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A GLOBAL DIGEST ON APPROACHES IN ADVANCED SOLID TUMORS

Report from the ESMO Immuno-Oncology Congress, 8th – 11th December 2021

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Preface

Dear Colleagues,

The ESMO Immuno-Oncology Congress 2021 took place online from 8th to 11th December 2021. Compared with the annual ESMO scientific congress, this meeting focused exclusively on the most exciting new data in the promising field of immuno-oncology. In total, 1,124 participants from 67 countries attended one of the 31 on-demand sessions featuring over 193 abstracts, 178 e-posters, 146 presentations and 20 educational sessions. The interest for such a specialized oncology meeting confirms the importance of immune checkpoint inhibition as established part of the antitumoral therapy.

The aim of this congress was to provide a comprehensive overview of immunotherapy-based solid tumor treatments and to discuss the role of the immune system in controlling different tumor types, biomarkers for immunotherapy, the mechanisms of action of immune agents administered alone or in combination. The numerous oral and poster presentations enabled to learn more about interesting topics such as the paradigm of host-cancer interactions, the complexity of tumor heterogeneity, the role of tumor microenvironment or microbiome, the tumor mutational burden for prediction of outcomes in patients treated with immune checkpoint inhibitors, the incidence of immune-related toxicities and their management, or new therapeutic strategies in immuno-oncology with practice-changing potential. The highlight of this year's ESMO IO meeting was certainly the combination of immunotherapy with other anticancer targeted therapies or chemotherapy which are in the focus of this special issue.

Although tumor immunology and immunotherapy – one of the four pillars next to surgery, chemotherapy and radiotherapy – play a central role and checkpoint inhibitors have definitely revolutionized cancer treatment, there are still several open questions:

Why do some tumors not respond to ICIs? How can the severity of treatment-related toxicities, especially late ones, be reduced? Which patient population benefits the most? How and when to de-escalate immunotherapy?

To face these important current and future challenges in immuno-oncology,

it deserves dedicated meetings like ESMO IO to apprehend the extend of its therapeutic applications across different tumor entities to move the field even further and thus enable giving the right treatment, at the right time, to the right patient.

Prof. Wolf H. Fridman
Centre de Recherche des Cordeliers, Sorbonne Université, Institut national de la santé et de la recherche médicale, Université de Paris, Paris, France

Immune checkpoint blockade combined with chemotherapy in solid tumors

Pooled analysis of PD-1 inhibitor versus bevacizumab in NSCLC

Non-small cell lung cancer (NSCLC) is a severe disease with poor outcomes since the majority of patients present with stage IV disease at diagnosis [1]. Approved treatment options in the first-line setting of advanced NSCLC (aNSCLC) with wildtype *EGFR/ALK* include bevacizumab - a VEGF targeting monoclonal antibody - and PD-1/PD-L1 inhibitors in combination with chemotherapy. Current guidelines preferentially recommend PD-1/PD-L1 antibodies over bevacizumab based on extrapolation of previous studies, since no randomized head-to-head trials exist to date [2]. With the aim of providing evidence to support clinical practice, Meng et al. presented a prospective analysis from three clinical trials at the ESMO IO congress 2021 with the aim to compare the survival benefit of PD-1 inhibitors versus bevacizumab in addition to chemotherapy for the treatment of advanced non-squamous NSCLC without targetable genetic mutations [2].

Data were pooled from three randomized trials (ORIENT-11, NCT03607539; CameL, NCT03134872; Bevacizumab trial, NCT02954172) with 466 patients who received the PD-1 inhibitors camrelizumab (also known as SHR-1210) or sintilimab in combination with pemetrexed (500 mg/m²) and platinum (cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min), and 432 patients who received bevacizumab (15 mg/kg) plus paclitaxel (175 mg/m²) and carboplatin (AUC 6 mg/mL/min). In total, 375 patients in each arm were matched 1:1 using a propensity

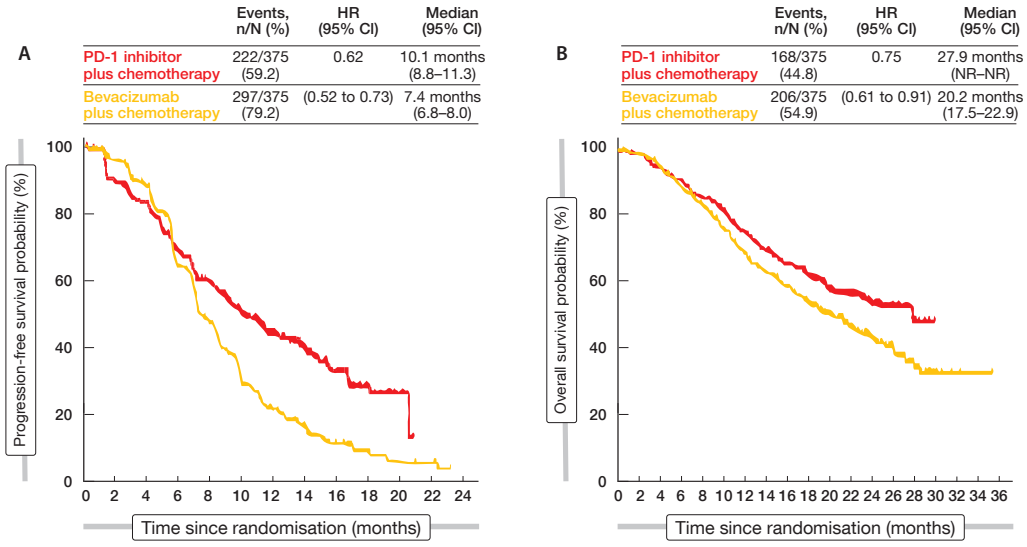

Figure 1: Pooled analysis of PD-1 inhibitors versus bevacizumab: **(A)** PFS and **(B)** OS.

score matching to balance baseline characteristics of the two arms. The endpoints of this analysis included progression-free survival (PFS), overall survival (OS), and objective response rate (ORR).

With a median follow-up of 23 months, the PD-1 inhibitors plus chemotherapy demonstrated significant longer median progression free survival (mPFS) and median overall survival (mOS) compared to bevacizumab plus chemotherapy. Indeed, the mPFS was 10.1 months in the PD-1 inhibitor arm compared with 7.4 months in the bevacizumab arm (HR, 0.62; 95% CI, 0.52 - 0.73; p < 0.001), while the OS reached 27.9 months with PD-1 inhibitors versus 20.2 months with bevacizumab (HR, 0.75; 95% CI, 0.61 - 0.91; p = 0.004) **(Figure 1)**. The ORR in the PD-1 arm reached 56.8% versus 45.1% in bevacizumab arm.

This pooled analysis showed a significant survival benefit of PD-1 inhibitor plus chemotherapy compared to bevacizumab plus chemotherapy in patients with aNSCLC. However, an exploratory subgroup analysis indicated comparative survival outcomes in the PD-L1-negative and older patient (≥ 65 years) subgroups, thus, treatment with bevacizumab plus chemotherapy still mattered in this patient population.

POSEIDON study: no ADA effects of durvalumab and tremelimumab in NSCLC

Administered therapeutic agents like immune checkpoint inhibitors (ICIs) are recognized by the immune system and may lead to the generation of anti-drug antibodies (ADAs). ADAs, by binding to the drug, can result in a reduction of the treatment activity via different mechanisms (e.g. neutralizing antibodies) or lead to increased toxicities by the generation of an immune response against the ADA-drug complex [3]. The clinical impact of ADAs upon treatment with PD-1/PD-L1 inhibitors is not well defined, and so far, data are contradictory [3, 4].

The global phase III trial POSEIDON (NCT03164616) investigated the efficacy and safety of the PD-L1 inhibitor durvalumab plus the CTLA-4 inhibitor tremelimumab. In total, 1013 patients with EGFR/ALK wild-type metastatic NSCLC were randomized 1:1:1 to durvalumab plus chemotherapy or durvalumab plus tremelimumab plus chemotherapy or chemotherapy alone as first line treatment. Main study results were published previously and showed that the combination of durvalumab plus tremelimumab plus chemotherapy significantly extended mPFS and mOS compared with chemotherapy alone [5]. Using the data set from the POSEIDON trial, Reinmuth et al. evaluated the pharmacokinetics (PK) and immunogenicity of durvalumab and tremelimumab, as well as the potential impact of ADAs on PK and safety; results of this study were presented at the ESMO IO 2021 congress [4].

PK data of 327 patients in the triplet combination arm and of 330 patients in the doublet combination were available for this analysis and showed similar profiles for durvalumab indicating that tremelimumab has no effect on durvalumab PK when administered in combination. Moreover, treatment induced-ADAs (TE-ADAs) reached 10.1% (29/286) in the durvalumab plus tremelimumab plus chemotherapy arm and 6.7% (19/285) in the durvalumab plus chemotherapy arm. In total, less than 3% (8/286 and 7/285, respectively) of patients were persistently ADA-positive and about 1% had neutralizing antibodies. Immunogenicity data for tremelimumab showed that 13.7% (38/278) of patients had TE-ADAs, 11.2% of ADA-evaluable patients had neutralizing antibodies, and 7.9% (22/278) of patients were persistently ADA-positive with a low ADA titer.

Adverse Events (AEs) reported in patients positive for ADAs were similar to those reported in patients who were negative for ADAs. There were no new types of events, or events clearly suggestive or indicative of immune complex disease. Based on pooled data from prior studies, PK and immunogenicity profiles for durvalumab and tremelimumab were within expected ranges and provided no evidence that PK or safety of either treatment was adversely affected.

RATIONALE 309: tislelizumab in nasopharyngeal cancer

Nasopharyngeal cancer, a relatively rare epithelial carcinoma accounting for approximately 133,000 new cases and 80,000 deaths per year worldwide, has

distinct geographical distribution and is particularly common among Asian and African populations [6, 7]. The first-line treatment with standard of care (SoC) chemotherapy has a poor prognosis with a mPFS of seven months and a mOS of 22.1 months [8, 9]. Tislelizumab - a humanized monoclonal anti-PD-1 antibody specifically designed to minimize the binding to FcγR on macrophages to abrogate the antibody dependent cellular phagocytosis - has been approved in China in December 2019 and is investigated in a broad clinical program combining various anticancer agents [10].

The randomized, double-blind, phase III trial RATIONALE 309 (NCT03924986) evaluates the efficacy and safety of tislelizumab combined with chemotherapy versus placebo plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer (RM-NPC); results of the interim analysis were presented at ESMO IO 2021 congress [11].

A total of 263 patients were randomized 1:1 to receive either tislelizumab (200 mg intravenously [IV] every three weeks [Q3W]) plus chemotherapy (gemcitabine 1 g/m² IV Day 1 (D1), D8 and cisplatin (80 mg/m² D1, Q3W, 4-6 cycles) (arm A) or placebo plus chemotherapy (arm B). The primary endpoint was progression-free survival (PFS) assessed by an independent review committee (IRC), while the IRC-assessed objective response rate (ORR) and duration of response (DoR), overall survival (OS), investigator-assessed PFS, health-related quality of life (HR-QoL) and safety were secondarily evaluated. Stratification factors included gender and liver metastases. Data review was performed by an independent data monitoring committee (iDMC); crossover to tislelizumab was allowed after disease progression or intolerable toxicity.

The median age of the patient population was 50 years, 78 % of the subjects were male, about half of them were never-smoker, a large majority of them had a primary metastatic disease (> 90 %) and 43 % suffered from liver metastases at baseline. In total, 80 % of patients in arm A and 72 % in arm B displayed an EBV DNA level ≥ 500 IU/ml, while 61 % and 64 %, respectively, had a PD-L1 expression ≥ 10 %. As of March 26, 2021, after a median follow-up time of ten months, the RATIONALE 309 study achieved its primary endpoint by demonstrating a statistically significant improvement of the mPFS with tislelizumab plus chemotherapy compared to chemotherapy alone (9.2 vs 7.4 months; stratified HR, 0.52; 95 % CI, 0.38 - 0.73; p < 0.0001) in the ITT population **(Figure 2)**. The PFS rates at six, nine, and twelve months were 66.1 %, 51.0 % and 35.7 % in arm A, compared to 53.0 %, 21.6 %, and 12.2 % in arm B. Further analysis showed a significant benefit for tislelizumab plus chemotherapy in almost all subgroups. The ORR was 69.5 % versus 55.3 % in favor of tislelizumab, including 21 patients with a complete response (CR), 70 with a partial response (PR) in arm A and 9 CRs and 64 PRs in arm B. The mDoR reached 8.5 months versus 6.1 months, respectively.

The RATIONALE 309 trial showed a manageable safety profile consistent with previous reports; all patients (100 %) in arm A and 99.2 % of arm B experienced at least one treatment-emergent adverse event (TEAE) of any grade. Grade ≥ 3 TEAEs were reported in 106 patients (80.9 %) in arm A, compared to 108 patients (81.8 %) in arm B, including anemia, decreased white blood cell count, decreased neutrophil count and leukopenia. Serious TEAEs grade ≥ 3 were reported in 22.9 % of patients in arm A, compared to 26.5 % in arm B. Only 1.5 % of TEAEs in arm A and 2.3 % in arm B led to a permanent treatment discontinuation.

The authors concluded that these promising interim results support the potential of tislelizumab combined with chemotherapy as a new standard of care for the first-line treatment of RM-NPC.

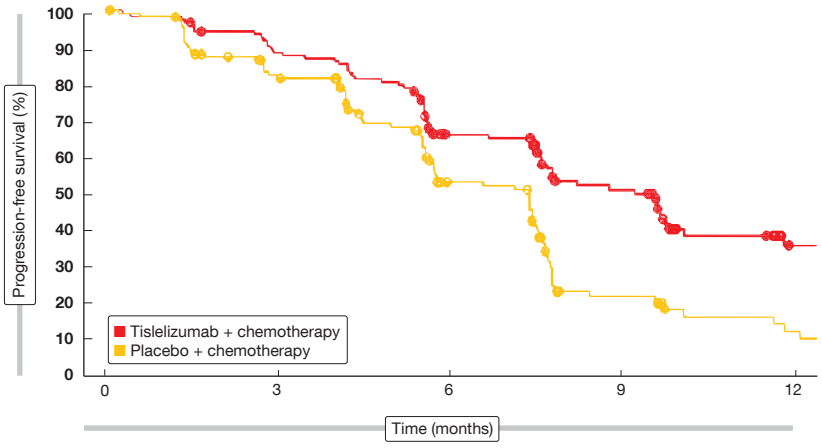

Figure 2: RATIONALE 309 trial: PFS of RM-NPC patients treated with tislelizumab plus chemotherapy versus placebo plus chemotherapy.

Neoadjuvant chemotherapy plus camrelizumab in HNSCC

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide with approximately 890,000 newly diagnosed cases and a mortality rate of 51 % in 2018 [12]. Previous studies showed that neoadjuvant anti-PD-1/PD-L1 immunotherapy for resectable HNSCC was well tolerated and might be a promising therapeutic option for this patient population [13]. A phase II trial (ChiCTR1900025303) investigated the antitumoral activity and safety of the neoadjuvant anti-PD-1 antibody camrelizumab combined with chemotherapy in patients with locally advanced HNSCC; study results were presented at ESMO IO 2021 [14].

Overall, 30 eligible patients (≤ 70 years) with a histologically confirmed resectable local advanced high-risk oral, oropharyngeal, hypopharyngeal or laryngeal squamous cell carcinoma were enrolled. They received chemotherapy with either docetaxel (75 mg/m², Day 1) plus cisplatin (75 mg/m², Day 1) or nanoparticle albumin-bound paclitaxel (260 mg/m², Day 1) plus cisplatin (75 mg/m², Day 1) and camrelizumab (200 mg, Day 1) for three 21-day cycles, followed by a 10-week break, surgery, and an adjuvant radiotherapy.

As of August 1, 2021, the median age of patients was 58 years, most of them were male (86.7 %), half of the patients were none-smokers, about one third were non-drinkers, and 20 % of patients were positive for HPV. The ORR reached 96.7 % and the disease control rate (DCR) 100 %. Three patients refused surgery, and 27 underwent surgery without delay, with an R0 resection rate of 92.6 %. The throat and hypopharyngeal function retention rate

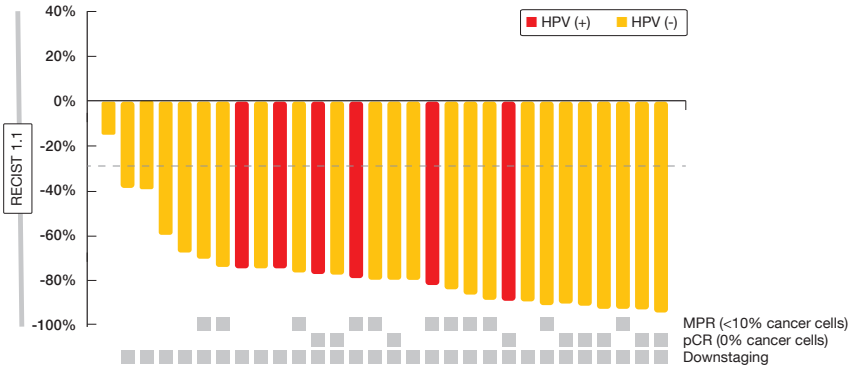

Figure 3: Tumor response per RECIST v1.1 and pathological assessment according to HPV status.

was 84.6 %. The pathological complete response (pCR) rate, which was the co-primary endpoint with safety, reached 33.3 % after a median follow-up of 10.5 months; the major pathological response rate was 74.1 % and the disease-free survival (DFS) not reached **(Figure 3)**.

Most of the neoadjuvant TRAEs were mild. Grade 3 rash, pruritus, and thrombocytopenia were experienced by one patient each. No grade 4 or 5 TREAs were observed.

Neoadjuvant chemotherapy plus camrelizumab demonstrated a strong anticancer activity with an acceptable safety profile and might thus be considered a new treatment option for locally advanced HNSCC in the neoadjuvant setting.

1L toripalimab combined with chemotherapy in advanced thymic carcinoma

Thymic epithelial tumors (TETs) include thymomas (Ts) and thymic carcinomas (TCs); TCs, which account for approximately 15 to 20 % of TETs, represent an aggressive disease with poor prognosis [15]. TCs highly express PD-L1 and previous data indicate a promising antitumoral effect of pembrolizumab monotherapy [16, 17].

At ESMO IO 2021 meeting, Hu et al. presented the study design of an open-label, single-arm, phase II study (ChiCTR2000039155), which aims to investigate the efficacy and safety of the PD-1 inhibitor toripalimab combined with paclitaxel and carboplatin in treatment-naïve patients with advanced TCs [18]. Key eligible criteria include the following: ≥18 years, ECOG PS ≤2, histologically or cytologically confirmed Masaoka stage III or IV TC, no prior systemic anticancer therapy for advanced TCs, at least one measurable lesion per RECIST v1.1 and adequate organ function. Patients with symptomatic brain metastases or controlled symptoms for less than one month are ineligible for enrollment, as well as patients who had a prior allogeneic hematopoietic stem cell- or organ transplantation. Approximately 30 patients will be enrolled and receive toripalimab (240 mg, Day 1) in combination with paclitaxel (175 mg/m², Day 1) and carboplatin (AUC=5, Day 1), Q3W, for six cycles. Patients whose disease did not progress will continue treatment with toripalimab (240 mg, Day 1, Q4W) until disease progression, intolerable toxicity, or withdrawal following patient's request. Investigator-assessed PFS according to RECIST v1.1 is the primary endpoint of the study, while secondary endpoints are ORR, OS, DCR, DoR, time to response (TTR) and safety.

The enrollment into this single-center trial has started in March 2021 in Beijing, China.

Dual targeting with ociperlimab plus tislelizumab combined with cCRT in NSCLC

About 85 % of lung cancers – the most common cancer worldwide – are NSCLCs [19]. Approximately one third of patients first diagnosed with NSCLC present with locally advanced stage III disease and have a poor long-term prognosis [19]. Combined chemoimmunotherapy showed a synergistic anticancer activity in the first-line treatment of advanced NSCLC [20]; however, most patients still suffer from disease recurrence [21]. However, immunotherapy after chemoradiotherapy (cCRT) was shown to improve survival outcomes in patients with locally advanced unresectable disease [22]. Tislelizumab, a humanized IgG 4 monoclonal antibody, was designed to abolish the antibody-dependent phagocytosis, a potential mechanism of resistance to anti-PD-1 therapy [10]. The in-

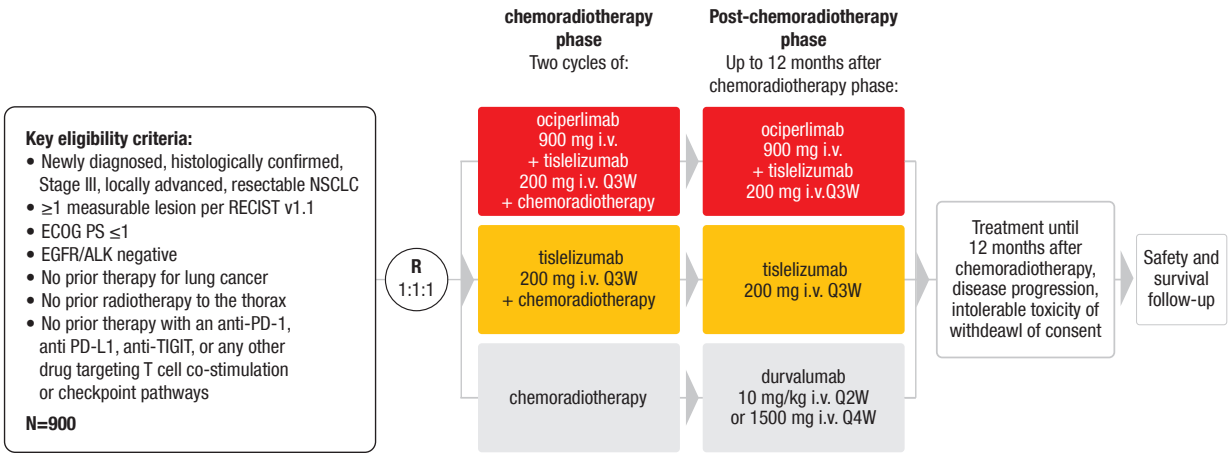

Figure 4: AdvanTIG-301 study design

vestigational humanized anti-TIGIT antibody ociperlimab binds specifically to TIGIT and blocks its interaction with the poliovirus receptor (CD155) and poliovirus receptor-related (CD112) ligands on tumor cells, resulting in activation of T-cell mediated antitumor immune response [23, 24].

Xing et al. presented the study design **(Figure 4)** of an ongoing randomized phase III trial named AdvanTIG-301 (NCT04866017) at ESMO IO 2021. This multicenter, randomized, open-label study, where patients are randomized 1:1:1, is investigating the efficacy and safety of ociperlimab plus tislelizumab plus cCRT followed by ociperlimab plus tislelizumab (arm A) compared with tislelizumab plus cCRT followed by tislelizumab (arm B) or cCRT followed by durvalumab (arm C) in previously untreated, locally advanced, unresectable NSCLC [24]. Key inclusion criteria are: i) untreated, newly diagnosed, histologically confirmed, locally advanced stage III unresectable NSCLC in absence of EGFR or ALK genomic tumor aberrations; ii) ECOG PS ≤ 1; and iii) no prior therapies (listed in **Figure 4**). Co-primary endpoints to be assessed by an IRC according to RECIST v1.1 are PFS and complete response rate (CRR). Secondary endpoints include OS, ORR, DoR, time to death or distant metastasis, HR-QoL, safety and tolerability, serum concentrations of ociperlimab and tislelizumab, immunogenic response to ociperlimab and tislelizumab as well as the evaluation of PD-L1 and TIGIT expression. An exploratory analysis will additionally evaluate biomarkers and patient-reported outcomes (PROs).

Recruitment is currently ongoing in various study sites of the United States and Australia. ■

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Established and novel chemo-free combinations in immuno-oncology

LEAP-007: pembrolizumab plus lenvatinib in first-line NSCLC

Immunotherapy was the major breakthrough in the treatment of lung cancer in the past years [1]. The PD-1 inhibitor pembrolizumab is approved for the treatment of various tumor entities including advanced or metastatic non-small cell lung cancer (a/mNSCLC), more precisely, as 1L therapy for NSCLC as monotherapy in patients with PD-L1 positive tumors or in combination with chemotherapy regardless of PD-L1 expression [2]. Lenvatinib, a multikinase inhibitor and anticancer agent that is so far approved for certain solid tumors but not NSCLC, already showed promising antitumoral effects and a manageable safety profile when combined with pembrolizumab in a phase Ib/II trial [3].

The double-blind phase III study LEAP-007 (NCT03829332) investigated the efficacy and safety of pembrolizumab with or without lenvatinib in adults with PD-L1-positive treatment-naïve NSCLC; first results were presented at ESMO IO congress 2021 [4]. Eligible patients (n=623) were random-

ized 1:1 to receive either pembrolizumab (200 mg intravenously [IV] every three weeks [Q3W)] for up to 35 cycles) plus oral lenvatinib (20 mg daily) or pembrolizumab plus placebo. Stratification factors were geographic region (East Asia versus non-East Asia), ECOG PS (0 versus 1), and PD-L1 TPS (1 - 49 % versus ≥ 50 %). Progression-free survival (PFS) according to RECIST v1.1 assessed by a blinded independent central review (BICR) and overall survival (OS) as co-primary endpoints, while secondary endpoints enclosed objective response rate (ORR), safety, quality of life (QoL) and patient-reported outcomes (PROs).

Baseline patient characteristics were well balanced between both arms. Median age was 66 years, about three quarter of patients were male, one third were enrolled in Asia, most were current or former smokers, while 44 % had a PD-L1 TPS ≥ 50 % and 56 % a PD-L1 TPS 1 - 49 %. The median overall survival (OS) was 14.1 months for pembrolizumab plus lenvatinib versus 16.4 months for pembrolizumab plus placebo (HR, 1.10; p = 0.79744), while the median PFS reached 6.6 versus 4.2 months, respectively (HR, 0.78; p = 0.00624). The ORR reached 40.5 % (including 7 patients with a complete response [CR] and 118 with a partial response [PR]) for pembrolizumab plus lenvatinib versus 27.7 % (including 6 CRs and 81 PRs) for pembrolizumab plus placebo.

After a median duration of treatment of approximately six months, pembrolizumab plus lenvatinib was associated with higher rates of grade 3-5 treatment-related adverse events (TRAEs) (57.9 vs 24.4 %), as well as AEs leading to discontinuation or death, compared with pembrolizumab plus placebo. The most common grade ≥ 3 TRAEs experienced with the combined therapy were hypertension, proteinuria, diarrhea, and fatigue. No new safety signals were reported.

Based on the prespecified futility analysis provided to the independent data monitoring committee (DMC), the benefit/risk profile for pembrolizumab plus lenvatinib was not considered favorable versus pembrolizumab plus placebo in patients with mNSCLC presenting a PD-L1 TPS ≥1%. Thus, treatment with pembrolizumab plus lenvatinib was discontinued, but patients were allowed to continue on open-label pembrolizumab plus placebo for up to 35 cycles.

Further phase III studies evaluating pembrolizumab plus lenvatinib in NSCLC patients are ongoing. The authors concluded that pembrolizumab monotherapy remains a standard of care for first-line metastatic NSCLC with PD-L1 TPS ≥ 1 % whose tumors are not presenting with *EGFR/ALK* alterations.

Novel surufatinib combined with toripalimab in solid tumors

Surufatinib, a novel angio-immuno kinase inhibitor, selectively targets vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, fibroblast growth factor receptor type 1 (FGFR1) and colony stimulating factor-1 receptor (CSF-1R). In December 2020, this small molecule received its first approval in China for the treatment of late-stage, well-differentiated, extra-pancreatic neuroendocrine tumors (NET). A U.S. FDA submission for surufatinib has been filed and a submission to the EMA is planned for pancreatic and extra-pancreatic NET, too [5]. Surufatinib, which was evaluated in a dose-escalating phase I trial in combination with the humanized IgG4 PD-1 antibody toripalimab in patients with advanced solid tumors, showed encouraging antitumor activity (NCT03879057) [6].

Results of an ongoing multicenter phase II trial investigating the efficacy and safety of surufatinib (250 mg per oral (PO) once daily) plus toripalimab (240 mg IV Q3W) in patients with unresectable or metastatic advanced solid tumors was presented at ESMO IO 2021 (NCT04169672) [7]. At the time of data cut-off (August 1, 2021), 62 patients were assigned in this open-label study into three cohorts of patients with advanced neuroendocrine carcinoma (NEC, n=21), gastric or gastroesophageal junction adenocarcinoma (G/GEJ, n=21), or advanced esophageal squamous cell carcinoma (ESCC, n=20) who progressed after 1L systemic chemotherapy. The median age was 60 years in the NEC and ESCC cohort and 58 years in the G/GEJ group. The number of male patients was slightly higher in the G/GEJ cohort than in the NEC and ESCC groups (81.0 %, 71.4 % and 70.0 %, respectively). Most of the patients had one previous anticancer therapy; approximatively 10 % of participants in the G/GEJ and ESCC cohorts had two or more prior lines of treatment. PD-L1 positivity according to low CPS (≥ 1 to < 10) was found in 61.9 %, 47.6 %,

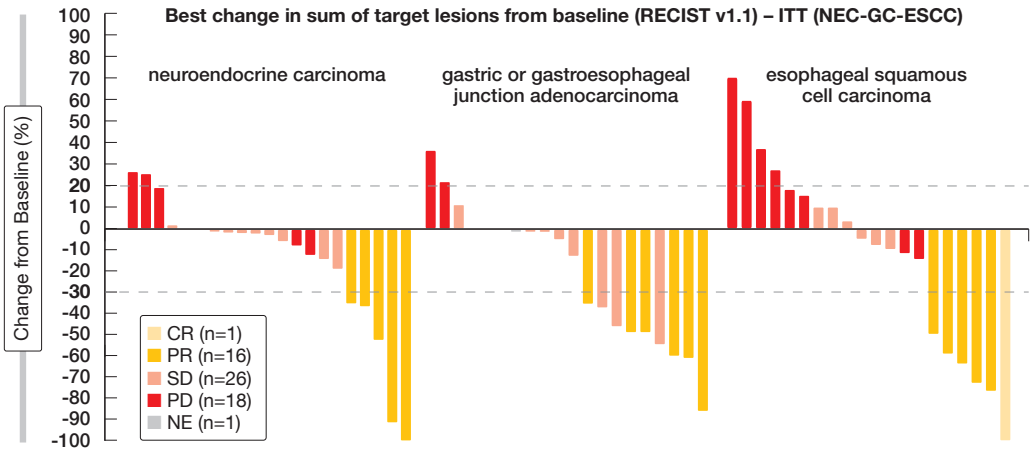

Figure 1: Waterfall plot of tumor response in the three cohorts.

and 45.0 % of patients in the NEC, G/GEJ and ESCC cohorts, and PD-L1 high CPS (≥ 10 to < 50) was detected in 19.0 %, 28.6 %, and 35.0 % of subjects in the NEC, G/GEJ and ESCC groups, respectively.

In the NEC cohort patients reached a confirmed ORR - the primary endpoint - of 23.8 %, with 5 patients with a PR, ten with a stable disease (SD) and six with a progressive disease (PD). A similar ORR of 30.0 % was reached in both G/GEJ (6 PRs, 10 SDs, 3 PDs) and ESCC cohorts (5 PRs, 6 SDs, 8 PDs) **(Figure 1)**. One patient in the ESCC cohort had a CR. The duration of response (DoR) was 4.11 and 4.28 in the NEC and G/GEJ cohort, and not evaluable in the ESCC group. The median PFS (mPFS) – secondary endpoint - was 4.14, 4.11, and 2.73 months in the NEC, G/GEJ, and ESCC cohorts, while the mOS was 10.87, not reached, and 9.72 months, respectively.

Surufatinib in combination with toripalimab showed a manageable toxicity without any new safety signals. In total, 56.5 % of the patients in the overall group (n=62) suffered from treatment-emerged adverse events (TEAEs) of grade three or higher. Hypertension (8.1 %) as well as anemia, decreased white blood cell- and neutrophil count, and malignant neoplasm progression (6.5 % each) were the most common TRAEs.

Surufatinib in combination with toripalimab exhibited promising efficacy in patients with advanced NEC, G/GEJ and ESCC. To confirm these findings, a multicenter phase III trial in advanced NEC patients is currently ongoing in China (NCT05015621).

Sintilimab plus anlotinib in second- or later line ED-SCLC therapy

Small cell lung cancer (SCLC) is still a poorly understood, aggressive disease with high relapse and mortality rates. Recently, immune checkpoint inhibitors (ICI) in combination with front-line chemotherapy significantly improved disease responses and changed the therapeutic algorithm of extensive-disease (ED)-SCLC in the first-line setting [8]. Nevertheless, treatment options for second- or later lines are limited [9].

At this year's ESMO IO meeting, Ma et al. presented results from a phase II single-arm, open-label clinical trial; this study evaluated anlotinib - a novel receptor tyrosine kinase inhibitor (RTKi) targeting VEGFR 2 and 3, FGFR 1–4, platelet-derived growth factor receptor (PDGFR) α and β, c-KIT and RET - in combination with sintilimab - an anti-PD-1 inhibitor - in 26 patients with recurrent or ED-SCLC, who had been pretreated with at least one platinum-based chemotherapy regime [10]. Eligible patients (median age of 57 years, 76.9 % male, 23.1 % with second-line therapy, 61.6 % with stage IVb) received anlotinib (12 mg PO on Day 1-14 Q3W) combined with sintilimab (200 mg IV on D1 Q3W). After a median follow-up of nine months, the primary endpoint PFS reached 5.8 months (95 % CI, 2.8-9.4) and the mOS was 11.4 months (95 % CI, 6.2-NR). The ORR reached 41.7 %, including two patients with a CR and eight patients with a PR, and the disease control rate (DCR) was 87.5 %.

In total, all patients had TRAEs, the most common ones being thyroid dysfunction (42.3 %), hypoproteinemia and anemia (34.6 % each). Lymphocytopenia (11.5 %) and hypoproteinemia (3.8 %) were the most frequent grade 3-4 TRAEs. In three patients TRAEs led to drug discontinuation.

Given the promising efficacy and an acceptable toxicity, sintilimab in combination with anlotinib represents a potential second-line or later therapy in pretreated patients with ED-SCLC. This single center-study is currently ongoing for recruitment in China.

Pembrolizumab plus olaratumab in pretreated STS patients

Soft-tissue sarcoma (STS) is a heterogeneous group of tumors that develop from mesenchymal tissue; affected patients have a short life expectancy of approximately twelve to 18 months [11]. In a phase II study, the anti-PDGFRα antibody olaratumab in combination with doxorubicin showed an improved survival outcome in patients with STS (NCT01185964) which could not be confirmed in a subsequent phase III trial (NCT02451943). On the other hand, pembrolizumab, an anti-PD-1 antibody, has shown clinical activity in some histological subtypes of STS [12]. The addition of olaratumab to pembrolizumab might thus induce a change of the tumor microenvironment allowing pembrolizumab to elicit a more robust immune response.

An open-label phase Ia/b study assessed the safety and efficacy of the addition of pembrolizumab (200 mg IV on Day 1 of a 21-day cycle for up to 35 cycles) to olaratumab during a phase Ia (dose escalation, 15 mg/kg IV starting dose or 20 mg/kg IV escalated dose on Day 1 and 8) and a phase Ib (dose-expansion with the recommended dose of 20 mg/kg IV) study in patients with unresectable locally advanced or metastatic STS, not amenable to curative treatment and after failure of standard therapies (NCT03126591). Patients with brain metastasis were not eligible for enrollment in this trial. The primary objectives were safety and tolerability, while secondary objectives included the ORR, DCR, DoR, PFS and OS per RECIST v1.1. Study results were recently presented at ESMO IO 2021 meeting [13].

Most patients were female with an age < 65 years, and two patients hat PD-L1-positive tumors. All patients in phase 1a and > 90 % in phase 1b had received prior systemic therapy with 10 patients in phase Ia (n=13) and 13 patients in phase Ib (n=28) experienced ≥ three prior lines of therapy while ten subjects received prior olaratumab. The majority of patients in phase Ib had leiomyosarcoma (35.7 %), followed by undifferentiated pleomorphic sarcoma (10.7 %), rhabdomyosarcoma (7.1 %), as well as synovial sarcoma, alveolar soft part sarcoma, and dedifferentiated liposarcoma (3.6 % each).

In phase Ib, the ORR was 21.4 %, including six patients with PR. The DCR was 53.6 % (including additional 9 patients with SD), with a mDoR of 16.2 months, while mPFS and mOS reached 2.7 and 14.8 months, respectively. To note, no response was observed in both patients presenting with PD-L1-positive tumors.

In total, 73.2 % of the safety population (n=41) had at least one TRAE, whereas 22 % experienced grade 3 or 4 TRAEs, most commonly diarrhea and anemia (4.9 % each). Treatment discontinuation due to TRAEs occurred in two patients in phase 1a (increased lipase) and two patients in phase 1b (infection and diarrhea).

Overall, the addition of olaratumab to pembrolizumab was safe and well-tolerated in patients with advanced STS. Antitumor activity was observed in 21 % of patients in the dose-expansion cohort. Further studies with a larger sample size

are needed to confirm the promising antitumor effect of this combination.

Sitravatinib combined with tislelizumab in ovarian cancer

Ovarian cancer (OC) is one of the most common gynecologic cancers, the high mortality rate is mainly caused by its diagnosis in the advanced stage because of a delayed onset of symptoms, lack of proper screening and asymptomatic and secret growth of the tumor. A platinum/taxane-based chemotherapy with or without bevacizumab is the standard of care for advanced OC [14]. The ORR of the primary treatment reaches usually 60–80 % but 70 % of patients relapse within five years and drug-resistance remains a major challenge [15]. Early phase clinical studies investigating the efficacy of ICIs have shown an antitumor activity in patients with advanced OC [15]. Tislelizumab, an PD-1 antibody, is currently investigated in a broad clinical program combining various anticancer agents [16]; among them, sitravatinib, an oral spectrum-selective kinase inhibitor that potentially inhibits TAM family receptors (TYRO3, AXL, MERTK) and split family receptors (VEGFR2, KIT) [17]. An open-label, multicenter, multicohort phase Ib study (NCT03666143) evaluated the safety and efficacy of tislelizumab in combination with sitravatinib in patients with advanced solid tumors; updated results from the cohort E (anti-PD-1/PD-L1 antibody-naïve recurrent platinum-resistant epithelial OC) have been presented at ESMO IO 2021 [18]. Safety/tolerability was the primary endpoint, while the key secondary endpoints were investigator-assessed ORR, DCR, DoR and PFS. Additionally, OS, potential pharmacodynamic biomarkers, retrospective analysis of PD-L1 expression have been exploratory analyzed.

As of March 29, 2021, 63 patients were enrolled into cohort E who received sitravatinib (120 mg PO daily) plus tislelizumab (200 mg IV Q3W) of which 27 patients (42.9 %) remained on treatment. The median age of patients was 66 years, most of them were white (79.4 %) and had serous epithelial carcinoma (95.2 %) or mucinous, endometrioid and clear cell OC (1.6 % each). In these heavily pretreated patients (median of four prior regimens), 34.9 % received bevacizumab, while 42.9 % of them had a PD-L1 expression of 10 % or higher. The median follow-up was 8.9 months.

In the efficacy evaluable population (n=59), the ORR was 28.8 % (17 PRs) and the DCR 79.7 % (with 30 additional SDs); nine patients (15.3 %) had a PD **(Figure 2)**. The overall population reached a median DoR of 5.6 months, mPFS and mOS were 4.1 and 11.8 months, respectively. After a median follow-up of 11.7 months, OS data were still immature. PD-L1 expression was not related to the clinical efficacy. Post-treatment changes of plasma VEGF, VEGFR2, and serum IP-10 were observed.

The median duration of exposure was 16 weeks for sitravatinib and 18 weeks for tislelizumab. Most patients experienced TRAEs of any grade (95.2 %) and 42.9 % grade ≥ 3 TRAEs. Frequently observed TEAEs were diarrhea (68.3 %), nausea (55.6 %) and fatigue (50.8 %), while the most common TEAEs of grade 3 or higher were hypertension (17.5 %) and fatigue (9.5 %). There were five fatal TEAEs which were unrelated to the treatment. Most patients (88.9 %) had sitravatinib dose modification.

Compared with the primary analysis (data cut-off, October 13, 2020), this two-month longer follow-up confirmed the manageable safety profile and antitumor activity of sitravatinib in combination with tislelizumab. Further investigation in this patient group is warranted.

Effect of TQ-B240 plus anlotinib in NSCLC

Although ICI monotherapy has shown unclear PFS benefit and limited OS advantage compared to docetaxel alone in the second-line treatment of NSCLC [19, 20], ICIs combined to antiangiogenic agents showed a good antitumoral efficacy [21, 22]. Anlotinib, a novel multi-target anti-angiogenic RTKi, was approved in May 2018 by the China national medical products administration (NMPA) as third-line treatment for NSCLC patients after ≥ 2 lines of chemotherapy; this approval is based on the results of the phase III ALTER0303 trial, in which anlotinib significantly prolonged OS (9.6 versus 6.3 months) and PFS (5.4 versus 1.4 months) versus placebo in this patient population (NCT02388919) [23].

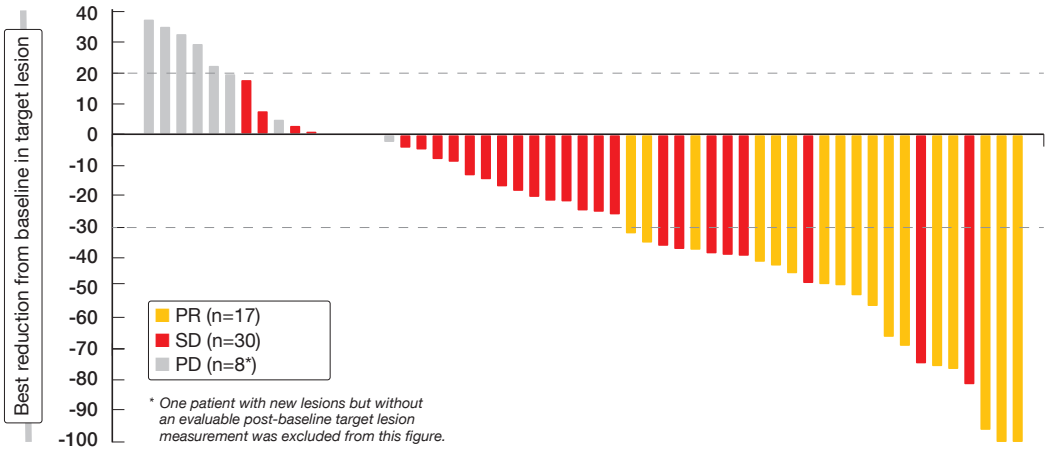

Figure 2: Best change in target lesions related to baseline in OC patients receiving sitravatinib plus tislelizumab.

At ESMO IO 2021 meeting, Han et al. presented the results of a multicenter, randomized, double-blind phase Ib study investigating the safety and efficacy of TQB-2450, an investigational humanized anti-PD-L1 antibody, combined with or without anlotinib in patients with advanced NSCLC pretreated with ≥1 line of chemotherapy (NCT03910127) [24]. A total of 101 patients (*EGFR/ALK* wildtype, PD-L1 TPS unrestricted) were randomized 1:1:1 to receive either TQ-B2450 (1200 mg IV D1 Q21D) plus anlotinib (12 mg or 10 mg daily Day 1-14 of a 21-day cycle) or TQ-B2450 plus placebo; as the average daily exposed dosage of anlotinib was 10.2 mg, both TQ-B2450 plus anlotinib groups were then merged as TQ-B2450-ALTN (TQ-B2450 + anlotinib) group. The median age was 60 years in the TQ-B2450 group compared to 61.5 years in the TQ-B2450-ALTN group with 82 % and 70 % being male. Most of the patients received one previous line of treatment (70 % and 76 %), and were ever smokers (67 % and 60 %).

Nearly two third of the patients (63 %) had an adenocarcinoma in both treatment groups, followed by squamous carcinoma (27 % in the TQ-B2450 and 21 % in the TQ-B2450-ALTN group, respectively). The tumor pathology was mainly stage IV (83 % and 86 %), about

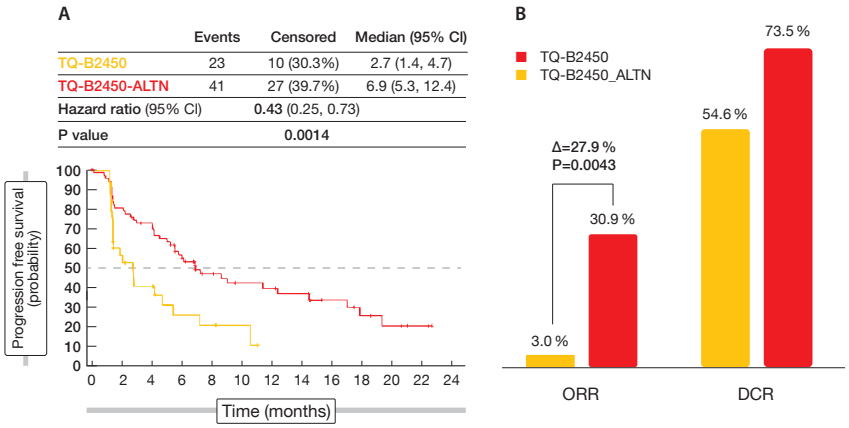

Figure 3: PFS **(A)** as well as ORR and DCR **(B)** benefit with TQ-B2450 plus anlotinib in advanced NSCLC patients.

one quarter of patients had brain metastases at baseline (27 % and 19 %) and half of the patients showed PD-L1 low expression (TPS 1-49 %, 50 % and 49 %).

After a median follow-up of 11.1 months, TQ-B2450 plus anlotinib demonstrated a longer median PFS compared to TQ-B2450 alone (6.9 vs 2.7 months; HR, 0.43; 95 % CI, 0.25-0.73; p=0.0014) **(Figure 3A)**. The ORR was significantly in favor of TQ-B2450 plus anlotinib (p=0,0043) with 30.9 % versus 3.0 %, while the DCR was 73.5 and 54.6 %, respectively (PR, 21 vs 1; SD, 29 vs 17) **(Figure 3B)**.

Overall, 46 (67 %) patients in the combination arm and seven (21 %) in the TQ-B2450 arm experienced grade ≥3 TEAEs. The most common TRAEs in the TQ-B2450 plus anlotinib arm included hypertension (19 %) and hypertriglyceridemia (9 %). Overall, 21 % of patients discontinued the combined treatment because of TRAEs.

TQ-B2450 combined with anlotinib significantly improved PFS and ORR compared to TQ-B2450 monotherapy. Thus, this combination therapy might be a promising treatment for advanced NSCLC patients having received prior systemic therapy. A randomized phase III study of TQ-B2450 plus anlotinib versus pembrolizumab in the first-line setting of NSCLC patients with PD-L1 ≥1 % is ongoing (NCT04964479). ■

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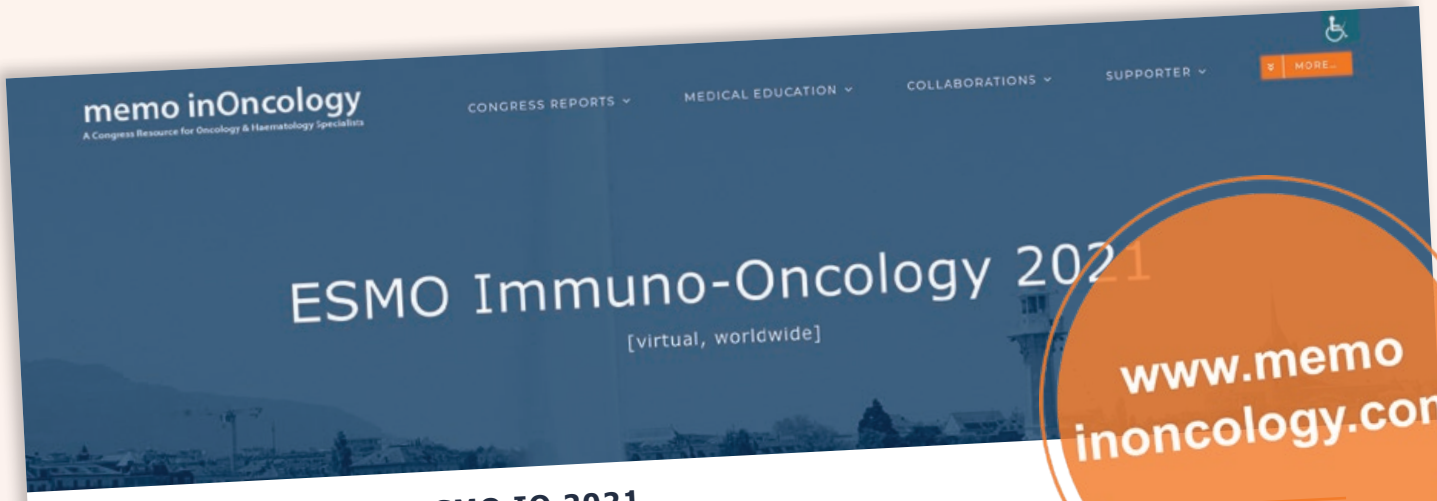

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Expert interviews at ESMO IO 2021

Mark G. Kris outlines the potential of circulating tumor DNA along the neoadjuvant cancer treatment timeline, explains which correlations have been observed between changes in ctDNA levels and clinical outcomes in patients with early-stage lung cancer and how monitoring of ctDNA can potentially be utilized in clinical practice to guide the management of these patients, while also depicting the limitations of this approach. The excitement in the field of lung cancer about new drugs targeting KRAS in combination with immunotherapy for first line treatment in stage IV NSCLC is addressed, too.

David McDermott deals with the question if combination therapy is superior to single agent PD-1/PD-L1 blockade in the adjuvant setting, highlights tools/biomarkers for appropriate patient selection for immune checkpoint inhibitor therapies, future strategies to potentially overcome resistance to ICIs, potential new outcome parameters for clinical trials investigating ICIs and highlights the most relevant findings presented at ESMO IO 2021 in terms of immuno-oncology.

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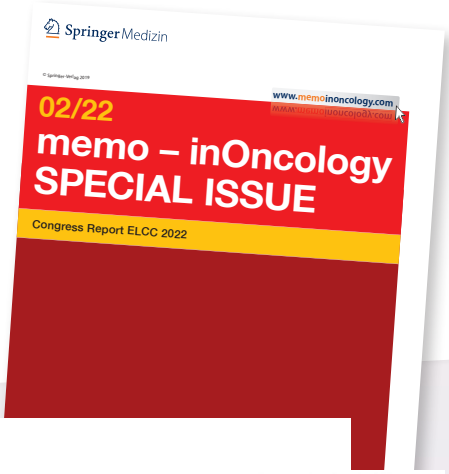

Forthcoming Special Issue

This special issue will be offering a synopsis from the ELCC 2022 that will be held in March 2022. The report promises to make for stimulating reading, as the ELCC Congress itself draws on the input from a number of partner organizations, representing a multidiscplinary approach to lung cancer treatment and care. Stay tuned for the latest news in oncology and its subspecialties.

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