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Congress Report ESMO Immuno-Oncology 2022

A GLOBAL DIGEST ON APPROACHES IN ADVANCED SOLID TUMORS

Report from the ESMO Immuno-Oncology Congress, 7th – 9th December 2022

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Preface

Dear Colleagues,

The ESMO Immuno-Oncology Congress took place in Geneva, Switzerland, and virtually from 7th to 9th December 2022. In total, more than 2,000 participants from more than 100 countries attended one of the 31 sessions featuring over 249 presented abstracts, 6 late breaking abstracts, 6 proffered paper, 14 mini orals and 229 posters. The 80 presenters provided a comprehensive overview of the fast-developing field of cancer immunotherapy, particularly concerning innovative therapeutic combinations with other anticancer strategies, such as chemotherapy and targeted therapies or recent developments on immune modulation.

This issue of memo inOncology presents findings of this year's ESMO IO in the areas of clinical research, immunological mechanisms, and new therapeutic agents. The AdvanTIG-105 trial outcomes showed encouraging antitumor activity with chemotherapy plus anti-TIGIT plus anti-PD-1 blockade as first-line treatment in therapeutically challenging ES-SCLC. Moreover, optimal treatment after failure of immunotherapy is still under investigation. Here, long-term follow-up results of the phase I trial demonstrated the promising activity of an anti-PVRIG antibody plus PD-1-targeted therapy. Additionally, neoadjuvant administration of a novel bifunctional fusion protein, targeting both PD-L1 and TGF-ß, rendered a quarter of unresectable stage III NSCLC patients eligible for surgery and resulted in a favorable efficacy in resected patients. Innovations with a histone deacetylase inhibitor in combination with an anti-PD-1 inhibitor plus chemotherapy in the 1L setting of advanced NSCLC, updated results on the combination of a covalent KRASG12C inhibitor and anti-PD-1 therapy as well as conventional chemotherapy combined with PD-(L)1 inhibitors are also discussed.

Last but not least, this issue looks at emerging therapies in various metastatic solid tumor entities, like the interplay between interleukin-8 signaling pathway, anti-PD-1 and anti-CTLA4-blockade or anti-PD-1 and a multikinase inhibitor.

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Once again, the ESMO IO congress offered an outstanding platform of exchange for international experts to transfer the latest findings from immuno-oncology research into practice-orientated therapeutic approaches combating cancer on multiple fronts, with the goal of remission and elimination.

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New strategies with PD-1/PD-L1 blockade in lung cancer

Small-cell lung cancer (SCLC) accounts for about 15 % of all diagnosed cases of lung cancer and is characterized by a high proliferative rate, an early development of widespread metastases and a poor prognosis [1]. The five-year survival rate is less than 7 % [2]. More than two-thirds of patients with this highly aggressive neuroendocrine tumor are diagnosed with advanced or extensive-stage disease (ES-SCLC) [3]. For more than two decades, the standard upfront treatment was platinum-based chemotherapy (CT), associated with a median survival time of less than one year [4]. Recently, the addition of immune checkpoint inhibitors (ICIs) targeting the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) to standard CT have demonstrated sustained OS benefit and have rapidly emerged as the current standard-of-care in the first-line setting [5]. Despite this progress, resistances emerge in virtually all patients; therefore, ES-SCLC remains a therapeutically challenging disease.

AdvanTIG-105 trial: 1L ociperlimab plus tislelizumab plus CT

T-cell immunoglobulin and immunoreceptor tyrosine–based inhibitory motif (ITIM) domain (TIGIT) is an coinhibitory receptor primarily expressed on activated T-cells, Tregs and natural killer (NK) cells (7). It is a promising target in the field of ES-SCLC immunotherapy. Combining TIGIT inhibitors with programmed PD-1/PD-L1 inhibitors has

previously demonstrated antitumor activity in advanced solid tumors [6, 7]. Ociperlimab is a novel humanized Fc-intact IgG1 monoclonal antibody (mAb) designed to bind to TIGIT with a high specificity and affinity [8] whereas tislelizumab is an anti-PD-1 mAb with low Fcγ binding affinity on macrophages [9].

At this year's ESMO IO meeting, Jun Zhang reported on the dose-expansion study of the ongoing phase 1b AdvanTIG-105 trial (NCT04047862) investigating the combination of ociperlimab plus tislelizumab and chemotherapy (CT) in patients with ES-SCLC [10]. A preliminary dose-escalation study (phase I) has previously demonstrated the antitumor activity and tolerability of this combination in patients with advanced solid tumors [11].

Patients included in the dose-expansion phase (Cohort 4) had a confirmed ES-SCLC, no prior systemic treatment for metastatic disease and an ECOG scorings of 0 or 1. They first received four cycles of the recommended phase II dose (RP2D) of ociperlimab (900 mg, intravenously [IV] every three weeks [Q3W]) plus tislelizumab (200 mg, IV, Q3W) and CT (cisplatin [75 mg/m²] or carboplatin, area under the curve [AUC] 5, on Day 1 plus etoposide [100 mg/m² on Days 1 to 3]). After four cycles, patients were administered with the RP2D of ociperlimab and tislelizumab until disease progression (PD) or intolerable toxicity. The primary endpoint was the overall response rate (ORR) as assessed by the investigator per RECIST v1.1. Key secondary endpoints included the investigator-assessed progression-free survival (PFS), the duration of response (DoR), the disease control rate (DCR) per RECIST v1.1, and safety.

Out of 42 patients enrolled in Cohort 4 (data cut-off date of June 20, 2022), 40 were evaluable for efficacy, as defined by 1 or more evaluable post-baseline tumor response assessment. The median age was 65.5 years, and most patients were male (76.2 %). The median follow-up was 24.9 weeks (range, 3.0-67.9).

In total, 65 % of the patients achieved a confirmed ORR (95 % CI, 48.3-79.4; partial response [PR], 65 %; complete response [CR], 0 %), while 25 % of the cohort had a stable disease (SD) and 5 % a progressive disease (PD). The median DoR was 4.3 months (95 % CI, 3.2-5.6), the median PFS 4.9 months (95 % CI, 4.2-5.7), while the 6-month PFS rate reached 27.3 % **(Figure 1)**.

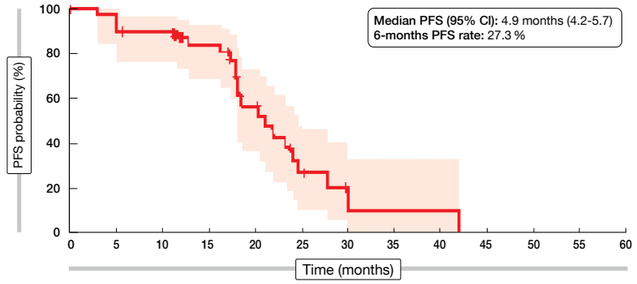

Figure 1: AdvanTIG-105 trial - Kaplan-Meier curve of the progression-free survival of patients treated with ociperlimab and tislelizumab plus chemotherapy.

Grade ≥ 3 treatment-emergent adverse events (TEAEs) occurred in 59.5 % of the patients, of these, decreased neutrophil count (33.3 %) and white blood cell count (16.7 %) were the most frequently reported ones. Overall, 40.5 % of the patients had serious TEAEs and 28.6 % experienced immune-mediated TEAEs, including two patients with grade ≥ 3. Moreover, two patients died following AEs (one of pneumonia unrelated to treatment and one of cardiac arrest). In total, 4.8 % of the AEs led to ociperlimab discontinuation.

The authors concluded that the combination of ociperlimab plus tislelizumab with cisplatin or carboplatin plus etoposide showed encouraging antitumor activity as first-line treatment in patients with ES-SCLC accompanied by an acceptable safety profile.

2L COM701 ± nivolumab

Several agents, such as the novel 1st-in-class immune checkpoint inhibitor (ICI) COM701, are currently under investigation in a post-ICI second line setting. COM701 is a humanized IgG4 monoclonal antibody with a high affinity to poliovirus receptor related immunoglobulin domain containing (PVRIG) [12]. PVRIG blockade leads to enhanced activation of T-cells and NK cells. Historical data with Lung-MAP demonstrated the superiority of combining immunotherapeutic agents (ramucirumab - an anti-vascular endothelial growth factor (VEGF) antibody and pembrolizumab - an anti-PD-1 ICI) over the standard-of-care, with a median OS of 14.5 months vs 11.6 months, respectively [13].

Sullivan et al. evaluated the antitumor activity of COM701 with or without nivolumab in an ongoing phase I trial (NCT03667716) conducted in patients with metastatic NSCLC who have received prior PD-1/PD-L1 inhibitor(s) [14]. Preliminary safety and tolerability outcomes have previously been reported at ASCO 2021 meeting [12]. At this year's ESMO IO conference, Ryan Sullivan presented long-term follow-up results.

Key inclusion criteria were a histologically confirmed locally advanced or metastatic solid malignancy with no available standard treatment, an ECOG of 0 or 1, and one or more prior lines of PD-1/PD-L1 inhibitor therapy. Patients with an active autoimmune disease requiring a systemic treatment, or a prior anti-PVRIG treatment or a history of immune-related toxicities leading to treatment discontinuation were excluded from the study. Patients received COM701 with or without nivolumab at variable doses. The co-primary endpoints were safety and tolerability of the mono- or combined therapy, while anti-tumor activity was set as a secondary endpoint. Other exploratory outcomes were COM701 immunogenicity, pharmacodynamics effect in blood, as well as cytokines and immunophenotype variations.

A total of seven patients were enrolled at the time of data cut-off (July 17, 2022). Out of five patients receiving COM701 monotherapy, one took part in the dose escalation phase at a dose of 0.01 mg/kg (IV, Q3W), while four were enrolled during the dose expansion phase at a dose of 20 mg/kg (IV, Q4W) which was the recommended dose for expansion. Two patients received the combination therapy during the dose escalation phase: one received COM701 (3 mg/kg, IV, Q3W) plus nivolumab (360 mg, IV, Q3W) and one received COM701 (10 mg/kg, IV, Q4W) plus nivolumab (480 mg, IV, Q4W).

Four patients (57 %) were over 65 years old and most of them were female (n = 6). The median number of prior lines of therapy was four (range, 3-6). All patients had received at least one prior line of ICI, and four of them (57 %) were administered more than two prior ICI lines. Overall, 71 % of the patients had a controlled disease (CR = 0 %, PR = 0 %, SD = 71 %), whereas 29 % had a progressive disease. For two patients with SD, the response was prolonged over six months. The median PFS in all patients was 84 days (95 % CI, 22-231) and was longer with the combination therapy than compared with the monotherapy (5.72 months [95 % CI, 3.15-NA] vs 2.69 months [95 % CI, 1.71-NA]). The median OS was 9.5 months (95 % CI, 2.7-11), with a median OS of 9.53 months (95 % CI, 4.11-NA) in the monotherapy group and 10.10 months (95 % CI, 8.57-NA) in the combination group.

The combination of COM701 plus nivolumab for the treatment of NSCLC patients post ICI showed promising results in terms of antitumor activity. A phase I trial in NSCLC patients post-ICI treatment evaluating COM902 plus COM701 with a PD-1 inhibitor versus COM902 plus COM701 with chemotherapy is planned.

Neoadjuvant SHR-1701 in unresectable NSCLC

Consolidation immunotherapy after chemoradiation is the actual standard-of-care for stage III unresectable NSCLC (uNSCLC) [15]. In patients with resectable NSCLC, neoadjuvant immunotherapy combined with CT has already proved to elicit strong tumor-specific T-cell response as well as to induce tumor and nodal downstaging [16-18]. At this year's ESMO IO meeting Yi-Long Wu presented the preliminary data of a phase II trial (NCT04580498), conducted in uNSCLC stage III naïve patients, evaluating the combination of a neoadjuvant immunotherapy with a PD-L1 expression-dependent CT, followed by surgery or radiotherapy (RT) [19]. Patients received a novel bifunctional fusion protein, SHR-1701, targeting both PD-L1 and transforming growth factor beta (TGF-β). This promising molecule has previously been evaluated in a phase I trial (NCT03710265) and demonstrated an encouraging antitumor activity, as well as an acceptable tolerability in advanced solid tumors [20].

This multicenter, open-label phase II trial included patients with unresectable stage III NSCLC, with an ECOG performance status of 0 or 1, no prior systemic therapy nor radiotherapy of the thorax, and no sensitizing EGFR/ALK alterations. Patients with a PD-L1 tumor proportional score (TPS) < 50 % received SHR-1701 (30 mg/kg, Day 1) plus paclitaxel (175 mg/m², Day 1) plus carboplatin (AUC 5, Day 1), Q3W for three cycles (Arm A). Patients with a PD-L1 TPS score ≥ 50 % were randomized 1:1 to receive either SHR-1701 (30 mg/kg, Day 1) plus paclitaxel (175 mg/m², Day 1) plus carboplatin (AUC 5, Day 1), Q3W for three cycles (Arm B) or SHR-1701 (30 mg/kg, Day 1) Q3W for three cycles (Arm C). Following multidisciplinary consultation, patients of the three arms allocated to either definitive surgery or definitive RT (60 Gy/30 fractions) plus concurrent cisplatin (30 mg/m², QW), followed by SHR-1701 (30 mg/kg), Q3W for 16 cycles or until PD or unacceptable toxicity. The co-primary endpoints were post-induction ORR and event-free survival (EFS), while secondary endpoints included OS, time to distant metastasis (TTDM) and safety. Other key exploratory endpoints were the major pathological response (MPR) and the surgical rate.

At the data cut-off date (July 31, 2022), a total of 107 patients were enrolled in the study. Out of them, 82.2 % had a PD-L1 TPS < 50 % (Arm A) and 17.8 % a PD-L1 TPS ≥ 50 % (Arm B, n = 9 or Arm C, n = 10). The median age was about 59 years. Overall, 73.8 % presented with NSCLC of squamous histology.

Post-induction ORR was 56.1 % (95 % CI, 46.2-65.7) in all patients (Arms A + B + C). Patients responded better to a combination therapy (Arms A + B) than to SHR-1701 monotherapy (Arm C); median ORR, 57.7 % in Arms A + B vs 40.0 % in Arm C, respectively. The median DCR was 92.5 % (95 % CI, 85.8-96.7) in all patients (Arms A + B + C). In more details, the post-induction CR, PR and SD rates of Arms A + B versus Arm C accounted for 1.1 %, 56.7 % and 35.1 % versus 0 %, 40.0 % and 50.0 %, respectively. The ORR based on assessments throughout the treatment course including RT-treated patients accounted for 71.1 % in Arms A +B compared to 60.0 % in Arm C **(Figure 2)**.

The overall median EFS was 18.2 months (95 % CI, 11.8-NR), 14.9 months in the combination therapy arm (Arms A + B), and not yet reached in the monotherapy arm. A total of 27 patients (25.2 %) had surgery (Arm A, n = 77.8 %; Arm B, n = 11.1 %; Arm C, n = 11.1 %), of which ten patients had a stage IIIA disease,

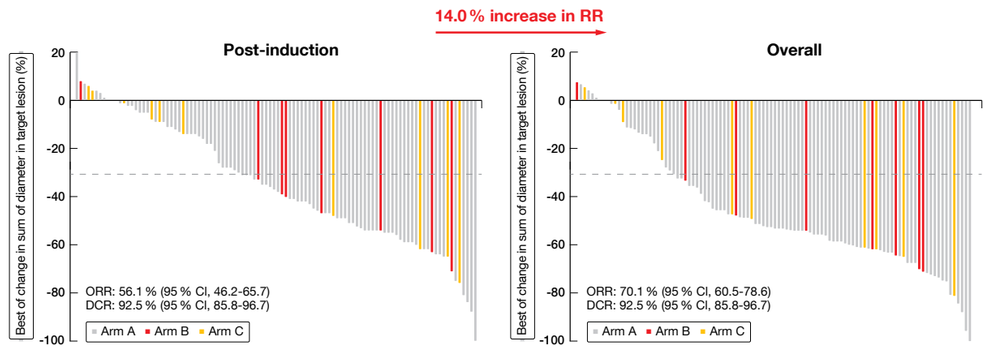

Figure 2: Radiographic assessment of best change in lesion tumor size after neoadjuvant SHR-1701 in patients with unresectable NSCLC.

twelve a stage IIIB disease and five a stage IIIC disease at enrollment. In total, 74.1 % of patients had had a post-induction radiographic PR and the rest a stable disease. About two-third of the patients showed a pathological nodal downstaging. The MPR rate (defined as ≤ 10 % residual viable tumor cells in the resected primary tumor) was 44.4 % and the pCR rate (defined as no residual viable tumor cells in the resected primary tumor and lymph nodes) was 25.9 %. The EFS was not reached (95 % CI, 11,8-NR) in resected patients and 14.9 months (95 % CI, 11.4-NR) in RT-treated patients. Moreover, the 12-month EFS rate was 74.4 % in resected patients compared to 55.9 % in patients who received definitive RT.

In total, 72 % experienced grade ≥ 3 TRAEs, including a decrease in neutrophil, white blood cell and lymphocyte counts as the most frequent ones. The rate of TRAEs leading to SR-1701 discontinuation was 15.9 % and the rate of immune-related AEs was 57.0 %. Three patients died in Arms A + B.

The neoadjuvant administration of SHR-1701 with or without CT followed by surgery or RT induced a promising antitumor activity with an acceptable safety in patients with uNSCLC. Importantly, this neoadjuvant regimen rendered 25.2 % of unresectable patients eligible for surgery and resulted in a favorable efficacy in resected patients.

1L HDACi + tislelizumab + CT

The regulation of histone acetylation, which is an important epigenetic regulation mechanism controlled by histone acetyltransferases (HATs) and histone deacetylases (HDACs), is associated with resistance to immunotherapy. Aberrant expression of HDACs have frequently been observed in various human cancers. HDAC inhibitors (HDACis) have displayed a therapeutic potential in treating cancer and are now emerging agents in cancer therapy [21]. Moreover, HDACis have been suggested to potentially synergize with PD-1 antibodies by inducing and activating the activation of the NK and cytotoxic T-cell - mediated cellular immunity, thus probably resulting in a delayed or prevented resistance to ICI [22]. At the ESMO IO 2022 meeting, Lijie Wang reported data of a phase II trial (chiCTR2000041542) evaluating the antitumor activity and tolerability of combed chidamide (a subtype-selective HDACi) and with tislelizumab (an anti-PD-1 monoclonal antibody approved for the first line treatment of NSCLC) plus chemotherapy [23].

To participate in this open-label, non-randomized study, patients were required to have a histologically confirmed squamous or non-squamous NSCLC of clinical stage IIIB to IV, no prior systemic treatment and an ECOG performance status of 0 or 1. Exclusion criteria were an EGFR/ALK mutation or fusion and symptomatic brain metastases. Patients received chidamide (20 mg, twice a week [BIW], per os [PO]), tislelizumab (200 mg, Q3W, IV) and CT (Q3W) for four to six cycles. The maintenance regimen consisted of chidamide (20 mg, BIW, PO) and tislelizumab (200 mg, Q3W, IV) until progression, unacceptable toxicity, withdrawal of consent or death. The ORR was set as the primary outcome, while DCR, PFS and safety were secondarily analyzed. Tumor response was assessed per RECIST v1.1.

Among the 20 patients included in this study, the median age was 63.5 (range, 49-75) years. All patients were male, and only 10 % of them were never-smokers. Ten patients (50 %) presented with an adenocarcinoma and ten (50 %) with a squamous cell carcinoma. Most of them (95 %) had a clinical stage of IV and 40 % had a PD-L1 status ≥ 1 %. At the time of data cut-off (September 15, 2022), 70 % of the patients were still on study therapy, and 19 patients were evaluable for efficacy. The ORR was 73.7 % (95 % CI, 63.6-83.8), including one patient (5.3 %) with a CR and 13 patients (68.4 %) with a PR. Of note, the ORR was higher in patients with a squamous cell carcinoma histology than in those with adenocarcinoma (88.9 % vs 60 %). All study participants reached a disease control (DCR = 100 %). After a median follow-up of 10.7 months, the median PFS was 13.8 months (95 % CI, 5.4-22.2) and the 1-year PFS rate reached 76.6 % (95 % CI, 64.3- 88.9).

Overall, grade ≥ 3 TRAEs were detected in 55 %, the most frequent ones being leukopenia (25 %), neutropenia (20 %) and thrombocytopenia (15 %). Immunotherapy discontinuation occurred in 20 % of the patients, followed by pneumonia (10.0 %), diarrhea (5.0 %), or dermatitis (5.0 %).

This preliminary analysis demonstrated an encouraging antitumor activity of HDACi combined with anti-PD1 antibody and CT in the 1L setting of advanced NSCLC. The safety profile was favorable and updated follow-up data are expected shortly.

KRYSTAL-1 and -7 trials: adagrasib plus pembrolizumab

About 14 % of patients with NSCLC harbor *KRAS*^{G12C} mutations. Adagrasib, a covalent KRAS^{G12C} inhibitor, has a half-life of 23-hours, dose-dependent pharmacokinetics, and the capability to penetrate the central nervous system. In the phase I/Ib part of the KRYSTAL-1 study, adagrasib already showed a favorable clinical activity accompanied by an acceptable tolerability in patients with *KRAS*^{G12C}-mutant cancers including NSCLC [24]. Several preclinical data support combining adagrasib with immunotherapy as a potential antitumor strategy.

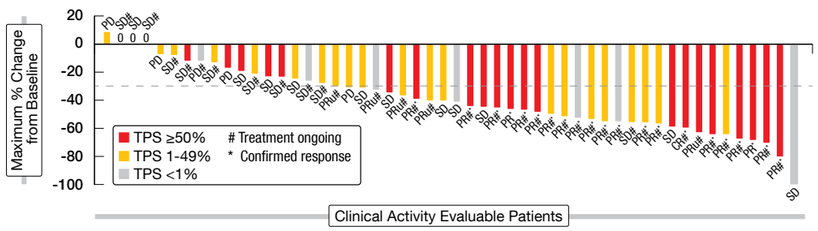

Figure 3: Best change in tumor size after adagrasib plus pembrolizumab in *KRAS*^{G12C} mutated NSCLC (KRYSTAL-7 trial).

In this context, adagrasib administration has been shown to reverse an immunosuppressive tumor microenvironment and to induce tumor sensitization to ICI in mice [25]. KRYSTAL-1 (NCT03785249) phase Ib and KRYSTAL-7 (NCT04613596) phase II trials evaluates the safety and efficacy of adagrasib plus pembrolizumab in treatment naïve (TN) patients harboring a *KRAS*^{G12C} mutation. Preliminary study data were presented at this ESMO IO 2022 by Pasi A. Jänne [26].

Patients' eligibility criteria include advanced, unresectable, or metastatic NSCLC with *KRAS*^{G12C} mutation, and no prior systemic therapy for locally advanced or metastatic disease. Stable brain metastases are tolerated. In the KRYSTAL-1 phase Ib trial, the primary endpoint is safety, while the secondary endpoints enclose the ORR as assessed per RECIST v1.1, DoR, PFS and OS. In the KRYSTAL-2 phase II trial, patients with a PD-L1 TPS < 1 % are allocated to Cohort 1a, whereas patients with a PD-L1 TPS ≥ 1 % are allocated to Cohort 2. The primary outcome is the ORR as assessed by RECIST v1.1, while DoR, PFS, OS, safety and PK are set as secondary outcomes. Both cohorts receive adagrasib (400 mg, BID) and pembrolizumab (200 mg, IV, Q3W).

At the time of data cut-off (August 30, 2022), seven patients had already been enrolled in the KRYSTAL-1 trial and 75 in KRYSTAL-7 (Cohort 1a, n = 11; Cohort 2, n = 64). Among KRYSTAL-1 participants, four out of seven patients attained an objective response (ORR = 57 %) and the disease control rate (DCR) was 100 %. Responses occurred in 2/2 patients with PD-L1 TPS ≥ 50 %, 1/4 patients with PD-L1 TPS 1–49 %, and 1/1 patient with PD-L1 TPS < 1 %. All four responding patients had a DoR of at least nine months and two still receiving treatment beyond 18 months. Overall, four patients experienced grade 3 TRAEs, whereas no patient had grade 4 or 5 TRAEs.

Patients of the KRYSTAL-7 trial were followed for a median duration of 3.5 months and were treated for a median time of two months. Out of 75 enrolled patients, 53 were clinically evaluable (≥ 1 post-baseline tumor assessment) and 25 were enrolled for at least six months before the data cut-off date. The median age of the enrolled patients was 66 years (range, 40-84). In total, 1 % of them were never smokers and 15 % had a PD-L1 TPS < 1 %. The ORR was 49 % (95 % CI, 35-63) and the DCR 89 % (CR, 2 %; PR, 47 %; SD, 40 %) **(Figure 3)**. Responses were observed in 59 % of patients with PD-L1 TPS ≥ 50 %, 48 % with PD-L1 TPS 1–49 %, and 30 % with PD-L1 TPS < 1 %, respectively. The median time to response was 1.4 months. Out of the 26 responding patients, six had a delayed response (> 2 months). So far, 35 of 53 patients, including all responding patients, were still on treatment at the time this analysis was performed.

Grade 3 TRAEs occurred in 40 % of patients with increased aspartate aminotransferase (AST, 9 %) or alanine aminotransferase (ALT, 8 %) being the most frequent ones. TRAEs led to adagrasib dose reduction in 31 %, dose interruption in 41 %, discontinuation of both drugs in 3 % and of pembrolizumab in 3 %. Grade 4 TRAES (4 %) comprised one case each of pneumonitis, neutropenia, and pulmonary embolism. No grade 5 TRAEs were observed.

According to those preliminary data, adagrasib plus pembrolizumab induced a clinically meaningful antitumor activity across all PD-L1 subgroups in patients *KRAS*^{G12C}-mutated NSCLC. The safety profile was manageable and similar to that observed of each agent as monotherapy. Further phase III trials comparing this combination versus standard-of-care in this patient population are planned. ■

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Emerging therapies in solid tumors

BMS-986253 plus nivolumab and ipilimumab

Interleukin-8 (IL-8), also known as chemokine (C-X-C motif) ligand 8, is a pro-inflammatory chemokine that exerts direct pro-tumorigenic effects primarily by recruiting immunosuppressive cells into the tumor microenvironment such as neutrophils and myeloid-derived suppressor cells. IL-8 has also been shown to promote cancer progression and resistance to therapy, by inducing angiogenesis, epithelial-mesenchymal transition (EMT), and cancer stem cell (CSC) self-renewal. Moreover, elevated serum levels have been associated with a poor prognosis in patients with different solid tumors and a reduced clinical benefit from immune checkpoint inhibitors (ICIs) therapy [1, 2]. BMS-986253 is a novel fully humanized monoclonal antibody that prevents IL-8 signaling, through the C-X-C motif chemokine receptors 1 and 2, by binding free IL-8 [3]. IL-8 blockade results in the inhibition of myeloid-derived suppressor cells recruitment to the tumor environment, in improved T-cell activity, decreased tumor growth, angiogenesis, and metastasis of cancer cells. Matteo Simonelli presented updated data of the initial part of a phase I trial (NCT03400332) designed to explore dosing and safety of BMS-986253 plus nivolumab with or without ipilimumab in patients with advanced solid tumors at ESMO IO 2022 [4].

Patients recruited in the dose finding phase of the trial (part 1A and 1B) had different selected metastatic solid tumors (melanoma, NSCLC, SCCHN, UCC, or RCC), and a baseline IL-8 serum level of more than 10 pg/mL. They received different doses and schedules of BMS-986253 (2400 mg, 1200 mg, or 600 mg, every four weeks [Q4W]; 3600 mg, 2400 mg, or 1200 mg, Q2W) given in combination with nivolumab (480 mg, Q4W) **(Figure 1)**. Patients included in the safety part (1C) had solid tumors (NSCLC not included) and any baseline IL-8 serum level. They received BMS-986253 (3600 mg, Q2W) plus four doses of nivolumab (1 mg/kg) and ipilimumab (3 mg/kg, Q3W), followed by BMS-986253 (3600 mg, Q2W) plus nivolumab (480 mg, Q4W).

As of the data cut-off date (August 4, 2022), 144 patients received the doublet combination of BMS-986253 plus nivolumab (part 1A + 1B) and 15 patients the triplet combination (part 1C). BMS-986253 plus nivolumab was well-tolerated with no dose-proportional increase in toxicity and no dose-limiting toxicities (DLTs) observed at any dose level. Since, 3600 mg BMS-986253 (Q2W) plus nivolumab showed a good tolerability, it was selected as the recommended phase II dose. In the dose expansion group (part 1A + 1B), eleven patients (8 %) experienced a grade ≥ 3 TRAEs and only two (1 %) patients discontinued due to serious TRAEs (one grade 4 infusion-related reaction and one grade 3 increase in AST/ALT). In the triplet group (part 1C), 33 % of patients experienced grade ≥ 3 TRAEs and 13 % discontinued because of TRAEs. The safety profile in this group compared favorably to that of the CheckMate 067 trial, which used the same nivolumab plus ipilimumab dosing regimen [5, 6].

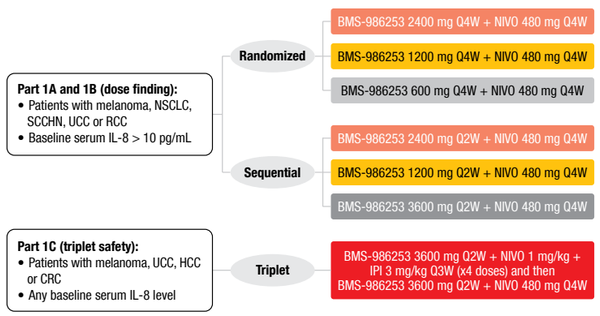

Figure 1: Design of the phase 1 trial evaluating BMS-986253 safety evaluation and dose exploration. IPI, ipilimumab; NIVO, nivolumab

In the dose exploring cohort (part 1A + 1B), six (13 %) out of 46 patients with melanoma achieved a durable response, as assessed per RECIST v1.1. All responding patients had received prior anti-PD-1 therapy and five out of six of them had received also a previous an anti-CTLA-4 therapy. Overall, 26 % remained on therapy for more than six months and 9 % for more than twelve months. In the triplet therapy cohort (part 1C), one out of six patients with melanoma obtained a partial response (PR). BMS-986253 exposure increased in a dose-dependent manner and treatment resulted in a concentration-dependent free serum IL-8 reduction that correlated with tumour-IL-8 suppression.

The authors concluded that BMS-986253 plus nivolumab with or without ipilimumab proved to be safe, while inducing a durable antitumor activity with concentration-dependent reductions in free serum IL-8 in a heterogenous patient population with advanced cancer. Furthermore, these findings support the opening of the second part of this trial, currently ongoing, which is a double-blind randomized study confronting the triplet (BMS-986253 + Nivo + Ipi) vs Nivo plus Ipi and placebo in patients with melanoma progressed on or after previous anti–PD-1 therapy.

1L tislelizumab plus lenvatinib

In hepatocellular carcinoma (HCC), that accounts for the sixth most prevalent cancer worldwide [7], emerging therapies include e.g. tislelizumab, a monoclonal antibody characterized by a high binding affinity for PD-1 and a reduced Fcγ receptor binding on macrophages [8]. The previous phase III RATIONALE-301 trial has demonstrated the non-inferiority of tislelizumab versus sorafenib as 1L monotherapy in patients with unresectable HCC (uHCC) in terms of overall survival (OS) [9].

At the ESMO IO 2022 meeting, Li Xu reported on the preliminary outcomes of a phase II trial conducted in systemic treatment-naïve patients with uHCC to assess efficacy and safety of tislelizumab plus lenvatinib, a multikinase inhibitor approved as first-line treatment in uHCC patients [10, 11].

Eligible patients had a locally advanced or metastatic uHCC, no prior systemic therapy, a BCLC stage C or B disease not amenable to or progressed after loco-regional therapy, a class A Child-Pugh score, at least one measurable lesion per RECIST v1.1, an ECOG performance status ≤ 1 and no tumor thrombus involving main trunk of portal vein or inferior vena cava. In part 1 of the study (safety run-in), patients received tislelizumab (200 mg, Q3W, IV) plus lenvatinib (body weight [BW] ≥60 kg, 12 mg; BW <60 kg, 8 mg; QD, PO). During the expansion phase (part 2), patients received tislelizumab (200 mg, Q3W, IV) plus lenvatinib (12 mg [BW ≥ 60 kg] or 8 mg [BW < 60 kg], QD, PO) until progression, unacceptable toxicity, 12-month treatment duration completion or death. The primary endpoint was ORR as assessed per RECIST v1.1 by an independent review committee (IRC), with a statistical assumption that ≥ 18 responders were needed in 60 efficacy evaluable patients to claim statistical superiority to a historical control ORR of 18.8 % per RECIST v1.1 (from lenvatinib arm of phase 3 REFLECT study [10]). Secondary endpoints consisted in safety and tolerability, and the ORR, DoR, DCR and PFS as assessed respectively per RECIST v1.1, mRECIST and iRECIST by IRC and investigator (except for primary endpoint).

Six patients were enrolled in the safety run-in phase and 58 patients in the expansion phase. In total, 21.9 % of the patients were still on therapy at the time of data cut-off (July 7, 2022). The median age was 52.5 years (range, 28.0-70.0) and they presented mainly with a BCLC staging of C (73.4 %) at study entry, as well as Child-Pugh score of 5 (90.6 %).

The median follow-up time was 12.5 months. Among the 62 evaluable patients for efficacy, 23 of the first 60 patients responded to the treatment. The confirmed ORR was 38.7 % (CR, 0 %; PR, 38.7 %) per RECIST v1.1 by IRC and 41.9 % (CR, 1.6 %; PR, 40.3 %) per RECIST v1.1 by investigator review, while DCR reached 90.3 % and 85.5 %, respectively. The ORR outcomes were globally similar across RECIST v1.1, mRECIST and iRECIST assessment methods. The median DoR per RECIST v1.1 was not reached, while the median PFS was 9.6 months (95 % CI, 6.8-NE) and 8.5 months (95 % CI, 5.3-NE) by IRC and investigator review, respectively. Reductions in tumor size of target lesion were observed in 74.2 % and 80.6 % of the patients, respectively.

During the safety run-in phase, no DLT was reported. Treatment-related adverse events (TRAEs) grade ≥ 3 and treatment-related serious AEs occurred in 28.1 % and 9.4 % of patients. Overall, 3.1 % of TRAEs grade ≥ 3 led to treatment discontinuation and 1.6 % to death.

This study met its endpoint of statistical superiority over a historical control (lenvatinib arm of the phase III REFLECT study [10]) in the 1L setting in uHCC patients, with a confirmed ORR of 38.7 % per RECIST v1.1 by IRC review. Tislelizumab plus lenvatinib was efficient and generally well tolerated in uHCC patients, while showing a promising mPFS. ■

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Conventional chemotherapy combined with PD-1/PD-L1

Neoadjuvant camrelizumab plus albumin-bound paclitaxel and cisplatin

Neoadjuvant chemotherapy (CT), which has been the standard-of-care for resectable NSCLC, resulted only in modest survival benefits of approximately 5 %. However, CT combined with neoadjuvant immunotherapy is a promising strategy in improving survival outcomes of patients with resectable NSCLC [1]. Hence, several small single-arm phase II studies are ongoing in this setting, all including patients with stage III disease [2-4].

Camrelizumab has previously demonstrated a survival benefit in patients with

advanced NSCLC when combined with CT in a first-line setting of advanced NSCLC [5, 6]. At this year's ESMO IO meeting, Jie Lei reported on the final analysis of a phase II trial (NCT04338620) evaluating the neoadjuvant combination of camrelizumab - an anti-PD-1 antibody - and CT in resectable NSCLC patients [7].

This randomized, controlled, multicenter trial was conducted in treatment-naïve patients diagnosed with resectable stage IIIA or IIIB (T3 N2 M0) NSCLC (according to the 8th edition of the AJCC/UICC TNM staging system), aged 18 to 70 years, presenting with an ECOG performance status of 0 or 1. Patients were randomized (1:1) to receive either three cycles of camrelizumab (200 mg, IV, Q3W) plus three cycles of CT (albumin-bound paclitaxel plus carboplatin [AUC 5 at Day one] or plus cisplatin [75 mg/m² at Day 1] or plus nedaplatin [100 mg/m² at Day 1]) or three cycles of CT alone. Four to six weeks post-treatment, all patients had surgery. The primary study endpoint was the complete pathologic response (pCR) - defined as no residual viable tumor cells in both the primary tumor and sampled lymph node-, while MPR, ORR, EFS and safety were secondarily analyzed.

A total of 88 patients received neoadjuvant treatment (n = 43 for camrelizumab plus CT and n = 45 for CT alone). The median age was 61 years, and the majority of patients was male. The most frequent tumor type was squamous cell carcinoma (62.8 % in the camrelizumab + CT arm and 71.1 % in the CT arm, respectively) and most of the patients had clinical stage IIIA (69.8 % in the camrelizumab + CT arm and 80.0 % in the CT arm, respectively). Regarding surgery, most patients had a lobectomy (90 % in the camrelizumab + CT arm and 81 % in the CT arm, respectively). An R0 resection was achieved in 92.5 % and 85.7 % of the patients, respectively. The median duration from final treatment to surgery was 4.7 versus 4.6 weeks, respectively.

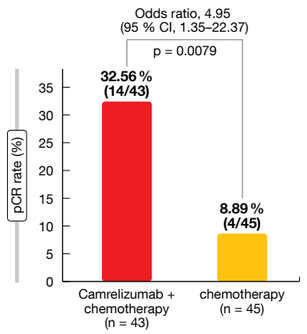

Figure 1: Complete pathologic response (pCR) rate with neoadjuvant camrelizumab plus chemotherapy versus chemotherapy in patients with resectable NSCLC (modified ITT population)

Overall, neoadjuvant camrelizumab plus CT was associated with a significantly higher pCR rate (32.56 % vs 8.89 %; odds ratio [OR] = 4.95; 95 % CI, 1.35-22.37; p = 0.0079) and MPR rate (65.12 % vs 15.56 %; OR = 10.13; 95 % CI, 3.32-32.76; p < 0.0001) compared with CT alone **(Figure 1)**. At the time of data cut-off (August 31, 2022), the median EFS and DFS were not reached; however, there was a trend in favor of camrelizumab plus CT over CT alone (24-month EFS rate = 76.9 % vs 67.6 %; 24-month DFS rate = 78.4 % vs 71.7 %). More patients responded to the treatment in the camrelizumab + CT group than in the CT group (ORR = 72.09 % vs 53.33 %; OR = 2.26; 95 % CI: 0.85-6.08; p = 0.0814) and a higher number of patients achieved a CR (CR: 11 vs 4 patients, respectively; PR: 20 patients in both groups).

The overall incidence of grade ≥ 3 TRAEs in the modified intention-to-treat (ITT) population was 25.6 % in the camrelizumab plus CT arm and 11.1 % in the CT arm. The most frequent grade ≥ 3 TRAEs were a decrease in white blood cell count (14.0 % vs 4.4 %, respectively) and a decrease in neutrophil count (7.0 % vs 11.1 %). Immune-related AEs (irAEs) < grade 3 occurred in 53.5 % of the patients, the most frequent ones being reactive cutaneous capillary hyperplasia (RCCEP, 44.2 %), hypothyroidism (7 %) and hyperthyroidism (2.3 %). Of note, a grade ≥ 3 surgery-related AE - a perioperative death following a cardiovascular accident - occurred in one patient treated with camrelizumab plus CT.

These data demonstrated that combining neoadjuvant camrelizumab plus CT was superior to CT alone in terms of pCR and MPR in resectable patients with stage IIIA or IIIB NSCLC. The safety profile was acceptable, with no new signals observed. This combination proved to be an effective and safe new potential neoadjuvant treatment option for this patient population.

RATIONALE-307 trial: 1L tislelizumab plus chemotherapy

Tislelizumab is an anti PD-1 monoclonal antibody with reduced Fcγ receptor binding specificity on macrophages [8]. The combination of tislelizumab with a platinum-based CT has been assessed in the open-label phase III RATIONALE-307 trial (NCT03594747) as first-line treatment for patients with advanced squamous NSCLC. In this context, a previously reported interim analysis showed a significantly prolonged PFS and higher tumor response rates with this combination compared to CT alone [9]. At the ESMO IO 2022 meeting, Jie Wang presented updated results from the final analysis of the RATIONALE-307 trial after a median of 10.1 months additional follow-up since the last interim cut-off [10].

Patients included in this study had treatment naïve stage IIIB (not eligible to curative surgery or radiotherapy) or IV squamous NSCLC. They were equally randomized to receive either tislelizumab (200 mg, IV, Q3W) plus four to six cycles of paclitaxel and carboplatin (Arm A) or tislelizumab (200 mg, IV, Q3W) plus nab-paclitaxel and carboplatin (Arm B), or four to six cycles of paclitaxel and carboplatin only (Arm C). Tislelizumab was administered for 1 hour on D1 of cycles 1 and 2 and for 30 minutes in subsequent infusions. Tislelizumab treatment continued every three weeks until lack of clinical benefit or intolerable toxicity. Doublet chemotherapy was given until completion of 4 to 6 cycles (at the investigator's discretion), occurrence of disease progression, or intolerable toxicity, whichever occurred first. Patients in arm C could cross over to receive tislelizumab monotherapy if it was determined that they had independent review committee (IRC)–confirmed disease progression [11]. The primary endpoint was the PFS as assessed by an independent review committee (IRC) in the ITT population. The OS, ORR as assessed by an IRC, DoR and safety were secondary endpoints.

At the time of data cut-off (September 30, 2020), a total of 360 patients had been randomized (Arm A, n = 120; Arm B, n = 119; Arm C, n = 121). The overall median age was 62 years, 91.7 % were male and 2/3 had a stage IV disease at baseline. In total, 38.3 % had a PD-L1 expression rate of less than 1 %, and 34.7 % a rate of 50 % or more. The median study follow-up was 18.7 months. At the time of data cut-off, 25.8 % of the patients were still on treatment in Arm A and 28.6 % in Arm B, while all patients in Arm C had completed their four to six cycles of chemotherapy. The interim analysis had previously demonstrated a PFS superiority of the combined treatments (Arms A and B) over chemotherapy alone (Arm C). At the final analysis cut-off, the benefit of tislelizumab plus CT over CT alone in terms of PFS was maintained in both Arms A and B (median PFS in Arm A vs Arm C: 7.7 vs 5.5 months; HR = 0.45; 95 % CI, 0.33-0.62 **(Figure 2)** and in Arm B vs Arm C: 9.6 vs 5.5 months; HR = 0.43; 95 % CI, 0.31-0.60). The outcome was consistent in all PD-L1 expression subgroups. More patients in Arms A and B compared to Arm C responded to the treatment (ORR = 74.2 % and 73.9 %, vs 47.9 %, respectively), achieved a CR (5.8 % and 6.7 % vs 0.8 %) and had a prolonged median DoR (8.4 months and 8.6 months vs 4.3 months). The ORR benefit of tislelizumab plus CT versus CT alone was also observed in all analyzed PD-L1 expression subgroups.

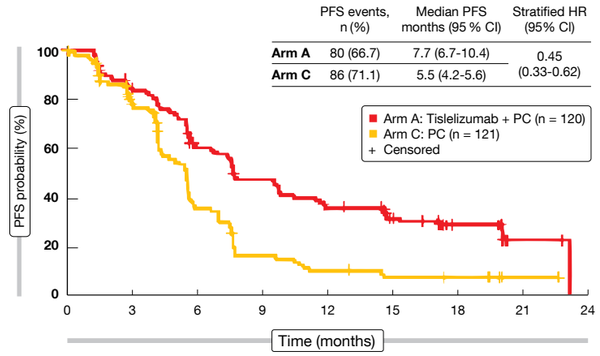

Figure 2: Progression-free survival (PFS) of patients with advanced squamous NSCLC receiving tislelizumab plus CT (Arm A) versus CT alone (Arm C) in the RATIONALE-307 trial.

According to the final analysis, 63.6 % of patients in Arm C received subsequent immunotherapy (92.2 % of them received tislelizumab) after a median time of 10.3 weeks after the last CT cycle. In contrast, a subsequent treatment with immunotherapy was required by 15.0 % of patients in Arm A and 10.9 % of patients in Arm B, only.

Safety data were similar to that of the interim analysis and no new safety signals were reported. Overall, the combination of tislelizumab plus CT proved to be tolerable.

With a longer follow-up, the final analysis of RATIONALE-307 trial demonstrated that the addition of tislelizumab to chemotherapy is clinically beneficial as first-line treatment of advanced squamous NSCLC versus chemotherapy in terms of PFS, ORR and DoR.

AK105-302 study: 1L penpulimab plus carboplatin and paclitaxel

Penpulimab, a novel humanized IgG1 monoclonal antibody directed against PD-1, has been engineered to eliminate Fcγ receptor binding, and therefore to reduce antibody-dependent cellular toxicity and phagocytosis. In 2021, penpulimab received its first approval in China for the second-line treatment of relapsed or refractory classic Hodgkin's lymphoma [12]. Penpulimab is currently investigated in a phase III trial (NCT03866993) in combination with carboplatin and paclitaxel for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC. At ESMO IO 2022, Baohui Han presented the final analysis of this randomized, double-blind, placebo-controlled, multicenter trial [13].

Eligible patients had a histologically or cytologically confirmed diagnosis of stage IIIB-IV squamous NSCLC, no EGFR, ALK or ROS 1 mutations, at least one measurable tumor lesion according to RECIST v1.1, an ECOG performance status or 0 or 1 and any rate of PD-L1 expression. Patients were randomized 1:1 to receive four cycles of CT (paclitaxel [175 mg/m², IV] and carboplatin [AUC 5, IV] Q3W) plus either penpulimab (200 mg, IV, Q3W) or placebo (IV, Q3W) on Day 1 of each cycle, followed by penpulimab or placebo as maintenance therapy until disease progression or for a maximum of 24 months. Of note, patients in the placebo arm were allowed to cross-over to penpulimab monotherapy (open-label) at any time during the 24-month study duration. The primary endpoint was PFS, as assessed by an IRC in the ITT population and in the PD-L1 positive population (TPS PD-L1 ≥ 1 %). Overall survival, ORR, and DoR, as assessed by an independent regulatory review commission (IRRC) and by the investigators as well as the PFS evaluated by the investigators, were secondarily analyzed. Patients were stratified by PD-L1 expression status and gender.

A total of 175 patients were enrolled in each study group. The median age was 68 years and most of them were males (92 %). Overall, 18 % of the patients had a PD-L1 expression status over 50 %. Patients who received penpulimab plus CT had a significantly longer PFS than patients treated with placebo plus CT (7.6 months vs 4.2 months; HR = 0.44; 95 % CI, 0.34-0.56; p < 0.0001). The 12-month and 24-month PFS rates were also more prominent in the penpulimab plus CT group than in the placebo plus CT group (37.1 % vs 9.2 % and 23.8 % vs 5.9 %, respectively). A PFS-benefit of adding penpulimab to CT was also demonstrated in the PD-L1 positive population (8.1 months vs. 4.2 months; HR = 0.37; 95 % CI, 0.27-0.51; p < 0.0001). At the time of data cut-off (June 1, 2022), the median follow-up was 23.56 months. Although the median OS was not reached, there was an obvious trend in favor of penpulimab plus CT (NR vs 19.8 months; HR = 0.55; 95 % CI, 0.40-0.75; p = 0.0002) and a significantly higher 24-month OS rate in this group compared to placebo plus CT (61.1 % vs 41.6 %). More patients responded to the treatment in the penpulimab plus CT arm (ORR, 71.4 % vs 44.0 %) and the response was also more durable for these patients (mDoR, 8.25 months vs 2.96 months).

The incidence of grade ≥ 3 TRAEs was 63.6 % in the penpulimab plus CT group and 62.9 % in the placebo plus CT group. The incidence of serious TRAEs was 28.3 % vs 26.9 %, respectively. In total, 5.2 % vs 3.4 %, respectively, of

patients experienced TRAEs leading to treatment discontinuation.

Combining penpulimab with CT demonstrated to be an effective and well-tolerated first-line treatment option for patients with advanced squamous NSCLC. This trial is the second randomized study (after investigating tislelizumab in the RATIONALE-307 trial [9]) suggesting that the abrogation of Fcγ receptor interactions may lead to higher response rates and lower toxicity.

EMPOWER-LUNG 3 trial: 1L cemiplimab plus CT plus ipilimumab

Cemiplimab is a monoclonal antibody directed against PD-1, which has been first developed, investigated, and approved for the treatment of advanced cutaneous squamous cell carcinoma [14]. When administered as monotherapy, cemiplimab demonstrated (NCT03088540) its survival benefit over chemotherapy in the EMPOWER-Lung 1 trial [15]. Thus, it was approved in the USA and the European Union as first-line treatment for patients with advanced NSCLC, PD-L1 ≥ 50 % and without EGFR, anaplastic ALK or ROS1 genomic aberrations. Moreover, in patients with low PD-L1 expression, the combination of ipilimumab - an anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody - and CT has been shown to potentialize the effects of anti–PD-1 therapy. At this year's ESMO IO meeting, Ana Baramidze reported on the phase III EMPOWER-Lung 3 trial part 1 (NCT03409614), which evaluated the combination of cemiplimab plus ipilimumab and CT as first-line treatment of patients with advanced squamous or non-squamous NSCLC with PD-L1 expression < 50 % [16].

Eligible patients had a histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or IIIC (not amenable to definitive concurrent chemoradiation) or stage IV (with no prior systemic treatment for recurrent or metastatic disease) disease, at least one radiographically measurable lesion per RECIST v1.1 criteria and an ECOG performance status of 0 or 1.

Patients were randomized (1:1:1) to receive either cemiplimab (350 mg, IV, Q3W for up to 108 weeks) plus four cycles of standard platinum-based doublet CT (CC Arm), or cemiplimab plus a reduced CT regimen (2 cycles) plus ipilimumab (50 mg, IV, Q6W for up to four cycles) (CIC Arm), or four cycles of standard platinum-based doublet CT (StC Arm). The primary endpoint was the OS, while the PFS, ORR, patient-reported outcomes (PROs) and safety were secondarily analyzed.

Of note, part 1 of this trial was stopped prematurely as patients were then reprioritized to standard CT plus cemiplimab regardless of PD-L1 expression. Thus, only descriptive statistical analyses comparing the combination of cemiplimab plus ipilimumab with a reduced course of CT (CIC Arm) with a standard CT regimen (StC Arm) were done and presented at the ESMO IO 2022 meeting [16].

A total of 323 patients, 85 % males, were enrolled in the study with a median followed-up of 35.5 months. Almost half of the patients (49 % in each group) presented with a PD-L1 expression < 1 %, while there was no patient with a PD-L1 expression > 50 %. Patients in the CIC arm (n = 109) showed a longer OS than those in the StC arm (n = 106) with a median OS of 20.1 months versus 13.9 months (HR = 0.615; 95 % CI, 0.441-0.857), respectively. The median PFS was 6.4 months versus 6.3 months (HR = 0.813; 95 % CI, 0.596-1.108), respectively. Overall, 35.8 % of patients in the CIC Arm responded to the treatment (ORR) compared to 28.3 % in the StC Arm. The median DoR was longer for CIC-treated patients compared to those having received the standard CT regimen alone (15.9 months vs 6.3 months, respectively).

Safety outcomes were comparable to known historical safety data, with an incidence of grade ≥ 3 TEAEs of 43.1 % in the CIC Arm and 42.7 % in the StC Arm. TEAEs leading to treatment discontinuation occurred in 6 % versus 2 % of the patients, respectively, while the rate of TEAEs leading to death was 4.6 % versus 4.9 %, respectively.

Although only descriptive data were presented, this trial showed that the addition of cemiplimab plus ipilimumab to a reduced CT regimen prolonged the overall survival in patients with PD-L1 expression < 50 %. ■

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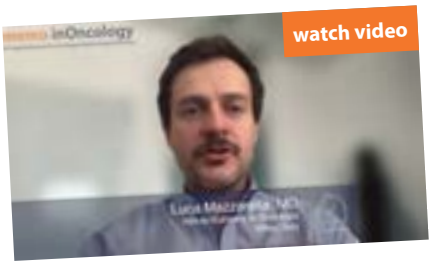
Expert interviews at ESMO IO 2022



Luca Mazzarella discusses the effects of modifying the pharmacology of anti-PD1 agents on their efficacy/toxicity in patients with advanced squamous NSCLC, explains potential therapeutic benefits of adding anti-CTLA4 or de-escalating chemotherapy to anti-PD1 blockade and highlights the role of individual or combined predictive biomarkers and biostatistics tools.

For those who are not only interested in immuno-oncology but also in the latest advances in nuclear medicine or neuroendocrine tumors please check out our congress reports from the 35th Annual Congress of the European Association of Nuclear Medicine as well as the North American Neuroendocrine Tumor Society (NANETS) Annual Medical Symposium on our microsite or recommend it to a colleague.

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This special issue will be offering a synopsis from the ASCO 2023 that will be held in June 2023. The report promises to make for stimulating reading, as the ASCO Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to cancer treatment and care. Stay tuned for the latest news in oncology and its subspecialties.

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