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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO 2018

Immuno-Oncology Congress

13-16 December 2018

Geneva, Switzerland

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Introduction

The annual Immuno-Oncology Congress of the European Society for Medical Oncology (ESMO) was held from 13 to 16 December 2018, in Geneva, Switzerland. Oncology professionals from across the globe gathered together to hear the newest research and to discuss the current issues, including future strategies for innovation in this fast-paced field of cancer treatment.

There were 1'031 attendees at this relatively new congress, including 859 delegates, 88 faculty, 30 merit award recipients, 43 industry exhibitors, and 11 members of the press. Delegates came from 60 countries in Europe, the Middles East, Asia, Africa, Australia and the Pacific region, as well as North, Central, and South America. The host country, Switzerland, was represented by the most delegates (20.9%), while 12.7% of delegates traveled from the United States of America, 7.5% came from the United Kingdom, 6.3% from France, and 5.6% from Germany, followed by the Netherlands and Belgium, which each accounted for approximately 3.5% of the delegate population. Denmark, Italy, and Spain each were represented by approximately 2.4% of delegates. The attendees were mostly in the 31 to 60 year age range, and nearly half (45.4%) were women.

Clinicians comprised the largest proportion of attendees (55.4%), with basic researchers making up 34.3%. Pharmacists, statisticians, medical students, undergraduate science students, nurses, and patient advocates accounted for 4.4% to 0.6% of delegates. The primary activities of delegates within these broad classifications included medical oncology, which made up 29.2% of delegates, followed by industry medical staff (12.1%), basic research/science (10.1%), industry commercial staff (9.1%), clinical research (7.1%), clinical oncology (5.8%), biology (5.7%), immunology (5.4%), haemato-oncology (3.5%), surgical oncology (1.8%), radiation oncology (1.5%), and 1.2% each of delegates cited oncology pharmacist and data specialist as their occupation. Chest physicians, paediatric oncologists, gastroenterologists, nurses, and other healthcare professionals represented from 0.1% to 1.0% of delegates.

Congress participants expressed interest in a broad range of topics across the spectrum of oncology that brought them to this congress. In all, 37.9% of attendees indicated that non-small cell lung cancer was their primary interest, followed by all gastrointestinal malignancies (37.4%), breast cancer (34.1%), melanoma (26.3%), small-cell lung cancer (23.6%), and colon/rectal cancer (22.7%). Other delegates commented that the topics they most wanted to hear about at the congress included all chest malignancies (20.8%), prostate cancer (16.8%), gynaecological malignancies (16.6%), haematological malignancies (16.6%), and genitourinary cancers (15.7%). Other topics of interest were skin, gastric, pancreatic, and ovarian cancer, as well as renal cell carcinoma, sarcoma, central nervous system malignancies, and mesothelioma (14.5% to 10.1%).

More than half of the delegates (53.2%) stated that they were interested in learning about the latest in immunotherapy, while 46.0% stated an interest in tumour immunology followed

by clinical research (44.5%), and cancer biology (44.1%). Translational research was cited by 36.3% of respondents as their primary topic of interest, basic science by 22.8%, and 20.3% of delegates said personalised cancer medicine was the topic that brought them to ESMO Immuno-Oncology 2018.

Of the 210 scientific submissions received, 116 were presented that covered these topics plus a host of others. The largest percent of submissions came from the United States (12.4%) and the United Kingdom (10%), with Spain, China, Italy, and France contributing 8.1% to 6.2% of submissions. The Russian Federation, Netherlands, Republic of Korea, and Germany completed the top 10 contributors of scientific papers. Eighteen of the accepted abstracts were presented in oral or mini-oral sessions, with the remainder being presented as quality posters.

ESMO Immuno-Oncology 2018 assembled a faculty of experts in this rapidly evolving field to provide a discourse on the increasing number of trials testing immunotherapy as monotherapy and in chemotherapy combination treatments. Therapeutic strategies for utilising immunotherapy in the first-line setting and beyond were discussed, including in rare cancers where patients currently have limited treatment options, as well as the use of immunotherapy as adjuvant and neo-adjuvant treatment in many cancer types. A brief summary of the advances in immunotherapy that were presented at the ESMO 2018 Immuno-Oncology Congress follows.

BIOMARKER DEVELOPMENT

Similar incidence of fast progression observed following atezolizumab or docetaxel treatment in NSCLC

David R. Gandara, Internal Medicine, Haematology-Oncology, University of California Davis Cancer Centre, Sacramento, USA presented data on behalf of colleagues from a study designed to determine whether fast progression was more predominant in non-small cell lung cancer (NSCLC) patients who were treated with atezolizumab than those receiving docetaxel in the OAK trial. This analysis used fast progression (FP) as a surrogate for the rare phenomenon, hyper-progressive disease (HPD), which has emerged in some patients treated with immunotherapy in clinical trials. HPD is characterised by rapid tumour growth rate and accelerated disease progression following PD-L1 checkpoint inhibitor therapy. HPD has been associated with age more than 65 years,[1] and the presence of epidermal growth factor receptor (EGFR) mutation,[2] and is characterised by poorer overall survival (OS). Since assessment of HPD requires an evaluation of pre-treatment tumour growth rates, this study used the surrogate of FP, which was defined as an increase of 50% or more in the sum of the longest diameters of tumours (SLD) from baseline to first assessment at 6 weeks, or upon death due to disease progression (PD). PD was evaluated by the investigator without a post-treatment scan within 12 weeks of treatment.

The phase III OAK study compared checkpoint inhibition with atezolizumab versus docetaxel chemotherapy in the second- and third-line settings in 850 patients with NSCLC. In OAK, superior median OS of 13.8 months was observed with atezolizumab compared to 9.6 months with docetaxel (hazard ratio [HR] 0.73) in the intent to treat (ITT) population. In order to examine FP, the investigators first categorised fast progressors in the two treatment arms; similar numbers of patients in both treatment arms met the criteria for FP and/or HPD. The investigators then reviewed the baseline characteristics of FP and non-FP patients for selected pre-treatment factors that could be correlated with FP for a comparison between the atezolizumab and docetaxel treatment arms. The OS per arm was evaluated according the selected factors, which included early treatment failure with the previous therapy, lactate dehydrogenase (LDH) levels ≥225 units/L, SLD ≥80 mm, and ≥3 metastatic sites. The proportion of patients having the selected baseline factors for fast progression was equivalent in the two treatment arms; 44 (10.4%) patients on atezolizumab compared to 41 (9.6%) patients on docetaxel met the criteria for fast progression. The overall baseline characteristics were generally similar between arms, except the atezolizumab arm contained more male patients, more non-smokers, and fewer (10 [31%] versus 15 [44%], atezolizumab versus docetaxel) patients that had demonstrated early failure to prior treatment. In both arms, the majority of patients had been heavily pre-treated.

Regarding the cohort of patients having baseline indicators for fast progression, 24 (55%) patients in the atezolizumab arm versus 21 (51%) patients in the docetaxel arm had baseline LDH ≥225 units/mL, and 21 (48%) versus 18 (44%) patients had baseline SLD ≥80 mm, respectively. In the respective cohorts, 32 (73%) versus 28 (68%) patients had 3 or more

metastatic sites at baseline and 10 (31%) versus 15 (44%) had experienced failure of their previous treatment within 180 days of initiation. In addition, 21 (48%) versus 20 (49%) patients were aged ≥65 years, and 3 (7%) versus 2 (5%) patients were EGFR mutation positive, therefore, having factors associated with HPD. Another variable associated with poor prognosis is PD-L1 expression on tumour or immune cells; PD-L1 was expressed in 25 (57%) patients on atezolizumab versus 24 (59%) of patients on docetaxel, and PD-L1 was as not expressed in 19 (43%) versus 17 (42%) of patients, respectively.

An evaluation of OS according to each pre-treatment risk factor for FP indicated median OS was improved overall with atezolizumab over docetaxel; the superior benefit with atezolizumab was consistent across all subgroups defined by baseline factors associated with aggressive disease. Median OS was 8.9 months with atezolizumab versus 6.2 months with docetaxel in patients showing early progression on prior treatment. Patients with high baseline LDH levels had median OS of 11 versus 8.9 months, median OS was 9.4 versus 6.9 months in patients with high SLD, and patients with ≥3 metastatic sites demonstrated median OS of 11.7 versus 8.6 months with atezolizumab versus docetaxel, respectively. Twenty (45%) patients receiving atezolizumab and 12 (29%) patients on docetaxel demonstrated an SLD change ≥50% from baseline within 6 weeks. In the respective treatment arms, 24 (55%) versus 29 (71%) patients died due to disease progression within 12 or fewer weeks of treatment. Equivalent proportions of patients in each treatment arm experienced fast progression, which suggested to the authors that rapid post-baseline progression is not specific to atezolizumab or anti–PD-L1 therapy in general. NCT02008227. Gandara *et al.* Abstract LBA1

Practice point and future research opportunities

Similar proportions of patients treated with atezolizumab or docetaxel showed post-treatment fast progression. The OS was improved across all subgroups of patients with NSCLC treated with atezolizumab compared with chemotherapy, including patients with poor prognostic factors. Additionally, this analysis found no evidence of quicker disease progression with the PD-L1 monoclonal antibody atezolizumab compared to docetaxel chemotherapy, suggesting this may not be a phenomenon solely related to cancer immunotherapies, as has been previously suggested.

Citations:

1. Champiat S, Dercle L, Ammari S, *et al.* Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. *Clin Cancer Res* 2017; 23(8):1920-1928.

2. Kato S, Goodman A, Walavalkar V, *et al.* Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. *Clin Cancer Res* 2017; 23(15):4242-4250.

Advanced CT imaging reveals features defining distinct tissue immune profiles with prognostic utility in NSCLC

Giulia Mazzaschi, Medicine and Surgery, University Hospital of Parma, Parma, Italy and colleagues used computed tomography (CT) scans to investigate the tumour immune microenvironment (TIME), with the aim of providing a non-invasive approach to identifying new prognostic factors in patients with non-small cell lung cancer (NSCLC).

The study comprised 60 patients that had undergone surgical resection; of these, the histology was adenocarcinoma in 31 patients and squamous cell carcinoma in 29 patients. TIME was defined by the quantitative assessment of PD-L1 expression plus detailed morphometric evaluation of tumour infiltrating lymphocytes (TILs). Using tumour associated images, the investigators extrapolated 841 CT radiomic features with open-source (3-D Slicer) software.

The investigators found high levels of tissue PD-L1 in radiologic lesions having a solid texture and any effect on the surrounding parenchyma ($p < 0.05$), whereas TILs-rich areas were characterised by well-defined CT margins ($p < 0.05$).

An analysis determining whether predetermined risk factors from TIME and CT texture revealed a strong association with clinical outcome. Patients having low PD-1 expression on CD8+ TILs and CT evidence of tumour effect on parenchyma showed significantly increased overall survival (OS) compared to patients without PD-L1 expression; median OS was 50 versus 30 months, respectively (hazard ratio [HR] 16.82). Prolonged survival of 46 versus 35 months was also observed in patients having well-defined CT margins and a high ratio of CD8-to-CD3 TILs versus patients whose tumours were without these tumour characteristics (HR 2.66; $p < 0.05$). When the investigators applied an unsupervised hierarchical clustering model they identified two clusters with oppositely regulated features: 57 cases showed further branching into two continuous different clusters, whereas tumour samples from 3 patients shared similar profiles: genetic (EGFR and KRAS mutations), an immunologic (PD-L1, CD3+, and CD8+ TILs, and PD-1/CD8 ratio), and radiologic profile (similar shape, effect, texture and structure), and clinical (regarding relapse and death). Mazzaschi *et al.* Abstract 1O

Practice point and future research opportunities

The authors propose that a highly significant prognostic score can be obtained in NSCLC by integrating TIME with CT features. This study shows distinct tissue immune backgrounds that may contain imaging textures, which may potentially be able to characterise a radiologic signature in lung cancer.

Greater response to anti-PD-L1 therapy is observed in patients with multiple tumour types and *BRCA2, NFE2L2, ARID1A* and *NOTCH1* somatic mutations

Michael Kuziora, Translational Medicine, MedImmune, Gaithersburg, USA and colleagues investigated whether somatic mutations in specific genes can sensitise tumours to immunotherapy by determining the association between mutations detected in circulating tumour DNA (ctDNA) and outcomes following anti-PD-L1 therapy with durvalumab. The investigators used data from patients with non-small cell lung cancer (NSCLC) or PD-L1-positive head and neck squamous cell carcinoma (HNSCC) participating in 3 nonrandomised phase II trials. All patients had advanced solid tumours and were treated with durvalumab at 10 mg per kg every 2 weeks. A next-generation sequencing (NGS) panel comprised of 73 genes was used, and ctDNA mutations in a discovery set of 116 NSCLC and 33 urothelial carcinoma (UC) pre-treatment samples were examined. This evaluation identified 7 genes harbouring mutations that enriched for response according to RECIST v1.1. These genes were then tested in a validation cohort containing samples of 217 NSCLC, 130 UC, 48 gastroesophageal cancer, 36 hepatocellular carcinoma, 52 microsatellite instability positive cancers, 40 ovarian cancer, 32 pancreatic cancer, 50 HNSCC, 34 triple negative breast cancer, 16 small-cell lung cancer, 18 sarcoma, 21 HPV-positive cancers, 22 uveal melanoma, 18 cutaneous melanoma, and 6 nasopharyngeal carcinoma samples.

Analysis of the discovery cohort, showed that patients responding to durvalumab had higher prevalence of mutations in the *BRCA1* and *2, NFE2L2, NOTCH1, PIK3CA, ARID1A,* and *APC* genes than non-responders (odds ratio [OR] 1.3-9). In the validation cohort, which comprised multiple tumour types, associations between *BRCA2, NFE2L2, NOTCH1* and *ARID1A* mutation and response were consistently observed (OR 1.9-2.3). Mutations in the *BRCA2, NFE2L2, NOTCH1,* and *ARID1A* genes were associated with significantly higher tumour mutational burden (TMB) in multiple tumour types in the Cancer Genome Atlas (TCGA). The prevalence of these mutations ranged from 0 to 26% or from 0 to 20% in the TCGA or a ctDNA clinical database, respectively.

The authors observed that somatic mutations in specific genes sensitise tumours to anti-PD-L1 treatment across multiple tumour types. Patients in the validation cohort with *BRCA2* mutations had an objective response rate (ORR) of 26% (95% confidence interval [CI], 16% - 38%) compared to patients with *BRCA2* wildtype (ORR 13%; 95% CI 11%, 16%; p = 0.006). Patients with *BRCA2* mutation also showed longer numerical median duration of response (DoR) of 12.4 months compared to 8.4 months with wildtype across all tumour

types. Patients with mutations in *NFE2L2* had an ORR with durvalumab of 27% (95% CI 12%, 46%) compared to wildtype, ORR 14% (95% CI 11%, 16%; p = 0.059). Mutation in *NFE2L2* occurred in the Neh2 domain, which binds the negative regulator KEAP1, activating this transcription pathway. Patients with mutations in the *NOTCH* and *ARID1A* treated with durvalumab had ORR of 23% and 21% versus ORR 14% and 13% in patients with wildtype, respectively. NCT01693562, NCT02087423, NCT02207530. Kuziora *et al.* Abstract 2O

Practice point and future research opportunities

While tumour TMB has emerged as a promising predictive biomarker for anti-PD-1/anti-PD-L1 therapies, this study demonstrated that somatic mutations in specific genes can sensitise several tumour types to immunotherapy with durvalumab. An association was determined between mutations detectable in ctDNA and outcomes on durvalumab therapy. Mutations in specific genes also associated with higher TMB. This seems a promising approach to identifying a biomarker for response to immunotherapy that warrants further consideration.

CELL THERAPY

T cell therapy with EBV-specific cytotoxic T-lymphocytes shows promise in patients with nasopharyngeal carcinoma

Although nasopharyngeal carcinoma (NPC) is an Epstein-Barr virus (EBV)-related malignancy that is highly chemo-radiosensitive, approximately one-third of patients are deemed incurable due to metastatic or recurrent disease, according to Paolo Pedrazzoli, Oncology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. Malignant cells express antigenic viral proteins providing a good target for immunotherapeutic strategies. Most of the clinical data using EBV specific T-cell therapy is from the setting of EBV-related post-transplant lymphoproliferative disorders; however, this therapeutic approach has been recently applied to solid tumours. This observation prompted Professor Pedrazzoli and colleagues to investigate EBV-specific T-cell therapy in patients with NPC failing conventional treatment.

The investigators noted that feasibility of expanding EBV-targeted cytotoxic T lymphocytes (CTLs) by stimulation with EBV-transformed lymphoblastoid cell lines (LCLs) has been demonstrated, and previous clinical trials have administered 2 or more doses of EBV-CTLs at a dose of 4-40 x 10^7/dose, supported by in vivo rhIL-2 infusion and, in some cases, pre-treatment with lymphodepleting chemotherapy or immunotherapy. To date, more than 60 patients in various centres have received this therapy for refractory/relapsed advanced NPC. The objective response rate is approximately 20%, which included some complete responses. Safety for this treatment had been demonstrated with patients having no or limited adverse events. The investigators are testing ways to enhance clinical activity and improve these encouraging results by administering the CTL therapy in earlier stages of disease, such as, immediately after first-line chemotherapy in relapsed patients. This attempt seems to improve overall survival as compared with conventional therapies, and justifies a prospective trial in this specific setting. Additionally, sequential combination of CTL therapy with other agents, such as checkpoint inhibitors, could yield optimal results. Perdrozzoli *et al.* Abstract 31O

Practice point and future research opportunities

EBV-specific CTL therapy has demonstrated safety and is associated with clinical benefit in patients with refractory or metastatic NPC. These encouraging results warrant further study.

Combined interferon-alpha and adoptive T cell therapy demonstrates clinical benefit in patients with metastatic melanoma who failed all prior therapies

Monique K. van der Kooij, Department of Medical Oncology, Leids Universitair Medisch Centrum (LUMC) in Leiden, Netherlands, explained that standard-of-care immunotherapies in melanoma target the interaction between the tumour and T cells. However, many patients have insufficient numbers of tumour-specific T cells present, which prompted Professor van

der Kooij and colleagues to investigate whether these patients could benefit from adoptive cell transfer (ACT) with melanoma-specific T cells. The study enrolled 24 patients with progressive metastatic melanoma who had failed at least one previous treatment for melanoma; 19 of the enrolled patients had failed extensive prior treatment with a BRAF/MEK inhibitor and/or and anti-PD-1, and/or and anti-CTLA4 agents.

Patients usually receive pre-ACT conditioning, which comprises lymphodepleting chemotherapy with or without total body irradiation and post-transfusion high-dose IL-2. However, the investigators employed low-dose interferon-alpha instead of this more toxic lymphodepletion regimen. One week prior to the first infusion the patients received daily subcutaneous interferon-alpha injections, which was continued as maintenance treatment following the infusions. All patients received up to 3 infusions with ex vivo, expanded tumour infiltrating lymphocytes (TILs) every 3 weeks. Each infusion ranged between 1 to 10 x 10^8 T cells. Total blood count was measured prior to the initiation of interferon-alpha and before each TIL infusion and serum and peripheral blood mononuclear cells were also collected at these time-points. A radiological response evaluation was done on each patient 12 weeks after the first TIL infusion.

Seven (29%) patients showed clinical benefit following the combination treatment and maintained stable disease for an average of 36 weeks. Of the responding patients, 5 (26.3%) continue to maintain stable disease following ACT. Interferon-alpha caused a mild lymphopenia, neutropenia and leukopenia, which decreased after one week of interferon-alpha. The persistence of leukopenia and, particularly, neutropenia was found to be predictive of the response to TIL therapy. Local Ethics Committee P04.085. Van der Kooij *et al.* Abstract 32O

Practice point and future research opportunities

Combination treatment with interferon-alpha and ACT was well tolerated by patients with metastatic melanoma who were resistant or refractory to all prior therapies, including immunotherapy with an anti-PD-L1 agent. Combined interferon-alpha and ACT may represent a new treatment option for this patient population. Furthermore, a biomarker for response was determined in this study; high leukocyte/lymphocyte and platelet/lymphocyte ratios were predictive for response.

Anti-MUC1 CAR-T cells combined with PD-1 knockout engineered T cells shows tumour shrinkage in some patients with non-small cell lung cancer

Size Chen, Department of Oncology, First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China, pointed out that treatment of solid tumours with chimeric antigen receptor (CAR) T-cell technology remains an enormous challenge. Dr. Chen and a team of investigators reasoned that combinational immunotherapy could provide increased efficacy in solid tumours. The team evaluated an anti-MUC1 CAR-T cell construct combined with PD-1 knockout T cells in patients with non-small cell lung cancer (NSCLC). This pilot

study represents the first use of PD-1 engineered knockout technology in human solid cancer. MUC1-specific CARs were constructed using the SM3 scFv. PD-1 gene knockout in the CAR positive T cells was achieved using the CRISPR-Cas9 system and validated by sequencing. The efficiency of transgenic expression was assessed by flow cytometry after lenti-MUC1 CAR retroviral transduction. MUC1-CAR+/PD-1- KO engineered T cells at a dose of $2.5x10^6$/KG were infused in patients over 60 minutes. Following treatment, the patients' general condition, levels of lymphocytes, IL-6, hs-CRP, PCT, CYFRA21, NSE(E), and SCC were monitored at regular intervals. Changes in tumour size were detected by MRI scans.

Data from 6 of the 8 patients enrolled in the study were reported. The patients were aged 36 to 84 years and had stage IIIb to IV NSCLC. All patients showed significant symptom improvements within the first 2 weeks after infusion. Decreased serum CYFRA 21 was observed following infusion, which increased 4 weeks following treatment. Changes in tumour size varied among patients. The efficacy of the combined therapy was case specific with NSCLC patients responding well, while no noticeable response was observed in others. Two patients manifested significant shrinkage in the size of their lung tumours within 4 weeks of infusion; one patient's tumour was reduced from 25x19x22mm to 14x10x26mm. Limited effects on metastasis have been observed with this treatment to date. The noteworthy individual patient response to treatment suggested to the investigators that other unknown factors may confer more sensitivity in a subset of patients. Cytokine release syndrome (CRS) did not occur in any patients, although cytokine levels were increased in 3 of the 6 patients. No other adverse effects were reported. NCT03525782. Chen *et al.* Abstract 33O

Practice point and future research opportunities

Findings from this study suggest that combined MUC1-CAR+/PD-1-knockout therapy is safe and well tolerated by patients. The response was highly individual with some patients demonstrating impressive tumour shrinkage while others showed no noticeable effect. Importantly, no CRS was observed. These intriguing results merit further study.

Tabelecleucel shows promise in patients with rare Epstein Barr virus-associated leiomyosarcomas

Lead author Lauren S. Kurlander, Department of Pediatrics, Weill Cornell New York Presbyterian Hospital, New York, USA pointed out that Epstein Barr virus (EBV) is widespread in all human populations and persists as a lifelong, asymptomatic infection that has been implicated in a wide range of lymphoproliferative disorders, including lymphomas and other cancers. EBV-positive leiomyosarcoma is a rare cancer that develops in patients with immune deficiency that responds poorly to both radiation and chemotherapy.[1] As a result, these patients have limited treatment options and poor outcomes, indicating an unmet medical need. Dr. Kurlander presented an analysis of data from two single-centre, open-label studies, and a multi-centre expanded access protocol study evaluating the safety

and efficacy of tabelecleucel. Tabelecleucel is an investigational, off-the-shelf, genetically unmodified, allogeneic T-cell immunotherapy targeting EBV antigens in patients with EBV-positive leiomyosarcoma that received FDA Breakthrough Therapy Designation in February 2015 for EBV-positive post-transplant lymphoproliferative disorder following allogeneic haematopoietic cell transplant.

In each study, tabelecleucel was administered at a 1.0–2.0 x 10^6 cells/kg/dose on days 1, 8, and 15 of every 4 to 6-week cycle, and imaging was performed before the first dose of each cycle.

Ten of the 12 patients receiving ≥ 1 dose of tabelecleucel were assessed for response; one patient was not evaluable and one patient was too early to assess. In these 10 patients, the objective response rate was 17%; two patients achieved partial response by CT-based RECIST v1.1 criteria. Stable disease was observed in the remaining 8 patients. Survival was median 77.4 months (95% confidence interval, 18 - NE months). Studies having longer follow-up demonstrated that 6 of the 8 responding patients survived 27 or more months. At the time of the analysis, metabolic response data were available for 4 patients participating in study 3. These data showed that 3 (75%) patients had a metabolic response. Tabelecleucel was well tolerated in this population; no new safety signals were observed and the safety profile was consistent with previous reports.[2] NCT00002663, NCT01498484, NCT02822495. Kulander *et al.* Abstract 34O

Practice point and future research opportunities

This analysis represents one of the larger prospective studies of patients with EBV-positive leiomyosarcoma. This study demonstrates that tabelecleucel may provide clinical benefit, based on the combination of CT-based and metabolic responses observed in this study, in a disease that is typically radiation and chemotherapy resistant. Tabelecleucel may be a treatment option for patients with this rare disease.

Citations:

1. Wang Z, Shi N, Naing A, et al. Survival of patients with metastatic leiomyosarcoma: the MD Anderson Clinical Center for targeted therapy experience. Cancer Med 2016; 5(12):3437-3444.

2. Prockop SE, Li A, Baiocchi RA, et al. Efficacy and Safety of ATA129, Partially Matched Allogeneic Third-Party Epstein-Barr Virus-Targeted Cytotoxic T Lymphocytes in a Multicenter Study for Post-Transplant Lymphoproliferative Disorder. Blood 2017; 130:4520.

CLINICAL PRACTICE (INCLUDING TOXICITIES)

PD-1 inhibitor based therapies are less effective for the treatment of metastatic melanoma in patients on proton pump inhibitors

Krisztian Homicsko, Service of Immune Oncology, CHUV in Lausanne, Switzerland and colleagues conducted this retrospective analysis of data from 140 participants in the CheckMate 069 phase II clinical trial. In CheckMate 069 patients with previously untreated, unresectable, or metastatic melanoma received immunotherapy consisting of ipilimumab monotherapy or ipilimumab combined with nivolumab. Although immunotherapy has demonstrated extraordinary results across multiple tumour types in CheckMate and other clinical trials, there is a paucity of data explaining the effect of medications taken for co-morbidities on immunotherapy efficacy, which prompted this analysis.

The investigators compared response rates, progression-free survival (PFS), and overall survival (OS) in patients receiving one or more concomitant treatments with 11 different classes of co-medications. They also compared variables such as disease stage, LDH levels, BRAF status, sex, age, and body mass index. A protein array was also performed for 440 analytes in 135 patients with available pre-treatment serum samples. The investigators conducted univariate analysis, which showed patients with melanoma receiving proton pump inhibitors (PPIs) for co-morbidities derived approximately half the clinical benefit from immunotherapy consisting of nivolumab plus ipilimumab as patients receiving the same combination but not on PPI medication. PPIs are considered to be the most effective drugs for inhibiting gastric acid secretion, and are also sometimes prescribed in asthma.

The effect of PPIs on the efficacy of combination treatment remained consistent across multiple comparisons and in multivariate analysis. Evaluation of the pre-treatment serum samples showed changes in NCAM1/CD56 and CSF3R levels in PPI users, both of which are expressed on neutrophil granulocytes. In accordance with the serum protein analysis, PPI users had significantly increased neutrophil levels at baseline. The impact of PPIs on efficacy was confirmed in an independent cohort of 93 first-line melanoma patients who were treated with nivolumab or pembrolizumab monotherapy. Reduced efficacy was not apparent with patients on PPIs receiving ipilimumab monotherapy. This effect remained consistent across multiple comparisons and in multivariate analysis. The authors suggested that PPIs administered prior to initiating immune therapy may produce a unique inflammatory immune status that interferes with treatment efficacy that interferes with treatment efficacy and PPIs may negatively affect the benefit from PD-1 based therapies in melanoma. NCT01927419. Homicsko *et al.* Abstract LBA2

Practice point and future research opportunities

Patients with melanoma receiving proton PPIs for co-morbidities derived approximately half

the clinical benefit from immunotherapy consisting of nivolumab plus ipilimumab as patients receiving the same combination but not on PPI medication. This analysis of data from the CheckMate 069 trial did not show the same negative impact with ipilimumab monotherapy in patients on PPIs. These results suggest that PPIs should be avoided when possible in patients diagnosed with melanoma and recommended for PD-1-based immunotherapies. It remains unclear if PPI initiation during PD-1 based therapy will have a similar impact. Further studies are required to precisely define the exact mechanism of PPIs impact on systemic immunity. These findings may have additional implications for the design of future immunotherapy clinical trials.

Antibiotics and proton pump inhibitors lessen the efficacy of atezolizumab and docetaxel in NSCLC patients

Myriam Chalabi, Gastrointestinal Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands, discussed the results of a retrospective analysis of pooled data from the phase III OAK and phase II POPLAR trials. The rationale for the analysis came from preclinical data showing that antibiotics and proton pump inhibitors (PPIs) may modulate the microbiome and from recent retrospective analyses of clinical trial data suggesting reduced benefit with immune checkpoint inhibitors in patients treated with antibiotics. Professors Chalabi and colleagues reviewed data from patients with non-small cell lung cancer (NSCLC) on antibiotics and PPIs who received atezolizumab or chemotherapy in these studies. Both trials randomised patients with previously treated metastatic NSCLC to receive either atezolizumab or docetaxel. All patients from these studies were included in the analysis; 757 were treated with atezolizumab and 755 received docetaxel. The primary objective of this study was to evaluate the impact on overall survival (OS) of antibiotic or PPI use within 30 days before and after treatment initiation. Hazard ratios (HR) were estimated using univariate and multivariate cox regression models adjusting for baseline variables, such as treatment arm, histology, ECOG number of metastatic sites and age.

Antibiotic use was identified in 169 (22.3%) patients receiving atezolizumab and 202 (26.8%) patients on docetaxel, whereas PPIs were used by 234 (30.9%) and by 260 (34.4%) patients in the respective treatment arms. Univariate analysis showed that antibiotic use overall was associated with shorter OS (HR 1.21; 95% confidence interval [CI], 1.05-1.39), as was PPI use (HR 1.29 [95% CI 1.13-1.48]). These associations remained significant in multivariate analysis in the overall population. The univariate analysis according to treatment arm showed OS was shorter in the atezolizumab arm in patients also receiving antibiotics (HR 1.32; 95%CI, 1.06-1.63) or PPIs (HR 1.45; 95% CI, 1.20-1.75), which was not confirmed by the multivariate analysis where the relationship was not statistically significant. NCT0190399, NCT02008227. Chalabi *et al.* Abstract 50O

Practice point and future research opportunities

Taken together with previously published data, this retrospective analysis suggests that antibiotic or PPI use 30 days before and after beginning treatment in patients with metastatic

NSCLC may interfere with immunotherapy treatment and be associated with lower efficacy of atezolizumab. Future study is warranted on cancer immunotherapy, which should elucidate the effects of concomitant medications and the role of the microbiome.

First-line durvalumab does not improve overall survival in metastatic NSCLC but shows activity in patients with high tumour mutational burden

Naiyer Rizvi, Division of Hematology/Oncology, Columbia University Medical Centre in New York, USA presented mixed results from the phase III MYSTIC trial of front-line durvalumab with and without tremelimumab in patients with metastatic non-small cell lung cancer (NSCLC). The open-label, MYSTIC trial enrolled 1,118 patients who did not have EGFR sensitising mutations or ALK rearrangement and had not received prior immunotherapy or chemotherapy for metastatic NSCLC. The patients were randomised equally to receive durvalumab monotherapy at 20 mg/kg i.v. every 4 weeks, or durvalumab at the same dose plus tremelimumab at 1 mg/kg i.v. every 4 weeks for a total of 4 cycles, or platinum-based chemotherapy for up to 6 cycles; pemetrexed maintenance was allowed for eligible patients. The patients were stratified by histology and according to tumour cell (TC) PD-L1 expression (≥25% versus <25%) as determined using the VENTANA PD-L1 (SP263) assay.

The primary endpoints were overall survival (OS) for durvalumab versus chemotherapy, and OS and progression-free survival (PFS) by blinded independent central review per RECIST v1.1 for durvalumab plus tremelimumab versus chemotherapy in patients with 25% or greater tumour cell PD-L1 expression.

While durvalumab has previously demonstrated activity in advanced NSCLC and the combination of durvalumab and tremelimumab has shown durable responses in metastatic NSCLC, neither durvalumab monotherapy nor the combination provided statistically significant OS in this trial. Results from the 488 (44%) of patients with PD-L1 expression ≥25% showed OS was 16.3 months with durvalumab monotherapy compared to 12.9 months with platinum-based doublet chemotherapy (hazard ratio [HR] 0.76; 97.54% confidence interval [CI], 0.564- 1.019; p = 0.036).

The 2-year OS rates were 39% with durvalumab plus tremelimumab, 30% with durvalumab monotherapy, and 18% with chemotherapy. More patients (median 39.5%) on chemotherapy received subsequent immunotherapy after treatment discontinuation compared to 6.1% of patients on durvalumab and 3.1% of patients on the combination.

Dr. Rizvi also discussed findings from an exploratory analysis of 40% of MYSTIC patients having high blood tumour mutational burden (TMB), defined as 16 or more mutations per megabase. These patients had median OS of 16.5 months with durvalumab plus tremelimumab versus 10.5 months with chemotherapy (HR 0.64). Patients with low TMB (less than 16 mutations/megabase) had median OS of 8.5 months with durvalumab plus tremelimumab, 12.2 months with durvalumab, and 11.6 months with chemotherapy.

The safety profile was consistent with previous reports for the two agents. The incidence of grade 3/4 treatment-related adverse events was 14.6%, 22.1%, and 33.8% with durvalumab, durvalumab plus tremelimumab, and chemotherapy respectively. NCT02453282. Rizvi *et al.* Abstract LBA6

Practice point and future research opportunities

Although statistical significance was not achieved, durvalumab monotherapy provided clinically meaningful improvement in median OS compared with chemotherapy in patients with 25% or greater PD-L1 expression. In addition, the results of the exploratory analysis need to be validated in a future trial, as the CheckMate 227 trial also showed that first-line immunotherapy combinations work best in advanced NSCLC patients with high TMB. TMB is measured with a simple blood test and may be an easy way to select patients for this treatment.

Immunotherapy has rapidly become a first-line treatment option in NSCLC, as shown in the 2018 ESMO Clinical Practice Guidelines for metastatic disease. The ESMO Immuno-Oncology Congress showcases cutting edge developments in this fast moving field, such as the highly anticipated MYSTIC trial. The analysis shows that appropriate biomarkers are needed to select the patients most likely to benefit from combination immunotherapy in first-line. The challenge now is to prospectively validate them prior to implementation in clinical practice.

Patient reported outcomes favour atezolizumab plus carboplatin and etoposide in extensive stage small-cell lung cancer

Raffaele Califano, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK and colleagues evaluated patient reported outcomes (PROs) that were collected as part of the phase III IMpower133 trial. IMpower133 randomly assigned 201 patients with extensive stage small-cell lung cancer (ES-SCLC) to atezolizumab at 1200 mg plus carboplatin (CP) AUC 5 / etoposide (ET) 100 mg/m^2 and 202 patients to placebo plus CP/ET i.v. every 3 weeks for 12 weeks, followed by atezolizumab or placebo maintenance every 3 weeks until disease progression, intolerable toxicity, or clinical benefit loss occurred. Using the EORTC QLQ-C30 and QLQ-LC13 scales (score range 0–100), the investigators determined descriptive analyses of change from baseline, cumulative distribution function curves of change at week 12, and time to deterioration (TTD) with the treatments. A ≥10-point change from baseline was prespecified as clinically meaningful.

At weeks 27 and 54, 108 and 34 patients on atezolizumab versus placebo remained on study and completed the QoL questionnaires, respectively. These patients reported that physical function improved from baseline until week 51 and also reported clinically meaningful health-related quality of life (HRQoL) improvements that persisted at most visits through week 54.

First-line atezolizumab plus CP/ET was associated with greater improvements in physical daily function and HRQoL than placebo plus CP/ET. Early notable lung cancer symptom palliation was reported by patients receiving both treatments, with numeric trends of greater improvement favouring the atezolizumab treatment arm where a greater proportion of patients reported lung cancer symptom relief by week 12. At this timepoint, 124 patients on atezolizumab versus 131 on placebo reported decreases from baseline in arm or shoulder pain of -7.0 versus -2.5, chest pain of -7.8 versus -4.1, and dyspnoea of -6.5 versus -2.3, respectively. Differences in TTD of cough or chest pain were not apparent, although a numeric delay in TTD of dyspnoea favoured atezolizumab plus CP/ET (hazard ratio [HR] 0.75; 95% confidence interval [CI], 0.55–1.02). No difference in the decrease from baseline between treatments was observed for cough, where both treatment arms showed clinically meaningful improvement (decrease from baseline -14.8 versus -15.5, respectively). NCT02763579. Califano *et al.* Abstract 49O

Practice point and future research opportunities

Atezolizumab plus CP/ET treatment provided a significant improvement in survival, as well as immediate and tangible improvements in patient reported lung cancer symptoms. This analysis of PROs from IMpower133 trial, indicating sustained function and improved HRQoL with minimal impact from treatment toxicities, support the positive benefit-risk ratio of atezolizumab plus CP/ET versus placebo and CP/ET that further support atezolizumab plus CP/ET as a first-line treatment option for ES-SCLC.

Real-world analysis of time on treatment with first-line pembrolizumab in patients with metastatic PD-L1-positive NSCLC compares favourably to clinical trial findings

Vamsidhar Velcheti, Cancer Institute, New York University in New York, USA presented findings from a study estimating the real-world time on treatment (rwToT) for first-line pembrolizumab monotherapy in a clinically matched real-world non-small cell lung cancer (NSCLC) database. The time on treatment was compared to the median treatment duration of 7.9 months reported in a recent update of the KEYNOTE-024 trial. Pembrolizumab monotherapy was approved for first-line treatment of metastatic NSCLC in patients with PD-L1 tumour proportion score (TPS) ≥50% in October 2016 in the US, based on the findings from KEYNOTE-024 trial.

Dr. Velcheti and colleagues reviewed the Flatiron Health electronic health records-derived advanced NSCLC database for patients with a stage IV NSCLC diagnosis, ECOG performance status (PS) 0-2, and tumour proportion score (TPS) ≥50% who received at least one dose of pembrolizumab monotherapy in the first-line setting. The Flatiron database includes structured and unstructured de-identified patient-level data from active records of more than 2 million patients with cancer in the United States that is refreshed monthly. The structured data include laboratory values, limited biomarker information, and prescribed drugs, while unstructured data includes physician's notes in the medical record and detailed

biomarker, radiology, and pathology reports. The investigators determined Kaplan-Meier estimates for rwToT, which was defined as the length of time between the first and last administration of pembrolizumab. Patients receiving a subsequent line of therapy or whose last activity date was 120 days or more from the last administration date or who died were considered discontinued; others were censored. They also determined the restricted mean (rMean) rwToT at the maximum time-point where at least 10% of patients had not discontinued, landmark on-treatment rates, and rMean rwToT at 24 months. All results were stratified into ECOG PS 0-1 and ECOG PS 2 for comparison that was similar to data in the KEYNOTE-024.

ECOG PS 0-1 was recorded for 454 patients and 172 patients had ECOG PS 2; the median age of these patients was 70.7 and 72.7 years, respectively. The median follow-up was 10.8 months. Patients with ECOG PS 0-1 NSCLC and PD-L1 TPS ≥50% demonstrated median rwToT of 6.9 months (95% confidence interval [CI], 5.7- 8.5). The extrapolated mean rwToT at 12 and 24 months was 6.9 (95% CI, 6.4- 7.4) and 10.4 (95% CI 9.3 - 11.8) months, respectively. The on-treatment rates in this patient population at 6, 12 and 18 months were 54.1%, 36.8%, and 31.7%, respectively. A total of 220 (48.5%) patients receiving first-line pembrolizumab in a US community setting discontinued treatment.

The duration of pembrolizumab use tended to be shorter in a real-world population of patients with ECOG PS 2, who are commonly excluded from clinical trials. These patients demonstrated median rwToT of 2.3 (95% CI, 1.4 - 3.1) months. The mean rwToT at 9 and 24 months was 3.7 (95% CI, 3.2 - 4.3) and 6.6 (95% CI 4.8-8.4) months, respectively. Just the 6-month on-treatment rate was recorded in this cohort, which was 32.0%. Velcheti *et al.* Abstract 51O

Practice point and future research opportunities

This study demonstrates that the duration of pembrolizumab use for first-line metastatic NSCLC in the real world is similar to the treatment duration reported in KEYNOTE-024 when restricted to a trial-matched population of patients with ECOG PS 0-1 and TPS ≥50%. These findings suggest that real world patients may obtain similar clinical benefit from pembrolizumab in the clinical setting as was observed in the clinical trial.

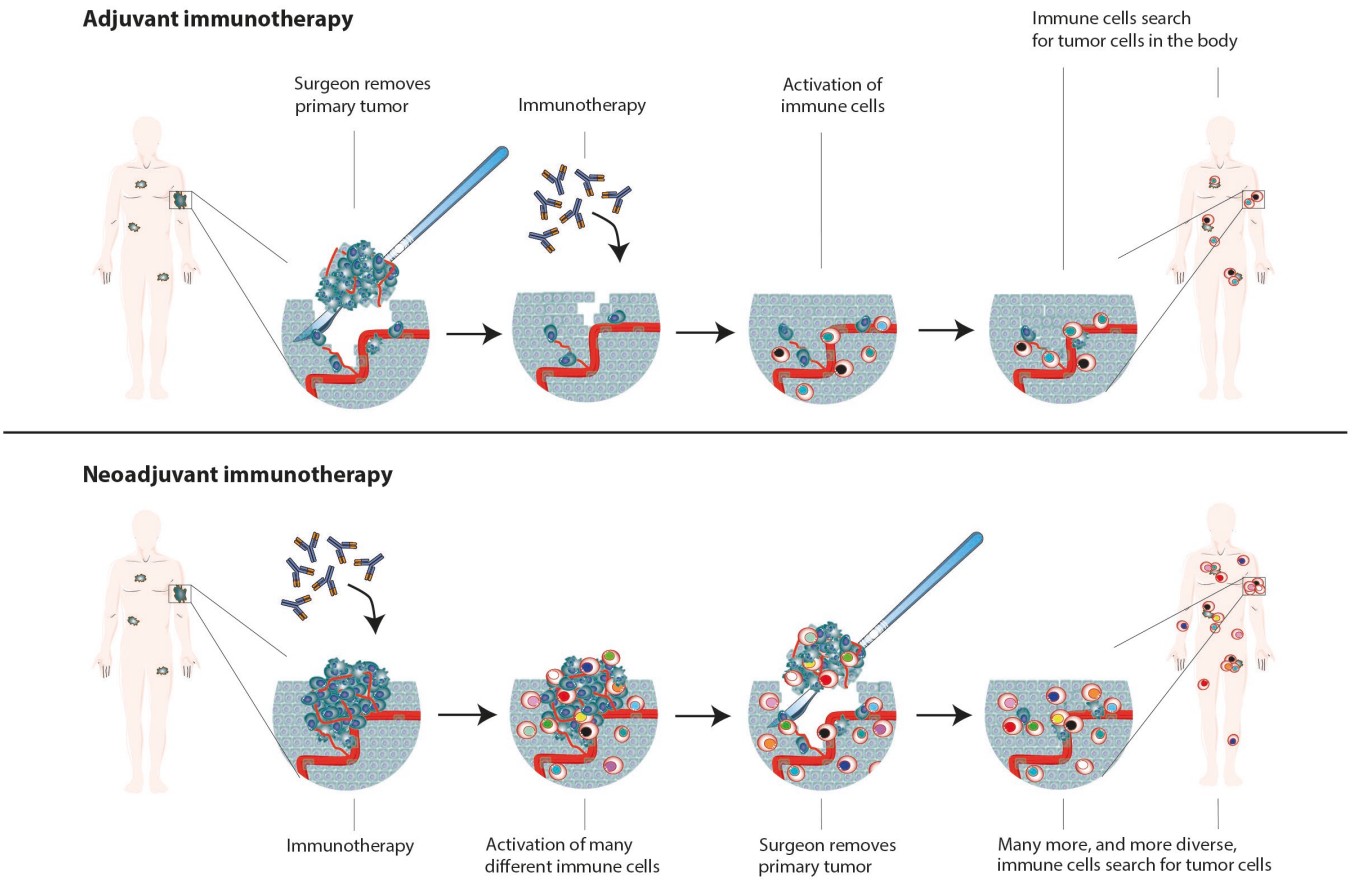
THERAPEUTIC DEVELOPMENT

Neoadjuvant ipilimumab plus nivolumab demonstrates promising overall survival and relapse-free survival in stage III melanoma

Elisa A. Rozeman, Medical Oncology, The Netherlands Cancer Institute, Amsterdam, Netherlands and colleagues conducted the phase Ib OpACIN feasibility trial to test ipilimumab in combination with nivolumab administered as neoadjuvant or adjuvant therapy (Figure 1) in patients with high-risk stage III melanoma. OpACIN was based on the premise that patients with high-risk stage III melanoma generally have a poor outcome, with less than 50% of patients surviving 5 years. Adjuvant ipilimumab has been shown to improve 5-year relapse-free survival (RFS) and overall survival (OS) rates, and RFS was improved even more with adjuvant anti-PD-1 therapy; in stage IV disease the combination of ipilimumab plus nivolumab has been shown to induce higher response rates.

From August 2015 to October 2016, OpACIN enrolled 20 patients with high risk, stage IIIB/IIIC melanoma and palpable nodal disease. Patients were randomised to receive ipilimumab at 3 mg/kg plus nivolumab at 1 mg/kg, either in 4 adjuvant courses, or to receive the same doses split into 2 neoadjuvant plus 2 adjuvant courses. Pathological response was defined as <50% viable tumour cells as reviewed by a blinded pathologist.

Figure 1. Illustration of adjuvant and neoadjuvant immunotherapy.



After median follow-up of 31.6 months (minimum 23.5 months) none of the 7 patients achieving a pathologic response in the neoadjuvant arm have relapsed; however, the two patients in this arm who did not achieve a pathological response have relapsed. The estimated 30-month RFS rate was 80% in the neoadjuvant arm. The OS rate at 30 months was 90% with neoadjuvant treatment.

In the adjuvant arm, 4 patients have relapsed and the 30-month RFS rate was 60%. The 30-month OS rate with adjuvant treatment was 67%.

One patient in the neoadjuvant arm and 3 patients in the adjuvant arm died. At the time of the analysis, 16 patients were alive.

Ninety percent of patients developed one or more grade 3/4 adverse events; all of these patients recovered to ≤ grade 1, except for 8 (50%) patients with ongoing endocrine toxicities, which required hormonal supplementation therapy. NCT02437279. Rozeman *et al.* Abstract LBA3

Practice point and future research opportunities

The OpACIN trial was the first trial investigating the combination of ipilimumab plus nivolumab as neoadjuvant treatment in patients with macroscopic stage III melanoma and, therefore, represents the longest follow-up of this regimen. None of the patients demonstrating pathologic response has relapsed, suggesting that pathologic response could become a primary read-out for subsequent neoadjuvant immunotherapy trials, as well as a marker for RFS and OS. These updated data of the OpACIN study demonstrated high response rates upon neoadjuvant therapy with ipilimumab plus nivolumab and a very promising long-term clinical outcome.

Improved long-term overall survival demonstrated with pembrolizumab over docetaxel in advanced non-small cell lung cancer

Roy S. Herbst, Medical Oncology, Yale University School of Medicine in New Haven, USA presented long-term findings from the global, open-label, phase II/III KEYNOTE-010 trial that enrolled adult patients with previously treated advanced non-small cell lung cancer (NSCLC) and PD-L1 tumour proportion scores (TPS) ≥1%. The patients were randomised 1:1:1 to receive pembrolizumab at 10 mg/kg or 2 mg/kg every 3 weeks for up to 35 cycles, or to docetaxel at 75 mg/m^2 every 3 weeks for the maximum number of cycles allowed per local guidelines, until disease progression or intolerable toxicity. Response assessments per RECIST v1.1 were made every 9 weeks by independent central review, and survival was evaluated every 2 months post-treatment. No difference between pembrolizumab doses was demonstrated in the primary analysis, thus doses were pooled in this analysis. Previously reported results from this trial showed overall survival (OS) was improved with pembrolizumab over docetaxel in subgroups of patients with high and low PD-L1 expression levels, defined as PD-L1 TPS ≥50% and ≥1% with median follow-up of 13.1 months.

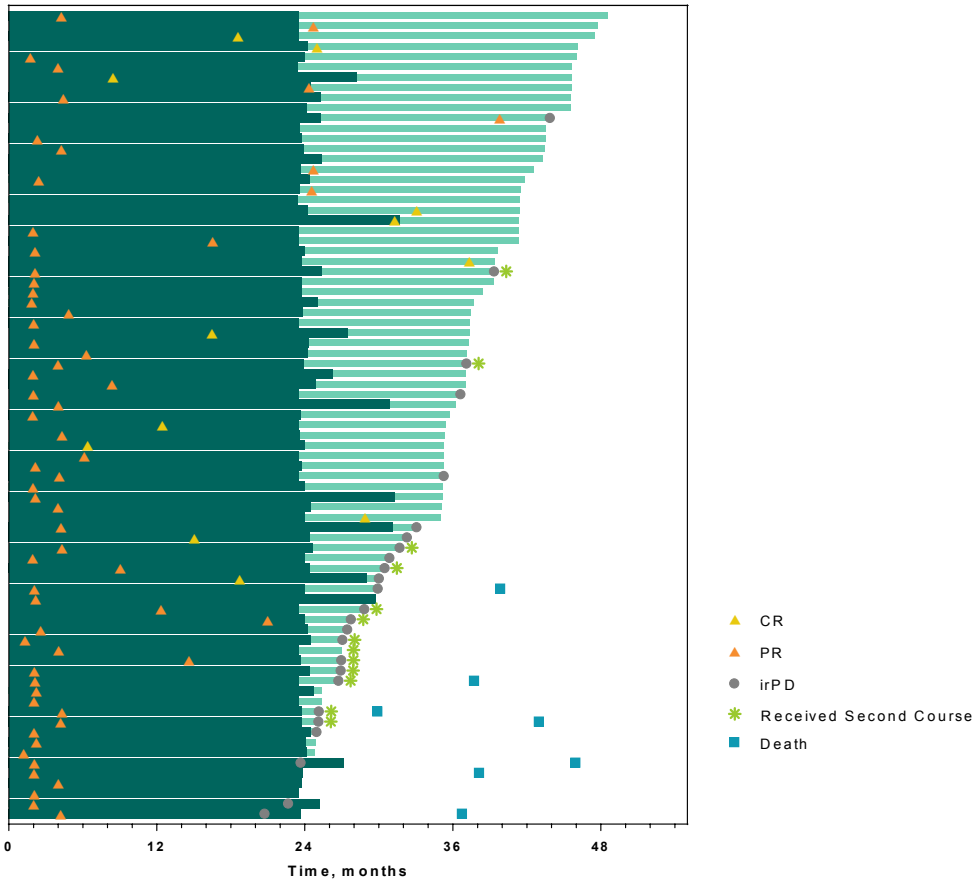
At the ESMO Immuno-Oncology Congress, Dr. Herbst reported updated OS and safety results with 43 months median follow-up in the study overall, and long-term results for patients who had completed 35 cycles or approximately 2 years of pembrolizumab, and for patients who received a second course of pembrolizumab therapy. After median follow-up of 42.6 months (range, 35.2 to 53.2 months), OS in the overall population of 1033 patients was improved with pembrolizumab over docetaxel.

Patients with PD-L1 TPS ≥50% demonstrated significantly improved OS with pembrolizumab compared to docetaxel. Median OS was 16.9 (95% confidence interval [CI], 12.3–21.4) months with pembrolizumab versus 8.2 (95% CI 6.4–9.8) months with docetaxel (hazard ratio [HR] 0.53; 95% CI 0.42–0.66; p < 0.00001). In this cohort, the 36-month OS

rates were 35% versus 13%, respectively. Similarly, OS was improved with pembrolizumab versus docetaxel in patients with TPS ≥1% (HR 0.69; 95% CI, 0.60–0.80; p < 0.00001). Progressive disease was observed in 25 (32%) patients, per investigator. A second course of pembrolizumab was delivered to 14 patients, of whom 5 patients completed 17 cycles. In this group, 11 (79%) patients remained alive, with 6 (43%) patients achieving partial response, and 5 (36%) patients showing stable disease

Thirty-five cycles or 2 years of pembrolizumab had been delivered to 79 of 690 patients. Among patients completing the 35-cycle (2 year) course of pembrolizumab, extremely high rates of response (Figure 1) and OS were observed; the 36-month OS rate was 99%. Ninety-five percent of these patients achieved complete or partial response as the best response, and 48 (64%) had an ongoing response. The median duration of response was not reached (range, 4 to 46+ months). Of the patients who completed 35 cycles or 2 years of pembrolizumab, 72 (91%) patients remained alive.

Figure 1. Treatment duration and time to response among patients who completed 35 cycles (2 years) of pembrolizumab[a].



CR, complete response; irPD, disease progression, per irRC by investigator review; PR, partial response. [a]Bar lengths indicate duration of treatment (dark green) and months of follow-up (light green). Follow-up was defined as date of progression or date of the last investigator assessment the patient was alive. Data cutoff: March 16, 2018.

The safety profile was similar to that reported for the primary analysis. Grades 3 to 5 treatment-related adverse events occurred in 16% of pembrolizumab-treated patients overall compared to 37% of docetaxel patients. NCT01905657. Herbst *et al*. LBA4

Practice point and future research opportunities

Findings from this study support the use of pembrolizumab in patients with advanced NSCLC. Long-term pembrolizumab treatment was superior to docetaxel. The clinical benefit with pembrolizumab was especially pronounced in patients remaining on treatment for 2 years, where the 3-year OS rate was a remarkable 99%.

Nivolumab is not superior to chemotherapy in the second-line setting for patients with small-cell lung cancer

Martin Reck of the Lung Clinic Grosshansdorf, German Centre of Lung Research in Grosshansdorf, Germany discussed the need for additional treatment options in small-cell lung cancer (SCLC), stating that patients with SCLC often show high initial response rates, bust most patients relapse soon after first-line treatment. These relapsing patients have few treatment options and have a poor prognosis. To address the lack of second-line treatment options for these patients, Professor Reck and colleagues conducted the CheckMate 331 study evaluating nivolumab, which has been approved in the USA for treatment of patients with SCLC who progress after platinum-based chemotherapy and one or more other lines of treatment. CheckMate 331 was a global, open-label, phase III trial comparing nivolumab to chemotherapy. The trial enrolled 569 patients with limited or extensive relapsed metastatic SCLC who progressed after first-line platinum-based chemotherapy. The patients were randomly assigned 1:1, with 282 patients receiving nivolumab and 285 receiving chemotherapy with topotecan or amrubicin, according to local approval. The patients were stratified by platinum sensitivity (90 days) and the presence of CNS metastases. Both treatments were continued until progression, or clinical benefit was no longer observed with nivolumab, or until unacceptable toxicity occurred. Overall survival (OS) with nivolumab versus chemotherapy served as the primary endpoint.

The primary endpoint of improved OS with nivolumab was not met. After a minimum follow-up of 15.8 months, 225 (79%) OS events occurred with nivolumab compared to 245 (86%) with chemotherapy. No statistically significant improvement in OS was seen with nivolumab compared to chemotherapy; median OS was 7.5 months versus 8.4 months with nivolumab versus chemotherapy, respectively (hazard ratio [HR] 0.86; 95% confidence interval [CI], 0.72–1.04]). The one-year OS rates were 37% with nivolumab versus 34% with chemotherapy. Interestingly, the OS curves showed delayed separation after month 12 favouring nivolumab.

With the respective treatments, progression-free survival (PFS) was median 1.5 versus 3.8 months (HR 1.41; 95% CI, 1.18-1.69) and the one-year PFS rates were 11% versus 10%. The objective response rates were 39% versus 47%. The duration of response (DoR) was longer with nivolumab; in responding patients the DoR was median 8.3 (95% CI 7.0-12.6) months with nivolumab versus 4.5 (95% CI 4.4-5.8) months with chemotherapy. In patients with platinum-resistant SCLC, the HR for OS with nivolumab versus chemotherapy was 0.71 (95% CI, 0.54–0.94).

Nivolumab demonstrated a better safety profile. All-grade treatment-related adverse events (TRAE) occurred in 55% versus 90% and grade 3–4 TRAE occurred in 4% versus 73% of nivolumab versus chemotherapy treated patients, respectively. Two treatment related deaths occurred with nivolumab and 3 deaths occurred that were chemotherapy related. NCT02481830. Reck *et al.* Abstract LBA5

Practice point and future research opportunities

Although nivolumab did not improve OS over chemotherapy in the second-line setting, the late separation of curves and potential activity in the platinum-refractory setting suggests possible long-term benefit for some patients.

Prostate stem cell antigen-directed GoCAR-T™ cells show clinical benefit in advanced pancreatic tumours

Approximately 60% to 80% of pancreatic tumours express the prostate stem cell antigen (PSCA), according to Carlos Becerra, of Baylor Health Care System, in Dallas, USA. PSCA is naturally produced in the bodies of both men and women and is found on the surfaces of cells. The protein was initially identified as a tumour antigen in prostate cancer, but subsequent investigations have revealed an upregulation in other cancers, including pancreatic cancer. GoCAR T cells (BPX601) are an autologous, T-cell product engineered to contain a PSCA-CD3ξ chimeric antigen receptor (CAR) plus the small molecule rimiducid-inducible MyD88/CD40 costimulatory domain. BPX601 has been optimised for antigen-directed and independent T cell activation, proliferation and persistence, which potentially enhances efficacy in solid tumours versus traditional CARs.

Dr. Becerra and colleagues carried out this first-in-human open label dose escalation study to evaluate safety and the biological and clinical activity of BPX601 plus the small molecule rimiducid in select PSCA-positive cancers. Results were reported from the ongoing dose escalation part 1 of this 2-part study, which evaluated the recommended BPX601 cell dose given in combination with a fixed, single rimiducid dose.

The study enrolled 9 patients with previously treated metastatic pancreatic cancer (mPDAC) with measurable disease and positive PSCA expression. Patients were given only cyclophosphamide for lymphodepletion within 3 days before BPX601 infusion on day 0. Three patients in each treatment arm received BPX601 at 3 cell dose levels: $1.25x10^6$ cells/kg without rimiducid, or $1.25x10^6$ cells/kg, and $2.5x10^6$ cells/kg plus a single fixed dose of rimiducid at 0.4 mg/kg on day 7. All of the patients had received ≥2 prior therapies for mPDAC.

No evidence of lymphodepletion due to the cyclophosphamide treatment was observed; however, rapid cell engraftment by day 4 was observed in all patients.

Data were available from 6 patients who were treated with rimiducid and cell infusion. Of these patients, 2 patients had cell expansion of 10- to 20-fold within 7 days of treatment initiation and 2 patients showed cell persistence for more than 3 weeks. All patients showed elevated serum cytokines (IP-10, TNFα), which correlated with cell expansion. The best response was evaluated after one or more scans, which demonstrated two patients had minor responses that were not confirmed; one patient showed matched CA19-9 decrease. Four patients achieved stable disease lasting for 8 or more weeks. Two patients had disease progression. In the responding patients, disease control was maintained without new therapy for 16 weeks in one patient and is ongoing for more than 11 weeks in 3 patients.

The most commonly reported adverse events (AEs) were fatigue and nausea. No dose limiting toxicities occurred at either dose level, and no treatment related serious AEs, neurotoxicity, or cytokine release syndrome events were reported.

Part 2 of this trial is planned to open soon and will include cyclophosphamide plus fludarabine for lymphodepletion to maximize engraftment and will enroll patients with pancreatic cancer, as well as gastric and prostate cancers. NCT02744287. Becerra *et al.* Abstract 68O

Practice point and future research opportunities

GoCAR-T™ cells are a unique T cell construct targeting the prostate stem cell antigen that is activated by the small molecule rimiducid that provided cell expansion at 2 dose levels and responses in previously treated patients with metastatic pancreatic cancer. This promising construct warrants further evaluation.

Encouraging preclinical activity observed with small molecule human PD-1/PD-L1 inhibitors

Marta Vilalta-Colomer, Research Department, ChemoCentryx, Inc., in Mountain View, USA presented results demonstrating that small molecule human PD-1/PD-L1 inhibitors are able to promote T cell immune activation and reduce tumour growth in a preclinical model. The investigators aimed to produce new therapeutic options providing improved anticancer immune responses, increased tumour penetration, and a shorter half-life to better manage immune-related adverse events at a lower cost. The investigators developed a number of small molecules targeting the PD-1/PD-L1 immune checkpoint based upon the crystal structure of human PD-1/PD-L1 complex. Compound activity was identified by an ELISA assay measuring inhibition of the PD-1/PD-L1 interaction, followed by functional cell-based reporter and mixed lymphocyte reaction (MLR) assays. In order to evaluate the inhibitors specifically, which specifically block human PD-1/PD-L1 interaction, it was necessary to co-implant A375 human melanoma cells along with human peripheral blood mononuclear cells (PBMCs) into immunodeficient NOD/SCID mice to test the inhibitor efficacy in vivo.

The human PD-1/PD-L1 inhibitors demonstrated potent activity in both the cell-based reporter and MLR assays. A lead compound, CCX4503, was identified that reduced tumour growth in vivo with similar activity to that of the positive control, an anti-human PD-L1 antibody. The investigators observed that anti-tumour activity was completely dependent on the presence of human PBMCs. In addition, an analysis of the tumour microenvironment indicated that the anti-tumour activity of CCX4503 was accompanied by a significantly higher $CD8^+$ T-Cell/$CD4^+$ T-cell ratio. An X-ray structure of CCX4503 co-crystallized with PD-L1 provided information about the structural basis by which the compound disrupts the PD-1/PD-L1 immune checkpoint interaction. Vilalta-Colomer *et al.* Abstract 69O

Practice point and future research opportunities

Using rational design, this study has identified and evaluated the activity of unique small molecule inhibitors of the human PD-1/PD-L1 complex. One molecule resulting from these efforts, CCX4503, exhibited marked inhibition of the PD-1/PD-L1 interaction and signalling in vitro, and demonstrated clear anti-tumour effects in vivo in a NOD/SCID mouse model system.

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Affiliations and Disclosure

Affiliation

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Disclosure

No conflicts of interest to disclose.

Acknowledgement

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

ESMO would like to thank Drs Elisa A. Rozeman, Jacqueline Staring and Roy S. Herbst for giving their permission to publish the images from the studies presented during the ESMO 2018 Congress in the ESMO Scientific report.

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