reported updated findings from KEYNOTE-059 indicating that patients with recurrent or metastatic advanced gastric or gastro-oesophageal junction (GEJ) cancer continued to show benefit from pembrolizumab. Previously reported results from the global, phase II study showed manageable safety and promising antitumour activity both for single agent pembrolizumab and for pembrolizumab plus chemotherapy in patients with gastric or GEJ cancer.

In KEYNOTE-059, patients were enrolled into 3 cohorts; 259 and 25 patients regardless of tumour PD-L1 expression were enrolled into cohorts 1 and 2, respectively, and cohort 3 comprised 31 patients with confirmed PD-L1-positive tumours and a combined positive score of $\geq 1\%$ per the PD-L1 immunohistochemistry 22C3 pharmDx assay. All cohorts received pembrolizumab at 200 mg every 3 weeks for up to 2 years. Pembrolizumab was delivered following ≥ 2 prior lines of therapy in cohort 1, in combination with cisplatin plus 5-fluorouracil or capecitabine (in Japan only) as first-line in cohort 2, and as first-line monotherapy in cohort 3. Primary endpoints included safety in all 3 cohorts and objective response rate (ORR) per RECIST v1.1 by central review in cohorts 1 and 3. The key secondary endpoints were ORR in cohort 2 and duration of response (DoR) by RECIST v1.1, progression-free survival (PFS), and overall survival (OS). The median follow-up in cohorts 1, 2, and 3 was 6 (range 2 to 25), 14 (range 2 to 24), and 18 (range 2 to 21) months, respectively.

The confirmed ORR with pembrolizumab in cohort 1 was 12% (95% confidence interval 8, 17%); among PD-L1 positive patients the ORR rose to 16% (95% CI 11, 23), and the ORR was 6% (95% CI 3,13) in patients with PD-L1-negative tumours. The median PFS was 2.0 months (95% CI 2, 2) and median OS was 6 (95% CI 4, 7) months.

Cohort 1: Best Percentage Change and Longitudinal Change in Target Lesion Size



^aOnly patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥ 1 postbaseline assessment were included (n = 223); assessment was nonevaluable in 1 patient.

^bLongitudinal change in the sum of the longest target lesion diameters from baseline in responders (n = 31).

+No progressive disease at last disease assessment.

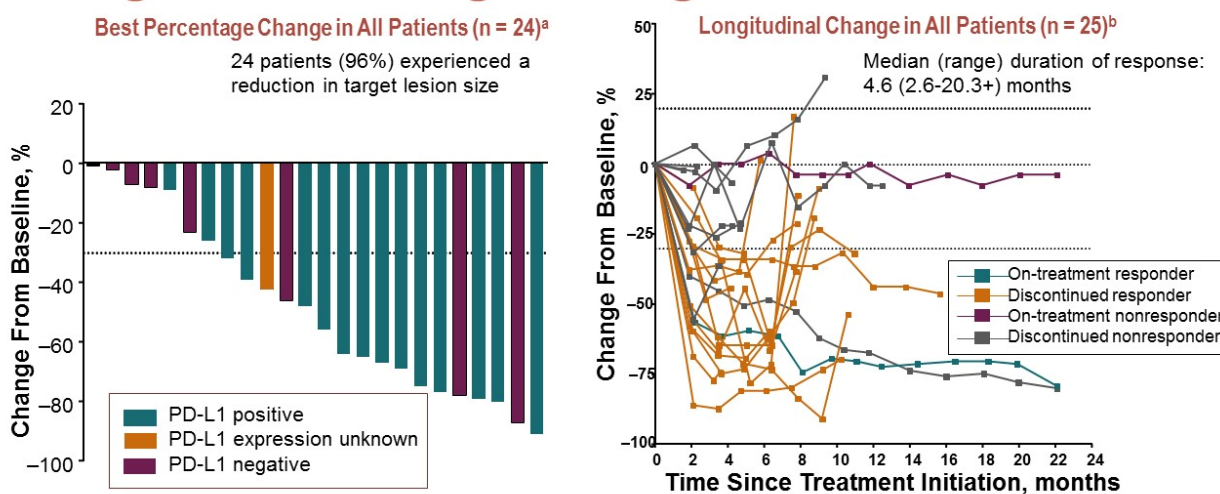
Data cutoff: April 21, 2017.

MADRID 2017 ESMO congress

© Zev Wainberg.

Cohort 2, patients receiving pembrolizumab plus chemotherapy had a confirmed ORR of 60% (95% CI 39, 79), which increased to ORR 73% (95% CI 45, 92) in patients with PD-L1-positive tumours and decreased to ORR 38% (95% CI 9, 76) in patients with PD-L1-negative tumours. Median PFS was 7 (95% CI 6, 11) months and median OS was 14 (95% CI 9, not estimable) months.

Cohort 2: Best Percentage Change and Longitudinal Change in Target Lesion Size



^aOnly patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥ 1 postbaseline assessment were included (n = 25); assessment was nonevaluable for 1 patient.

^bLongitudinal change in the sum of the longest target lesion diameters from baseline in patients with ≥ 1 postbaseline assessment (n = 25).

+No progressive disease at last disease assessment.

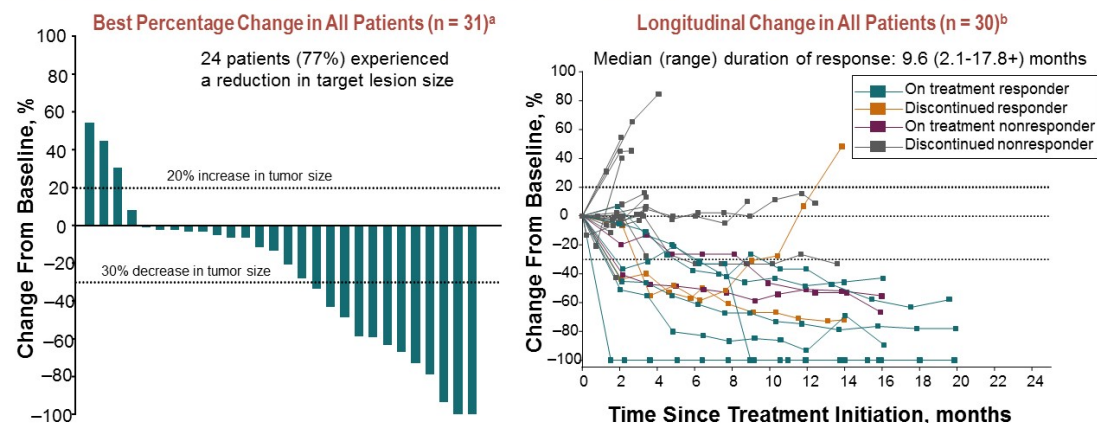
Data cutoff: April 21, 2017.

MADRID 2017 ESMO congress

© Zev Wainberg.

The patients in cohort 3 with confirmed PD-L1 expressing tumours that received pembrolizumab as a first-line monotherapy had a confirmed ORR of 26% (95% CI 12, 45). Median PFS was 3 (95% CI 2, 6) months and median OS was not reached (95% CI 9, 21) months.

Cohort 3: Best Percentage Change and Longitudinal Change in Target Lesion Size



^aOnly patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥ 1 postbaseline assessment were included (n = 31) and assessments were nonevaluable/not available in 3 patients.

^bLongitudinal change in the sum of the longest target lesion diameters from baseline in patients with CR or PR (n = 30).

+No progressive disease at last disease assessment.

Data cutoff: April 21, 2017.

MADRID 2017 **ESMO** congress

© Zev Wainberg.

The incidence of grades 3 to 5 treatment-related adverse events (TRAEs) in cohorts 1, 2 and 3, was 18%, 76%, and 23%, respectively. TRAEs led to discontinuation by 3% of cohort 1 patients and 12% of cohort 2 patients. TRAEs led to death in two cohort 1 patients and one patient in cohort 3.

On September 22, 2017, the US Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients who received at least 2 prior lines of therapy for recurrent or advanced gastric or GEJ adenocarcinoma and with tumours expressing PD-L1 as determined by an FDA-approved test. (NCT02335411). Wainberg *et al.* Abstract LBA28_PR

Practice point and future research opportunities

Although anti-PD antibodies will have a role in the management of advanced gastric adenocarcinoma, the role of PD-L1 expression has to be clarified, predictive biomarkers have to be developed, the role of anti-PD agents in early lines and in combination with chemotherapy has to be clarified and established; the optimal combination and sequence have to be established as well.

These updated results demonstrated manageable safety and showed promising antitumour activity for pembrolizumab administered either alone or with chemotherapy in patients with advanced gastric/GEJ cancer and were the basis for FDA approval of pembrolizumab in September 2017 for these patients.

Biomarker analysis reveals lenvatinib and sorafenib upregulate different genes in unresected HCC

Richard S. Finn, Division of Haematology/Oncology, Geffen School of Medicine, UCLA Medical Center, Santa Monica, CA, USA and an international team of investigators conducted an analysis of serum and tissue biomarkers in patients participating in a trial comparing lenvatinib to sorafenib as first-line treatment for unresectable hepatocellular carcinoma (HCC). Lenvatinib is an oral multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFR α , RET, and KIT, whereas sorafenib is a VEGFR inhibitor with activity against RAF kinase.

In the open label phase III trial, 954 patients who were previously untreated in the first-line for unresectable HCC, were randomised 1:1 to frontline treatment with lenvatinib at either 8 mg or 12 mg once per day based on body weight (n = 478) or sorafenib at 400 mg twice daily (n = 476). The trial's primary endpoint was overall survival (OS). Archival tumour tissue was collected at baseline and blood samples were obtained prior to treatment and at specified time points during treatment. Using clinical data and patient samples from this trial, the investigators performed biomarker analyses on serum samples to identify potential markers of benefit to each agent.

First-line lenvatinib was found to be non-inferior for OS compared with sorafenib; the median OS with lenvatinib was 13.6 months compared with 12.3 months for sorafenib, the current standard of care (hazard ratio [HR], 0.92; 95% confidence interval [CI] 0.79, 1.06).

The biomarker subgroup analysis set included 119 patients with both archival tissue and serum samples. The investigators assessed these serum samples at baseline and over time using the ELISA protocol or chemiluminescence for VEGF, ANG2, FGF21, FGF23, and PIVKA-II. Of 119 patients in the biomarker set, 58 tissue samples passed quality assurance. Serum assays were done on samples from 66 patients in the lenvatinib arm and 48 patients in the sorafenib arm. A trend was observed between lower VEGF, ANG2, and FGF21 serum levels at baseline and better outcomes with both agents. Both lenvatinib and sorafenib treatments resulted in an increase in serum VEGF over time that was greater for lenvatinib. Only lenvatinib modulated ANG2, FGF19, and FGF23 levels. Data with FGF19 and FGF23 were not consistent.

Gene-expression analysis was performed in 34 patients receiving lenvatinib and 24 patients on sorafenib. Supervised clustering was performed using angiogenic and growth-factor pathway gene expression based on 36 genes that identified 3 groups of expression. Median OS was longer with lenvatinib in patients having higher VEGF- and FGF-family gene-expression levels but, conversely, OS was longer with sorafenib in patients having lower VEGF- and FGF-family gene-expression levels. Additionally, the change in biomarker levels after lenvatinib and sorafenib treatments differed according to the agent used. NCT01761266. Finn *et al.* Abstract LBA30.

Practice point and future research opportunities

Biomarker analyses in HCC is challenging due to molecular heterogeneity, clonal evolution driving drug resistance, and being often conducted in uncontrolled studies. This study was a preplanned, exploratory, optional biomarker analysis to identify blood and tumour biomarkers correlating with clinical outcomes. Investigators are to be credited for their efforts to identify

clinically useful biomarkers. Due to the small number of patients and the differences in the baseline, the results can be considered only hypotheses generating. The efficacy observed in the biomarker defined subgroups may support lenvatinib as a new first-line treatment option (non-inferior compared to sorafenib). These results are hypotheses generating and require confirmation.

GENITOURINARY TUMOURS, PROSTATE

Addition of abiraterone acetate or docetaxel plus prednisone to standard of care improves response in patients with high-risk prostate cancer

Matthew R. Sydes, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, UCL, London, UK, presented data from a subset of the STAMPEDE head-to-head comparison of two combination therapies in patients with high-risk prostate cancer at the onset of long-term androgen deprivation therapy (ADT).

STAMPEDE was a multi-arm multi-stage platform randomised controlled protocol recruiting patients at initiation of standard of care (SOC) therapy consisting of ADT for 2 or more years for high-risk locally-advanced or metastatic prostate cancer. Recruitment of patients for the comparison of docetaxel/prednisone plus SOC versus SOC overlapped for 16 months with the recruitment of patients for abiraterone acetate and prednisone plus SOC versus SOC. Data were presented on these contemporaneously randomised patients. Patients were stratified and randomised to SOC plus docetaxel at 75 mg/m² every 3 weeks for 6 courses and prednisone at 5 mg twice daily (n=189), or to SOC plus abiraterone acetate at 1000 mg plus prednisone at 5 mg daily until disease progression (or for a maximum of 2 years in 377 non-metastatic patients planned to receive radiotherapy as part of SOC). Sixty percent of patients were classified M1 at entry, and 76% had Gleason scores of 8 to 10; the patients' median age was 66 years and median PSA was 56 ng/ml. The analyses used Cox proportional hazards and flexible parametric models, adjusted for stratification factors. The primary outcome was death from any cause.

At a median follow-up of 4 years, 149 deaths had occurred; of these 45 were in the docetaxel plus SOC/prednisone arm and 111 had occurred in the abiraterone acetate plus SOC/prednisone arm; the survival comparison was hazard ratio (HR) 1.16 (95% confidence interval [CI] 0.82, 1.65). Comparison of the two treatment arms for failure-free survival was HR 0.51 (95% CI 0.39, 0.67), progression-free survival, HR 0.65 (95% CI 0.48, 0.88), metastatic progression-free survival, HR 0.77 (95% CI 0.57, 1.03), and the comparison for symptomatic skeletal events was HR 0.83 (95% CI 0.55, 1.25), with all comparisons indicating similar benefit.

The incidence of grades 3, 4, and 5 toxicity, respectively, was 36%, 13%, and 1% with docetaxel plus SOC/prednisone versus 40%, 7%, and 1% with abiraterone plus SOC/prednisone.

Both treatments demonstrated practice-changing benefits over the previous SOC of first line ADT. Further treatments were administered on relapse, with a choice of different treatments at progression. Many patients were exposed to the treatment opposite that received in the trial. (NCT00268476). Sydes *et al.* Abstract LBA31_PR

Practice point and future research opportunities

Adding abiraterone acetate plus prednisolone to ADT is a clinically effective treatment option offering an alternative to docetaxel for men who are starting treatment for the first time. Future research will need to address which of these two agents or whether their combination is most effective, and for whom. The STAMPEDE trial offers a direct, randomised, comparative

analysis of two new standards for patients with hormone naive prostate cancer. This comparison was possible only because of the novel platform design of this protocol. Failure-free and progression-free survival clearly favoured abiraterone plus SOC/prednisone, and metastasis-free survival, with less certainty.

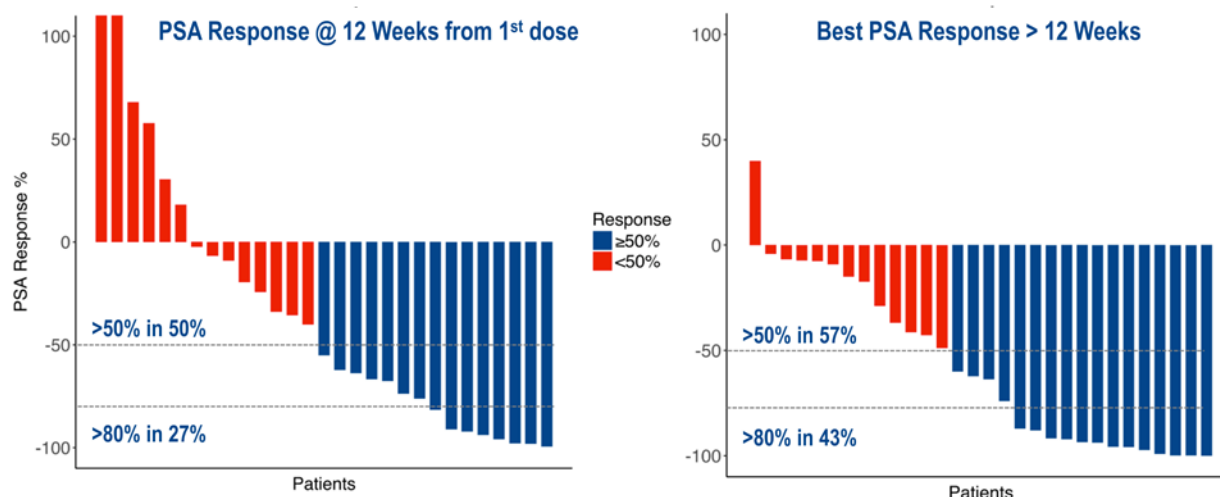
However, the design means that abiraterone was given at progression whereas docetaxel was given as a short course at start of therapy, meaning docetaxel patients had more salvage options at relapse, including docetaxel rechallenge. This explains the discrepancy between failure and progression-free survival favouring abiraterone but with no ultimate difference seen on overall or cause-specific survival. The proportion of patients having at least one “severe” toxicity was similar between the arms but the type of toxicities was quite different. These data will help clinicians and patients to choose appropriately where both drugs are available options.

¹⁷⁷Lu-PSMA617 demonstrates significant clinical activity in mCRPC

Associate Professor Michael Hofman of the University of Melbourne, Peter MacCallum Cancer Centre, Australia headed a team of researchers in this study of ¹⁷⁷Lu-PSMA617, a radiotherapeutic under evaluation in metastatic castration resistant prostate cancer (mCRPC) comprising a Lutetium-177 radiolabelled small molecule that binds with high affinity to prostate specific membrane antigen (PSMA) enabling beta particle therapy that specifically targets mCRPC. In this phase II prospective trial, ¹⁷⁷Lu-PSMA617 was administered every 6 weeks for up to 4 cycles to 30 enrolled patients with PSMA-avid mCRPC who progressed after standard therapies. ¹⁷⁷Lu-PSMA617 was manufactured in the hospital radiopharmacy and patients received a mean dose of 7.5 GBq. The trial’s primary endpoints were the decrease in prostate specific antigen (PSA) according to Prostate Cancer Working Group 2 (PCWG2) criteria and toxicity by common terminology criteria for adverse events (CTCAE) v4. Other endpoints were quality of life (QoL) as measured on the EORTC QLQ-C30, the Bone Pain Inventory (BPI) questionnaires relating to bone pain, dosimetry, progression-free survival (PFS), and overall survival (OS).

The patients were enrolled between October 2015 and December 2016 and had a median age of 69 years. Overall, 87% of patients had received prior chemotherapy, 47% had progressed after second-line cabazitaxel, and 83% of patients had received prior abiraterone and/or enzalutamide. Only patients with high uptake on PSMA PET were eligible for treatment.

The primary endpoint (shown on graph below) of a PSA decrease greater than 50% was achieved in 17 (57%) of 30 patients. Remarkably, 12 (40%) patients showed a deep response with PSA decrease of >80%.



© Michael Hofman.

The PFS and OS data have not yet matured and will be presented at the time of the final data analysis.

The most commonly reported adverse events (AEs) included grade 1 xerostomia in 19 (63%) of patients and nausea in 15 (50%) patients. Grade 3 or higher haemotoxicity that was attributable to LuPSMA occurred in 5 (17%) patients.

QoL, as measured by the global health scale, showed scores improved significantly directly after the first cycle of LuPSMA. Eleven (37%) patients showed improvement in global health scores of ≥10 points, and 9 of 12 (43%) patients experiencing bone pain showed a significantly improved mean severity scores of ≥ 10 points. Hofman *et al.* Abstract 785O

Practice point and future research opportunities

This phase II trial of ¹⁷⁷Lu-PSMA617 provided promising antitumour activity data in men with mCRPC who failed conventional therapies, but more data are needed, including response according to RECIST, and in larger populations. There was a good tolerance, not much grade 3 toxicity but significant transitory grade 1-2 dry mouth or nausea. There is a good therapeutic ratio for many, but not all, patients. QOL improvement is difficult to interpret in single arm studies. It remains to be seen if we can identify predictive biomarkers of response and good combination strategies should be pursued.

Germline mutations in DNA repair genes lowers survival in mCRPC

Elena Castro, Prostate Cancer Unit, CNIO - Spanish National Cancer Centre in Madrid, Spain explained that certain germline mutations in DNA repair genes have been associated with poor outcomes in metastatic castration resistant prostate cancer (mCRPC) but there were no conclusive data on the response to currently approved survival-prolonging therapies (SPT) and survival in mCRPC. Dr Castro and a multidisciplinary research team led by Dr David Olmos conducted the prospective multicentre observational PROREPAIR-B study of patients with newly diagnosed mCRPC and germline mutation that was unknown at study entry.

The study enrolled 419 eligible patients in 38 Spanish institutions who were treated with either abiraterone, enzalutamide, docetaxel, cabazitaxel, or Ra-223 according to physician-choice. The investigators looked for *BRCA1*, *BRCA2*, *ATM*, and *PALB2* germline mutations in patient samples and explored their impact on cancer specific survival (CSS) from the time of diagnosis of mCRPC and first line therapy with a SPT. Enrolment of a minimum 408 patients was required and 171 deaths must have occurred to demonstrate a CSS hazard ratio (HR) of germline mutation carriers compared to non-carriers equal to 3 ($\alpha=0.05$ & $\beta=0.20$). Secondary endpoints included the association of those mutations to the response to SPT.

In all, 26 (6.2%) patients were identified as carriers of germline mutations, including 14 *BRCA2*, 8 *ATM*, and 4 patients had *BRCA1*. Sixty-three percent of carriers versus 46% of non-carriers had received a taxane as the first SPT, and 37% versus 53% had received a novel androgen receptor (AR) targeting therapies (ART), respectively. A non-significant trend was observed for carriers to be younger compared to non-carriers, with median ages of 66.5 versus 71.6 years, respectively ($p = 0.16$). Other statistically non-significant baseline characteristics at the start of SPT included that carriers were more likely to have ECOG performance status of 0 versus 1, which was more often seen in non-carriers (92% versus 88%) and carriers versus non-carriers, median prostate-specific antigen (PSA) was 27.9 versus 31.0 ng/mL, and metastasis to bone was reported in 96% versus 86%, lymph nodes in 48% versus 52%, and viscera in 12% versus 16% of the respective groups.

Carriers also had a shorter median time from initiation of ADT to development of mCRPC compared to non-carriers of 23.7 versus 26.7 months, respectively ($p = 0.22$); this was especially pronounced in patients in the *BRCA2* subgroup where time to mCRPC was 18 months ($p = 0.24$). Prostate-cancer specific deaths occurred in 207 patients after a median follow-up of 36 months. The median CSS from mCRPC was 28.5 months in carriers versus 36.0 months in non-carriers ($p = 0.5$); again the shortest CSS of 17.4 months was observed in patients in the *BRCA2* subgroup ($p = 0.02$).

Carriers of germ-line mutations versus non-carriers receiving taxane treatment demonstrated median CSS in of 17.3 versus 24.5 months, respectively ($p = 0.6$) and 12.8 months in the *BRCA2* subgroup ($p < 0.01$, as compared to non-carriers) Median PFS was 7.8 versus 7.1 months ($p = 0.4$), respectively, and 5.7 months in the *BRCA2* subgroup ($p = 0.3$ in comparison with non-carriers).

ART treated patients showed CSS from ART initiation of 25.4 months in carriers versus 26.6 months in non-carriers ($p = 0.9$), and 27.6 months in *BRCA2* carriers ($p = 0.5$) and PFS was 8.2 versus 9.4 months, respectively ($p = 0.8$) and 5.8 months in the *BRCA2* subgroup ($p = 0.4$). NCT03075735. Castro *et al.* Abstract LBA32

Practice point and future research opportunities

This is a prospective study designed to assess the predictive value of a biomarker and we need more studies like it or even better randomised for testing, not for treatment. However, there are contradictory data among different studies in the last year. It remains questionable whether treatment with a PARP inhibitor, or platinum can change outcome in this population. Based on the currently available data, patients with DDR germline mutations should be discouraged from receiving standard therapy with taxanes, abiraterone, or enzalutamide. The comparison of carriers to non-carriers of specific germline mutations showed non-significant

trends to worse CSS from mCRPC from the start of the first taxane and the first ART. Pre-planned subgroup analyses suggest that BRCA2 mutations associated with significantly poorer outcomes.

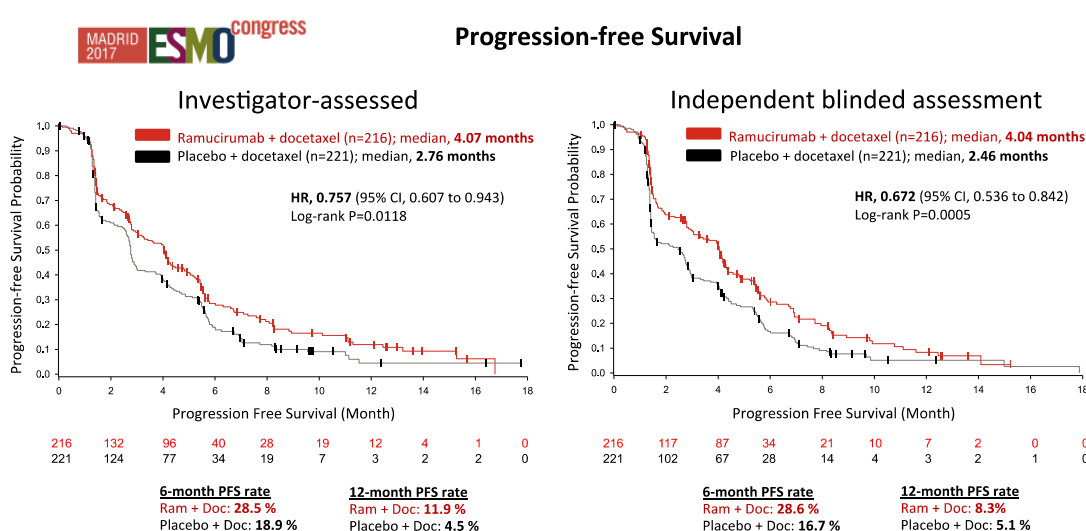
GENITOURINARY CANCERS, NON-PROSTATE

Improved PFS with ramucirumab in patients with platinum refractory advanced urothelial carcinoma

Daniel P. Petrylak of the Department of Medical Oncology, Yale University School of Medicine in New Haven, USA and colleagues conducted the randomised, double-blind, phase III RANGE trial to confirm phase II results seen in a similar patient population showing significantly improved progression-free survival (PFS) with ramucirumab plus docetaxel of 5.4 versus 2.8 months with docetaxel, hazard ratio (HR) 0.389; 95% confidence interval (CI) 0.235, 0.643 ($p = 0.0002$).

RANGE enrolled 530 patients with progressive advanced or metastatic urothelial carcinoma after platinum-based chemotherapy. Prior treatment with one immune checkpoint inhibitor was allowed. The investigators randomised 263 patients to docetaxel at 75 mg/m² plus ramucirumab at 10 mg/kg, and 267 patients to docetaxel at the same dose plus placebo on day 1 of a 21-day cycle until disease progression or other discontinuation criteria. Radiographic assessment was done every 6 weeks. Primary investigator assessed PFS was the primary endpoint, and secondary outcome measures included overall survival (OS), objective response rate (ORR), safety, and quality of life (QoL).

Prolonged PFS was demonstrated by investigator (shown on image below) assessed PFS that was consistent with a blinded central analysis. Patients treated with ramucirumab/docetaxel had significantly longer median PFS of 4.1 months compared to 2.8 months with placebo/docetaxel, HR 0.757; 95% CI 0.607, 0.943 ($p = 0.0118$). These results were consistent with PFS results from a blinded central analysis, HR, 0.672; 95% CI 0.536, 0.842 ($p = 0.0005$).



Median follow-up duration in the full ITT population was 5.0 months (interquartile range [IQR], 2.3–8.9).

© Daniel P. Petrylak

The response was nearly doubled by the addition of ramucirumab: the ORR was 24.5% (95% CI 18.8, 30.3) with ramucirumab/docetaxel versus 14.0% (95% CI, 9.4-18.6) with placebo/docetaxel. The OS data are not yet mature.

The safety data in the RANGE study were also consistent with earlier findings. Grade 3 or higher adverse events (AEs) were reported at a similar frequency in both arms with no unexpected toxicities. The most commonly reported grade 3 or higher AE was neutropenia, which occurred in 15% of patients in the ramucirumab arm versus 14% of patients with placebo/docetaxel. The QoL analysis revealed that the mean scores for global QoL were relatively unchanged over time, with no differences between arms. NCT02426125. Petrylak *et al.* Abstract LBA4_PR

Practice point and future research opportunities

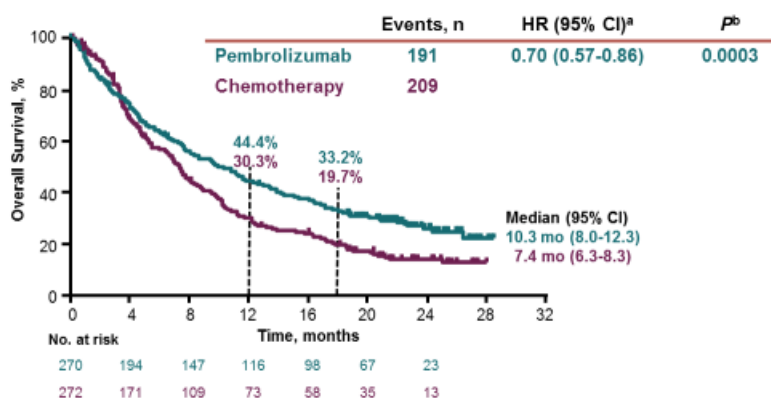
Ramucirumab plus docetaxel may be the treatment chosen post immune checkpoint inhibition (ICI) for most clinicians, however the issues with this trial are insufficient number of patients in subgroup analyses to suggest that ramucirumab plus docetaxel may not be active in post ICI, many patients (approximately 60%) do not receive any subsequent treatment after ICI failure, and there is no evidence of efficacy of ramucirumab on visceral disease. It is questionable whether ramucirumab is active and well-tolerated in unselected patients in daily practice, since the study inclusion criteria were restrictive to patients with good performance status, no untreated brain metastasis, no recent cardiovascular event, and no thromboembolic event within 6 months of prior treatment.

Pembrolizumab continues to show greater benefit over chemotherapy in recurrent, advanced urothelial carcinoma

Ronald de Wit, Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands presented mature results from the phase III, multicentre, open label KEYNOTE-045 study, which confirmed earlier findings that pembrolizumab significantly improved overall survival (OS) compared to investigators' choice of chemotherapy, including paclitaxel, docetaxel, or vinflunine in patients with recurrent, advanced urothelial carcinoma. KEYNOTE-045 randomly assigned 270 patients with recurrent, advanced urothelial carcinoma to pembrolizumab at 200 mg every 3 weeks and 272 were assigned to investigators' choice of chemotherapy.

As of 19 May 2017, median follow-up was 22.5 months in both arms. The median OS was significantly longer with pembrolizumab compared to chemotherapy in the overall patient population. Median OS (shown on image below) was 10.3 with pembrolizumab compared to 7.4 months with chemotherapy, hazard ratio [HR] 0.70 ($p = 0.0003$).

Overall Survival



Data cutoff: May 19, 2017.

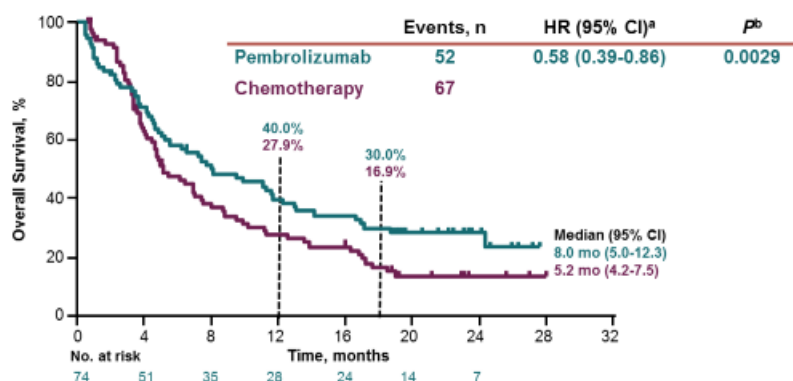
^aBased on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).

^bOne-sided P value based on stratified log-rank test.

© Ronald de Wit.

This significantly improved OS was maintained regardless of the level of PD-L1 expression, as measured by combined positive score (CPS), with patients having CPS ≥10% demonstrating median OS of 8.9 with pembrolizumab versus 5.2 months with chemotherapy, HR 0.58 (p = 0.003), as shown on image below.

Overall Survival: CPS ≥10



Data cutoff: May 19, 2017.

^aBased on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo).

^bOne-sided P value based on stratified log-rank test.

© Ronald de Wit.

Importantly, OS was longer with pembrolizumab versus chemotherapy regardless of age, liver metastases, haemoglobin, the presence of visceral disease, and the choice of chemotherapy. The 18-month OS rates according to Kaplan-Meier estimate, were 33.2% (95% CI 27.5, 38.9) compared to 19.7% (95% CI 14.7, 24.8) with pembrolizumab versus chemotherapy, respectively.

Similar progression-free survival (PFS) was observed between the treatments; median PFS was 2.1 versus 3.3 months with pembrolizumab versus chemotherapy, respectively, HR 0.96

($p = 0.32$). The objective response rate (ORR) was nearly doubled with pembrolizumab, which provided more durable responses. The ORR was 21.1% (95% confidence interval [CI] 16.4, 26.5) versus 11.0% (95% CI 7.6, 15.4) and the median response duration was not reached (range 1.6+ to 24.6+ months) versus 4.4 months (range 1.4+ to 24.0+ months) with pembrolizumab versus chemotherapy, respectively.

The incidence of any grade treatment-related adverse events (TRAEs) was 62.0% versus 90.6%, and the incidence of grade > 3 TRAEs was 16.5% versus 50.2% with pembrolizumab compared to chemotherapy, respectively. NCT02256436. de Wit *et al.* Abstract LBA37_PR

Practice point and future research opportunities

Pembrolizumab continues to demonstrate statistically significant and clinically meaningful OS benefit versus chemotherapy with longer follow-up. Pembrolizumab is the first immunotherapy to demonstrate superior OS over chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy and should be considered a standard of care for these patients.

On 20 July 2017, the Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a new indication for pembrolizumab as monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy. The US Food and Drug Administration (FDA) approved pembrolizumab in May 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy and as monotherapy in patients ineligible for platinum based chemotherapy.

First-line nivolumab and ipilimumab therapy improves response over sunitinib in patients with advanced or metastatic RCC and intermediate to high risk

Bernard Escudier, Institut Gustave Roussy, Villejuif, France presented the results of the phase III, randomised, open-label CheckMate-214 trial of nivolumab plus ipilimumab compared to sunitinib in patients with previously untreated advanced or metastatic renal cell carcinoma (RCC). The study enrolled adult patients with measurable clear-cell metastatic RCC, Karnofsky performance score ≥ 70 , and available tumour tissue, who were stratified by International Metastatic Renal Carcinoma Cell Database Consortium (IMDC) score and by region, and then randomised to receive the nivolumab/ipilimumab combination or sunitinib. The 550 patients in the combination arm received nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg every 3 weeks for 4 doses, followed by nivolumab at 3 mg/kg every 2 weeks, and 546 patients received sunitinib at 50 mg once daily for 4 weeks and 2 weeks off in 6-week cycles. The co-primary endpoints of CheckMate-214 were overall response rate (ORR), progression-free survival (PFS) per independent committee and overall survival (OS) in the cohort of patients at intermediate or poor-risk. Efficacy was also evaluated according to IMDC risk group and baseline tumour PD-L1 expression.

After approximately 17.5 months of follow-up, CheckMate-214 met the co-primary endpoint of ORR in intermediate/poor risk patients, which was 41.6% for the combination compared to

26.5% for sunitinib ($p < 0.0001$). Complete response (CR) was achieved by 9.4% of patients receiving combination nivolumab/ipilimumab therapy compared to 1.2% of patients on sunitinib. The median duration of response (DoR) with nivolumab/ipilimumab was not reached (95% confidence interval [CI] 21.82, NR) versus 18.2 months with sunitinib (95% CI 14.82, NR). Improved median PFS was seen with the combination in this cohort; median PFS was 11.6 months for the nivolumab and ipilimumab combination versus 8.4 months with sunitinib, hazard ratio [HR] 0.82 ($p = 0.03$).

In patients with favourable risk, both the ORR and PFS were higher with sunitinib over combination; ORR was 29% versus 52% ($p = 0.0002$), and median PFS was 15.3 (95% CI 9.7, 20.3) versus 25.1 (95% CI 20.9, NR) months, with nivolumab plus ipilimumab and sunitinib, respectively, HR 2.17 (95% CI 1.46, 3.22; $p < 0.0001$).

Baseline tumour PD-L1 expression was lower in the cohort of patients at favourable risk where 11% of patients on combination had PD-L1 levels $\geq 1\%$ versus 12% of patients on sunitinib, compared to 26% versus 29% of patients at intermediate or poor risk in the respective treatment arms.

Both the ORR per independent committee and PFS significantly favoured nivolumab plus ipilimumab over sunitinib in intermediate/poor risk patients having baseline PD-L1 expression $\geq 1\%$ where the ORR was 58% versus 25%, and median PFS was 22.8 (95% CI 9.4, NR) months versus 5.9 (95% CI 4.4, 7.1) months, respectively, HR 0.48; 95% CI 0.28, 0.82 ($p = 0.0003$).

No significant ORR difference between treatments was demonstrated in the overall composite of patients at any risk, ($p = 0.0191$) or PFS ($p = 0.819$). According to the investigators, these findings support the use of nivolumab plus ipilimumab as a first-line treatment for patients with intermediate/poor risk metastatic RCC, particularly those patients having tumour PD-L1 expression $\geq 1\%$, but not in good risk patients.

Any grade drug-related adverse events (AEs) occurred in 509 (93%) of patients in the nivolumab/ipilimumab cohort and in 521 (97%) of patients receiving sunitinib. With the combination, 54% of patients had a grade 3 to 4 AE, and with sunitinib 63% of patients had a grade 3 to 5 AE. Discontinuation due to an AE was reported for 22% of combination patients and 12% of sunitinib patients. Of the 159 deaths that occurred in the combination cohort, seven (1%) were considered drug-related, whereas 4 (1%) of the 202 deaths occurring in the sunitinib cohort were considered drug related. Escudier *et al.* NCT02231749. Abstract LBA5

Practice point and future research opportunities

When trying to address if superiority of nivolumab plus ipilimumab over sunitinib is a paradigm change in metastatic RCC first-line treatment, to some extent, yes as sunitinib has never been defeated before. It was brave to choose sunitinib as a comparator. Nivolumab plus ipilimumab induces a high rate of objective responses. The quality of the response is highlighted by the rate of complete remissions, the duration of response and its translation into OS benefit. Checkpoint inhibitor first-line treatment may be a new standard of care (with massive impact), however this is not the final picture. Once we are able to properly address the biology of a patient's individual tumour, we may pick out the best individual treatment among various first-line options. Furthermore, multiple combinations are currently under

investigation in phase III trials; some of these combinations will most likely be included in the standard of care. These data are also encouraging news for those conducting phase III trials with immuno-oncology-VEGF-inhibitor combinations versus sunitinib.

Progression-free rate unaffected by the sequence of cytoreductive nephrectomy and sunitinib in patients with synchronous metastatic RCC

Axel Bex, Surgical Oncology-Urology, The Netherlands Cancer Institute in Amsterdam, Netherlands and colleagues investigated whether the outcome after sequential cytoreductive nephrectomy (CN) followed by targeted therapy with sunitinib could be improved with the opposite sequence. They randomised 99 patients with metastatic renal cell carcinoma (RCC) to immediate CN followed by sunitinib (n=50) versus 3 cycles of sunitinib followed by CN plus sunitinib (n=49). The study included patients with histologically confirmed clear-cell subtype, and a resectable asymptomatic primary tumour plus 3 or fewer surgical risk factors per Culp, *et al.*¹

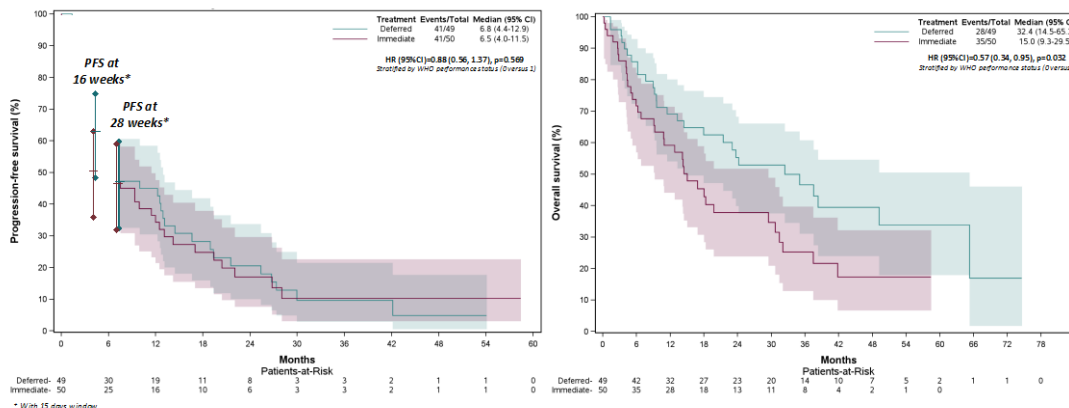
Due to poor accrual, it was decided to report the progression-free rate (PFR) at week 28 as the primary endpoint, which required 98 patients, instead of median progression-free survival, which required 380 events to detect a 3-month increase (hazard ratio [HR] = 0.75) with deferred CN with a 2-sided 5% logrank test at 80% power. Overall survival (OS), adverse events (AEs) and post-operative progression in both arms were secondary endpoints.

After 5.7 years the study included 99 patients from 19 centres. Fifty patients were in the immediate CN arm and 49 in the deferred CN arm. The majority of patients were male, with a median age of 60 compared to 58 years, and MSKCC intermediate risk was reported for 86% versus 87.7% of patients, respectively. In the respective arms, WHO performance status (PS) was 0 and 1 in 72% and 28% versus 63.3 % and 36.7%; 86% versus 93.9% of patients had ≥ 2 measurable metastatic sites, with mean (standard deviation) primary tumour size of 93.1 (37.8) mm versus 96.8 (31.3) mm.

At a median follow-up of 3.3 years, 46 of 50 patients underwent CN in the immediate CN arm and 40 of these patients had received post-CN sunitinib. In the deferred CN arm, 48 of 49 patients had been treated with sunitinib prior to CN; of these patients, 40 underwent CN and 26 also received post-CN sunitinib. Sunitinib treatment of primary tumours prior to CN did not improve the PFR at 28 weeks over immediate CN followed by sunitinib but an OS signal was seen for deferred CN, and post surgical complication rates were also better with deferred versus immediate CN.

No significant difference between the treatment sequence was observed in PFR, which was 42.0% (95% confidence interval [CI] 28.2, 56.8) versus 42.9% (95% CI 28.8, 57.8) in the immediate and deferred arms, respectively ($p > 0.99$). However, patients demonstrated different OS benefit with each sequence. The OS stratified by WHO PS of the intention to treat (ITT) population showed a two-fold advantage favouring deferred versus immediate CN; the overall HR was 0.57 (95% CI 0.34, 0.95; $p = 0.032$) and the median OS was 32.4 (95% CI 14.5, 65.3) months versus 15.1 (95% CI 9.3, 29.5) months, respectively.

The PFS and OS in the ITT analysis of deferred versus immediate CN in all patients are shown on graph below.



© Axel Bex.

In addition, fewer surgical complications were seen in the deferred arm where complication occurred in 27.5% of patients compared to 43.5% of patients treated with immediate CN.

The rate of progression at 16 weeks was 46% of patients after immediate CN, compared to 32.7% in patients in the deferred arm, which was prior to planned CN. The protocol recommended not performing deferred CN in patients with progression. EORTC 30073 SURTIME NCT01099423. Bex *et al.* Abstract LBA35

Citation: 1. Culp SH, *et al.* *Cancer* 2010;116(14):3378-88.

Practice point and future research opportunities

The role of nephrectomy in metastatic RCC remains unclear. Information is still lacking regarding the effect of nephrectomy on early progression. Delaying cytoreductive nephrectomy in metastatic RCC is a viable option. The authors should consider including their data in a meta-analysis with other neoadjuvant trials, like Panther, Atlas and Carmena.

GYNAECOLOGICAL CANCERS

Neoadjuvant chemotherapy followed by surgery is not superior to concurrent cisplatin and radiation therapy in patients with stage IB2 to IIB squamous carcinoma of cervix

Sudeep Gupta from Tata Memorial Centre, Mumbai, India, presented findings from a large randomised trial that demonstrated neoadjuvant chemotherapy followed by surgery (NACT–surgery) was not superior to concurrent cisplatin and radiation therapy (CTRT) in patients with stage IB2 to IIB squamous cervical cancer. The trial enrolled 633 patients with stage IB2–IIB squamous cell carcinoma of the cervix; trial accrual was halted after 635 patients were randomised, which included 2 eligibility violations. The remaining 633 patients were stratified by disease stage and randomised, 316 to NACT-surgery at 3 cycles of paclitaxel at 175 mg/m² plus carboplatin at AUC 5-6 every 3 weeks followed by radical hysterectomy and 317 patients to CTRT consisting of standard pelvic radiation plus 5 cycles of cisplatin at 40 mg/m² once weekly. Overall, there were 113 (17.9%) IB2, 158 (25.0%) IIA, and 362 (57.2%) stage IIB patients. The treatment arms were balanced for stage, age, haemoglobin, performance status and radiological pelvic lymph node status. Post-operative radiation was administered per protocol. The primary endpoint was disease-free survival (DFS), and the earliest occurring relapse or death, while secondary end points included overall survival (OS) and toxicity. The trial was designed to demonstrate 10% absolute increase in 5-year DFS in the NACT-surgery arm, assuming 65% DFS in CTRT (control) arm (2-sided $\alpha = 0.05$, power=80%) with a planned sample size of 730 patients.

At the data cut-off on 30 March 2017 the median follow-up was 58.5 months and the number of DFS events and deaths in NACT-surgery arm were 105 and 80 and those in CTRT arm were 87 and 80, respectively. The trial did not meet the primary endpoint; CTRT provided a significantly higher 5-year DFS rate of 76.7% compared to 69.3% with NACT–surgery hazard ratio [HR] 1.38 ($p = 0.038$). No significant difference in 5-year OS was observed between the respective treatment arms; 5-year OS was 74.7% versus 74.8%, HR 1.025 ($p = 0.87$). The toxicity observed with either treatment was acceptable. NCT00193739. Gupta *et al.* Abstract 928O

Practice point and future research opportunities

It took 12 years to complete this trial, which provides important clinical information. Although NACT–surgery did not prove to be superior to CTRT in terms of efficacy, a positive impact on quality of life was observed particularly in young patients that cannot be excluded. A recently completed European Organisation for Research and Treatment of Cancer trial addressing the same comparison will help to clarify this extremely relevant outcome.

Maintenance rucaparib shows clinical benefit in patients with recurrent ovarian cancer

Jonathan Ledermann, Professor of Medical Oncology at UCL Cancer Institute and UCL Hospitals, London, UK presented findings from the double-blind, multinational phase III ARIEL3 trial of rucaparib as a maintenance therapy compared to placebo in women with high-grade ovarian, fallopian tube, or primary peritoneal cancer. The women had platinum-

sensitive disease defined as disease progression 6 or more months after penultimate platinum and had received ≥ 2 prior platinum-based therapies, demonstrating a complete or partial response per RECIST v1.1 or by Gynaecologic Cancer InterGroup CA-125 criteria to the most recent platinum therapy. All patients were required to have CA-125 less than the upper limit of normal. The patients were randomised in a 2 to 1 ratio; 375 patients received 600 mg of rucaparib twice daily and 189 received placebo.

The primary endpoint was investigator-assessed progression-free survival (PFS) in 3 prospectively-defined nested subgroups in a step-down manner. The nested subgroups were: *BRCA* mutant with a deleterious germline or somatic *BRCA* mutation, homologous recombination deficient (HRD) comprising either *BRCA* mutant or *BRCA* wild-type/loss of heterozygosity (LOH) high, and the intent-to-treat (ITT) population. The PFS as assessed by blinded independent central review was a key secondary endpoint and LOH status in patients with *BRCA* wildtype ovarian cancer was an exploratory endpoint.

Median PFS favoured rucaparib at 10.8 months versus 5.4 months in the intent-to-treat population, according to investigator review, hazard ratio [HR] 0.36 ($p < 0.0001$). By independent review, rucaparib improved PFS by 8.3 months over placebo, HR 0.35 ($p < 0.0001$). In the HRD subgroup, which included patients with *BRCA*-mutant tumours and patients with wild-type/LOH high tumours, median PFS by investigator review was 13.6 months with rucaparib versus 5.4 months with placebo, HR 0.32 ($p < 0.0001$) and median PFS by independent review was 22.9 months versus 5.5 months, respectively, HR 0.34 ($p < 0.0001$). The *BRCA* mutant subgroup demonstrated median PFS of 16.6 months with rucaparib versus 5.4 months with placebo by investigator review, HR 0.23 ($p < 0.0001$). The PFS advantage associated with rucaparib was more pronounced by independent review where median PFS was 26.8 months versus 5.4 months, respectively, HR 0.20 ($p < 0.0001$).

Efficacy by LOH status in patients with *BRCA* wild-type ovarian cancer, the exploratory endpoint, showed patients with *BRCA* wild-type/LOH-high tumours had median PFS of 9.7 months with rucaparib versus 5.4 months with placebo, HR 0.44 ($p < 0.0001$) by investigator review and median PFS by independent review was 11.1 months versus 5.6 months, respectively, HR 0.55 ($p = 0.0135$). The subgroup of patients with *BRCA* wild-type/LOH low tumours showed the poorest median PFS with rucaparib of 6.7 versus 5.4 months with placebo by investigator review, HR 0.58 ($p = 0.0049$) and median PFS by independent review was 8.2 months versus 5.3 months, respectively, HR 0.47 ($p = 0.0003$).

The most common grade 3 or higher treatment-emergent adverse events (AEs) with rucaparib or placebo were anaemia, which occurred in 18.8% and 0.5%, and alanine/aspartate aminotransferase increase in 10.5% and 0% of patients, respectively. Discontinuation of study drug due to treatment-emergent AEs (excluding disease progression) occurred in 13.4% and 1.6% of rucaparib and placebo patients and 1.6% and 1.1% of patients died due to AEs (including disease progression), respectively. NCT01968213. Ledermann *et al.* Abstract LBA40_PR

Practice point and future research opportunities

Rucaparib is another option as maintenance therapy in platinum sensitive patients responding to platinum. There are clear signs of activity also in *BRCA* wild-type patients. LOH is not able to separate unresponsive patients. Maintenance rucaparib significantly improved PFS compared to placebo in all primary analysis groups of patients with platinum-sensitive,

recurrent ovarian cancer. Improvement in PFS, albeit less, was observed in non-nested subgroups of patients with *BRCA* wild-type ovarian cancer with both LOH-high and LOH-low tumours.

ICON8 confirms carboplatin plus paclitaxel every 3 weeks as standard of care in epithelial ovarian cancer

Andrew Clamp, from The Christie NHS Foundation Trust and The University of Manchester, UK presented findings from the practice confirming, phase III ICON8 trial of carboplatin and paclitaxel administered every 3 weeks as first-line treatment of epithelial ovarian/fallopian tube/primary peritoneal carcinoma. Recently a trial conducted in Japanese women reported prolonged progression-free survival (PFS) was achieved with a dose-dense weekly regimen, albeit at the expense increased toxicity¹, prompting Clamp and a team of investigators to compare standard chemotherapy to two dose-dense weekly regimens in a predominantly European patient group.

ICON8 enrolled 1566 women with FIGO stage IcG3-IV epithelial ovarian cancer who were randomised 1:1:1 to arm 1 with standard chemotherapy with carboplatin AUC5/6 plus paclitaxel 175 mg/m² every 3 weeks, or arm 2 with carboplatin AUC5/6 every 3 weeks plus paclitaxel 80 mg/m² weekly, or to arm 3 consisting of weekly carboplatin AUC2 plus paclitaxel 80 mg/m² weekly. Patients were enrolled following immediate primary surgery or neo-adjuvant chemotherapy with planned delayed primary surgery. The patients' median age was 62 years, 72% had serous histology, 93% were ECOG performance status 0/1, 48% had received immediate primary surgery, 50% had planned delayed primary surgery, 2% of patients were inoperable.

Completion rates were highest with the standard treatment with 72%, 60%, and 63% of patients in arms 1, 2, and 3 completing 6 cycles of protocol-defined treatment. The completion rate for 6 cycles platinum was 88% overall with 90%, 89%, and 85% of patients in the respective arms receiving the full dose. Paclitaxel dose-intensification was achieved with median total doses of 1011, 1234, 1274 mg/m² delivered, respectively.

Importantly, no significant increase in PFS was observed with dose intensification provided by either weekly treatment regimen (log-rank $p = 0.45$ arm 2 versus arm 1; $p = 0.56$ arm 3 versus arm 1; non-proportionality $p = 0.02$). Furthermore, the restricted mean survival time was 24.4, 24.9, and 25.3 months in arms 1, 2, and 3, respectively. Median PFS in the respective arms was 17.9, 20.6, and 21.1 months, hazard ratio [HR] 0.92 for arm 2 versus 1, and HR 0.94 for arm 3 versus arm 1.

Grade 3/4 toxicity, which mostly comprised uncomplicated low neutrophil levels, occurred in 42%, 63%, and 53% of arm 1, arm 2, and arm 3 patients. The incidence of grade 3/4 febrile neutropenia was 4%, 6%, and 3%, respectively whereas and \geq the incidence of grade 2 sensory neuropathy was similar across all arms. At data cut-off, 64% patients overall had experienced disease progression. ISRCTN: ISRCTN10356387, EUDRACT: 2010-022209-16, CTA: 2010-022209-16, ENGOT: OV-13, MREC: 11/LO/0043. Clamp *et al.* Abstract 929O_PR

Citation: 1. Katsumata N, *et al. Lancet Oncol* 2013;14:1020-1026.

Practice point and future research opportunities

Although weekly dose-dense chemotherapy can be delivered successfully as first-line epithelial ovarian cancer treatment without substantial toxicity increase, it does not significantly improve PFS compared to standard 3-weekly carboplatin/paclitaxel.

Quality of life maintained during maintenance niraparib treatment in patients with platinum sensitive ovarian cancer

Amit M. Oza, Division of Medical Oncology and Haematology, Princess Margaret Cancer Centre, University Health Network in Toronto, Canada, presented quality of life (QoL) findings on behalf of colleagues from the ENGOT-OV16/NOVA trial of niraparib as maintenance therapy in patients with recurrent ovarian cancer who achieved complete or partial response on platinum-based chemotherapy. Previously published results¹ from ENGOT-OV16/NOVA demonstrated improved progression-free survival (PFS) regardless of the patients' germline BRCA (gBRCA) mutation or homologous recombination deficiency (HRD) status; patients in the overall non-mutated gBRCA group had PFS of 9.3 months with niraparib versus 3.9 months with placebo (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.34, 0.61). In the cohort of patients with gBRCA mutated tumours, PFS was 21.0 versus 5.5 months (HR 0.27; 95% CI 0.17, 0.41), and PFS was 12.9 months versus 3.8 months in the non-gBRCA cohort of patients with HRD tumours in patients on niraparib versus placebo, respectively (HR 0.38; 95% CI 0.24, 0.59; $p < 0.001$ for all comparisons)

New findings were presented at ESMO 2017 from an evaluation of QoL with niraparib compared to placebo that used the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI) and European Quality of Life Scale 5-Dimensions (EQ-5D-5L). A mixed-effects growth-curve model adjusting for baseline demographic values that included 3 stratification factors was used to model the relationship between treatment and the patient reported outcome (PRO) score for each measure.

According to the model, adjusted EQ-5D-5L health utility index (HUI) scores were similar in both arms at baseline. However, the average adjusted HUI pre-progression scores trended to be higher in the niraparib arm versus the placebo arm at 0.812 versus 0.803 in patients with gBRCA mutation compared to 0.845 versus 0.828 in non-gBRCA mutation cohort, respectively. Haematologic toxicities had no detrimental effect on the patients' overall health-related QoL.

Individual FOSI measures show a trend for niraparib treatment to improve fatigue and pain over time as shown on image below.

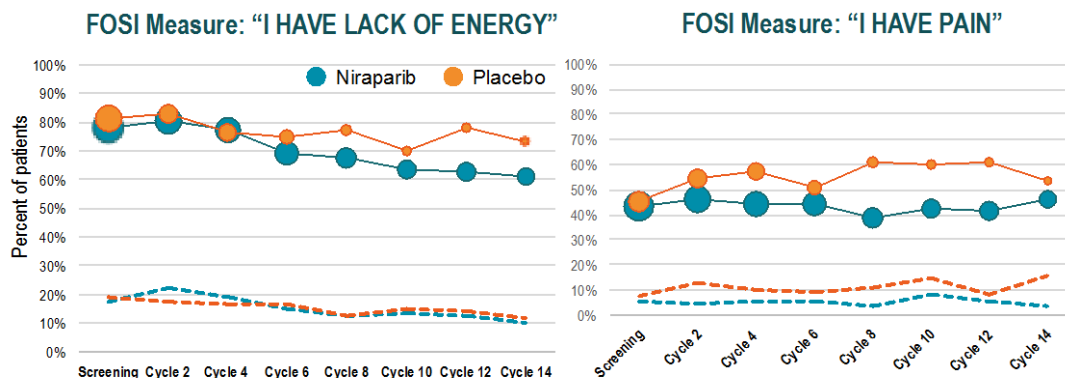


Figure 1. Individual FOSI measures show a trend for niraparib treatment to improve fatigue and pain over time. Data are presented as the percent of patients experiencing any symptom (solid lines) or severe symptoms (dashed lines). The size of the circles corresponds to the number of patients.

© Amit M. Oza.

NCT01847274. Oza *et al.* Abstract 9300

Citation: 1. Mirza *et al.* *NEJM* 2016; 375:2154-2164. DOI: 10.1056/NEJMoa1611310

Practice point and future research opportunities

These data suggest that patients with recurrent ovarian cancer treated with niraparib after achieving complete or partial response with platinum-based chemotherapy can continuously maintain their quality of life while on niraparib maintenance treatment.

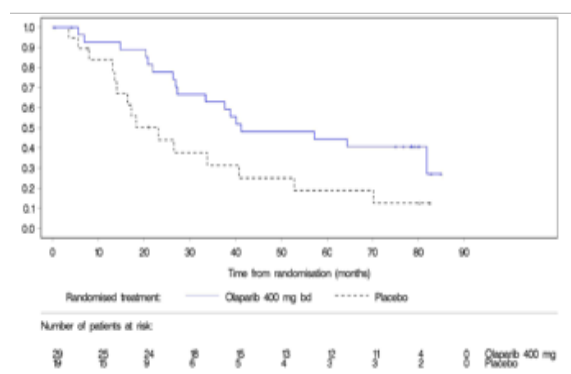
Patients with ovarian cancer and TP53 disruptive mutation status demonstrate an overall survival benefit with olaparib

Alejandro Martinez Bueno, Medical Oncology, Instituto Oncologico Dr Rosell, Hospital Quirón in Barcelona, Spain and colleagues evaluated overall survival (OS) and progression-free survival (PFS) according to *TP53* (disruptive versus non-disruptive) and *BRCA* mutation status in a cohort of 195 patients with ovarian cancer receiving olaparib or placebo after platinum-based chemotherapy. The investigators used data and anonymous tumour samples from the NCT00753545 study archived at Foundation Medicine. *TP53* status was assessed as disruptive or non-disruptive according to the degree of disturbance of p53 protein function and structure. Specifically, disruptive *TP53* mutations associate with a severe disturbance in the DNA repair activities of the p53 protein.

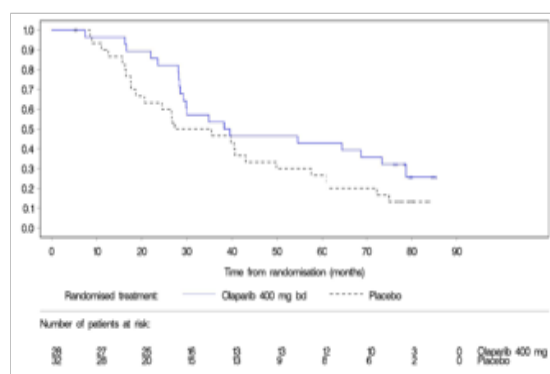
TP53 disruptive mutations were identified in 95 patients and 100 patients had *TP53* non-disruptive tumours as of data cut-off in May 2016. The analysis of *BRCA* mutated and *BRCA* wild-type patients showed PFS was similar between *TP53* disruptive and *TP53* non-disruptive subgroups, with both subgroups demonstrating comparable hazard ratios [HR] for PFS.

However, the comparison of disruptive to non-disruptive *TP53* according to *BRCA* status told a different story regarding OS. Patients having a *TP53* disruptive mutation showed a statistically significant OS benefit of median 39.5 months with olaparib compared to 24.0 months with placebo, HR 0.57 (95% confidence interval [CI] 0.35, 0.92) versus *TP53* non-disruptive patients, HR 0.73 (95% CI 0.46, 1.15), as shown on graph below.

OS Olaparib vs Placebo *TP53* D Total Population



OS Olaparib vs Placebo *TP53* ND Total Population



© Alejandro Martinez Bueno.

Analysis according to *BRCA* status showed that all 108 patients with *BRCA* mutation had an OS benefit with olaparib that was independent of *TP53* status, although this benefit seemed stronger in *TP53* disruptive where OS was 18 versus 7.5 months, with olaparib versus placebo, respectively. Patients with *TP53* disruptive mutations in the *BRCA* wild-type group (n=47) receiving olaparib demonstrated OS of 35.0 months compared to 25.5 months for similar patients on placebo, HR 0.80 (95% CI 0.40, 1.52). Only the mutational subgroup of 40 patients with *BRCA* wild-type and *TP53* non-disruptive mutation did not derive benefit from olaparib treatment, HR 1.58 (95% CI 0.77, 3.35). However, the authors pointed out that the number of patients/events for some of the subgroups were low and further validation is needed in a larger patient population.

These results provided the basis for olaparib approval in Europe as maintenance treatment after response to platinum-based chemotherapy in patients with relapsed, epithelial ovarian cancer who harbour a *BRCA* mutation. Olaparib inhibits PARP, which is important in repairing single strand DNA breaks. During cell division, these may become double strand breaks, which are lethal to cells; however, some types of tumour cells have a deficiency in the homologous recombination pathway that can repair double stranded breaks, for example mutations in the *BRCA1* and *BRCA2*, which may allow cells with faulty DNA to survive. NCT00753545. Martinez Bueno *et al.* Abstract LBA42

Practice point and future research opportunities

TP53 disruptive status seems to be a predictive factor for OS in patients with high-grade serous ovarian cancer treated with olaparib. For both *BRCA* mutated *TP53* disruptive and *BRCA* mutated *TP53* non-disruptive, olaparib achieved better OS. High-grade serous ovarian cancer patients who are *BRCA* wild-type and with *TP53* disruption mutations may derive a

survival benefit from olaparib treatment, whereas no benefit for wild-type *BRCA* and *TP53* non-disruptive is observed. The results of this *post-hoc* exploratory analysis should be interpreted with caution and further validation in larger patient population is needed.

HAEMATOLOGICAL MALIGNANCIES

GP2013, biosimilar rituximab shows equivalent efficacy to reference rituximab in previously untreated advanced follicular lymphoma

Wojciech Jurczak of the Department of Haematology, Jagiellonian University Kraków in Kraków, Poland and the ASSIST-FL researchers compared a GP2013-CVP regimen to rituximab(R)-CVP in terms of efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) in the confirmatory phase III, double-blind, randomised, controlled trial. The primary efficacy endpoint was equivalence in objective response rate (ORR) defined by a 95% confidence interval [CI] with a margin of $\pm 12\%$ standard deviation. Secondary endpoints were non-powered and included progression-free survival (PFS), overall survival (OS), PK, PD, and safety. The investigators randomised 629 patients with previously untreated, advanced-stage follicular lymphoma to 8 cycles of either GP2013-CVP (n=314) or R-CVP (n=315), followed by monotherapy maintenance for up to 2 years in responders.

GP2013-CVP met the primary endpoint of equivalence in ORR compared to rituximab-CVP in patients with previously untreated, advanced-stage follicular lymphoma. With median follow-up of 23.8 months, the ORR was 87.1% with GP2013 compared to 87.5% with rituximab, with a difference of -0.40% (95% CI 5.94, 5.14). Median PFS and OS have not been reached. However, the PFS rate was 69.9% versus 75.9%, hazard ratio [HR] 1.31 (90% CI 1.02, 1.69), and the OS rate was 92.6% versus 90.8%, HR 0.77 (90% CI 0.49, 1.22) for GP2013 versus rituximab, respectively.

According to Prof. Jurczak, the safety and immunogenicity profiles were similar between the tested agents. The PK and PD profiles were also similar and demonstrated a ratio of geometric means of 1.00 (90% CI 0.925, 1.09) for C_{max} at cycle 4 day 1 and 0.939 (90% CI 0.845, 1.04) for $AUEC_{0-21d}$ of peripheral B-cells.

In June 2017, the European Commission approved GP2013 (Rixathon®) for use in all indications of the reference medicine. The rituximab biosimilar, GP2013, was developed according to biosimilar development guidelines and had previously demonstrated equivalence in rheumatoid arthritis in a clinical trial. NCT01419665. Jurzak *et al.* Abstract 994O

Practice point and future research opportunities

In the last 20 years, thanks to rituximab, the survival of patients with B-cell lymphomas improved by 30%. It can be reasonably speculated that a biosimilar improvement in response rate will also improve PFS and OS. However, to be sure of that longer observation is needed. At present we should trust our health authorities, and feel safe in prescribing registered rituximab biosimilars. GP2013 represents an important option that may help to decrease the cost of cancer care, making it sustainable for patients that benefit from rituximab.

Increased risk of AML seen in patients receiving radioactive iodine for well-differentiated thyroid cancer

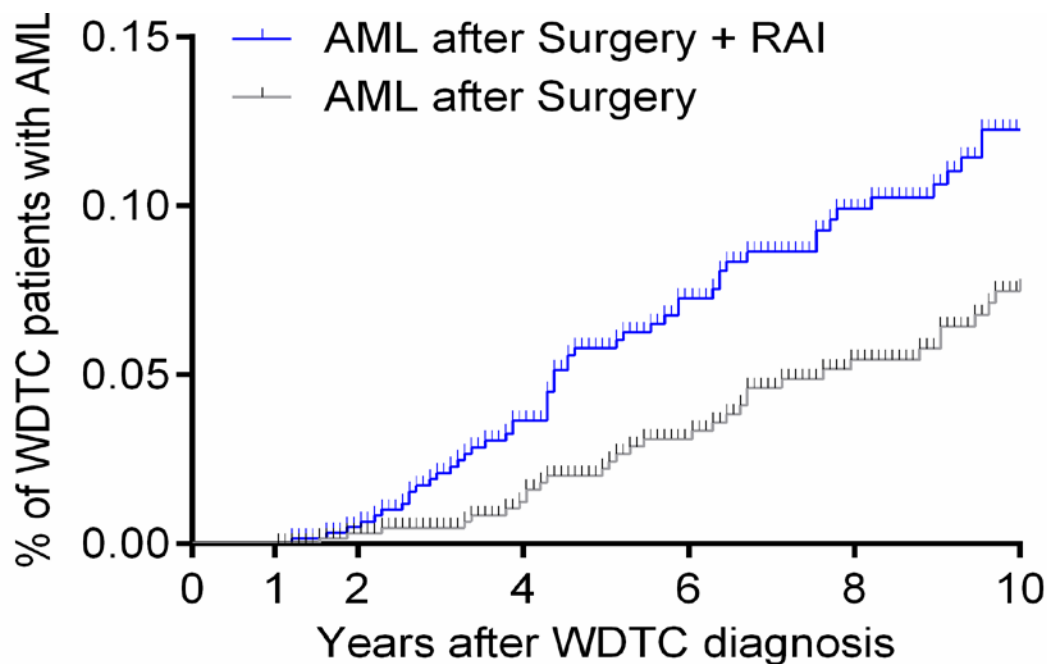
Remco J. Molenaar, Medical Oncology, Academic Medical Centre in Amsterdam, Netherlands commented that it is known that the risk of developing acute myeloid leukaemia (AML) is increased following radiation and radioactive iodine (RAI) treatment for well-differentiated thyroid cancer (WDTC); however, this risk had not been fully characterised. In this population-based study, Dr. Molenaar and colleagues reviewed all 18 registries contained in the Surveillance Epidemiology and End Results (SEER) database for WDTC cases treated solely with surgery or with surgery plus RAI. The risk dynamics of developing AML in WDTC survivors and the association of AML to RAI were also assessed. Case-control studies were used to investigate the clinical outcome of AML occurring *de novo* or following WDTC.

The researchers identified 148,215 patients who were diagnosed with WDTC from 1973 to 2014, of whom 55% were treated with surgery alone and 45% received surgery plus RAI. A median follow-up of 4.3 person years (interquartile range 1.9 to 7.4 years) disclosed that AML occurred in 44 patients after surgery compared to 56 patients receiving surgery plus RAI. Compared with the background rates in the general population, patients receiving surgery plus RAI had an increased risk of developing AML (relative risk [RR] 5.6, 95% confidence interval [CI] 3.8, 8.1; $p < 0.0001$) after correcting for age, sex and year of WDTC diagnosis. This risk peaked within the first 3 years following RAI and subsequently regressed to baseline rates.

In multivariate analysis correcting for sex and the WDTC tumour size, 3 variables emerged as independent prognostic factors for AML development: patient age, hazard ratio [HR] 1.03; 95% CI 1.02, 1.05 ($p < 0.001$), WDTC tumour stage, HR 1.36; 95% CI 1.04, 1.79 ($p = 0.03$), and receiving RAI treatment for WDTC as compared with thyroidectomy alone, HR 1.38; 95% CI 1.09, 1.75 ($p = 0.007$). Case-control analyses revealed that WDTC patients developing AML after surgery plus RAI survived one-third as long as matched control patients that were successfully treated for WDTC but did not develop AML; median overall survival (OS) was 7.4 years versus 24.4 years, respectively ($p < 0.0001$). In addition, patients that were diagnosed with AML after RAI treatment for WDTC had a significantly worse prognosis, with median OS of just 1.2 years compared to 3.5 years in patients with spontaneously occurring AML ($p = 0.004$).

The investigators concluded that the rates of AML in WDTC survivors are likely to continue to rise, due to the increasing incidence of WDTC, the young ages at which most WDTC diagnosis are made and the excellent survival of patients with WDTC. Furthermore, they found that RAI treatment associated with an increased risk of developing AML and patients with RAI-related AML had a poorer prognosis for survival that was similar to survival seen in patients developing therapy-related AML that occurs following radiotherapy or chemotherapy.

The percentage of WDTC patients that developed AML after initial treatment for WDTC, separated by WDTC treatment type, either surgery alone or surgery followed by RAI is shown on graph below.



© Remco J. Molenaar.

Molenaar *et al.* Abstract 996O

Practice point and future research opportunities

It is well established that prior chemotherapy or radiotherapy increases the risk of secondary AML. Relative risk increases according to the type and dose of therapy (e.g. 2-6-fold in various breast cancer studies). Risk is greater with larger doses of chemotherapy, larger portal of radiation encompassing active bone marrow, stem cell stress after autologous transplant, use of G-CSF. This current study from Molenaar and colleagues provides more information with a systematic approach using registry data: therapy related AML after RAI is rare (1/1000) but there is 1.8-fold increase in relative risk. The study will enable better counselling of patients and reduction in numbers of patients having unnecessary RAI for WDTC.

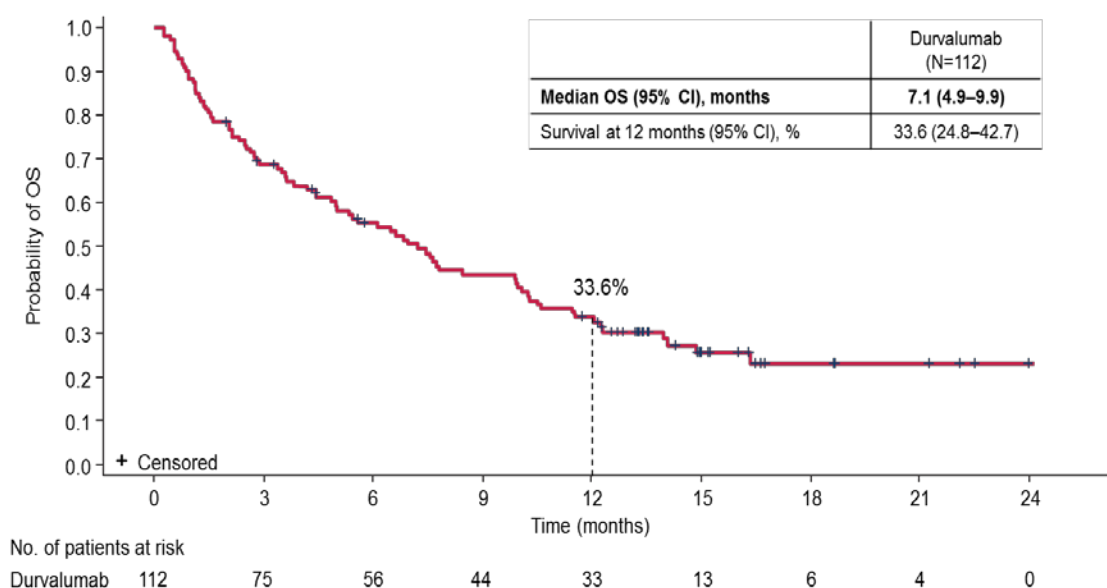
HEAD AND NECK CANCER

Promising clinical benefit with durvalumab in recurrent/metastatic head and neck squamous cell carcinoma

Reports that programmed cell death 1 (PD-1) and its ligand PD-L1 are frequently upregulated in head and neck squamous cell carcinoma (HNSCC) among other tumour types, prompted Dan P. Zandberg, Hematology/Oncology, University of Maryland Greenebaum Comprehensive Cancer Center in Baltimore, Maryland, USA, to investigate durvalumab as monotherapy in patients with recurrent/metastatic (R/M) HNSCC in the global, single-arm, phase II HAWK study. HAWK enrolled immunotherapy-naïve adult patients who progressed on or after one platinum-based chemotherapy. The patients' tumours had high PD-L1 expression, defined as $\geq 25\%$ staining of tumour cells using the VENTANA SP263 Assay. Durvalumab at 10 mg/kg was administered intravenously to 112 patients for up to 12 months or until progression, the initiation of another anticancer therapy, consent withdrawal, or unacceptable toxicity occurred. The patients came from 12 countries with a median age of 60 years, 71.4% were male, 34.3% were human papillomavirus (HPV)-positive, and 61.6% of patients were either current or former smokers. The primary endpoint of HAWK was objective response rate (ORR) by blinded independent central review according to RECIST v1.1; progression-free survival (PFS), and overall survival (OS) were secondary endpoints.

The median duration of treatment was 3.45 months and median follow-up was 6.13 months. Among the 111 patients with evaluable data, the ORR was 16.2% (95% confidence interval [CI], 9.9, 24.4). Of the 18 responding patients, 10 (55%) showed ongoing responses at data cut-off on 31 March 2017. The disease control rate at 24 weeks, which included patients with a complete or partial response plus those with stable disease, was 23.4%.

In the overall cohort, median PFS was 2.1 months (95% CI, 1.9, 3.7), median OS (shown on graph below) was 7.1 months (95% CI, 4.9, 9.9), and the 12-month survival rate was 33.6% (95% CI, 24.8–42.7).



© Dan P. Zandberg.

© Copyright 2017 European Society for Medical Oncology. All rights reserved worldwide.

An exploratory analysis according to HPV status revealed that patients who were positive for HPV demonstrated an ORR of 29.4%, compared with ORR 10.8% in patients who were negative for HPV.

Durvalumab had a manageable safety profile consistent with previous reports. The incidence of grade ≥ 3 treatment-related adverse events (TRAEs) was 8.0%. Only one patient discontinued durvalumab because of a TRAE and no deaths occurred due to a TRAE. NCT02207530. Zandberg *et al.* Abstract 1042O

Practice point and future research opportunities

Durvalumab demonstrated promising antitumour activity together with an acceptable safety profile in patients with R/M HNSCC and high PD-L1 expression. These data support the potential use of durvalumab in this patient population.

The EAGLE (NCT02369874) and KESTREL (NCT02551159) phase III studies of durvalumab alone and with tremelimumab in R/M HNSCC are ongoing.

Nivolumab demonstrates antitumour activity post-progression in recurrent/metastatic head and neck squamous cell carcinoma

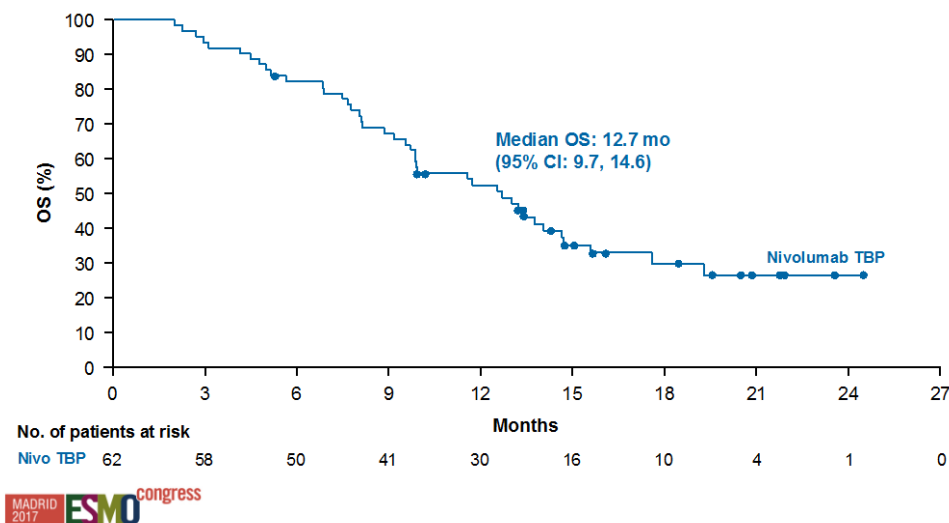
Robert Haddad of the Department of Medical Oncology, Dana-Farber/Harvard Cancer Center, in Boston, USA, presented updated data on behalf of the CheckMate 141 investigators that showed patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) continued to have responses to nivolumab after initial radiologic evidence of progression per RECIST v1.1. was observed. The investigators updated the clinical outcomes in patients in the CheckMate 141 nivolumab arm who met protocol-defined criteria excluding patients without progression or tumour assessment. CheckMate 141 was a randomised phase III study in patients with R/M HNSCC that compared nivolumab to investigator's choice of single-agent systemic therapy in 361 patients with progressive disease occurring within 6 months after platinum-based chemotherapy. Nivolumab was administered at a dose of 3 mg per kilogram every 2 weeks. Previously reported findings showed overall survival (OS) was significantly longer with nivolumab compared to standard single-agent therapy, hazard ratio [HR] 0.70; 97.73% confidence interval [CI] 0.51, 0.96).

At ESMO 2017, data from a September 2016 database lock with a minimum follow-up of 11.4 months were presented. Disease progression was detected in 146 (61%) of 240 patients randomised to nivolumab in CheckMate 141. One or more doses of nivolumab was delivered to 62 (42%) of these patients following progression (TBP group), and 84 (58%) patients were not treated beyond progression (NTBP group).

Updated findings showed that median OS was 12.7 months (95% CI 9.7, 14.6) with nivolumab in the TBP group.

Overall Survival, Patients Treated Beyond Progression

CheckMate 141: Nivolumab in R/M SCCHN After Platinum Therapy

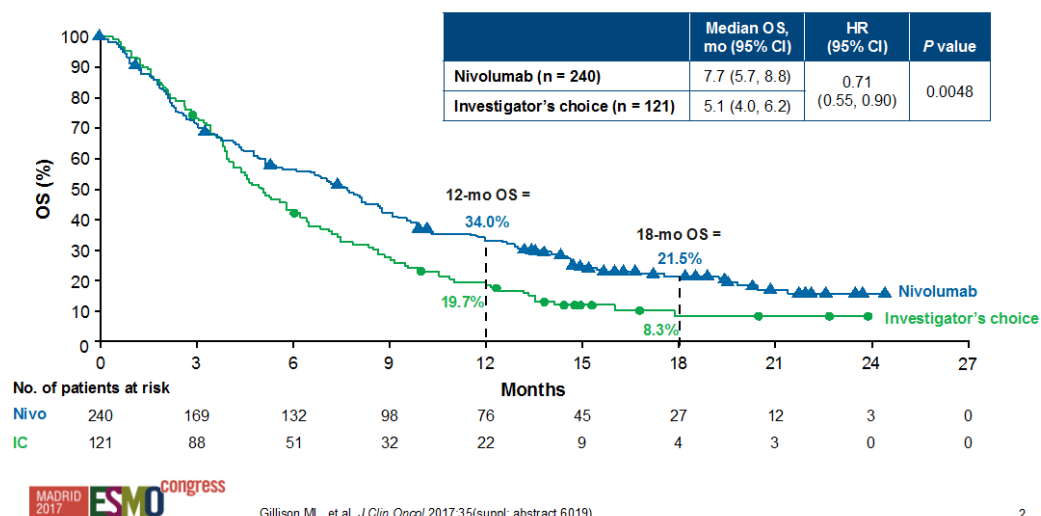


1

© Robert Haddad.

Overall Survival

CheckMate 141: Nivolumab in R/M SCCHN After Platinum Therapy



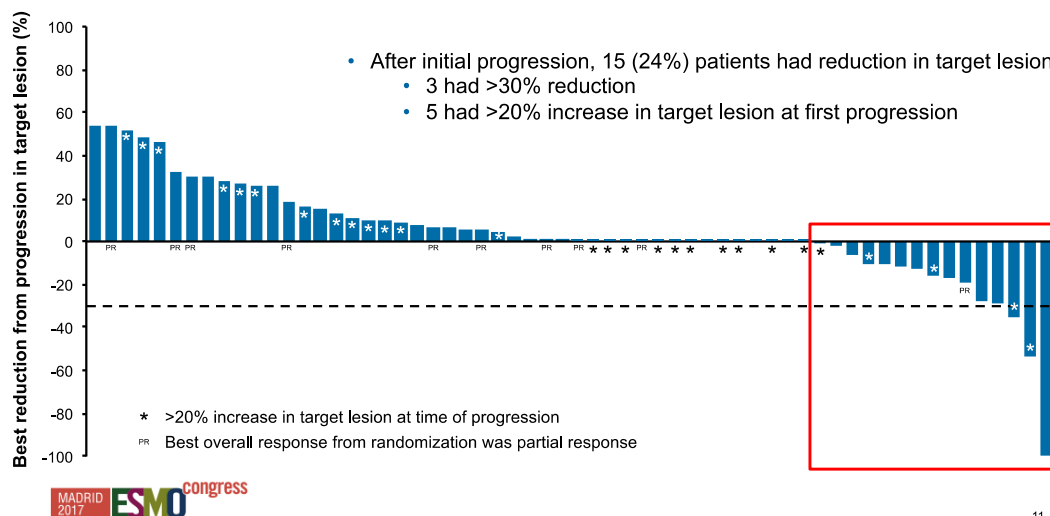
2

© Robert Haddad.

After the initial progression, 15 (24%) TBP patients had a reduction in the target lesion size, and 3 patients had a greater than 30% reduction.

Tumor Reduction in Patients Treated Beyond Progression

CheckMate 141: Nivolumab in R/M SCCHN After Platinum Therapy



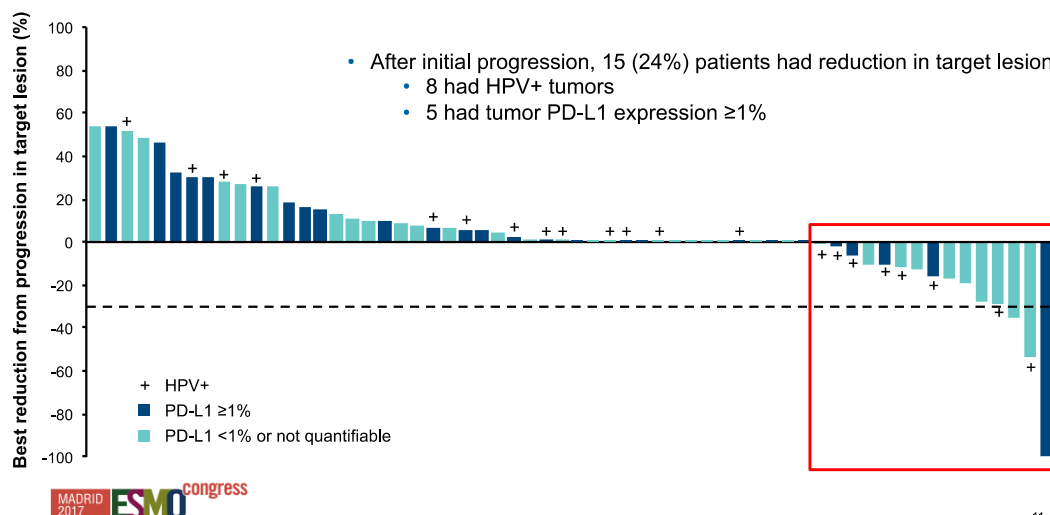
11

© Robert Haddad.

Of the 15 responding patients, 8 were human papilloma virus (HPV)-positive, 5 had PD-L1 tumour expression $\geq 1\%$, and 5 patients had shown a greater than 20% increase in target lesion at the first progression.

Tumor Reduction in Patients Treated Beyond Progression

CheckMate 141: Nivolumab in R/M SCCHN After Platinum Therapy



11

© Robert Haddad.

The investigators also conducted a biomarker analysis and immune cell phenotyping was done by flow cytometry that was associated to clinical response in patients having samples available for both treatment days 1 and 43. At day 1, the percentage of PD-1-positive CD8-positive effector T cells was lower in responders and TBP patients. On day 1, a lower percentage of PD-1-positive T-regulatory cells was also detected in TBP patients that was similar to the percentage detected in responders.

Nivolumab showed a safety profile that was in accord with previous reports. The rates of grade 3/4 treatment-related adverse events (TRAEs) were similar in the TBP and NTBP groups. NCT02105636. Haddad *et al.* Abstract 10430

Practice point and future research opportunities

Nivolumab-treated patients who experienced tumour reduction with treatment beyond progression had circulating cellular immune profiles that were similar to conventional responders. Nivolumab treatment beyond progression was associated with tumour size reductions, was well tolerated and can be considered as a potential treatment in some patients with R/M HNSCC.

Single agent atezolizumab shows promising efficacy in head and neck cancer

Rastislav Bahleda of the Early Drug Development Department, Gustave Roussy in Villejuif, France presented data from the phase Ia study evaluating the safety and clinical activity of atezolizumab monotherapy in patients with advanced head and neck cancer. Of the 32 enrolled patients, 84% were male with a median age of 62 (range: 32 to 78) years, 66% of patients were ECOG performance status 1, and the majority (66%) of patients reported current or previous tobacco use. All patients had been heavily pre-treated, with 53% of patients receiving ≥ 2 prior lines of therapy. Most (56%) patients had a primary tumour in the oropharynx and other primary tumour sites included the oral cavity in 22%, and nasopharynx in 13% of patients.

Atezolizumab was initially administered intravenously every 3 weeks for 16 cycles or up to 1 year but patients were subsequently treated until loss of clinical benefit was observed. The primary endpoint of this study was safety.

The duration of follow-up was 14 months or more and the median treatment duration was 3.4 months. Most (66%) patients experienced a treatment-related adverse event (TRAE). Grade 3 TRAEs of tumour lysis syndrome, hyponatremia, pruritus, and colitis occurred in 3 (9%) patients. One (3%) patient had grade 4 treatment-related cardiac tamponade. No grade 5 TRAEs were seen.

The first 10 patients were non-selectively enrolled; however, upon identification of PD-L1 as a potential biomarker, subsequent enrolment was based on PD-L1 status of $> 5\%$ expression on immune cells (IC2/3) as detected by immunohistochemistry using the VENTANA SP142 antibody. Determination of human papilloma virus (HPV) status was made by PCR. PD-L1 expression in immune cells was $<5\%$ (IC0/1) in 7 patients and $>5\%$ (IC2/3) in 25 patients.

In all patients, regardless of PD-L1 expression, the confirmed objective response rate (ORR) by RECIST v1.1 was 22%; median progression-free survival (PFS) was 2.6 months (range 0.5 to 48.4 months) and median overall survival (OS) was 6.0 months (range 0.5 to 51.6+ months). The subgroup of 25 IC2/3 patients with higher PD-L1 expression demonstrated an ORR of 24% that consisted entirely of partial responses, and the disease control rate (DCR) was 28%. In responding patients, the median duration of response (DoR) was 26.2 (range 2.8 to 45.8) months. The subgroup of 7 patients with low PD-L1 expression had ORR 14%, which represented one partial response. The DCR was 43% and the DoR was 7.4 months in responding patients. NCT01375842. Bahleda *et al.* Abstract 10440

Practice point and future research opportunities

Atezolizumab, an anti-PD-L1 checkpoint inhibitor that restores tumour-specific T-cell immunity by blocking the binding of PD-L1 to both PD-1 and B7.1, was well-tolerated in patients with advanced head and neck cancer. Encouraging responses and long-term survival were observed that was independent of both PD-L1 expression status on immune cells and the presence of HPV infection. These findings warrant further investigation.

IMMUNOTHERAPY OF CANCER

ISA 101 vaccine plus nivolumab shows promising efficacy in HPV-positive oropharyngeal cancer

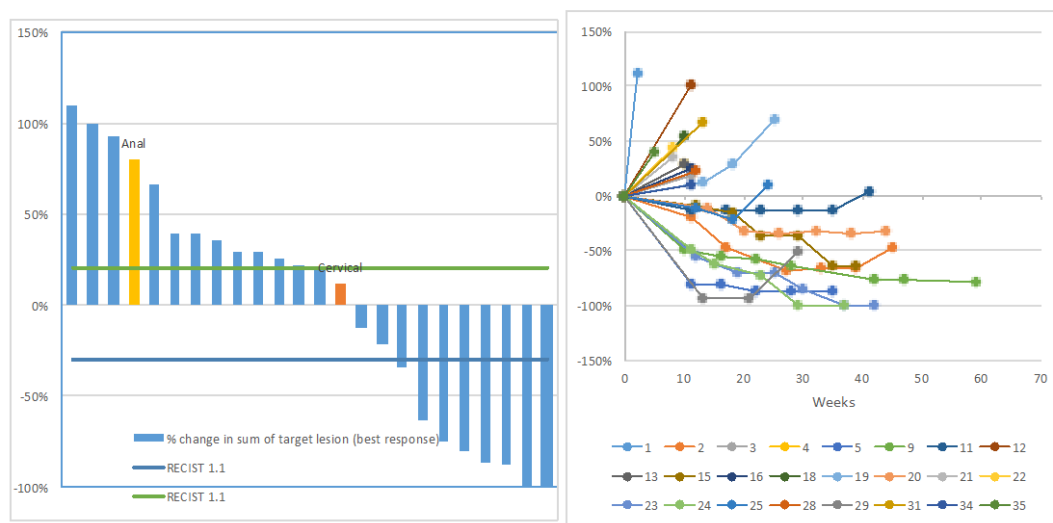
Reasoning that vaccine-induced T cell activity may be amplified by treatment with immune checkpoint antibodies such as nivolumab, Bonnie S. Glisson, professor at the University of Texas MD Anderson Cancer Center in Houston, USA and colleagues conducted a phase II trial of the synthetic long-peptide HPV16 vaccine, ISA 101, plus nivolumab in patients with incurable HPV16-positive cancer.

The trial was open to all patients with HPV16-related cancers regardless of organ of origin and accrued 24 patients; 22 patients had oropharyngeal cancer and one patient each had anal and cervical cancer. HPV-genotype 16 was confirmed using Cervista HPV16/18 in all tumours. The patients had ECOG performance status 0-1 and had received up to one prior regimen for recurrence; 18 (75%) patients had progressed within 6 months of receiving platin, 12 (50%) had received cetuximab, and just one patient was platin-naïve. Treatment with ISA 101 plus nivolumab was frontline for recurrence in 10 patients and second line in 14 of the 24 enrolled patients. All patients were treated with ISA 101 at 100 mcgs/peptide on days 1, 22, and 50 plus nivolumab at 3 mg/kg intravenously every 2 weeks beginning on day 8 for up to one year. Imaging was obtained at baseline, week 11 and every 6 weeks thereafter. The primary objective was assessment of overall response rate (ORR) with a target of 30%, and the secondary objectives included tolerability, progression-free survival (PFS), and overall survival (OS).

The ORR of 33% with combined nivolumab and ISA 101 exceeded the historical ORR of 16% demonstrated by nivolumab monotherapy in p16-positive oropharyngeal cancer.¹ The ORR of 33% was higher than the target, thus meeting the primary objective. The ORR included 2 complete response (CR) and 8 partial responses (PR), with one unconfirmed PR. Stable disease (SD) was achieved by 3 (13%) patients, and 13 (54%) patients showed progressive disease (PD). The median duration of response is not reached, 39+ weeks (range 21-59) with 5/8 remaining in response. Six of the patients achieving PR had progressed within 6 months of prior platin.

Percentage Change in Target Lesions

Phase II Nivolumab and ISA101



Presented by Bonnie Glisson at 2017 ESMO Congress

© Bonnie S. Glisson.

All responses were seen in patients with oropharyngeal cancer, where the ORR was 36% (8/22).

Regarding the secondary endpoints, at a median follow-up of 8.6 months the median PFS was 2.7 months (95% confidence interval [CI] 2.3, 8.0 months) and median OS was not reached. The 6-month PFS rate was 33%, (95% CI 16%, 52%) and the 6-month OS rate was 74% (95% CI 51%, 87%).

Response positively correlated with tumour cell PD-L1 positivity ($\geq 1\%$). PD-L1 $\geq 1\%$ on tumour cells was identified in 7 (39%) of 18 baseline tumour specimens and was associated with probability of response.

The combination of the ISA 101 vaccine plus nivolumab was well tolerated with only grades 1 and 2 toxicity, including fever in 5 patients, injection site reaction in 6, and transaminase elevation, fatigue, and nausea which each occurred in 3 patients. Grade 3 elevated transaminase and grade 4 lipase elevation each occurred in one patient.

ISA 101 comprises 13 synthetic long peptides derived from the E6 and E7 oncogenic proteins of the HPV16, which is responsible for 50% of human cervical cancers and cervical intra-epithelial neoplasias and approximately 80-90% of HPV-positive head and neck cancers, anal cancers and premalignant HPV-induced anal lesions, or anal intra-epithelial neoplasia. ISA 101 caused regression of vulvar intra-epithelial neoplasia, but is not active in invasive cervical cancer. Glisson *et al.* Abstract 1136O

Citation: 1. Ferris RL, *et al.* *NEJM* 2016; 375:1856-1867.

Practice point and future research opportunities

The strengths of the study are the strong rationale (HPV-positive tumour microenvironment is immunosuppressive), a strong translational research component (biopsies baseline/restaging, serial blood samples, HPV-specific immune responses, exploratory biomarkers), and promising results. However, the caveats are the clinical response was observed in this small non-randomised study, heterogeneity prior treatment, and in terms of translational research there is a skewing of data and a small number of evaluable tumours. As a proof of principle, a randomised controlled trial to confirm findings is needed.

These data support the hypothesis that the efficacy of vaccine-induced T cells can be augmented by anti-PD-1 therapy, thus mitigating the influence of an immunosuppressive microenvironment. The authors pointed out that the ORR of 36% in patients with oropharyngeal cancer compares favourably to the ORR of 16% demonstrated for nivolumab monotherapy in patients with p16-positive platin-refractory oropharyngeal cancer participating in the in Checkmate 141 study. These findings merit confirmation in a larger randomised trial, which is being planned.

Rocapuldencel-T shows potential benefit in metastatic renal cell carcinoma

Robert Figlin of the Division of Hematology Oncology, Cedars-Sinai Medical Center in Los Angeles, USA presented findings from the ongoing, phase III ADAPT trial of the novel individualised immunotherapeutic agent, rocapuldencel-T, plus standard of care (SOC) versus SOC. The ADAPT enrolled adult patients with newly diagnosed synchronous, clear cell metastatic renal cell carcinoma who were eligible for nephrectomy. ADAPT randomly assigned 462 patients 2:1 to receive either three 0.2 mL intradermal injections of rocapuldencel-T plus SOC or SOC alone.

At a median follow-up of 20 months, the majority of patients in both treatment groups were still alive. A review of data from 154 (44%) of the first third of patients randomised having the longest duration of follow-up and least censored data suggests a potential survival benefit for rocapuldencel-T. The researchers also observed a statistically significant correlation between overall survival (OS) and an increase in the number of rocapuldencel-T induced memory T cells (CD8+/CD28+/CD45RA-) in the 114 patients who had received 7 doses of rocapuldencel-T.

Rocapuldencel-T was well-tolerated and demonstrated a safety profile that was consistent with that shown in an earlier phase II trial.

These promising long-term data ADAPT come after trial discontinuation was advised. In February 2017 the ADAPT trial's Independent Data Monitoring Committee (IDMC) recommended that the study be halted following a planned interim data review that showed 75% of the targeted number of 290 events (deaths) had been reached and the OS hazard ratio in the rocapuldencel-T/SOC treatment arm was greater than the pre-defined futility boundary of 0.98 for the 3rd interim assessment.

The trial's sponsor discussed the preliminary trial data with the US Food and Drug

Administration and the decision was made to keep the ADAPT trial open, based upon the safety profile, maturing survival data, and the mechanism of action of rocapuldencel-T, which involves the induction of long-term memory immune responses. Rocapuldencel-T is an individualised immunotherapy formulated with RNA isolated from each patient's tumour, which activates autologous dendritic cells with tumour-specific antigens. Thus, an immune response is induced that includes tumour-specific memory T-cells targeting each patient's specific tumour antigens. Figlin *et al.* Abstract 1137O

Practice point and future research opportunities

While censoring may have impacted assessment of both median survival and potential tail-of-the curve effect, which is supported by phase II results, it remains doubtful that this will be a positive trial as >50% of subjects are censored in both treatment groups at the interim analysis. The IDMC recommended study discontinuation for futility; to the best knowledge, no trial has turned out to be positive when the IDMC recommendation is termination for futility. The ADAPT trial is ongoing to further evaluate the long-term effects of this well-tolerated individualised immunotherapy.

MELANOMA AND OTHER SKIN TUMOURS

Adjuvant dabrafenib plus trametinib significantly lowers risk of death in stage III *BRAF* V600–mutated melanoma

Axel Hauschild, University Hospital Schleswig-Holstein, Kiel, Germany and colleagues conducted the COMBI-AD study to investigate an adjuvant regimen for patients with melanoma and regional nodal involvement (stage III disease), who remain at high risk of relapse and death after a complete lymphadenectomy.

COMBI-AD was a randomised double-blind, placebo-controlled, phase III trial of the *BRAF* inhibitor dabrafenib plus the MEK inhibitor trametinib as an adjuvant treatment for patients with high-risk stage III *BRAF* V600E/K-mutated melanoma after complete surgical resection. The trial stratified 870 patients according to *BRAF* mutation (V600E versus V600K) and stage (IIIA versus IIIB versus IIIC); 18% of patients were stage IIIA, 41% IIIB, 40% were IIIC, and 1% of patients had unknown stage disease. COMBI-AD randomly assigned 438 patients to receive dabrafenib at 150 mg twice daily plus trametinib at 2 mg once daily, and 432 patients to matching placebo for 12 months. The primary endpoint was relapse-free survival (RFS), and secondary endpoints were overall survival (OS), distant metastasis-free survival (DMFS), freedom from relapse (FFR), and safety.

At a median follow up of 2.8 years, the primary endpoint of RFS was met; median RFS was not reached with dabrafenib/trametinib versus 16.6 months with placebo ($p < 0.001$). This RFS benefit was consistent across all patient subgroups. Risk of disease recurrence or death was reduced by 53% with the combination over placebo, hazard ratio [HR] 0.47 (95% confidence interval [CI] 0.39, 0.58).

Secondary endpoints also showed benefit; the hazard ratio for OS was 0.57 in favour of adjuvant dabrafenib/trametinib (95% CI 0.42, 0.79), for DMFS the HR was 0.51 (95% CI 0.40, 0.65), and FFR was HR 0.47 (95% CI 0.39, 0.57).

Grade 3/4 adverse events (AEs) occurred in 41% of patients receiving the combination compared to 14% of patients on placebo. Additionally, 26% of patients in the dabrafenib plus trametinib arm discontinued the trial due to an AE compared to 3% of patients in the placebo arm. The type and severity of treatment-related AEs did not differ from already known toxicities observed in randomised trials for advanced unresectable metastatic melanoma, leading to the FDA granting accelerated approval in 2014 to the combination of trametinib and dabrafenib as a treatment for patients with unresectable or metastatic melanoma who harbour *BRAF* V600E or V600K mutations. NCT01682083. Hauschild *et al.* Abstract LBA6_PR

Note: The COMBI-AD results have been published simultaneously in *The New England Journal of Medicine*. Long GV, Hauschild A, Santinami M, *et al.* Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma. *NEJM* 2017; 377:1813-1823.

Practice point and future research opportunities

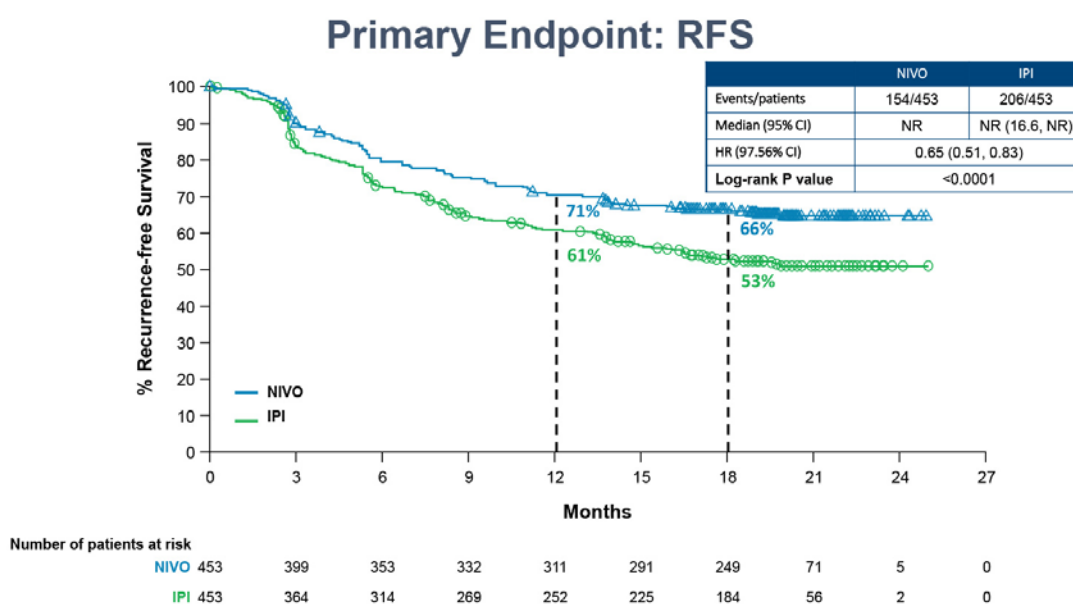
The combination of dabrafenib and trametinib is a convenient oral adjuvant treatment for patients with resected *BRAF*-mutant melanoma. Dabrafenib/trametinib adjuvant therapy

associated with improvements in RFS, OS, DMFS, and FFR, and demonstrated manageable safety in patients with high-risk, resected, stage III, *BRAF* V600E/K–mutated melanoma and may represents a treatment option in this setting.

Nivolumab outperforms ipilimumab as adjuvant therapy in resected melanoma

Jeffrey Weber of the Perlmutter Cancer Center, NYU Langone Health in New York, USA presented the first results of the CheckMate 238 trial on behalf of an international research team. CheckMate 238 is an ongoing phase III, randomised, double-blind study directly comparing nivolumab to ipilimumab as adjuvant therapy in patients older than 15 years of age with resected stage IIb/c/IV melanoma at high risk of recurrence. The trial randomised 906 patients, 453 patients per treatment arm, to receive either nivolumab at 3mg/kg i.v. every two weeks or ipilimumab at 10 mg/kg i.v. every 3 weeks for four doses and for 12 weeks thereafter until documented disease progression or unacceptable toxicity, up to a maximum treatment duration of one year. Overall, stage IIb, IIc, and IV disease was reported for 34%, 47%, and 19% of patients, respectively. Thirty-two percent of patients had ulcerated primary disease, 48% had macroscopic lymph node involvement, and 42% of patients were positive for the *BRAF* mutation. The primary endpoint in the study was recurrence-free survival (RFS), defined as the time between randomisation and the date of first recurrence or death.

RFS (shown on graph below) was significantly improved with nivolumab over ipilimumab at a median follow-up of 18.5 months; the 18-month RFS rates were 66.4% versus 52.7%, respectively, hazard ratio [HR] 0.65; 97.56% confidence interval [CI] 0.51, 0.83 ($p < 0.0001$).



© Jeffrey Weber.

Median RFS was not reached in either treatment arm.

Findings from prespecified subgroup analyses demonstrated consistent hazard ratios favouring nivolumab.

Nivolumab and ipilimumab are immune checkpoint inhibitors that restore immune anti-tumour activity by different mechanisms; nivolumab blocks the programmed death 1 (PD-1) receptor and ipilimumab targets the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) molecule on T cells. Both drugs have demonstrated significant benefit and have been approved for advanced melanoma. Ipilimumab has also been approved in the adjuvant setting for patients with resected stage III melanoma in the United States since 2015, based on results from the phase III international, double-blind EORTC 18071 trial, which showed that ipilimumab at a 10 mg/kg dose reduced the risk of recurrence by 25% versus placebo (HR 0.75; 95% CI, 0.64-0.90; $p < 0.002$)¹.

In CheckMate 238, safety results also favoured nivolumab. Fewer grade 3/4 treatment-related adverse events (TRAEs) were observed with nivolumab; grade 3/4 TRAEs occurred in 14% of nivolumab patients and 46% of patients on ipilimumab. Study discontinuation due to an adverse event of any grade was reported in 10% of nivolumab and 43% of ipilimumab patients. The incidence of grade 3/4 immune-related TRAEs for the following organ systems with nivolumab and ipilimumab was: gastrointestinal 2.0% versus 16.8%, hepatic 1.8% versus 10.8%, and skin 1.1% versus 6.0%.

No deaths due to study drug toxicity were reported for nivolumab; however, two (0.4%) deaths due to colitis and medullary aplasia occurred in patients more than 100 days after last ipilimumab dose. NCT02388906. Weber *et al.* Abstract LBA8_PR. The co-senior authors for this abstract are Dr. J. Larkin and Dr. P.A. Ascierto.

Note: The results of CheckMate 238 have been published simultaneously in *The New England Journal of Medicine*. Weber J, Mandala M, Del Vecchio M, *et al.* Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *NEJM* 2017; 377:1824-1835.

Citation: 1. Eggermont AM *et al.* *Lancet Oncol* 2015; 16 (5):522-530.

Practice point and future research opportunities

Nivolumab administered as adjuvant therapy significantly improved RFS compared to ipilimumab for patients with stage IIIb/c/IV melanoma at high risk of recurrence. Nivolumab also demonstrated a superior safety profile. Predicted implication of this trial for approvals in the USA is that nivolumab will fully substitute the approval of ipilimumab in all stages including stage IIIa in the adjuvant setting and, in Europe, nivolumab will be approved for stage IIIb and higher disease, with dabrafenib/trametinib approved for stages IIIa to IIIc. In terms of surgical and medical management of stage III melanoma, interferon and ipilimumab are no longer recommended in the adjuvant setting; these control arms should be discontinued in clinical trials. The adjuvant treatment options are nivolumab for all and dabrafenib/trametinib for BRAF mutant patients. The necessity of complete lymph node dissection is questionable and there is a need for urgent investigation. Neoadjuvant therapy is still experimental and must be applied in the context of clinical trials only.

Adjuvant vemurafenib in completely resected *BRAF*^{V600} positive melanoma at high risk of recurrence

Karl Lewis, associate professor of medicine, Division of Medical Oncology, at the University of Colorado Denver School of Medicine, in Aurora, USA presented results of the BRIM8 trial

comparing adjuvant vemurafenib to placebo in patients with completely resected V600E BRAF-mutated melanoma and a high risk of recurrence. BRIM8 was a randomised, double-blind, placebo-controlled, 2-cohort study that placed 498 adult patients with fully resected stage IIc, IIIa, or IIIb melanoma into cohort 1 and patients with stage IIc melanoma to cohort 2. Both cohorts were randomly assigned to vemurafenib at 960 mg twice daily or placebo for 52 weeks. In cohort 1, patients were also stratified by geographic region and disease stage.

The primary endpoint was disease-free survival (DFS). Secondary objectives included safety, distant metastasis-free survival (DMFS), and overall survival (OS). A hierarchical analysis of cohort 2 data prior to cohort 1 was prespecified.

As of the cut-off date for the primary analysis, cohorts 2 and 1 had a median follow-up of 34 and 31 months, respectively. Both cohorts had a similar exposure to study drug with a median duration of 364.0 days and the median dose intensity was approximately 80% overall. Cohort 2 contained 184 patients with resected stage IIc melanoma, including 93 patients on adjuvant vemurafenib and 91 patients on placebo. A trend towards improved DFS with adjuvant vemurafenib compared to placebo was observed; DFS events occurred in 52 (55.9%) versus 53 (58.2%) of patients, respectively, hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.54, 1.18 ($p = 0.2598$). The DMFS was also similar between treatment arms in cohort 2, HR 0.91 ($p = 0.6815$).

However, in cohort 1, which included patients with resected stages IIc, IIIa, or IIIb melanoma, adjuvant vemurafenib substantially improved DFS versus placebo. Of the 157 patients in each treatment arm, 45 (28.7%) versus 72 (45.9%) patients receiving vemurafenib versus placebo experienced a DFS event and the median time to event was 'not estimated' versus 36.9 months (95% CI 21, NE), respectively, HR 0.54; 95% CI 0.37, 0.78 ($p = 0.0010$). Cohort 1 data showed DMFS events occurred in 21.7% of vemurafenib patients versus 33.1% of placebo patients and the median time to DMFS event was not estimated for both groups, HR 0.58 ($p = 0.0133$). Subgroup analyses were conducted in cohort 1 by common disease and demographic covariates that showed results that were consistent with the overall analysis.

The OS data are immature for both cohorts.

Patients receiving vemurafenib in cohorts 1 and 2 had a similar incidence of serious adverse events (AEs) of 16.2% and 16.1%, respectively. Cohort 1 showed a slightly higher rate of treatment discontinuation due to a treatment related AEs of 22.7% compared to 15.1% in cohort 2. GO27826 v9. Lewis *et al.* Abstract LBA7_PR

Practice point and future research opportunities

The future for BRAF inhibition monotherapy in adjuvant melanoma is unclear. Although the study did not meet the primary DFS endpoint in patients with stage IIIC disease, adjuvant vemurafenib appeared to be well tolerated and effective in patients with resected stage IIc–IIIb *BRAF*^{V600} positive melanoma. Overall, the safety profile of adjuvant vemurafenib was consistent with previous data and no new safety signals were observed. The authors are continuing further follow-up to assess the OS benefit.

Current indications for vemurafenib include approval by the European Medicines Agency as a monotherapy or in combination with cobimetinib for the treatment of adult patients with

BRAF V600E mutation-positive unresectable or metastatic melanoma and US Food and Drug Administration approval for the treatment of patients with unresectable or metastatic melanoma with the *BRAF V600E* mutation as detected by an FDA-approved test.

NETs AND ENDOCRINE TUMOURS

First report of pembrolizumab activity in patients with PD-L1-positive pNETs and carcinoid tumours

Lead author Janice M. Mehnert of the Phase I and Developmental Therapeutics Program, Rutgers Cancer Institute of New Jersey in New Brunswick, USA presented findings from the pancreatic neuroendocrine tumours (pNETs) and carcinoid cohorts of the multicohort phase Ib KEYNOTE-028 study, which evaluated the safety and efficacy of pembrolizumab. The study enrolled patients with PD-L1-positive carcinoid tumours or well- or moderately-differentiated pNETs, and ECOG performance status (PS) ≤ 1 that had failed standard therapy. Pembrolizumab was administered at 10 mg/kg every 2 weeks for up to 2 years or until confirmed progression, intolerable toxicity, or withdrawal of consent. Response was assessed every 8 weeks for the first 6 months and every 12 weeks thereafter. The median ages of the patients were 61 and 63 years in the pNETs and carcinoid cohorts, respectively. The ECOG PS was 1 in 38% and 76% of patients, and 50% and 44% of patients with pNETs and carcinoid tumours, respectively, had received ≥ 2 prior therapies for metastatic disease. The primary endpoint of KEYNOTE-028 was objective response rate (ORR) per RECIST v1.1 by investigator review.

The benchmark of PD-L1-positivity was set at $\geq 1\%$ modified proportion score or interface pattern, according to immunohistochemistry using QualTek. PD-L1 expression is associated with higher tumour grade in patients with advanced carcinoid/neuroendocrine tumours. Of the 276 patients with tumour samples evaluable for PD-L1 detection, 36% were positive; of these 16 patients had pNETs and 25 patients had carcinoid tumours that included 9 with lung, 7 with gut, and 9 patients with other tumour locations.

The median follow-up was 20.1 (range 4.5 to 30.4) months in the pNET cohort and 18.9 (range 2.0 to 33.3) months in the carcinoid cohort. Objective responses were observed in one (6%) patient with pNET (95% confidence interval [CI] 0%, 30%) and in 3 (12%) carcinoid patients (95% CI 3%, 31%); 14 (88%) patients with pNETs and 15 (60%) patients with carcinoid tumours achieved stable disease. The durations of response were 17.6 months in the one responding patient with pNET, and 6.9, 9.2, and 11.1 months for the carcinoid lung, gut, and other location patients, respectively.

Treatment-related adverse events (TRAEs) were reported in 11 (69%) patients with pNET, including fatigue in 38% and diarrhoea in 25% of patients with pNETs. TRAEs occurred in 17 (68%) patients with carcinoid tumours that included diarrhoea in 28%, and fatigue in 20% of patients. No pNET patients had grade ≥ 3 TRAEs. Grade ≥ 3 TRAEs occurred in 8 (32%) carcinoid patients that included 3 patients with diarrhoea, and 2 patients each with AST and ALT increased. One grade 4 nontreatment-related adverse event of increased gamma-glutamyl transferase and one death of unspecified cause that also was unrelated to treatment occurred in the carcinoid cohort. NCT02054806. Mehnert *et al.* Abstract 427O

Practice point and future research opportunities

Moving to new targets in neuroendocrine tumours shows encouraging steps in clinical trials. It is about first results in prospective anti-PD1 antibody study. Whether PD-L1 is a good biomarker for pembrolizumab sensitivity in NETs remains unresolved. Pembrolizumab was

generally well tolerated in patients with heavily pre-treated carcinoid or pNET tumours, and provided clinically meaningful antitumour activity.

Immune landscape of PanNETs elucidated

Kate Young of The Royal Marsden NHS Foundation Trust presented findings from a study carried out under the leadership of Dr Anguraj Sadanandam of the Institute of Cancer Research (ICR) in Sutton, UK, who had previously developed a PanNETassigner signature which identified 3 molecular subtypes in pancreatic neuroendocrine tumours (PanNETs), MLP, intermediate, and insulinoma-like tumours. The current study aimed to profile the immune architecture of 48 PanNET patient samples across these subtypes PanNETassigner signature to determine whether immunotherapy may be a treatment option for some of these patients. Forty-eight patients with PanNETs were recruited by Prof. Aldo Scarpa at the ARC-Net Research Centre in Verona, Italy. RNA was isolated from fresh frozen tumour samples for immune gene expression profiling using microarray and the nCounter platform (Nanostring Technology). Computational analysis was also performed to assess immune cell enrichment.

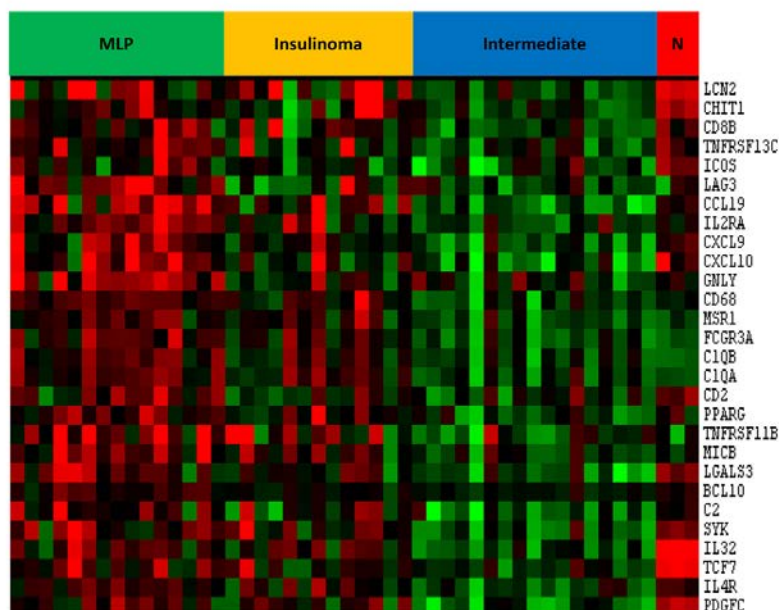
The 48 PanNET samples were classified according to the PanNETassigner gene signature and the tumours were categorised into immune high or immune dormant groups based on immune expression profile analysis. The majority of the MLP subtype tumours were determined as immune high, whereas most of the insulinoma and intermediate samples were immune dormant, although a small proportion of insulinoma samples were classified as immune high, which may reflect the heterogeneity of this tumour, according to the investigators.

Increased expression of *CD8B*, *LAG3*, *CD38*, *CXCL10*, *CXCL9*, *CCL19*, *CD28*, and *CD27* genes was apparent in the MLP subtype as compared to the other subtypes. Some of these genes, such as *CD38*, *CXCL10* are associated with chronic infection, whereas other genes, including *LAG3*, are markers of T cell exhaustion.

Differentially Expressed Genes

40% immune related genes studied were differentially expressed in the MLP and Intermediate subtypes

All of the differentially expressed immune genes had a higher expression in the MLP subtype and a lower expression in the Intermediate subtype



© Kate Young.

PD-1 was highly expressed in 2 of 15 samples classified as MLPs, and FOXP3 was highly expressed in a subset of 7 out of 16 MLP samples. PD-L1 expression was heterogeneous in MLP samples but was highly expressed in 7 of 13 insulinomas. This differential pattern of immune related gene expression is consistent with computational analysis for immune cell enrichment that was done using microarray data on an overlapping cohort of PanNET samples. Young *et al.* Abstract 428O

Practice point and future research opportunities

Immune profiling of samples obtained from patients with PanNETs demonstrated differential expression of immune related genes across 3 PanNET subtypes. Of these, the MLP subtype appears to be associated with an immune high phenotype identified by a pattern of immune-high gene expression, which may aid to inform patient selection approaches for immunotherapy and rational immunotherapy combinations for treating patients with PanNETs.

Improved survival demonstrated with NSCLC-chemotherapy in pulmonary large cell neuroendocrine carcinoma with *RB1* wild-type

The debate of which type of chemotherapy provides the most clinical benefit to patients with pulmonary large cell neuroendocrine carcinoma (LCNEC) may have been resolved by this analysis of genomic profiling of archival LCNEC samples. Citing the controversy surrounding whether LCNEC is better treated with chemotherapy designed to treat non-small cell lung cancer (NSCLC), such as platinum-gemcitabine/taxanes or by the platinum-etoposide therapy used for small cell lung cancer (SCLC), Anne-Marie Dingemans and Jules Derks of the GROW School for Oncology and Developmental Biology, Pulmonology Department,

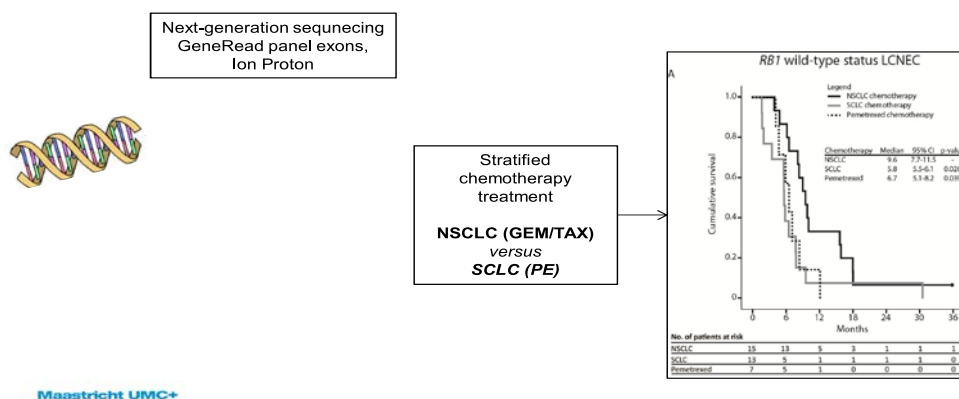
Maastricht University Medical Centre in Maastricht, Netherlands, and colleagues conducted this retrospective study to evaluate whether recently identified genomic LCNEC subtypes are clinically relevant for a chemotherapy outcome.

Two mutually exclusive genomic LCNEC subtypes have been identified by molecular studies: one shows co-mutated TP53 and RB1, which is similar to SCLC, and the STK11/KEAP1 subtype with predominantly RB1 wild-type that is similar to NSCLC. Reviewing clinical data and tumour specimens of 232 patients in the Netherlands Cancer Registry and Pathology Registry from 2003 to 2012, 148 patients who had been diagnosed with LCNEC were identified. Of these, samples from all patients receiving first-line chemotherapy for panel-consensus diagnosed LCNEC were included for next-generation sequencing (NGS) for the *TP53*, *RB1*, *STK11*, and *KEAP1* genes. RB1 (pRB1, 13A10) was analysed by immunohistochemistry, with samples having an H-score of ≥ 50 considered positive. The results of the NGS and pRB1 were correlated with overall survival (OS) and progression-free survival (PFS) by Kaplan Meier plots and Log-rank test.

Quality control determined that 79 samples were sufficient for NGS and that pRB1 could be analysed in 109 samples. RB1 mutations were identified in 37 (47%) samples and loss of pRB1 expression was found in 78 (72%) of samples. It was further determined that mutations in RB1 were mutually exclusive with mutations in the *STK11* gene that were identified in 8 samples ($p = 0.006$). Survival was longer with NSCLC (platinum-gemcitabine/taxane) than SCLC (platinum-etoposide) chemotherapy in the overall cohort, in patients with wild-type RB, and in patients with tumours expressing pRB1; however, no differences were observed in RB1 mutated LCNEC. The researchers assessed the utility of chemotherapy used to treat both NSCLC and SCLC, but omitted pemetrexed (which is used in some NSCLC cases) from the analysis due to reports of resistance in neuroendocrine carcinomas.

The OS was significantly longer overall in patients treated with chemotherapy for NSCLC than OS in patients receiving SCLC-chemotherapy. In the 15 patients with LCNEC treated with NSCLC-chemotherapy, median OS was 9.6 (range 7.7 to 11.6) months compared to OS of 5.8 (range 5.5 to 6.1) months demonstrated by the 13 patients receiving a SCLC-type chemotherapy regimen ($p = 0.026$).

“Improved Survival Demonstrated with NSCLC-chemotherapy in Pulmonary Large Cell Neuroendocrine Carcinoma with *RB1* wildtype”



© Jules Derks.

Patients with LCNEC tumours that expressed pRB1 also had longer OS when treated with a NSCLC chemotherapy regimen; of the patients treated with NSCLC-type chemotherapy, 14 patients with tumour expression of pRB1 had median OS of 9.6 (range 7.4, 11.8) months compared to 1.9 (range 1.7 to 2.1) months in 9 patients with tumours not expressing pRB1 ($p = 0.001$). Similarly, PFS was significantly longer in RB1 wild-type patients with NSCLC chemotherapy treatment than with SCLC chemotherapy ($p = 0.018$). Prolonged PFS also favoured NSCLC over SCLC treatment in patients with pRB1 ($p = 0.023$). However, OS and PFS did not significantly differ between NSCLC and SCLC chemotherapy in patients with tumours having RB1 mutation. Derks *et al.* Abstract 431O

Practice point and future research opportunities

The hypothesis has not been met, as there is no correlation between SCLC-like genomics and benefit from SCLC treatment and outcomes in patients with NSCLC-like tumours mirror those in unselected population. The authors called for the initiation of prospective studies to support the findings of this retrospective analysis. These findings demonstrated that survival was improved in patients with LCNEC and RB1 wild-type, who were treated with NSCLC type of chemotherapy as opposed to chemotherapy designed to treat SCLC. However, no differences in clinical outcomes were observed with either chemotherapy regimen in patients with RB1 mutated LCNEC. These data also suggest that genomic profiling may aid in informing treatment decisions for patients with LCNEC.

NSCLC, NON-METASTATIC

Durvalumab as consolidation therapy prolongs PFS in stage III patients with NSCLC without progression following platinum-based chemoradiotherapy

Presenting author Luis Paz-Ares, Medical Oncology, Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO in Madrid, Spain communicated interim results from the double-blind PACIFIC trial of durvalumab, which was carried out in patients with unresectable, locally-advanced, (stage III) non-small cell lung cancer (NSCLC). The patients were required to demonstrate no disease progression after ≥ 2 cycles of platinum-based chemoradiotherapy but could have any level of PD-L1 expression.

One to 42 days after undergoing chemoradiotherapy, 713 patients were randomised in a 2:1 ratio to durvalumab at 10 mg/kg i.v. every 2 weeks or placebo for up to 12 months. In all, 473 patients were treated with durvalumab and 236 received placebo. Patients were also stratified by age, sex, and smoking history. Progression-free survival (PFS) by blinded independent central review per RECIST v1.1 was a co-primary endpoint, along with overall survival (OS). Secondary endpoints included 12- and 18-month PFS rates, objective response rate (ORR), duration of response (DoR), time to death or distant metastasis (TTDM), and safety.

As of data cut-off on 13 February 2017, the median follow-up was 14.5 months. Median PFS was significantly longer with durvalumab at 16.8 months (95% confidence interval [CI] 13.0, 18.1) versus 5.6 months (95% CI 4.6, 7.8) with placebo, stratified hazard ratio [HR] 0.52; 95% CI 0.42, 0.65 ($p < 0.0001$). The 12- and 18-month PFS rates with durvalumab versus placebo were 55.9% versus 35.3%, and 44.2% versus 27.0%, respectively. The ORR was significantly higher with durvalumab at 28.4% compared to 16.0% with placebo ($p < 0.001$). Responding patients demonstrated a longer median DoR, which was not reached versus 13.8 months with placebo. Significantly prolonged median TTDM was observed with durvalumab over placebo; TTDM was 23.2 versus 14.6 months, respectively, stratified HR 0.52; 95% CI 0.39, 0.69 ($p < 0.0001$). The OS data were not yet mature at the time of the interim PFS analysis.

Adverse events (AEs) were similar between durvalumab and placebo, with grade 3/4 AEs occurring in 32.0% versus 27.8% patients; the most common AE was pneumonia, which occurred in 4.4% versus 4.3% of patients, respectively. Study treatment was discontinued by 15.4% of patients receiving durvalumab and by 9.8% of patients on placebo.

On 31 July 2017, the US Food and Drug Administration (FDA) granted breakthrough therapy designation to durvalumab for patients with locally advanced, unresectable NSCLC who do not relapse after platinum-based chemoradiation, based on data from this interim analysis of the phase III PACIFIC trial. NCT02125461. Paz-Ares *et al.* Abstract LBA1_PR

Note: The PACIFIC results have been simultaneously published in *The New England Journal of Medicine*. Antonia SJ, Villegas A, Daniel D, *et al.* Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *NEJM* 2017; 377(20):1919-1929.

Practice point and future research opportunities

These results represent a first strong “interim-PFS” positive phase III trial on systemic therapy for stage III NSCLC in over decades. Durvalumab is a promising therapeutic option in this

setting. The PACIFIC trial met its primary endpoint of improved PFS with durvalumab, an anti-PD-L1 (programmed death ligand-1) monoclonal antibody, in patients with locally advanced tumours for whom surgery was not an option.

Enhanced post-surgery surveillance does not equate to prolonged OS in NSCLC

Virginie Westeel, Thoracic Oncology, University Hospital of Besançon, France, and colleagues conducted the phase III IFCT-0302 trial to evaluate whether a maximal surveillance regimen could improve outcomes in patients with completely resected non-small cell lung cancer (NSCLC). They contrasted a minimal follow-up of physical examination together plus history and a chest x-ray with a maximal follow-up that added a computed tomography (CT) scan with contrast of the thorax and upper abdomen plus fibre-optic bronchoscopy, which was optional for patients with adenocarcinoma but mandatory for squamous and large cell carcinoma. The study randomised 1775 patients; 888 patients received minimal surveillance and 887 received the maximal follow-up. The patients' median age was 63 years (range: 34 to 88), 76.3% were male and 39.5% of patients had squamous and large cell carcinomas. Stage I, II, and III disease was reported in 68.1%, 13.7%, and 18.3% of patients, respectively. Most patients (86.6%) had undergone lobectomy or bilobectomy, with 8.7% also receiving pre- and/or post-operative radiotherapy, and 45% received pre- and/or post-operative chemotherapy. Histology included squamous (34%), adenocarcinoma (57%), and large cell (5.5%).

Dr. Westeel presented findings from a final analysis done at a median follow-up of 8.7 years showing a non-statistically significant trend toward improved overall survival (OS) with the experimental (maximal) regimen; median OS in the minimal arm was 8.2 years (95% confidence interval [CI] 7.4, 9.6) versus 10.3 years with maximal surveillance (95% CI 8.5, not reached), hazard ratio [HR] 0.92; 95% CI 0.8, 1.07 ($p = 0.27$). The 8-year OS rates were 51.1% (95% CI 47.2%, 55.1%) in the minimal arm versus 55.6% (95% CI 51.7%, 59.4%) maximal arms, respectively. The authors will continue follow-up to avoid missing a potential long-term OS benefit. NCT00198341. Westeel *et al.* Abstract 1273O *et al.*

Practice point and future research opportunities

The IFCT-0302 trial is the first randomised study of follow-up in resected NSCLC. The primary endpoint was not met. A longer follow-up is necessary not to miss a potential long-term OS benefit of CT-scan-based surveillance. Although no significant survival benefit was seen, there was a trend for an earlier diagnosis of recurrences and second primary cancers suggesting that maximal follow-up with CT scan may have a potential long-term benefit for patients at high risk for second primary cancers. The debate between chest x-ray versus CT-based follow-up after resection of early-stage NSCLC remains unsettled; additional data are needed to abandon CT-based follow-up during the first 2 years of resection.

NSCLC, METASTATIC

Front-line osimertinib poised to become standard of care in *EGFR*-mutation positive NSCLC

Suresh S. Ramalingam, professor of medical oncology and deputy director of the Winship Cancer Institute of Emory University in Atlanta, Georgia, USA reported results on behalf of an international team from the phase III double-blind, randomised FLAURA study of first-line oral osimertinib, which significantly prolonged progression-free survival (PFS) compared to the standard of care (SOC) among patients with Ex19del/L858R *EGFR* mutated advanced non-small cell lung cancer (NSCLC). The PFS was improved with osimertinib over SOC in patients both with and without central nervous system (CNS) metastasis. The trial enrolled adult patients who had not received previous *EGFR* tyrosine kinase inhibitor (TKI)/systemic anticancer therapy for advanced disease and included neurologically stable patients with CNS metastases with the caveat that definitive treatment or steroids had been completed for ≥ 2 weeks. The patients were randomly assigned to oral osimertinib (n=279) at 80 mg once daily orally or SOC *EGFR*-TKI (n=277) with gefitinib at 250 mg or erlotinib at 150 mg orally per day. Patients had been stratified by mutation status (Ex19del versus L858R) and race (Asian versus non-Asian). Patient characteristics across the osimertinib and SOC arms were well balanced with 57% versus 56% and 35% versus 32% of patients in the respective arms having Ex19del, and L858R mutation. The primary endpoint was PFS by investigator per RECIST v1.1.

Osimertinib is a third-generation, irreversible, *EGFR*-TKI that was designed to inhibit both *EGFR* sensitising and *EGFR* T790M resistance mutations. Although *EGFR*-TKIs are an effective SOC for patients with NSCLC and *EGFR* activating mutations, nearly 50 to 60% of patients that are initially responsive to this treatment eventually acquire resistance by developing a T790M mutation. Since osimertinib crosses the blood-brain barrier, it also has the potential to be active against CNS lesions.

As of data cut-off on 12 June 2017, a consistent PFS benefit was demonstrated across all subgroups, including patients having CNS metastasis at study entry. Median PFS with osimertinib was 18.9 months (95% confidence interval [CI] 15.2, 21.4) compared to 10.2 months (95% CI 9.6, 11.1) with SOC, hazard ratio [HR] 0.46; 95% CI 0.37, 0.57 ($p < 0.0001$). A total of 136 (49%) versus 206 (74%) patients had a PFS event with osimertinib versus SOC, respectively. Median overall survival (OS) was not reached in either arm and will be calculated at approximately 60% maturity; for the current OS comparison of osimertinib versus SOC, the HR was 0.63; 95% CI 0.45, 0.88 ($p = 0.0068$) at 21% data maturity. The objective response rate (ORR) was 80% with osimertinib compared to 76% with SOC. However, the duration of response (DoR) was doubled with osimertinib, where the median DoR was 17.2 (95% CI 13.8, 22.0) versus 8.5 (95% CI 7.3, 9.8) with SOC.

The median total treatment duration was 16.2 (range 0.1, 27.4) months with osimertinib compared to 11.5 (range 0, 26.2) months with SOC. The incidence of adverse events (AEs) of any cause by investigator was 98% with both osimertinib and SOC. Despite a higher median duration of exposure to osimertinib, grade ≥ 3 AEs was lower with osimertinib at 34% versus 45% with SOC. The most commonly occurring all causality AEs with osimertinib were diarrhoea in 58% and dry skin in 32% of patients, whereas 57% of patients on SOC had diarrhoea, and 48 had dermatitis acneiform. Grade ≥ 3 diarrhoea occurred in 2% versus 3%

of osimertinib and SOC patients, respectively. Thirteen percent of osimertinib patients discontinued the trial due to an AE compared to 18% of patients receiving SOC. During the study 58 (21%) of patients receiving osimertinib and 83 (30%) of patients receiving SOC died.

The European Medicines Agency and US Food and Drug Administration (FDA) granted approval for osimertinib 80 mg once-daily tablets for the treatment of patients locally advanced or metastatic EGFR T790M mutation-positive NSCLC. The summary of product characteristics states that it is important that the EGFR T790M mutation status is determined by a validated test performed using either tumour DNA derived from a tissue sample or circulating tumour DNA obtained from a plasma sample. In March 2017, FDA granted regular approval to osimertinib for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. NCT02296125. Ramalingam *et al.* Abstract LBA2_PR

Practice point and future research opportunities

The FLAURA trial is a winner, the question remains whether the winner takes all, meaning should all *EGFR* mutation positive patients receive first line osimertinib. There is sufficient evidence supporting first-line osimertinib for patients with CNS metastases. In comparison with second generation TKIs, a subgroup of *EGFR* mutation positive patients may attain a long duration of PFS but there is a higher toxicity profile with second generation TKIs. The optimal sequence to improve OS remains unclear, and remains pending on the final OS data from AURA 3 and FLAURA trials.

The authors concluded that osimertinib demonstrated a superior risk/benefit over SOC as first-line therapy in patients with advanced *EGFR* mutated NSCLC and these findings support frontline use of osimertinib in all *EGFR* mutated NSCLC.

Substantial clinical activity demonstrated in the first-line by combined dabrafenib plus trametinib in *BRAF V600E*-mutated metastatic NSCLC

David Planchard, Department of Medical Oncology, Institute Gustave Roussy in Villejuif, France presented the results of the third (cohort C) of three sequentially enrolled cohorts in the phase II study of patients with *BRAF V600E*-mutated metastatic non-small cell lung cancer (NSCLC). In this cohort, 36 patients received first-line treatment with 150 mg twice daily of dabrafenib and 2 mg once daily of trametinib. The patients had not received prior systemic therapy for metastatic disease. Dr. Planchard pointed out that substantial clinical activity had been previously demonstrated by the combination in patients with previously treated *BRAF V600E*-mutated metastatic NSCLC (cohort B), who showed an investigator-assessed confirmed overall response rate (ORR) of 67%, median progression-free survival (PFS) of 10.2 months, and median overall survival (OS) of 18.2 months.

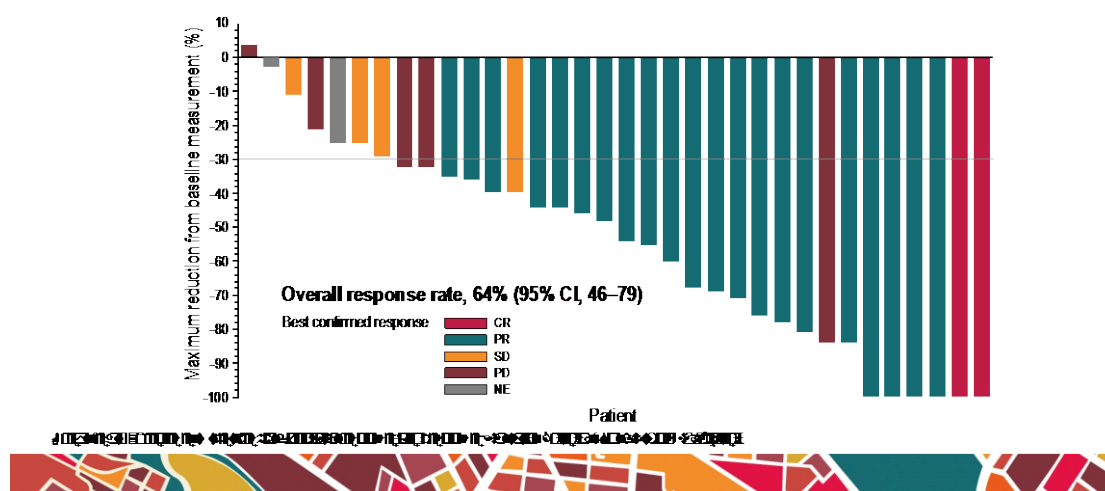
In the findings presented at ESMO 2017, the median age of cohort C patients was 67 (range 44 to 91) years, 61% were female, 83% were white, and 72% of patients were current or former smokers. Investigator-assessed ORR was the primary endpoint; secondary endpoints included duration of response (DoR), PFS, OS, and safety.

As off data cut-off on 8 April 2017, three-fourths of patients with previously untreated *BRAF V600E*-mutated NSCLC receiving a combination of a *BRAF* inhibitor dabrafenib plus a MEK

inhibitor trametinib, achieved complete or partial response or stable disease by both investigator assessment and independent review.

After a median follow-up of 15.9 months, the investigator assessed ORR was 64% (95% confidence interval [CI] 46%, 79%). Two (6%) patients receiving the combination experienced a complete response (CR), and 21 (58%) patients demonstrated partial response (PR). Overall, 4 (11%) patients had stable disease (SD) lasting ≥ 12 weeks as their best response, thus the disease control rate (DCR = CR+PR+SD) was 75% (95% CI 58%, 88%).

MADRID 2017 ESMO congress
**INVESTIGATOR-ASSESSED MAXIMUM CHANGE
IN TARGET LESION BY BEST RESPONSE**



© David Planchard.

The independent review committee assessment supported these results; investigator-assessed median DOR was 10.4 (95% CI 8.3, 17.9) months. Median PFS was 10.9 (95% CI 7.0, 16.6) months and median OS was 24.6 (95% CI 12.3, not estimable) months.

All (100%) of the patients experienced ≥ 1 adverse event (AE), and 69% had ≥ 1 grade 3/4 AE. Serious AEs (SAEs) occurring in >2 patients included alanine aminotransferase increase in 14%, pyrexia in 11%, aspartate aminotransferase increase in 8%, and ejection fraction decrease was reported in 8% of patients. Of the 24 patients who progressed or died, 17 patients died. One death was due to a cardiorespiratory arrest SAE that was determined to be unrelated to study treatment.

The US Food and Drug Administration (FDA) first approved the dabrafenib and trametinib combination for patients with metastatic melanoma in January 2014 and the European Commission approved the dabrafenib/trametinib combination for adults with unresectable or metastatic melanoma with a *BRAF* V600 mutation a year later. In April 2017, the European Commission approved the combination of dabrafenib and trametinib for patients with *BRAF* V600-positive advanced or metastatic NSCLC. In June 2017, the US FDA granted regular approvals to dabrafenib and trametinib administered in combination for patients with metastatic NSCLC with *BRAF* V600E mutation as detected by an FDA-approved test. NCT01336634. Planchard *et al.* Abstract LBA51

Practice point and future research opportunities

Dabrafenib plus trametinib is for good reasons approved in both first and later lines in BRAF V600-mutated NSCLC, but there is some toxicity. BRAF-mutational analysis should now be regarded standard of care in up-front diagnostics. Resistance remains a challenge; rebiopsies and collaborative molecular studies are warranted, and the results from the BRF113928 study are awaited.

Combined dabrafenib and trametinib represents a new targeted therapy with clinically meaningful antitumour activity and a manageable safety profile in patients with previously untreated BRAF V600E-mutated metastatic NSCLC. Activating mutations in the *BRAF* gene, which are generally mutually exclusive from *EGFR* mutations or *ALK* rearrangements, act as an alternative oncogenic driver in metastatic NSCLC. The most common of these mutations, *BRAFV600E*, is observed in 1–2% of lung adenocarcinomas. Combined *BRAF* and *MEK* inhibition has shown superior efficacy compared with *BRAF* inhibitor monotherapy in patients with BRAF-mutated metastatic melanoma, potentially contributing to sustained pathway inhibition and delay or prevention of resistance. These results support the recent approvals by the European Commission and US FDA.

Improved patient outcomes favour alectinib over chemotherapy in patients with previously treated ALK-positive NSCLC

Silvia Novello, from the Department of Oncology, University of Turin in Turin, Italy presented primary efficacy and safety findings from the phase III randomised, open label ALUR study comparing alectinib with chemotherapy. The ALUR enrolled 119 patients with ALK-positive non-small cell lung cancer (NSCLC) who had progressed following treatment with platinum-based doublet chemotherapy and crizotinib. The patients were randomised 2:1; 72 patients received alectinib at 600 mg twice daily and 35 patients received either pemetrexed at 500 mg/m² or docetaxel at 75 mg/m² administered every 3 weeks until disease progression (PD), death or withdrawal of consent. Upon PD, crossover to alectinib was permitted. The primary endpoint was investigator-assessed progression-free survival (PFS) and secondary endpoints included PFS by Independent Review Committee (IRC), overall response rate (ORR), and central nervous system (CNS) ORR by IRC, disease control rate (DCR), duration of response (DoR) and safety.

After follow-up of median 6.5 months with alectinib and 5.8 months with chemotherapy, significantly longer investigator-assessed PFS was observed with alectinib; median PFS was 9.6 versus 1.4 months, respectively, hazard ratio [HR] 0.15; 95% confidence interval [CI] 0.08, 0.29 ($p < 0.001$). According to IRC review, median PFS was 7.1 months with alectinib versus 1.6 months with chemotherapy, HR 0.32; 95% CI 0.17, 0.59 ($p < 0.001$). Other findings by IRC included ORR 36.1% with alectinib versus 11.4% with chemotherapy, demonstrating difference in response of 24.7%, 95% CI 0.05, 0.43. Overall, DoR was 9.3 months versus 2.7 months, and the DCR was 80.6% versus 28.6% with alectinib versus chemotherapy, respectively, demonstrating a treatment difference of 52%; 95% CI 0.33, 0.69.

In a companion poster presentation, Julie de Castro and colleagues reported on alectinib activity in the CNS from the ALUR study. A key secondary endpoint of the ALUR study was the CNS overall response rate (CORR) by IRC in patients with measurable CNS metastases at baseline, plus CORR in patients with measurable and non-measurable CNS metastases,

the 6-month cumulative incidence rate in the ITT, and patients with CNS metastases at baseline (CITT); CNS duration of response (CDoR) and disease control rate (CDCR); and safety. Of the patients with ALK-positive NSCLC who previously failed platinum-based doublet chemotherapy and crizotinib and were randomised in ALUR, 76 had baseline CNS disease; of these, 50 patients received alectinib and 26 were treated with chemotherapy (CITT population). Measurable CNS metastases (MITT population) were reported in 24 patients on alectinib and 16 on chemotherapy, and 36 patients had non-measurable CNS metastases, 26 on alectinib and 10 receiving chemotherapy.

CNS-related outcomes were significantly improved with alectinib compared to chemotherapy. In the ITT population, the 6-month cumulative incidence rate of CNS PD was 11% with alectinib compared to 48% with chemotherapy, whereas this rate was 15% versus 52% in the CITT population, and 0% versus 39% in patients who did not have baseline CNS disease, respectively with alectinib versus chemotherapy. CORR was 36% versus 0%, representing a difference between the respective treatment arms of 36% ($p < 0.001$). The CDoR was NE (95% 6.6, NE) versus 0, and the CDCR was 80% versus 26.9% respectively.

In the MITT population, CORR was 54.2% versus 0%, representing a difference between the respective treatment arms of 54% ($p < 0.001$). The CDoR was NE (95% 3.6, NE) versus 0, and the CDCR was 79.2% versus 31.3%, respectively with alectinib versus chemotherapy.

The median duration of treatment in the ITT population was 20.1 weeks versus 6.0 weeks with alectinib versus chemotherapy, respectively. Any grade adverse events (AEs) occurred in 77.1% versus 85.3% and with grade 3–5 AEs occurred in 27.1% versus 41.2% of patients receiving alectinib versus chemotherapy, respectively. One fatal AE was reported with chemotherapy. AEs leading to discontinuation or dose reduction occurred in 10% of alectinib patients and 20.6% of patients receiving chemotherapy. Patients with CNS disease demonstrated a similar safety profile. NCT02604342. Novello *et al.* Abstract 1299O_PR; de Castro *et al.* Abstract 1346P

Practice point and future research opportunities

Although the current standard of care in ALK-positive NSCLC is crizotinib, many patients experience progressive disease within a year, and often show CNS metastasis. Alectinib has shown systemic and CNS efficacy in prior phase II trials of patients following crizotinib failure. This study provides proof of clinically significant CNS efficacy for alectinib, which may translate to routine clinical care.

First-line alectinib demonstrates improved PFS and better control of CNS disease progression over crizotinib

Shirish Gadgeel, University of Michigan in Ann Arbor, USA discussed the open-label phase III ALEX study of alectinib versus crizotinib in 303 patients with treatment-naïve advanced ALK-positive non-small cell lung cancer (NSCLC). Of these, 64 patients in the alectinib arm and 58 in the crizotinib group had central nervous system (CNS) metastases at baseline. Overall, 43 patients had measurable lesions at baseline and 47 had received prior radiotherapy. The study randomised 122 patients to 600 mg of alectinib and 151 patients to 250 mg of crizotinib, both administered twice daily. The primary endpoint was improved progression-free survival (PFS).

In the overall population, median PFS was doubled with alectinib at 25.7 months versus 10.4 months with crizotinib, hazard ratio [HR] 0.47; 95% confidence interval [CI] 0.34, 0.65 ($p < 0.0001$). In the cohort of patients without CNS metastases, median PFS was not reached with alectinib compared with 14.8 months with crizotinib, HR 0.51; 95% CI 0.33, 0.80 ($p = 0.0024$). In patients with CNS involvement, median PFS was not reached with alectinib versus 7.4 months with crizotinib, HR 0.40; 95% CI 0.25, 0.64 ($p < 0.0001$). In the patients with CNS metastases who had received prior radiotherapy, the median PFS was not reached with alectinib compared to 12.7 months with crizotinib, HR 0.34; 95% CI 0.15, 0.78 ($p = 0.0078$), and patients with CNS metastasis but who had not received prior radiotherapy demonstrated median PFS of 14.0 months versus 7.2 months with alectinib versus crizotinib, respectively, HR 0.44; 95% CI 0.25, 0.78 ($p = 0.0041$).

While patients with CNS disease experienced progressive disease before those without CNS lesions in the crizotinib arm, patients on alectinib without CNS sites progressed before those having CNS disease. In patients having measurable CNS metastases who received prior radiotherapy, the CNS overall response rate (ORR) was 85.7% with alectinib versus 71.4% with crizotinib whereas, in patients not receiving prior radiotherapy, the CNS ORR was 78.6% with alectinib versus 40.0% with crizotinib.

In the overall ALEX population, grade 3/4 adverse events (AEs) were less frequent with alectinib (41%) versus crizotinib (50%). Moreover, alectinib versus crizotinib treatment associated with a lower incidence of fatal AEs at 3% versus 5%, fewer patients discontinuing due to AEs at 11% versus 13%, and patients receiving a dose reduction at 16% versus 21%, or interruption at 19% versus 25%, respectively. NCT02075840. Gadgeel *et al.* Abstract 1298O_PR

Practice point and future research opportunities

Findings from the subgroup analysis, focusing specifically on 122 patients with CNS metastases at baseline suggest that alectinib controls existing CNS metastases and inhibits the formation of new metastases better than crizotinib. The ALEX trial provided proof of clinically significant CNS efficacy for alectinib and indicates that CNS staging should be routine for optimal care of patients with ALK-positive lung cancer.

Alectinib also showed significantly superior CNS activity compared to crizotinib in patients having previously untreated advanced ALK-positive NSCLC that was irrespective of prior radiotherapy.

OTHER THORACIC MALIGNANCIES

Nivolumab plus ipilimumab slow disease progression as second or third line malignant pleural mesothelioma therapy

G rard Zalcman, Paris Diderot University in Paris, France and colleagues at the Intergroupe Francophone de Cancerologie Thoracique compared nivolumab monotherapy to dual checkpoint blockade with nivolumab plus ipilimumab in patients with histologically proved malignant pleural mesothelioma (MPM) in the MAPS2 trial. The trial enrolled 125 patients whose mesothelioma had progressed after one or two courses of pemetrexed and platinum chemotherapy. The patients were randomly assigned to nivolumab at 3 mg/kg every 2 weeks, or a combination of 3 mg/kg nivolumab every 2 weeks plus ipilimumab at 1 mg/kg every 6 weeks, until progression or unacceptable toxicity. The majority (80%) of patients was male with a median age of 71.8 years (range, 32.5 to 88.1 years). The performance status (PS) was 1 in 62.4% of patients who mostly (83.2%) had epithelioid tumours. One previous line of treatment had been received by 69.6% of patients but 70% of patients had received at least 3 cycles of either pemetrexed or platinum treatment. The primary endpoint was the disease control rate (DCR) at 12 weeks by BICR.

Primary analysis of the first 108 patients showed that the combination controlled disease progression in half of the patients at 12 weeks, thus meeting the primary endpoint; the 12-week DCR with nivolumab monotherapy in 54 patients was 44% (94% confidence interval [CI] 31.2, 57.7%) compared to 50.0% (95% CI 36.7, 63.3%) in 54 patients receiving combined nivolumab and ipilimumab. The objective response rate (ORR) was 18.5% (95% CI 8.2, 28.9%) versus 27.8% (95% CI 15.8, 39.7%) with nivolumab versus nivolumab/ipilimumab, respectively. After a median follow-up of 15 weeks, median PFS was 4.0 months (95% CI 2.8, 5.7) versus 5.6 months (95% CI 3.2, 8.4) and median OS was 13.6 months (95% CI 6.7, not reached [NR]) versus NR with nivolumab and nivolumab/ipilimumab, respectively. At one year, 51% of patients in the nivolumab group were alive compared to 58% the overall in the combination arm.

Grade 3/4 toxicities were slightly increased with the combination; grade 3/4 toxicities occurred in 22.9% of patients receiving combination treatment versus 3.3% patients on nivolumab. Three treatment-related deaths occurred with the combination.

PD-L1 expression levels by immunohistochemistry were available for 99 out of 125 patients, with 41.4% of patients showing 1% or greater PD-L1 expression on tumour cells. However, positive PD-L1 immunohistochemistry was not predictive of longer PFS or OS, either in the whole population or for each separate treatment group. NCT02716272. Zalcman *et al.* Abstract LBA58_PR

Practice point and future research opportunities

The trial's endpoint was reached in both treatment groups of patients with MPM receiving 2nd/3rd line nivolumab or nivolumab/ipilimumab without any unexpected toxicity. Meaningful increases in PFS and OS were observed; these results support a recent decision by the US Food and Drug Administration to grant orphan drug status to the combination immunotherapy for mesothelioma. There is currently no recommended standard treatment for patients with MPM who progress after first-line pemetrexed/platinum doublet.

PUBLIC HEALTH AND ECONOMICS

Comparison of clinical trials supporting US FDA approval of orphan versus non-orphan drugs according to the ESMO Magnitude of Clinical Benefit Scale

Consolación Molto Valiente, Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau in Barcelona, Spain presented findings from an analysis evaluating the criteria of clinical trials of agents obtaining US Food and Drug Administration (FDA) approval as an orphan or non-orphan drug according to the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) thresholds of meaningful clinical benefit. Professor Molto Valiente and colleagues identified anticancer drugs approved between January 2006 and December 2016 in a search of Drugs@FDA and categorised them as orphan or non-orphan drugs by FDA definition. Data on clinical trial design and methodology for each drug were compared using Mann Whitney U or Chi squared tests between the orphan and non-orphan drug classifications, and by applying an ESMO-MCBS grade for drugs studied in randomised clinical trials (RCTs). The ESMO-MCBS has been validated as a tool for ranking the clinical benefit that can be anticipated from new treatments developed for solid tumours.

RCTs composed 109 (80%) of the 137 trials assessed, which resulted in the approval of 63 individual drugs for 118 indications. Among these indications, 54 (46%) received orphan drug designation according to the Orphan Drug Act, which provides incentives, to manufacturers for the development of drugs targeting rare diseases.

This analysis found that trials supporting orphan drug approval had a smaller sample size of median 369 compared to median 687 patients in non-orphan drug trials ($p = 0.001$), were less often randomised, 73% versus 86%, respectively ($p = 0.047$). Orphan drug trials were less likely to evaluate experimental cytotoxic chemotherapy or endocrine therapy than targeted therapy (8% versus 21%; $p = 0.005$). In 71% of orphan drug trials versus 51% of non-orphan drug trials, intermediate endpoints were used as the primary objective instead of overall survival. Regarding trials testing drugs in the palliative care setting, similar proportions of orphan (29%) versus non-orphan drugs (27%) approved for palliative use met the ESMO-MCBS threshold for meaningful benefit ($p = 0.86$). There were too few studies performed in the curative setting ($n = 7$) to perform statistical testing. Molto Valiente *et al.* Abstract 1435O_PR

Practice point and future research opportunities

The ESMO-MCBS is a crucial component of ESMO's sustainable cancer care agenda, which is centred around advocating for access to quality treatment and for cancer prevention. Compared with trials used to approve non-orphan cancer drugs, trials for orphan drugs are smaller, more likely to explore experimental biological therapies, use single-arm trials and intermediate endpoints. A similarly low proportion of approved orphan and non-orphan drugs meet the ESMO-MCBS threshold for meaningful benefit.

Assessment of cancer therapies according to the French National Authority for Health and the ESMO Magnitude of Clinical Benefit Scale

Mathilde Grande, French National Authority for Health, Saint-Denis, France and colleagues reviewed the 77 trials that were tested by the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) 2015 publication for a comparison of the clinical added value (CAV) assessment with the CAV assessment done by the French National Authority for Health (HAS). The HAS provides CAV evaluations using a 5-point scale from I (major CAV) to V (no CAV) for pricing but not reimbursement decisions. The objective was to evaluate cancer drug affordability and to explain the need to base reimbursement and pricing decisions on the CAV of drugs in solid tumours.

The HAS evaluated 59 of the 77 trials tested using the ESMO-MCBS; 16 trials were not assessed and two remain under assessment. The HAS CAV and ESMO ranking were in agreement in approximately 23 (39%) of these 59 evaluations. Inconsistency between the two ranking systems was observed in 36 (61%) evaluations. The HAS CAV assessment was uniformly more strict, meaning that no indication had a higher HAS evaluation score than that received under ESMO evaluation. In 37 (62%) indications, the ESMO-MCBS indicated a substantial improvement in CAV, with 13 (48%) obtaining a similar ranking by the HAS. In all, 13 versus 2 indications were downgraded for toxicity by the HAS versus the ESMO-MCBS. Four indications that obtained the lowest scores on ESMO-MCBS received an unfavourable opinion for reimbursement according to the HAS. Grande *et al.* Abstract 1436O_PR

Practice point and future research opportunities

In most cases, disparities between the ESMO-MCBS and the HAS assessment of CAV were observed, with the HAS appearing to be more demanding in its appraisals, which are mainly based on the level of evidence, comparator relevance, interchangeability of the results, and safety. The French regulators urged that in case of a health technology evaluation, the possibility of an unfavourable opinion for drug access should be added to the ESMO-MCBS. Since the CAV impacts drug prices, using the ESMO-MCBS could have led to an increase in French cancer expenses. Nevertheless, the ESMO-MCBS provides an objective tool for health technology assessment bodies to rate CAV and the opportunity for HAS to use the ESMO scale should be further explored.

Report on the ESMO/SIOPE European Landscape project key results regarding the status and needs in AYA cancer care

Emmanouil Saloustros of the General Hospital in Heraklion, Greece underscored that adolescents and young adults (AYA) represent a distinct group of cancer patients. AYAs are poised at the interface between children's and adult's cancer services where specific clinical management and care are needed; therefore, the joint ESMO/SIOPE Cancer in AYA Working Group initiated a survey to explore the practice patterns, knowledge, and available services regarding AYA cancer care provided by health care providers. A link to this online survey was sent by e-mail to European Society for Medical Oncology (ESMO) national representatives plus all members of ESMO and to the European Society for Paediatric Oncology (SIOPE) and was further circulated to several European oncology groups. The questions covered demographics, education, and access to specialised cancer care for AYAs, research and supportive care opportunities, as well as demands for further education. Contingency tables

for each question were calculated and were further explored according to European sub regions using chi-squared and Fisher's exact test.

At ESMO 2017, results from the 266 practitioners responding from Europe were presented out of the 323 responses collected from all countries across the world. More than two-thirds (67%) of respondents reported that they do not have access to specialised centres for AYA with cancer. In addition, 69% of respondents reported not being aware of any cancer research studies or clinical trials focused on AYA, and 67% said they had no access to a specialist cancer service for late side effects management. The majority of the professionals responding said there had the ability to refer AYA patients to professional psychological support and specialised social workers. However, more than half reported no access to an age-specialised nurse, specialised AYA cancer education, or to AYA-specialised learning mentor. Furthermore, 38% of responding oncology professionals reported that their AYA cancer patients do not have access to fertility specialists, a figure that rose to 76% in Eastern Europe. In general, the lack of specialised AYA cancer care was more profound for practitioners from Eastern and South Eastern European countries. Saloustros *et al.* Abstract 1438O_PR

Note: The results from this survey have been simultaneously published in the *ESMO Open*. Saloustros E, Stark D, Michailidou K, *et al.* *ESMO Open*; Published online 8 September 2017. DOI: 10.1136/esmoopen-2017-000252

Practice point and future research opportunities

Less than one half of European health-care providers who treat AYA with cancer have access to specialised centres and research initiatives for this specific group of patients with unique needs. This survey revealed that specialised AYA cancer care is not uniformly available across Europe, with significant inequities existing in the provision of AYA cancer care. Improving care using education and research focused on AYA cancers is a growing priority for both ESMO and SIOPE.

Survey results show the delivery of paediatric radiation therapy varies across Europe

Lead author Charlotte Demoor-Goldschmidt of the French Institute of Health and Medical Research, Paris, France presented findings showing that increased focus has been placed upon improving the quality of care for children with cancer and to provide access to European trials in paediatric oncology. With colleagues, she prepared a survey regarding paediatric cancer care and invited experts in paediatric radiation oncology by email to complete the 21-point questionnaire. The investigators collected the 69 responses, which represented 24 countries (7 centres with proton) and visited 16 centres. The study was supported by the SIOPE, ESTRO, PROS, and several national paediatric haematology-oncology societies.

Although the respondents agreed that specific knowledge is needed to treat paediatric oncology patients, the access to paediatric radiotherapy treatment is unequal throughout Europe. The responses also showed that few (11.74%) radiation oncologists treat only children, which is in contrast with paediatric oncologists and surgeons where 93.44% and 71.67%, respectively, are dedicated to paediatric patients.

In 5 responding countries, paediatric radiotherapy was centralised in one centre. As to the techniques used, 12% of respondents reported using 2D- conventional radiotherapy 'sometimes,' meaning for some patients, 4% still use Cobalt, and 15% never or rarely use Intensity Modulated Radiotherapy (IMRT), whereas the majority (64%) use hypofractionated treatments, defined as at least 3 Gy per fraction, and 32% use hypofractionated treatments of 5 Gy or more.

Regarding the centres employed in paediatric oncology, 84% of respondents had access to paediatric devices for personalised immobilization and, when necessary, radiation treatments could be delivered under anaesthesia in 75% of the centres, or under hypnosis in 9% of centres located in 2 countries. The centres had an environment that was adapted to children, with dedicated waiting areas in 47% of centres, 98% of centres provided gifts to the patients, 93% offered the possibility to listen to music and 12% offered patients the opportunity to watch cartoons. Patient information was readily available in 83% of the centres. Demoor-Goldschmidt *et al.* Abstract 1439O_PR

Practice point and future research opportunities

This survey attempted to quantify the healthcare inequalities currently existing for children and adolescents who need radiotherapy in Europe. Nevertheless, an effort to guarantee quality treatment with the local environment was noted.

SARCOMA

Adjuvant imatinib shows benefit over control only in patients with high-risk GIST: Final results of the EORTC STBSG, AGITG, UNICANCER, FSG, ISG, and GEIS trial

Paolo Casali of the Adult Mesenchymal Tumour and Rare Cancer Medical Oncology Unit, Fondazione IRCCS - Istituto Nazionale dei Tumori in Milan, Italy presented final results from an intergroup, randomised trial of adjuvant imatinib versus no further therapy after R0-R1 surgery for gastrointestinal stromal tumour (GIST). The open label, multicentre, phase III trial was conducted at 112 hospitals in 12 countries. Patients were randomly assigned to two years of 400 mg imatinib daily (n=454), or no further therapy after surgery (n=454). The primary endpoint was imatinib failure-free survival (IFFS), and secondary endpoints included relapse-free survival (RFS), relapse-free interval (RFI), overall survival (OS) and toxicity.

At a median follow-up of 9.1 years, 835 patients were eligible for analysis. There was no significant difference between arms for IFFS or OS at 5 and 10 years. The 5- and 10-year IFFS rates were 87% and 75% with imatinib versus 83% and 74% in the controls (hazard ratio [HR] 0.87, 95.7% confidence interval [CI] 0.65, 1.15; $p = 0.31$). The 5-year OS rates were 93% versus 92% and 10-years OS rates were 80% versus 78%, in the imatinib and controls arms, respectively (HR 0.88, 95% CI 0.65, 1.21; $p = 0.43$).

However, RFS was significantly improved with imatinib; RFS at 5 years was 70% with imatinib versus 63% in the control arm and 10-year RFS was 63% versus 61% in the respective arms (HR 0.71, 95% CI 0.57, 0.89; $p = 0.002$). In addition, benefit with imatinib was seen in the subgroup of 526 patients with local pathology confirmed high-risk GIST. At 10 years, the IFFS rates were 69% versus 61%, and RFS rates were 48% versus 43% in the imatinib and control arms, respectively. Casali *et al.* Abstract LBA55

Practice point and future research opportunities

In terms of adjuvant treatment with KIT inhibitors, it seems that apoptotic rather than secondary resistance is the problem and will be addressed by future hypotheses in the field.

After 9.1 years of follow-up, a trend toward better long-term IFFS and RFS in imatinib treated patients was observed in the high-risk subgroup that was not statistically significant but was consistent with results reported by the Scandinavian/German trial, which demonstrated a small but sustained long-term OS benefit in high risk GIST patients receiving 3 years of adjuvant imatinib. These findings discourage the use of imatinib in low-risk patients with GIST.

DCC-2618, a novel pan-KIT and PDGFR α inhibitor, shows encouraging anti-tumour activity in patients with GIST

Filip Janku, Assistant Professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston, USA explained that the tyrosine kinase inhibitors (TKIs) already approved in the treatment of gastrointestinal stromal tumour (GIST) primarily target either exons 13 and 14 of the ATP binding pocket or a subset

of activation loop mutations found in exons 17 and 18 of KIT, but they are not active across both regions, which are known to mediate imatinib resistance, leaving a gap in the inhibitory coverage of known KIT resistance mutations. DCC-2618 is a potent kinase switch control inhibitor that has activity across a broad range of treatment emergent mutations.

Professor Jaku and colleagues conducted this dose-escalation study of oral DCC-2618, which was administered at doses ranging from 40 to 400 mg once or twice daily for 28 days in patients with pre-treated TKI resistant GIST. This phase was followed by an escalation phase wherein patients received DCC-2618 at 150 mg per day. KIT or PDGFR α -driven GIST was confirmed in 30 and 3 of the 42 enrolled patients, respectively. The patients had received a mean of 4.8 prior lines of therapy.

FDG-PET scans performed at baseline and after 3 weeks of treatment showed 15 (79%) of the 19 patients with KIT mutant GIST had a partial metabolic response by EORTC RECIST criteria. According to the authors, tumour metabolism is indicative of the response in patients with GIST and metabolic changes have been shown to precede a significant decrease in tumour size on computed tomography scans, which were done every 2 treatment cycles. Conversely, lack of metabolic response on FDG-PET may signal treatment resistance. Of the 23 evaluable patients, 2 patients achieved partial response. Six of the 11 evaluable patients receiving DCC-2618 at doses of ≥ 100 mg/day demonstrated progression free survival lasting more than 6 months, including 5 patients on DCC-2618 at cycle 10.

Next generation sequencing of plasma cell-free DNA was performed throughout the study revealed a reduction of mutation allele frequency (MAF) in KIT exons 9, 11, 13, 14, 17, and 18.

DCC-2618 was well tolerated by the 42 patients included in the safety analysis. Grade 3 /4 adverse effects (AEs) that were reported >1 patient included anaemia in 15 patients, asymptomatic lipase increase in 7, hypertension in 4, creatinine phosphokinase in 2, and lower gastrointestinal haemorrhage in 2 patients. Dose limiting toxicities of grade 3/4 lipase increase occurred in 2 of the patients receiving DCC-2618 at 100 mg and 200 mg twice daily and in one patient with CPK on 150 mg per day. NCT02571036. Janku *et al.* Abstract 1473O.

Practice point and future research opportunities

Patients with heavily pre-treated GIST showed promising objective responses and achieving prolonged stable disease after treatment with DCC-2618, novel pan-KIT and PDGFR α kinase switch control inhibitor.

The notable decreases in MAF of resistance mutations across all exons supports the use of DCC-2618 beyond imatinib resistance.

SUPPORTIVE AND PALLIATIVE CARE

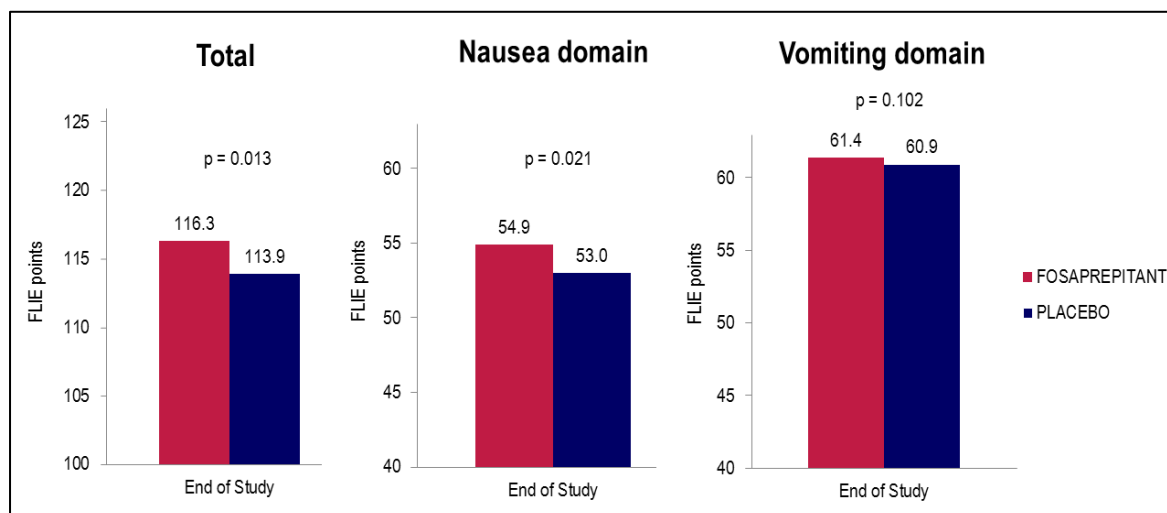
Neurokinin-1 receptor antagonist provides quality of life benefit during concomitant chemoradiotherapy for cervical cancer

Christina H. Ruhlmann of the Department of Oncology, Odense University Hospital, Odense, Denmark presented findings from data analysis supporting the secondary endpoint of the multinational, randomised, double-blind, placebo-controlled phase III GAND-emesis trial. GAND investigated the efficacy and safety of fosaprepitant, a neurokinin-1 receptor antagonist, combined with palonosetron and dexamethasone in preventing nausea and vomiting in women with cervical cancer receiving 5 weeks of fractionated radiotherapy and concomitant weekly cisplatin. The study demonstrated a 17% increase in the proportion of patients that were able to complete the full five weeks of treatment without vomiting with the addition fosaprepitant to palonosetron and dexamethasone¹. In the GAND-emesis trial, 118 patients received fosaprepitant and 116 patients received placebo. All patients completed the Functional Living Index – Emesis (FLIE) questionnaire comprising 18-items that measure the impact of nausea (9 items per domain) and vomiting (9 items per domain) on daily functional life baseline and at end of study (EoS). The scores for each domain and the total score were calculated according to the FLIE Manual with domain scores ≥ 54 and a total score ≥ 108 indicative of no, or minimal impact on daily life. Nine patients were excluded due to invalid questionnaires.

The findings presented at ESMO 2017 evaluated the difference in impairment of daily functional life between both treatment groups as a result of nausea or vomiting. The baseline point scores were similar between the fosaprepitant and placebo cohorts; patients receiving fosaprepitant had scores of 59.9 compared to 60.3 with placebo for the nausea domain ($p = 0.31$). The scores for the vomiting domain were 61.9 versus 62.1 ($p = 0.16$), and the total scores were 121.8 versus 122.4 for patients receiving fosaprepitant versus placebo, respectively ($p = 0.37$).

The difference between the fosaprepitant and placebo groups according to an analysis using the Kruskal-Wallis H test at EoS showed a statistically significant difference in the point scores for the nausea domain and the total score between the fosaprepitant and placebo cohorts. The nausea domain scores were 54.9 versus 53 ($p = 0.02$), the vomiting domain scores were 61.4 versus 60.9 ($p = 0.10$), and the difference in the total scores was 116.3 versus 113.9, in the fosaprepitant and placebo cohorts, respectively ($p = 0.01$).

Mean FLIE point scores at end of study are shown on graph below.



© Christina H. Ruhlmann.

EudraCT number: 2009-014691-21, NCT 01074697. Ruhlman *et al.* Abstract 1540O

Citation: 1. Ruhlmann CH, *et al. Lancet Oncol* 2016;17(4):509–518.

Practice point and future research opportunities

The authors are to be congratulated for providing data for the first time on a neurokinin-1 receptor antagonist containing regimen in chemo-radiotherapy induced nausea and vomiting in a randomised fashion, and moreover for first time showing data about the impact of nausea on daily function in chemo-radiotherapy.

The addition of fosaprepitant to palonosetron and dexamethasone improved emetic control and also provided a clinically and statistically significant reduction of the impact of nausea on patients' daily functional life.

Patients' viewpoint may not be reflected by investigator-reported clinical trial toxicity

Yvonne Brandberg of the Oncology-Pathology Department, Karolinska Institutet in Stockholm, Sweden, reported that patient experience assessed in health related quality of life (HRQoL) questionnaires does not mirror investigator toxicity reporting for many symptoms. Dr. Brandberg and colleagues compared HRQoL by patient assessment to toxicity reporting by physicians in clinical trials and found little agreement on many symptoms between the two, indicating that patients and investigators may not be on the same page regarding the overall patient clinical trial experience.

The investigators reviewed the agreement between toxicity items reported by physicians using the Common Terminology Criteria for Adverse Events, version 3.0. (CTCAEs) and patient-reported HRQoL items in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Data collected from assessments made at the end of treatment in PANTHER, a randomised phase III trial, was used for this analysis. The trial evaluated dose dense versus standard administration of adjuvant

chemotherapy in women with high-risk breast cancer, the majority of whom had node positive disease¹.

For this analysis, 3 researchers individually selected items from the EORTC QLQ-C30 that they considered comparable to CTCAE criteria, according to ordinal data that were analysed by Goodman and Kruskal gamma methods. The analysis included data from 1428 event-free patients and investigated the relation between 13 toxicities and 36 EORTC QLQ-C30 items, with some patients having more than one toxicity.

The investigators found little agreement between physician evaluated toxicities by CTCAE criteria and the true patient experience, as reported on HRQoL questions, prompting them to conclude that these findings should raise concerns on how to best evaluate HRQoL and toxicities in clinical trials.

A strong association (0.5 to 1.0) or strong agreement was seen between physician assessed toxicity and patient-reported outcomes for the HRQoL scale questions 17 “Have you had diarrhoea?” and 15, “Have you vomited?” The relation between the reports for diarrhoea was 0.53 (range 0.47 to 0.59) and the relation for vomiting was 0.50 (range 0.39 to 0.62).

The relation was moderate (0.30-0.49) for HRQoL questions 10, 12, and 8 relating to fatigue (relation 0.35, 0.35, and 0.42, respectively). Physician rated “pain” was moderately related to patient ratings on question 9, the relation was 0.31 (0.25 to 0.37).

All of the comparisons between the nine remaining physician-reported toxicities and patient-reported HRQoL scores and toxicity showed weak or no relation. Brandberg *et al.* Abstract 1422O.

Citation: 1. Foukakis T, *et al.* *JAMA* 2016;316(18):1888-1896.

Practice point and future research opportunities

This large trial provides a valuable perspective that can inform understanding of treatment toxicities. The questions arising from this study are who is right: patient or clinician, and are patient reported outcomes really that helpful. Patient and clinician reports of symptoms, particularly symptomatic toxicities during cancer treatment, provide discrepant yet complementary data. There are two potential views of the situation: 1. *more patient-centred view*: the patient is always right by definition because nobody (not even the most sensitive clinician) can truly know another person’s subjective experience; 2. *more traditional view*: the clinicians should be considered right because they have an “objective” perspective based on experience and training.

It is questionable whether it is possible to combine these views. Three potential approaches are: 1) “Independent reporting,” in which patient and clinician toxicity data are collected, analysed, and reported completely separately from each other; 2) “Merged reporting,” in which patient and clinician data are collected separately and then merged analytically into a single metric; and 3) “Collaborative reporting,” in which patients directly report symptomatic toxicity information, which is then provided to clinicians to inform their CTCAE reporting.

TRANSLATIONAL RESEARCH

Expanding the use of approved drugs: The CPCT's Drug Rediscovery Protocol

Daphne Van der Velden, Molecular Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital in Amsterdam, the Netherlands explained that following regulatory drug approval, the identification of signals of activity in cancer subsets outside the approved indication would benefit both patients and pharma. Whole Genome Sequencing is offered to systemically treated cancer patients by the Netherlands' precision oncology network, which allows the detection of a spectrum of potentially actionable genetic aberrations across all cancer types. In addition, the Drug Rediscovery Protocol provides access for patients with these aberrations to genetically matched treatment upon central review of their tumour profile.

Dr. Van der Velden and a team of researchers initiated this study, which enrolled adult patients with no standard treatment options for solid tumours, including glioblastoma, lymphoma or multiple myeloma. Patients were required to have a fresh tumour biopsy for biomarker research and they were enrolled in multiple parallel cohorts, each defined by one tumour type, one tumour profile and one treatment. Efficacy is analysed per cohort using a Simon-2-stage approach, aimed at achieving one or more clinical benefit of complete (CR) or partial response (PR) or stable disease (SD) lasting ≥ 16 weeks) per every 8 patients in stage I, and ≥ 5 per 24 in stage II (85% power, α error rate 7.8%). Currently, 23 hospitals are participating hospitals and 10 pharmaceutical companies have supplied 19 study drugs.

Since the study launch in September 2016, approximately 250 cases were submitted for review and about one-third of these patients began treatment. Clinical benefit was observed in 37% of the study patients, including 6% of patients with CR and 14% of patients with PR. SD ≥ 16 weeks was achieved by 17% of patients. All CRs and approximately 66.6% of PRs were ongoing at data cut-off and awaiting ≥ 30 days confirmation.

Approximately two-thirds of case submissions were not taken forward due to general protocol ineligibility (18%), current unavailability of matching study drugs (17%), no detection of actionable target (15%), negative evidence for target-drug-match (13%), eligibility for standard treatment (12%), eligibility for competing trials (11%), loss to follow up (10%) and where the genetic tumour profile had not yet been assessed (4%). NCT02925234; EudraCT 2015-004398-33. Abstract Van der Velden *et al.* LBA59_PR

Practice point and future research opportunities

These findings show that execution of a national multi-drug and multi-tumour precision oncology trial is feasible. Whole genome sequencing in many different cancer types, can identify subgroups of patients that may benefit from existing drugs outside of their registered indication. Therefore, this study accelerates translation of new findings to the clinic and increases the yield of existing therapies.

RELATED INFORMATION

Click [here](#) to access the Congress abstracts.

Click [here](#) to access the meeting webcast page.

Save the date

[ESMO 2018 Congress Munich, Germany, 19-23 October 2018.](#)

Affiliations and Disclosure

Affiliation

Dr Svetlana Jezdic, ESMO Head Office.

Disclosure

No conflicts of interest to disclose.

Acknowledgment

ESMO would like to thank you Virginia Powers, PhD for editorial assistance in preparation of this report.

ESMO would like to thank you Drs Laurie Gay, Miguel Martin, Suzette Delaloge, Nina Radosevic-Robin, Angelo Di Leo, Didem Şener Dede, Zev Wainberg, Michael Hofman, Daniel D. Petrylak, Ronald de Wit, Axel Bex, Amit M. Oza, Alejandro Martinez Bueno, Remco J. Molinar, Dan P. Zandberg, Robert Haddad, Bonnie S. Glisson, Jeffrey Weber, Kate Young, Jules Derks, David Planchard, Christina H. Ruhlmann.

for giving their permission to publish the images from the studies presented during the ESMO 2017 Congress in the ESMO Scientific report.

© Copyright 2017 European Society for Medical Oncology. All rights reserved worldwide.