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ESMO Solid Tumors 2022

A GLOBAL CONGRESS DIGEST ON SOLID TUMORS

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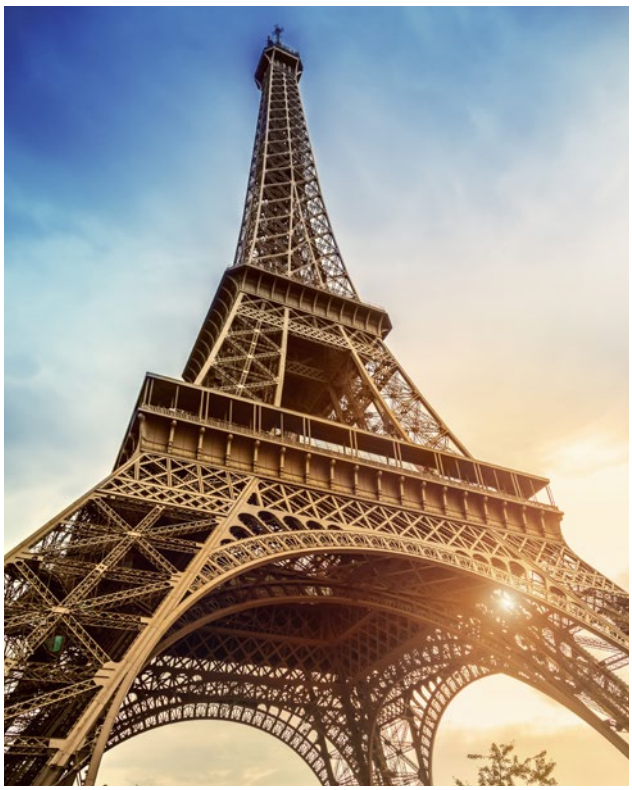

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Preface

Dear Colleagues,

At the ESMO congress held in Paris, France, and virtually from 9th – 13th September 2022, practice-changing data and high-quality education attracted more than 29,300 participants from over 150 countries. The 1,912 abstracts reported at the conference included 76 late-breaking abstracts; among them, 11 abstracts were selected for presidential symposia to discuss the very latest advances in the treatment of different solid tumor entities, including therapeutic innovations, translational research, patient advocacy, public policy, and many more, whilst offering a wealth of opportunities for exchange of ideas among delegates.

Thus, this issue of memo inOncology on solid tumors highlights new clinical insights in head and neck squamous cell carcinoma with new treatment strategies, including e.g. a 5-FU-free chemotherapy combination with pembrolizumab to overcome toxicities, as well as several longtime follow-up study data.

Moreover, multiple clinically relevant trials addressing open questions regarding first- or second-line mono- or combination therapies to further improve response and survival rates in patients with advanced hepatocellular carcinoma are summarized.

Additionally, at this year's meeting, a range of new practice-changing treatment strategies for all stages of gastric cancer and gastroesophageal junction adenocarcinoma were presented; these highlight the importance of selecting patients who are most likely to benefit from a specific therapy, biomarkers to predict response to treatment, prognostic stratification, as well as health-related quality of life.

In RCC, although several phase 3 trials – in the adjuvant and metastatic setting – did not meet their primary endpoints, novel three and two drug combinations showed encouraging clinical activity. The COSMIC-313 study demonstrated the efficacy and safety of a TKI plus two standard-of-care ICIs in previously untreated patients with advanced RCC. For treatment naïve, as well as for previously immunotherapy-treated patients, a new doublet combining an HIF-2α and a VEGF inhibitor showed promising antitumor activity, too.

At ESMO, the importance of genomic profiling to detect somatic variants, and thus identifying treatments specifically tailored to the molecular and pathological characteristics of colorectal cancer, was in the focus of several presentations where new therapeutic approaches showed their potential of becoming new standards-of-care.

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Finally, this report focuses on novel early clinical approaches in solid tumors, including CLDN6 CAR-T cell therapy, a GDF-15 neutralizing antibody, an MDM2 inhibitor, an antibody-drug conjugate, or even a new class of T-cell-redirecting bispecific fusion proteins, as well as an anti-TIGIT antibody to elicit a meaningful tumor response.

Once again, the scientific program at the EMSO meeting made this year's tagline "understanding the disease to provide better care for cancer patients" more than just a slogan. It was a great place to interact with colleagues and peers, as well as to debate the burning topics in oncology aiming at improving cancer care even further with new treatment paradigms and innovations. We hope you enjoy this issue!

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New clinical insights in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) was the sixth most common cancer in 2018, with more than 700,000 newly diagnosed cases per year and 350,000 cancer deaths worldwide [1]. Around 90 % of head and neck cancers are HNSCC, with oral cavity, oropharynx, hypopharynx, and larynx being the most commonly affected areas. The current standard of care (SOC) for locally advanced unresectable HNSCC is concurrent chemoradiotherapy (CRT) with high-dose cisplatin [2]. Pembrolizumab - a PD-1 immune checkpoint inhibitor - has been approved by the U.S. Food and Drug Administration (FDA) in June 2019 and by the European Medicines Agency (EMA) in November 2019 as first-line treatment for patients with metastatic or unresectable recurrent HNSCC either as monotherapy or in combination with platinum based chemotherapy [3, 4].

Primary results of the KEYNOTE-412 study

The randomized, double-blind, phase III KEYNOTE-412 (NCT03040999) study investigated the efficacy and safety of pembrolizumab versus placebo given concom-

itantly with CRT, followed by maintenance therapy with pembrolizumab or placebo in treatment-naïve patients with unresected locally advanced HNSCC (defined as T3-T4 [N0-N3] or any N2a-3 [T1-T4] larynx/hypopharynx/oral cavity/p16 negative oropharynx cancers and T4 or N3 p16 positive oropharynx cancer) [5]. At ESMO 2022, primary results of the KEYNOTE-412 trial were presented [6].

Overall, 804 patients (ECOG PS 0-1) were randomized 1:1 to receive either pembrolizumab (200 mg, IV) + cisplatin 100 mg/m² every three weeks (Q3W) + CRT (70Gy/35F)) or placebo (Q3W) + CRT, followed by maintenance therapy with pembrolizumab or placebo for 14 cycles. Pembrolizumab or placebo priming was given one week before CRT. Stratification factors included radiotherapy regimen (accelerated fractionation [AFX] versus standard fractionation [SFX]), tumor site/p16 status (oropharynx [p16 positive versus negative] or larynx/hypopharynx/oral cavity) and disease stage (III versus IV).

Patients baseline characteristics were well balanced between both investigational groups. In both arms, most patients (around 85 %) showed a PD-L1 combined positive score (CPS) ≥ 1 and 36 % of them had CPS ≥ 20. Human papillomavirus (HPV) was found in 27 % of patients in the pembrolizumab arm versus 26 % in the placebo arm. After a median follow-up of 47.7 months, 86 % of patients in the pembrolizumab plus CRT arm and 88 % in the placebo plus CRT arm completed concurrent CRT and had ongoing maintenance therapy. In total, 210 patients (60 %) in the pembrolizumab arm and 223 (63 %) in the placebo arm completed the maintenance therapy at data cut-off. Of note, the cumulative cisplatin exposure of ≥200 mg/m² was comparable in both arms (>87 %).

Event-free survival (EFS) - the primary endpoint - included death from any cause, progression according to RECIST v1.1 and pathologic proven relapse. A positive trend towards improved EFS was observed in favor of pembrolizumab plus CRT (NR vs 46.6 months with placebo; HR=0.83; 95 % CI, 0.68-1.03; p=0.0429), but the difference did not reach statistical significance. The 24-month EFS-rate was 63.2 % with pembrolizumab versus 56.2 % with placebo, while the 36-month rate was 57.4 % versus 52.1 %, respectively. Locoregional progressive disease (PD) was similar (13.2 % and 14.2 %) in both arms; however, distant PD was lower in the pembrolizumab arm (12.9 % versus 16.7 %). The non-significant benefit was observed in all prespecified subgroups analyzed except in the CPS < 1 group (HR=1.09; 95 % CI, 0.56-2.11). In a post-hoc analysis of the CPS ≥ 1 population, the 24-month EFS-rate was 63.7 % in the pembrolizumab arm versus 56.3 % in the placebo group, while the 36-month OS-rate achieved 71.4 % versus 70.2 %, respectively. Similar results were seen in the CPS ≥ 20 population, with a 24-month EFS-rate of 71.2 % in the pembrolizumab arm versus 62.6 % in the placebo group **(Figure 1)**, and a 36-month OS-rate of 79.1 % versus 73.0 %, respectively. The overall survival (OS) was similar in both treatment arms (HR=0.90; 95 % CI, 0.71-1.15), but the median OS was not reached.

No new safety signals were reported. In total, 367 (92.2 %) patients in the pembrolizumab arm and 352 (88.4 %) in the comparative group experienced grade 3-5 adverse events (AEs), with four and six treatment-related deaths, respectively. In the pembrolizumab arm, 8.6 % of patients suffered from grade 3-5 immune-mediated AEs and infusion reactions compared with 2.3 % in the placebo arm.

The primary results of the KEYNOTE-412 study showed a favorable trend towards an improved EFS with first-line pembrolizumab plus CRT in locally advanced HNSCC patients although the difference did not reach statistical significance.

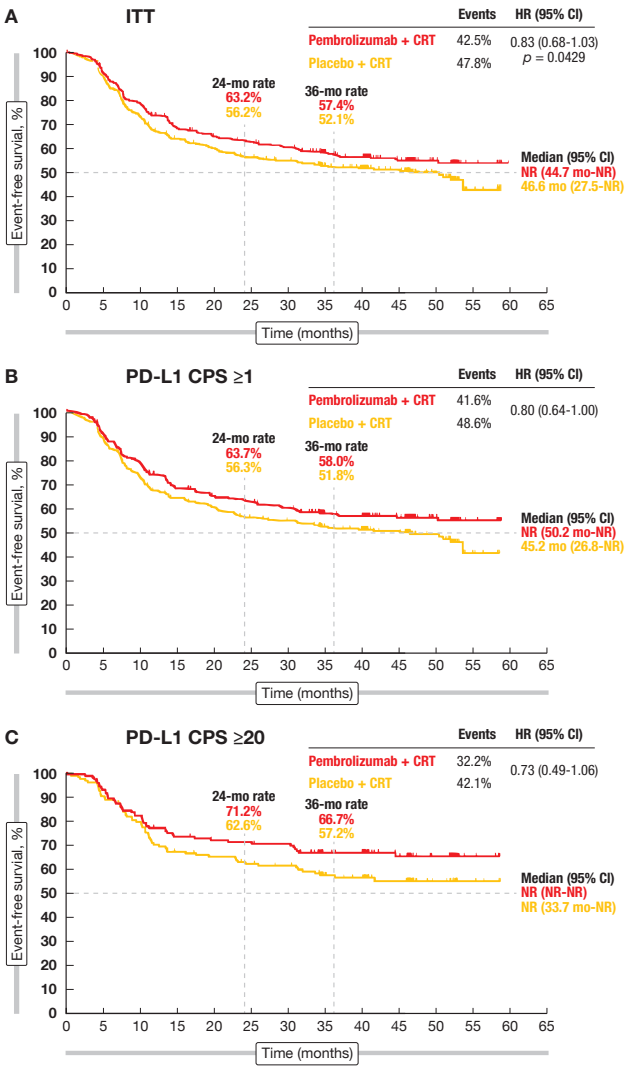

Figure 1: Event-free survival in the KEYNOTE-412 study in the ITT population **(A)**, in patients with PD-L1 CPS ≥1 **(B)** and PD-L1 CPS ≥20 **(C)**.

Long-term data of xevinapant in locally advanced HNSCC patients

Xevinapant (formerly known as Debio 1143) is an investigational first-in-class potent oral small-molecule inhibitor of apoptosis proteins (IAP) [7]. In preclinical studies, xevinapant restored the sensitivity of cancer cells to apoptosis and enhanced the effects of chemoradiotherapy (CRT) [8]. Efficacy and safety of xevinapant have been previously evaluated in a double-blind, multicenter, phase II study (NCT02022098) in 96 patients with previously untreated locally advanced HNSCC [9]. The locoregional control rate at 18 months after CRT, the primary endpoint, was significantly improved with xevinapant versus placebo (OR=2.74; 95 % CI, 1.15-6.53; p=0.0232) [10]. The 3-year progression-free survival (PFS), the key secondary endpoint, was also markedly improved with xevinapant (KM-estimate, 72 % versus 36 %; adjusted HR=0.33; 95 % CI, 0.17-0.67; p=0.0019) [10]. Long-term efficacy outcomes were presented at this year's ESMO meeting [10].

High risk previously untreated locally advanced HNSCC patients were randomized 1:1 and stratified according to primary tumor site (oropharynx versus other), lymph node involvement (N0-N1 versus N2-N3), and HPV-16 status. Eligible patients received either xevinapant (200 mg/day, orally) or placebo once daily on days 1-14 of 21-day treatment cycles, for three cycles + CRT (cisplatin 100 mg/m² on Day 2, Q3W for 3 cycles; intensity-modulated radiotherapy 70 Gy [2 Gy/day, 5 days/week for 7 weeks]).

Between January 2016 and April 2017, 96 patients were followed-up for disease progression until July 2020 and survival data were collected until April 2022 (5 years after last patient randomization). The risk of death was more than halved in the xevinapant + CRT arm versus the placebo + CRT arm (adjusted HR=0.47; 95 % CI, 0.27-0.84; p=0.0101). The median OS was not reached in the xevinapant arm versus 36.1 months (95 % CI, 21.8-46.7) in the placebo arm. For long-term OS, the median follow-up was 60.1 months in the xevinapant arm and 39.2 months in the placebo group. Xevinapant + CRT prolonged OS compared to placebo + CRT, with a 53 % (95 % CI, 37-66) OS rate after five years compared to 28 % (95 % CI, 15-42) with placebo **(Figure 2)**.

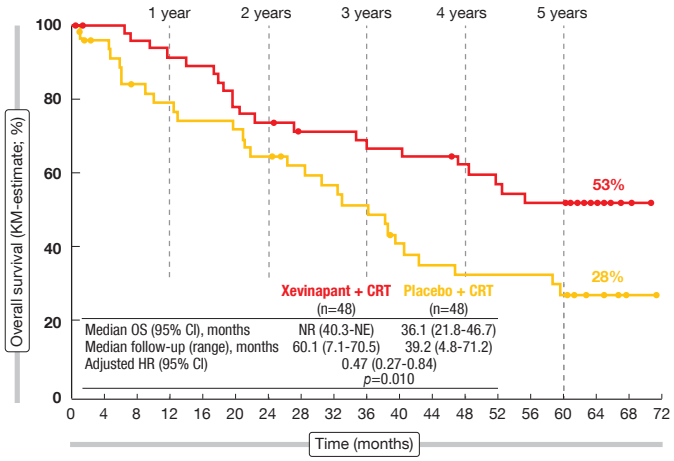

Figure 2: 5-year OS of xevinapant + CRT versus placebo + CRT in unresected locally advanced HNSCC.

The duration of response (DoR) was prolonged with xevinapant plus CRT. The risk of death or disease progression after initial response was markedly reduced by 79 % in the xevinapant arm versus placebo (DoR KM-estimate, 79 % vs 36 %; adjusted HR=0.21; 95 % CI, 0.08-0.54; p=0.0011).

The safety profile, including late-onset AEs, was similar in both investigational arms. The most frequent grade ≥ 3 AEs were dry mouth and dysphagia in the xevinapant group, compared to anemia and dysphagia in the placebo group. In total, eight patients in the xevinapant and seven in the placebo arm had to discontinue the study treatment prematurely.

When added to the standard of care CRT, xevinapant showed a significant OS-improvement in patients with locally advanced HNSCC. Based on these results, xevinapant plus CRT is currently being further investigated in the ongoing phase III TrilynX study (NCT04459715).

KEYNOTE-048: first-line pembrolizumab in R/M HNSCC long term follow-up

The phase III KEYNOTE-048 trial (NCT02358031) investigated pembrolizumab monotherapy and pembrolizumab plus chemotherapy versus cetuximab plus chemotherapy (EXTREME) in previously untreated recurrent or metastatic (R/M) HNSCC [11]. Previous analyses of KEYNOTE-048 showed a significant improvement of the median OS with pembrolizumab monotherapy or pembrolizumab plus chemotherapy in pre-specified subgroups, compared to cetuximab plus chemotherapy, with comparable safety. Five-year results from KEYNOTE-048 were presented at ESMO 2022 [12].

Eligible participants with R/M HNSCC of the oropharynx, oral cavity, hypopharynx, or larynx that was not curable by local therapy were randomly assigned 1:1:1 to either receive pembrolizumab (200 mg, Q3W for up to 35 cycles), pembrolizumab plus chemotherapy (carboplatin AUC 5 or cisplatin 100 mg/m² + 5-FU 1000 mg/m²/day for 4 days for 6 cycles (Q3W)), or cetuximab (400 mg/m² loading dose, then 250 mg/m² per week) plus chemotherapy given until PD, unacceptable toxicity, six cycles (chemotherapy), or 24 months (pembrolizumab). Stratification factors included ECOG (0 versus 1), p16 status in oropharynx, and PD-L1 expression (Tumor Proportion Score (TPS) ≥ 50 % versus < 50 %) [11].

After a median follow-up of 69.2 months, pembrolizumab monotherapy showed an improved 5-year OS versus EXTREME in the CPS ≥ 20 (19.9 % vs 7.4 %), CPS ≥ 1 (15.4 % vs 5.5 %) and total population (14.4 % vs 6.5 %) [12]. The ORR for pembrolizumab versus EXTREME was 16.9 % versus 36.0 %, and the DoR 22.6 months versus 4.5 months, respectively.

Similarly, pembrolizumab plus chemotherapy improved the 5-year OS versus EXTREME in the CPS ≥ 20 population (23.9 % versus 6.4 %), CPS ≥ 1 population (18.2 % versus 4.3 %), and in the total population (16.0 % versus 5.2 %). The ORR

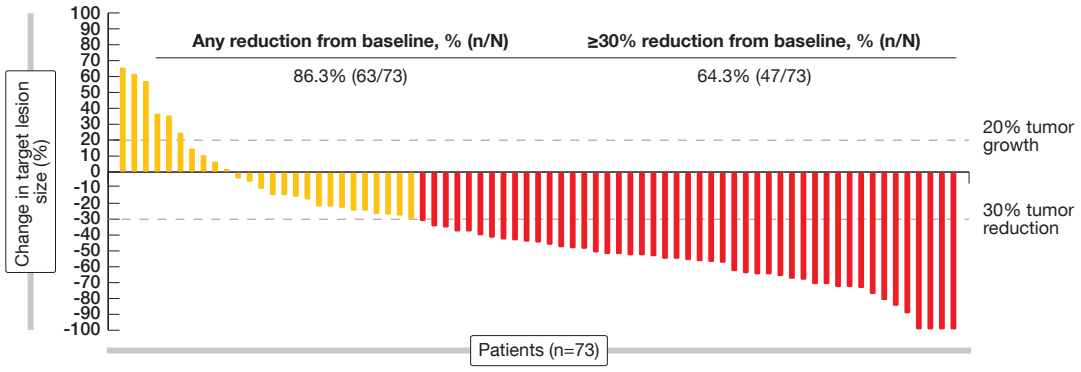

Figure 3: Waterfall-plot indicating the best percentage of change from baseline for target lesions.

was 37.0 % versus 36.3 % and the median DoR reached 6.7 months versus 4.3 months, respectively.

The safety profile was consistent to previous reports.

The authors concluded that, even after five years of follow-up, first-line pembrolizumab therapy continued to show a clinically meaningful benefit for patients with R/M HNSCC.

KEYNOTE-B10: pembrolizumab plus carboplatin/paclitaxel as first-line 5-FU-free therapy option in R/M HNSCC

Based on the positive outcomes of the pivotal KEYNOTE-048 trial, pembrolizumab combined with platinum plus fluorouracil (5-FU) has been approved as 1L therapy for R/M HNSCC [13]. However, alternatives to 5-FU are needed to overcome toxicities, costs and complications related to the continuous 4-day infusion of this drug [14]. The combination of cisplatin plus paclitaxel was shown to be as effective as cisplatin plus 5-FU in patients with R/M HNSCC [15]. Thus, the goal of the global, open-label, phase IV KEYNOTE-B10 study (NCT04489888) was to evaluate the antitumoral activity and safety of pembrolizumab combined with carboplatin and paclitaxel as first-line treatment in patients with R/M HNSCC. The primary analysis of this ongoing study was presented at ESMO 2022 [16].

Eligible patients with previously untreated R/M HNSCC of oral cavity, oropharynx, larynx, or hypopharynx received pembrolizumab (200 mg, Q3W for ≤ 35 cycles) plus paclitaxel (investigators choice for 6 cycles) and carboplatin (AUC 5 mg/mL/min, Q3W for 6 cycles). The primary study endpoint is ORR per RECIST v1.1 assessed by blinded independent central review (BICR), the secondary endpoints include DoR and PFS according to RECIST v1.1 by BICR, OS as well as safety and tolerability. The presented analysis enclosed 92 treated patients (of 100 planned patients); among them, 41 participants were still on treatment after a median follow-up of 8.2 months.

The median age of the patient population was 64 years, most of the patients were male (82.6 %) and white (87.0 %); three quarters of the patients had a paclitaxel dose of 175 mg/m² Q3W, 18.5 % had a PD-L1 expression CPS < 1, 66.3 % had distant metastasis, and 21.7 % of the oropharynx patients were p16 positive.

Out of 82 patients included in the efficacy analysis, 42.7 % had an objective response, with four patients showing a complete response (CR) and 31 a partial response (PR); moreover, 24 patients had a stable disease (SD), while 15 patients had a progressive disease (PD). The disease control rate (DCR) was 58.5 % and the median DoR reached 5.5 months. Most patients showed a reduction from baseline for target lesions **(Figure 3)**.

Nearly all patients (95.7 %) reported treatment related adverse events (TRAEs) any grade. Overall, 70.7 % experienced grade 3-5 TRAEs, including two deaths (2.2 %) due to TRAEs (sepsis and hypersensitivity). The most reported TRAEs with ≥ 10 % incidence were decreased neutrophil count, anemia, and fatigue. No new immune-mediated AEs and infusion reactions were detected.

This first global, prospective trial of pembrolizumab plus carboplatin and paclitaxel demonstrated antitumor activity in first-line R/M HNSCC independently of PD-L1 status with a manageable safety profile. The results of the KEYNOTE-B10 study may suggest this 5-FU-free chemotherapy combination with pembrolizumab as an alternative to the current SOC chemotherapy regime.

KEYNOTE-040 study: long-term follow-up

The open-label, phase III KEYNOTE-040 study (NCT02252042) compared the efficacy and safety of pembrolizumab with those of an investigator's SOC choice of methotrexate (40 mg/m², QW) or docetaxel (75 mg/m², Q3W) or cetuximab (250 mg/m², QW) in patients with R/M HNSCC who progressed during or after platinum-based chemotherapy within 3-6 months of multimodal therapy. Six-year follow up data of the KEYNOTE-040 trial were presented at ESMO 2022 [17].

After a median follow-up of 74.8 months, the 6-year survival rate accounted for 6.5 % in the pembrolizumab arm versus SOC regime with 2.4 %. For PD-L1 positive patients (CPS ≥ 1), the risk reduction of death with pembrolizumab was 28 % (8.7 versus 7.1 months; HR=0.72; 95 % CI, 0.59-0.89), with a 6-year OS rate of 7.1 % versus 2.1 %, respectively. For patients with TPS ≥ 50 %, the risk reduction of death remained at 38 % (11.6 months versus 7.9 months; HR=0.62; 95 % CI, 0.43-0.90), with a 6-year OS rate of 8.9 % versus 6.3 %, respectively.

After a follow-up of six years, pembrolizumab continued to show an OS benefit compared to SOC in R/M HNSCC patients. To note, an increased benefit was observed with increasing PD-L1 expression. Overall, these data further support the use of pembrolizumab as second-line treatment in appropriate patients with R/M HNSCC. ■

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Update on the treatment for advanced HCC

With more than 900,000 newly diagnosed cases in 2020, hepatocellular carcinoma (HCC) is the sixth most frequent malignant disease with a high mortality rate of approximately 92 % [1]. Current first-line treatment for advanced HCC includes atezolizumab plus bevacizumab [2], as well as the tyrosine kinase inhibitors (TKIs) sorafenib [3, 4] and lenvatinib [5].

Numerous trials are ongoing to investigate first- or second-line mono- or combination therapies to further improve response and survival rates in patients with advanced HCC.

1L camrelizumab plus rivoceranib in unresectable HCC

In advanced HCC, immune checkpoint inhibitors (ICIs) targeting PD-1 or PD-L1 did not provide any survival benefit over sorafenib in the first-line setting when used as single immunotherapeutic agents so far [6]. However, adding an anti-angiogenic tyrosine kinase inhibitor (TKI) to ICI monotherapy has shown promising improvements of survival outcomes in renal cell carcinoma and endometrial carcinoma [7]. Camrelizumab, an anti-PD-1 IgG4 antibody, and rivoceranib (also known as apatinib), a small-molecule VEGFR2-targeted TKI, have both been approved in China as second-line monotherapy agents in advanced HCC [8, 9]. Interestingly, camrelizumab in combination with rivoceranib showed encouraging preliminary antitumor activity and an acceptable tolerability in pretreated HCC in a phase I trial [10]. Moreover, a phase II study in patients with advanced HCC demonstrated promising efficacy with an overall response rate (ORR) of 34.3 %, a median progression-free survival (mPFS) of 5.7 months and an 18-month overall survival (OS) rate of 58.1 % [11]. A phase III trial (NCT03764293) presented at ESMO 2022 compared the efficacy and safety of this dual first-line therapy versus sorafenib in unresectable HCC [12].

Patients matching key eligibility criteria (including unresectable or metastatic HCC, BCLC stage B or C, no prior systemic therapy, ECOG 0 or 1, Child-Pugh score A and more than 1 measurable lesion as assessed by RECIST v1.1) were randomized 1:1 to receive either camrelizumab (200 mg, intravenously [IV], every second week [Q2W]) plus rivoceranib (250 mg, per os [PO], twice daily [BID]) or sorafenib (400 mg, PO, BID). The co-primary endpoints included PFS and OS. ORR was set as a key secondary outcome. PFS and ORR

were assessed by a blinded independent central review (BICR) per RECIST v1.1. Patients were stratified by tumor extent (extra-hepatic spread/macrovascular invasion or not), geographic origin (Asian or not) and baseline serum alpha-fetoprotein (< or ≥ 400 ng/mL).

Out of the 543 enrolled patients, 272 were included in the camrelizumab plus rivoceranib ITT population versus 271 in the sorafenib ITT population. At the time of data cut-off (February 8, 2022), 42 and 22 patients, respectively, were still receiving their treatment. A significant benefit of camrelizumab plus rivoceranib compared to sorafenib was demonstrated for both PFS (median PFS: 5.6 vs 3.7 months; HR, 0.52; 95 % CI, 0.41-0.65; one-sided p<0.0001) **(Figure 1A)** and OS (median OS: 22.1 vs 15.2 months; HR, 0.62; 95 % CI, 0.49-0.80; one-sided p<0.0001) **(Figure 1B)**. A pre-specified subgroup analysis showed that HRs of PFS and OS obviously favored camrelizumab plus rivoceranib in most subgroups. The ORR was also significantly improved in the camrelizumab plus rivoceranib arm versus sorafenib (25.4 % [1.1 % complete response/CR, 24.3 % partial responses/PR] vs 5.9 % [0.4 % CR, 5.5 % PR]; p<0.0001), while the disease control rate (DCR) was 78.3 % and 53.9 %, respectively. The median duration of response (DoR) reached 14.8 months in the camrelizumab plus rivoceranib arm versus 9.2 months in the sorafenib arm. Moreover, the rate of patients with reduction in the sum of diameters of target lesions was twice as high in the combination arm compared to sorafenib (72.8 % vs 35.6 %).

Grade ≥ 3 treatment-related adverse events (TRAEs) were more frequent within the combination arm (80.5 %), with hypertension (37.5 %), increased aspartate aminotransferase (16.5 %) and alanine aminotransferase (12.9 %) being the most frequent ones; compared to sorafenib (52.0 %), patients experienced most commonly palmar-plantar erythrodysaesthesia (15.2 %), hypertension (14.9 %) and increased gamma-glutamyl transferase (7.4 %). One patient in each treatment arm experienced a grade 5 TRAE. The number of TRAEs leading to discontinuation of treatment was similar in both groups (10 vs 12, respectively).

This first positive international phase III study of a TKI combined with an anti-PD1 agent supports this combination of rivoceranib plus camrelizumab as another new first-line treatment option for unresectable HCC.

RATIONALE-301: 1L tislelizumab monotherapy

Several single-agent ICI have been or are currently under evaluation in HCC [6, 13, 14]. Among those, tislelizumab - a new monoclonal antibody with high binding affinity for PD-1 - is currently being investigated as first-line treatment in adult patients with unresectable HCC. This antibody has been specifically engineered to minimize Fcγ receptor binding on macrophages because this was shown to have a negative impact on the anti-PD-1 antibody-mediated antitumoral activity [15, 16]. In the phase II RATIONALE-208 study (NCT03419897) durable responses and generally good tolerability of tislelizumab monotherapy were shown in patients with previously treated advanced HCC [17]. At this year's ESMO meeting, Kudo et al. presented the final analysis of the RATIONALE-301 trial, which evaluated the safety and the efficacy of first-line tislelizumab monotherapy versus sorafenib in patients with unresectable HCC [14].

RATIONALE-301 is a randomized, open-label, multicenter phase III study (NCT03412773). Eligible patients had histologically confirmed HCC, no prior treatment, BCLC stage C or B disease with no progression risk or event after loco-regional therapy, Child-Pugh score A, ≥ 1 lesions assessed by RECIST v1.1, no tumor thrombus, and ECOG 0 or 1. Patients were randomized 1:1 to receive either tislelizumab (200 mg, IV, Q3W) or sorafenib (400 mg, PO, BID) until disease progression or intolerable toxicity. The primary endpoint was OS in the ITT population, while other efficacy parameters (ORR, PFS and DoR) assessed by BIRC according to RECIST v1.1 and safety were secondarily analyzed. Stratifications factors included macrovascular invasion, extrahepatic spread, ECOG performance status, etiology, and geography.

Patients in the tislelizumab arm (n=342) and the sorafenib group (n=332), who were followed for a minimum of 33 months, had a median age of 62 and 60 years, respectively. According to the final median OS analysis, tislelizumab monotherapy demonstrated non-inferiority versus sorafenib (15.9 vs 14.1 months; stratified HR, 0.85; 95 % CI, 0.712-1.019; p = 0.0398). These results were consistently observed across all

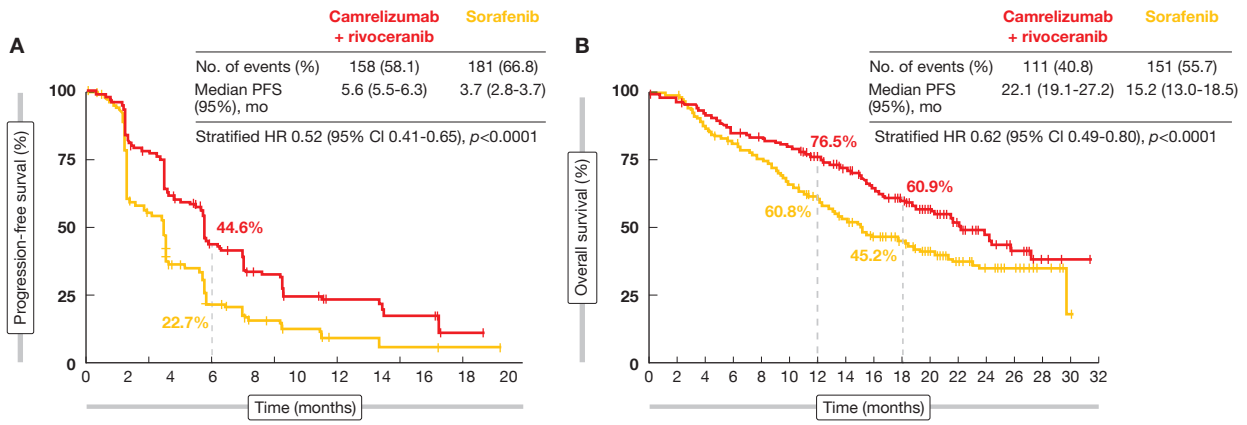

Figure 1: Progression-free survival (A) and overall survival (B) in the ITT population.

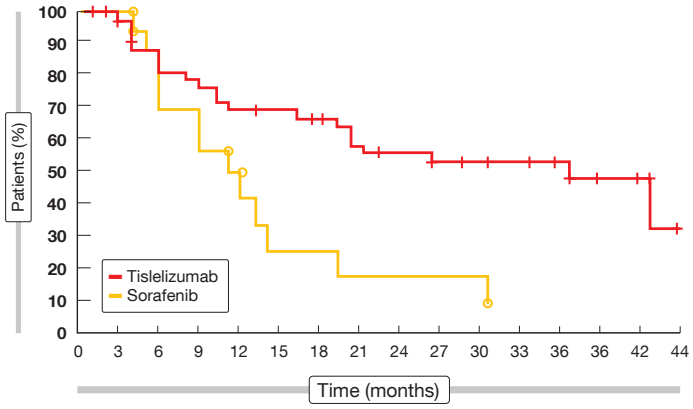

Figure 2: Duration of response in the ITT population of the RATIONALE-301 study.

prespecified subgroups. There was a benefit of tislelizumab (CR, 2.9 %; PR, 11.4 %) in terms of ORR (14.3 % vs 5.4 %) compared to sorafenib (CR, 0.3 %; PR, 5.1 %) and in terms of median DoR (36.1 vs 11.0 months) **(Figure 2)**. Of note, the median PFS was shorter with tislelizumab than with sorafenib (2.1 vs 3.4 months; stratified HR, 1.11; 95 % CI, 0.92-1.33).

Tislelizumab was well tolerated as it was associated with less grade ≥3 treatment-emergent AEs (TEAEs) (48.2 % vs 65.4 %) and TRAEs (22.2 % vs 53.4 %) compared to sorafenib. The most frequent TEAEs associated with tislelizumab were increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), and blood bilirubin, while those associated with sorafenib were PPES, diarrhea, and increased AST. Treatment discontinuations (10.9 % vs 18.5 %) and dose modifications (31.1 % vs 64.8 %) following TEAEs were less frequent in the tislelizumab arm compared to sorafenib.

RATIONALE-301 met its primary endpoint of OS non-inferiority with tislelizumab versus sorafenib demonstrating a clinically meaningful antitumor benefit with a favorable and manageable safety profile as 1L monotherapy for patients with unresectable HCC.

LEAP-002: 1L lenvatinib plus pembrolizumab

In the KEYNOTE-224 phase II trial, pembrolizumab has been evaluated as second-line monotherapy in advanced HCC; these results led to pembrolizumab's approval in the US after demonstrating promising ORR in sorafenib-pretreated patients [18]. Two phase III studies in HCC demonstrated a favorable benefit/risk profile despite a narrowly missed statistical significance for OS and PFS (KEYNOTE-240 global study [19]), significantly improved OS, PFS and ORR (KEYNOTE-394 Asian study [20]) and consistent improvements in OS, PFS and ORR (KEYNOTE-240 and KEYNOTE-394 meta-analysis [21]). Lenvatinib - a TKI inhibitor - has been approved as 1L treatment of advanced HCC after demonstrating OS non-inferiority versus sorafenib (REFLECT study [5]). The combination of lenvatinib plus pembrolizumab showed promising efficacy and safety in 1L unresectable HCC in a phase Ib study (study 111/KEYNOTE-524) [22]. At ESMO 2022, the outcomes of the LEAP-002 study investigating the first-line combination pembrolizumab plus lenvatinib in advanced HCC were presented [23].

The LEAP-002 study is a global, double-blind, placebo-controlled phase III study assessing lenvatinib plus pembrolizumab versus lenvatinib monotherapy in 1L advanced HCC (NCT03713593). Enrolled patients had confirmed HCC, were not eligibility to curative therapy, had no prior treatment, ECOG 0 or 1, Child-Pugh score class A, an esophagogastroduodenoscopy (EGD) within the last three months and no major portal invasion. Randomization occurred 1:1 with patients being administered lenvatinib (8 mg if body weight [BW] < 60 kg or 12 mg if BW > 60 kg, PO, BD) either combined with pembrolizumab (200 mg, IV, Q3W) or plus placebo (saline, IV, Q3W) for a maximum of 35 cycles. Dual primary endpoints were OS and PFS assessed by BICR according to RECIST v1.1. Secondary endpoints included ORR and DoR, assessed by BICR per RECIST v1.1 or mRECIST, as well as safety/tolerability. Patients were stratified by geographic region, macroscopic portal vein invasion/extrahepatic spread, alpha-fetoprotein (AFP) level and ECOG performance status.

A total of 794 patients were randomized from January 17, 2019, to April 28, 2020, resulting in 395 patients in the lenvatinib plus pembrolizumab arm and 399 patients in the lenvatinib plus placebo arm. Median age was 66 years in both groups. Median follow-up was 17.6 months for final PFS and 32.1 months for the final OS analysis. LEAP-002 did not meet its pre-specified statistical significance for both primary endpoints as neither the median OS (21.2 vs 19.0 months; HR, 0.840; 95 % CI, 0.708-0.997; p = 0.0227), nor the median PFS (8.2 vs 8.0 months; HR, 0.867; 95 % CI, 0.734-1.024; p = 0.0466) reached prespecified superiority thresholds in the final analysis for lenvatinib plus pembrolizumab versus lenvatinib plus placebo. However, a subgroup OS analysis favored lenvatinib plus pembrolizumab versus lenvatinib plus placebo in patients ≥ 65 years, macroscopic portal vein invasion/extrahepatic spread, hepatitis B virus or AFP levels > 400 ng/mL. More patients in the lenvatinib plus pembrolizumab arm attained an objective response (ORR, 26.1 % vs 17.5 %) with a longer DOR (16.6 vs 10.4 months).

No new safety concerns were reported. The frequency of TRAEs events was similar in both arms, with a higher number of grade 3-4 TRAEs in the lenvatinib plus pembrolizumab group (61.5 % vs 56.7 %), with hypertension, proteinuria, decreased platelet count, increased AST levels and diarrhea being the most frequently reported TRAEs. The number of treatment discontinuation was higher in the combination arm (18.0 % vs 10.6 %). Immune-mediated AEs (imAEs) and infusion reactions grade 3-4 were more frequent in the group receiving lenvatinib plus pembrolizumab than in the lenvatinib plus placebo group (8.9 % vs 2.3 %) - with 9.6 % and 1.8 % of patients requiring systemic corticoids.

As the study did not meet its pre-specified statistical significance for the primary endpoints of OS and PFS, this combination will not be added to the treatment algorithm of advanced stage HCC. A phase

III study (LEAP-012) testing the combination of transarterial chemoembolization (TACE) plus lenvatinib and pembrolizumab is currently under investigation (NCT04246177).

KEYNOTE-240: 2L pembrolizumab monotherapy

In sorafenib or oxaliplatin-based chemotherapy-treated advanced HCC patients from Asia, pembrolizumab demonstrated statistically significant and clinically meaningful benefit in the KEYNOTE-394 trial [20]. Although in the KEYNOTE-240 phase III trial, the statistical significance criteria for OS and PFS were narrowly missed [19], ORR data were consistent with those of the KEYNOTE-224 study [18], which led to the approval of pembrolizumab in the United States. At ESMO 2022 the updated outcomes from the KEYNOTE-240 trial after a 4.5-year follow-up were presented [24].

KEYNOTE-240 is a randomized, double-blind phase III study comparing pembrolizumab monotherapy with placebo in a second-line setting in participants with sorafenib-pretreated advanced HCC (NCT02702401). Patients with histologically, cytologically, or radiographically confirmed advanced HCC were randomly assigned at a 2:1 ratio to receive either pembrolizumab (200 mg, IV, Q3W) plus best supportive care (BSC) or placebo plus BSC for up to 35 cycles. Key eligibility criteria included a measurable disease per RECIST v1.1, a progression or intolerance to sorafenib, Child-Pugh liver class A, BCLC stage C or B not amenable or refractory to locoregional therapy and not amenable to curative treatment and ECOG 0 or 1. Dual primary endpoints were OS and PFS assessed by RECIST v1.1 by BICR, while ORR, DoR, DCR, time to progression (TTP) and safety were the secondary endpoints.

At the time of this updated analysis (data cutoff: September 22, 2021), the median follow-up time was 53.9 months for pembrolizumab (n = 278) and 54.1 months for placebo (n = 135). Compared to placebo, pembrolizumab treatment showed an improved median OS (13.9 vs 10.6 months; HR, 0.77; 95 % CI, 0.62-0.96), as well as median PFS (3.0 vs 2.8 months; HR, 0.73; 95 % CI, 0.58-0.91). Concerning the secondary endpoints, the ORR was higher in the pembrolizumab arm (18.3 %, including 10 patients with a CR and 41 with a PR) than in the placebo arm (4.4 %, including no patients with a CR and 6 patients with a PR). Overall, 63.3 % of pembrolizumab-treated patients versus 55.6 % of placebo patients were able to reach a disease control (DCR). The median DOR reached 13.9 months in the pembrolizumab arm versus 15.2 months in the placebo arm, while the TTP was 3.8 versus 2.8 months, respectively.

TRAEs grade 3-4 accounted for 19.7 % in the pembrolizumab arm and 7.5 % in the placebo arm. The most frequent grade 3 or 4 TRAEs were increased AST (5.7 % with pembrolizumab vs 1.5 % with placebo) and increased ALT (3.9 % vs 1.5 %). The immune-mediated AEs and infusion-related reactions were mild in severity (grade 3-4, 7.2 % in pembrolizumab arm vs 0.7 % in placebo arm).

The updated results of the KEYNOTE-240 study, together with data from KEYNOTE-224 and KEYNOTE-394, provide further evidence for a favorable benefit-risk profile of pembrolizumab monotherapy as treatment for patients with advanced HCC. ■

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Towards treating all stages of gastric cancer and gastroesophageal junction adenocarcinoma

Gastric and esophagus cancers were the fifth and the seventh most frequently diagnosed cancers worldwide in 2020, respectively. In the same year, these cancers ranked fourth and sixth in mortality, respectively [1]. Most patients with gastric cancer/gastroesophageal junction adenocarcinoma (GC/GEJA) present with inoperable or metastatic disease at the time of diagnosis; resulting in a strong need for efficient and tolerable first-line (1L) and second-line (2L) treatments [2].

Moonlight study: 1L FOLFOX induction vs combination therapy

The combination of leucovorin, fluorouracil (5-FU) and oxaliplatin (FOLFOX) plus nivolumab, an anti-PD-1 immune checkpoint inhibitor (ICI), has become the standard-of-care for first-line therapy of patients with esophagogastric adenocarcinoma [2]. Moreover, the CHECKMATE-036 trial had previously demonstrated the efficacy of nivolumab plus ipilimumab (anti-CTL4), whose combination was associated with meaningful antitumoral activity, durable response, encouraging long-term overall survival (OS) and satisfactory tolerance as second-line treatment for patients with chemotherapy-refractory esophagogastric cancer [3].

In the AIO-STO-0417 (Moonlight) trial, a four-arm phase II trial (NCT03647969), the combination of modified FOLFOX (mFOLFOX) chemotherapy plus nivolumab and ipilimumab (arm A) versus mFOLFOX alone (arm B) was evaluated as first-line therapy for patients with GC/GEJA [4]. To reduce toxicity, there is a need for an alternative treatment. Thus, in a second part of the Moonlight study **(Figure 1)**, short-term induction chemotherapy is under investigation. In this study, mFOLFOX plus nivolumab and ipilimumab (arm A1) versus induction therapy followed by nivolumab and ipilimumab (arm A2) were assessed for toxicity and efficacy. Outcomes were presented by Lorenzen et al. at ESMO 2022 [5].

Patients with previously untreated HER2 (human epidermal growth factor receptor 2) negative metastatic or locally advanced gastric/gastroesophageal junction adenocarcinoma (G/GEJA) were stratified according to ECOG (0 or 1) and tumor status (prior resection or not). Eligible patients were randomized (1:2) to receive either parallel treament (arm A1: mFOLFOX every second week [Q2W] plus nivolumab [240 mg, Q2W] plus ipilimumab [1 mg/kg, Q6W]) or sequential treatment (arm A2: 3 cycles of mFOLFOX induction treatment Q2W, followed by immunotherapy consisting of 4 administrations of nivolumab [240 mg, Q2W] and 2 administrations of ipilimumab [1 mg/kg, Q6W]). The primary endpoint was progression-free survival (PFS) at six months, while key secondary endpoints were OS, PFS, overall response rate (ORR) and safety.

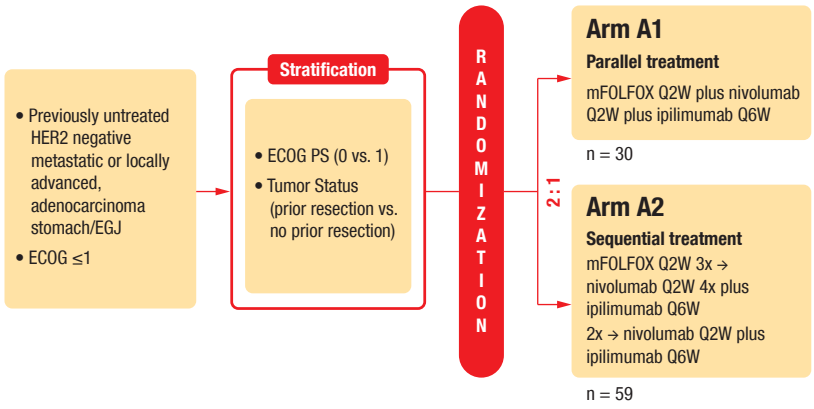

Figure 1: Design of the AIO-STO-0417 (Moonlight) trial (arms A1 and A2).

The parallel treatment was administered to 30 patients for a median of 11.5 cycles, while 60 patients received the sequential treatment for a median of eight cycles. At the time of data cutoff (July 22, 2022), the median follow-up was 9.3 months. The median age was 59.5 years in arm A1 and 63.5 years in arm A2. In total, 41 % of patients had a PD-L1 combined positive score (CPS) ≥ 1 (available in 74 % of patients). Progression-free survival at six months was twice as high in the parallel treatment arm compared to the sequential treatment arm (6-month PFS: 60 % in arm A1 vs 30 % in arm A2). The median PFS was longer in arm A1 than in arm A2 (7.29 vs 3.98 months; log rank p=0.0261), as well as the median OS (10.12 vs 7.85 months; log rank p=0.3604). Of note, a similar advantage was observed in the PD-L1 positive subpopulation for the parallel treatment (median OS, 16.46 months in arm A1 vs 6.87 months in arm A2; log rank p=0.4512). When comparing arm A1 and arm A2, a higher proportion of patients obtained a response (ORR, 46.7 % [10.0 % CR, 36.7 % PR] vs 30.0 % [6.7 % CR, 23.3 % PR], respectively). Moreover, the obtained responses were more durable in the parallel treatment arm than in the sequential one (8.4 vs 4.3 months).

However, patients in arm A1 experienced more grade ≥ 3 treatment-related adverse events (TRAEs) than those in arm A2 (70.0 % vs 43.3 %). The most common any-grade TRAEs across both arms were diarrhea, fatigue, nausea, decreased neutrophil count and peripheral sensory neuropathy. There was one treatment-related death in both groups.

Although associated with better tolerability, FOLFOX induction followed by nivolumab plus ipilimumab was less effective than FOLFOX plus nivolumab and ipilimumab. Thus, this study does not support the use of sequential treatment in the first-line setting. However,

the results must be interpreted with caution due to the small number of participants and a low PD-L1 expression rate in both treatment arms.

PRODIGE 59 - DURIGAST: 2L FOLFIRI plus ICI(s)

Although the combination of ICIs with chemotherapy has demonstrated its efficacy as first-line treatment of advanced G/GEJA [2], treatment options in second line remain limited and the current standard-of-care is still based on chemotherapy (paclitaxel, ramucirumab or irinotecan as monotherapy or in combination with 5-FU). Tougeron et al. presented the results of a first 2L study combining FOLFIRI (leucovorin, 5-FU and irinotecan) with one or two ICIs at this year's ESMO meeting [6].

PRODIGE 59 - DURIGAST is a French, randomized, non-comparative, phase II trial (NCT03959293) assessing the efficacy and safety of the combination of FOLFIRI plus durvalumab (anti-PD-L1) with or without tremelimumab (anti-CTLA-4) as 2L treatment of advanced G/GEJA. Platinum-based first-line chemotherapy pretreated patients with G/GEJA, who were ICI-naive and had a good performance status (ECOG 0 or 1) were equally randomized (1:1) to receive either FOLFIRI (intravenously [IV], Q2W) plus durvalumab (1500 mg, IV, Q4W) or FOLFIRI plus durvalumab plus tremelimumab (75 mg, IV, Q4W, 4 cycles only) until disease progression. The primary endpoint was PFS at four months.

In total, 92 patients were enrolled in this trial between August 2020 and June 2021. Most patients had GEJA (53.3 %) with intestinal subtype (50 %) and synchronous delay of metastatic disease (65.2 %), with the liver being the most frequent metastatic site (40.2 %). At the time of analysis, six patients receiving FOLFIRI plus durvalumab (FD) and twelve patients receiving FOLFIRI plus both ICIs (FDT) were still under treatment. The primary endpoint was not met, as the 4-month PFS was inferior to 70 % in both groups (44.7 % in FD and 55.6 % in FDT). There was no advantage of the combination of FD versus FDT in terms of either OS (13.3 vs 9.5 months, **Figure 2**) or disease control rate (DCR, 67.4 % vs 68.9 %). To note, a larger number of patients had a controlled disease at twelve months in the FDT arm (15.7 %, n = 7) as compared to the FD arm (4.3 %, n = 2); Moreover, about 30 % of the patients in both groups showed OS longer than twelve months.

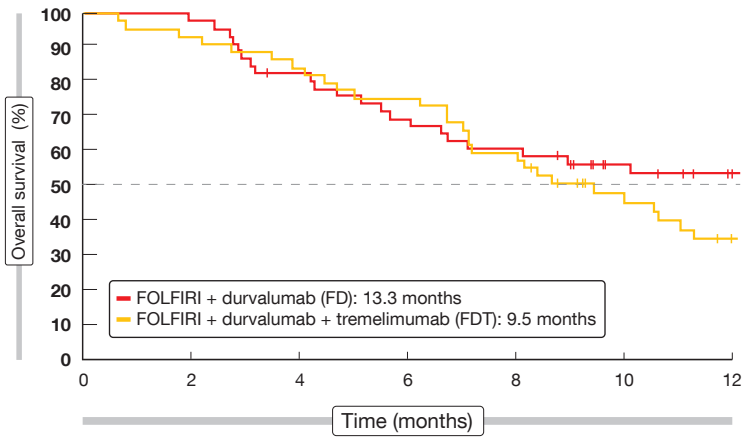

Figure 2: Overall survival in the PRODIGE 59 - DURIGAST trial

The safety profile of combining one or two ICIs to FOLFIRI was acceptable, with an equal proportion of grade ≥3 TRAEs (47.8 %). The most frequent grade ≥3 TRAEs were decreased neutrophil count (15.2 %) and vomiting (6.5 %) in the FD treatment group and decreased neutrophil count (23.9 %) and diarrhea (10.9 %) in the FDT treatment group.

Although the combination of FOLFIRI plus durvalumab or durvalumab plus tremelimumab did not meet its primary endpoint, both arms demonstrated a clinically relevant PFS, and an increased OS compared to historic data with chemotherapy alone. As the efficacy of both combinations seems promising in specific subgroups, predictive markers of efficacy (PD-L1 status, immune scores, tumor mutation burden and microbiota) are currently under investigation in ancillary studies.

DESTINY-Gastric02: 2L T-DXd in patients with HER2+ G/GEJA

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate consisting of a humanized HER2 targeting antibody with the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and DXd, a cytotoxic topoisomerase I inhibitor, as its released payload [7]. This targeted therapy was approved by the FDA for the treatment of locally advanced or metastatic HER2-positive G/GEJA, who previously received a trastuzumab-based regimen [8]. At this year's ESMO meeting, Ku et al. presented the updated analysis of DESTINY-Gastric02, an open-label, phase II study (NCT04014075) conducted in Western patients [9].

Eligible patients had a pathologically documented, unresectable or metastatic G/GEJA, a centrally confirmed HER2-positive disease (defined as immunohistochemistry (IHC) 3+ or IHC 2+/in situ hybridization (ISH)+) from a biopsy performed after progression on trastuzumab-based first-line regimen, and a good performance status (ECOG 0 or 1). All patients enrolled in this single-arm study received T-DXd (6.4 mg/kg, Q3W). The primary endpoint was confirmed ORR (cORR) as assessed by independent central review (ICR); the ICR-confirmed PFS, OS, duration of response (DoR), safety and patient-reported outcomes (PROs) based on health-related quality of life (HRQoL) were secondarily analyzed.

A total of 79 patients were included in this study. After a median follow-up of 10.2 months (data cut-off: November 8, 2021), a cORR of 41.8 % (5.1 % of patients with a complete response [CR], 36.7 % of them with a partial response [PR]) was reported. Confirmed DCR (81 %; 95 % CI: 70.6-89.0), median DoR (8.1 months; 95 % CI: 5.9-NE) and median time to response (TTR, 1.4 months; 95 % CI, 1.4-2.7) were similar to the results from the primary analysis (median follow-up of 5.9 months). The reported median OS was 12.1 months (95 % CI, 9.4-15.4) and the median PFS reached 5.6 months (95 % CI, 4.2-8.3).

The updated safety data were generally consistent with the established T-DXd safety profile [10]. Overall, 55.7 %

of patients experienced a grade ≥3 treatment-emergent adverse event (TEAE), the most common TEAEs being nausea (67.1 %), vomiting (44.3 %), and fatigue (41.8 %). A total of eight patients experienced an adjudicated drug-related interstitial lung disease (ILD)/pneumonitis (grade 1: 2.5 %, grade 2: 5.0 % and fatal grade 5: 2.5 %). Median time to onset of adjudicated drug related ILD/pneumonitis was 80.5 days, with a median duration of 36.0 days. The HRQoL was maintained during treatment with T-DXd from baseline throughout to cycle 7 without any worsening.

After seven months of additional follow-up, T-DXd continues to demonstrate a clinical benefit and a tolerable safety profile as well as maintained HRQoL as second-line treatment for Western patients with HER2-positive unresectable/metastatic G/GEJ cancer.

1L KN026/KN046 dual therapy in HER2+ G/GEJ

At ESMO 2022, Gong et al. presented the preliminary analysis of a phase II trial (NCT04521179) assessing the safety and the efficacy of a dual therapy in HER2-positive patients with locally advanced unresectable or metastatic gastric/gastroesophageal junction (G/GEJ) cancer without prior systemic treatment. This treatment combines two novel bispecific antibodies: KN026, an anti-HER2 antibody that binds simultaneously to two non-overlapping epitopes of HER2 and thus leading to a dual HER2 signal blockade; and KN046, a bispecific antibody preventing both the interaction of PD-L1 with PD-1 and CTLA-4 with CD80/CD86 [11].

Eligible patients received KN026 (30 mg/kg, Q3W on Cycle 1/Day 1 & Cycle 1/Day 8) combined with KN046 (5 mg/kg, Q3W) until disease progression or intolerable toxicity. The co-primary endpoints are ORR and DoR according to RECIST v1.1. Additionally, PFS, clinical benefit rate (CBR) and OS, are analyzed secondarily. Since January 30, 2022, a total of 31 patients (median age, 64 years) were enrolled so far, with 26 patients still receiving study treatment. HER2 status was determined with HER2 gene amplification in all patients (83.9 % had IHC3+ and 16.1 % IHC2+). Most patients (80.6 %) presented with ECOG 1; most of them had distant lung (61.3 %) or liver (12.9 %) metastases at enrollment.

Overall, 27 patients were evaluable for efficacy at the time of the preliminary analysis with twelve confirmed PRs, nine unconfirmed PRs, four stable disease (SD) and two progressive disease (PD) **(Figure 3)**. The ORR was 77.8 %, while 92.6 % of the patients had a controlled disease (DCR).

Considering safety, 80.6 % experienced at least one TRAE, most frequently being diarrhea (32.3 %), pyrexia (32.3 %) and leukopenia (22.6 %). Most TRAES were mild to moderate; however, grade ≥3 TRAES occurred in 16.1 %, with diarrhea (6.5 %) and pyrexia (3.2 %) being the most commonly reported ones and almost all patients recovered. However, three patients discontinued their treatment following KN046-treatment related AEs, while there was no treatment discontinuation related to KN026 treatment. No treatment-related death was reported.

Although preliminary, these clinical data demonstrate a synergistic antitumoral activity and a manageable safety of KN026 combined with KN046 treatment in HER2-positive G/GEJ cancer systemic therapy-naïve patients. Further studies are warranted to confirm these outcomes.

First-in-human trial of TST001

Targeted therapy and immunotherapy have revolutionized treatment of various cancers in the past decade, and are currently developed to identify ideal monoclonal antibodies specific to tumor proteins only. One of these investigated proteins is claudin 18.2 (CLDN18.2), which is involved in tumor development, as well as in cancer progression [12]. TST001 is a recombinant humanized antibody presenting a high affinity to CLDN18.2, that can eliminate cancer cells via antibody-dependent cytotoxicity and complement dependent cytotoxicity. In combination with chemotherapy, TST001 has already shown synergistic effects in preclinical studies [13].

At this year's ESMO meeting, Shen et al. reported on an updated analysis of the open label, phase I, first-in-human trial of TST001 (NCT04495296) [14]. In this dose escalation and expansion study safety, tolerability, and preliminary efficacy of TST001 combined with capecitabine and oxaliplatin (CAPOX) as first-line treatment in locally advanced or metastatic G/GEJ cancer are evaluated. Patients recruited in the dose escalation phase had no prior systemic treatments and undetermined CLDN18.2 expression level. However, a positive CLDN18.2 expression confirmed by a central laboratory was required to be enrolled in the dose expansion phase of this trial.

As of August 4, 2022, 51 patients had been enrolled and dosed with TST001 (1, 3, 6 or 8 mg/kg) plus CAPOX Q3W, following a 3+3 design. After the dose escalation phase, the regimen of the expansion phase was determined as 6 mg/kg TST001 plus CAPOX Q3W with which 36 patients were treated. Median follow-up was 65 days on average (median age, 56 years). Most patient had GC (92.2 %) and 1-3 metastases. No patients experienced dose limiting toxicity and 36 patients were still on treatment at the time of the presentation.

TST001 combined with CAPOX was well tolerated; 89.7 % of patients treated with 6 mg/kg experienced any grade

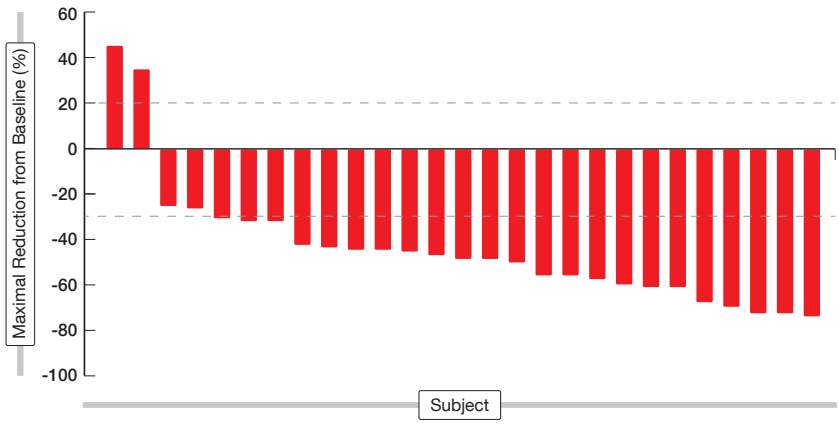

Figure 3: Waterfall plot of individual patient response to first-line KN026 plus KN046 treatment in advanced HER2 positive G/GEJ cancer.

TEAEs and 17.9 % grade ≥ 3 TEAEs with hypertension (5.1 %) being the most common one. No patient had to discontinue treatment due to TEAEs, however, twelve patients experienced dose delay, five a dose reduction and eleven a dose interruption. One patient died after treatment discontinuation for unknown reason. According to pharmacokinetics analysis, the elimination half-life of TST001 was four to seven days, regardless of the administrated dose.

Amongst the 15 patients in the expansion phase with a measurable disease and at least one tumor assessment, 73.3 % had a partial response (PR) and 26.7 % a stable disease (SD). Disease control rate was 100 %.

This interim analysis confirmed the safety of the novel agent TST001 in combination with CAPOX as first-line treatment for G/GEJ cancer. Efficacy data of this combination were also encouraging, although a correlation of antitumor activity with CLDN18.2 expression thresholds needs to be evaluated. TST001 is currently investigated in other combinations and in various indications (NCT05190575, NCT04495296) and a phase III trial is under consideration.

PANDA trial: neoadjuvant atezolizumab in HER2+ G/GEJA

The standard-of-care for non-metastatic, resectable G/GEJA currently consists of perioperative docetaxel-based triplet FLOT (5-FU plus leucovorin, oxaliplatin and docetaxel) chemotherapy [15]. This therapy is associated with a 16 % pathological complete response (pCR) and a 37 % major (complete plus subtotal) pathologic response (MPR) [16]. The clinical efficacy of anti–PD-(L)1 drugs has already been established in advanced unresectable tumors and supports the evaluation of immunotherapy against earlier disease stages [17].

The PANDA study presented at ESMO 2022 by Chalabi et al. is a single-center, phase II trial (NCT03448835) exploring the safety and the feasibility of atezolizumab (anti-PD-L1) based neo-adjuvant therapy in non-metastatic, primary resectable G/GEJA treatment-naïve patients [18]. The investigational treatment consists of one cycle of atezolizumab monotherapy (1200 mg) followed by four cycles of atezolizumab plus docetaxel-oxaliplatin-capecitabin (A-DOC), followed by surgery seven weeks after the last A-DOC cycle. Baseline tumor-staging was assessed via an oesophagoduodenoscopy, biopsies, a CT scan or/and FDG-PET-CT for all patients; an ultrasound endoscopy in GEJA patients or a diagnostic laparoscopy in diffuse type G cancers was additionally performed to exclude metastatic conditions. A radiological (via CT scan or/and FDG-PET-CT) post-treatment staging was also done prior to the last cycle of treatment. Tumor samples were collected at baseline, after atezolizumab monotherapy, after first A-DOC and at resection. The primary endpoint was safety and feasibility. Secondary endpoints were disease-free survival (DFS), pCR, MPR and translational analyses (immunohistochemistry [IHC], as well as DNA and RNA sequencing).

Twenty patients (median age, 62 years) were enrolled and followed-up over a median of 29 months. Patients' clinical stage ranged from N0 to N3 (N0, 25 %; N1, 50 %; N2, 20 %; N3, 5 %). At the time of data cut-off (June 15, 2022), 75 % of patients were alive and disease-free. In almost half of the patients, tumor and lymph node regression was reported (pCR, 45 %; 95 % CI, 23-68). In total, a MPR (≤10 % residual vital tumor) was attained in 70 % (95 % CI, 46-88). At the time of data cut-off, disease recurrence occurred only in non-responders (NR) presenting with more than 50 % residual vital tumor (30 %; 95 % CI, 12-54), after a median time of ten months post-surgery.

Overall, 10 % of patients had immune-related grade 3 adverse events (irAEs), consisting of headache, hepatitis, and diarrhea. Chemotherapy-related grade 3 AEs were experienced by 20 %, including febrile neutropenia (n = 3) and diarrhea (n = 1), while 50 % of patients had surgery-related grade 3 AEs, to the same extent as historical data [15, 19].

Besides efficacy and safety evaluation, biomarker analysis highlighted differences between responders and non-responders. Following atezolizumab monotherapy, responders presented with increased transcription of immunological markers such as IFNγ, CD8, CXCL1, PD-L1 and PD-1. Moreover, according to baseline IHC analysis, there was a significantly higher CD8/PD-1-positive T cell infiltration in responders compared to non-responders. There was no difference between the two groups regarding the tumor mutational burden.

These preliminary results of the PANDA trial, showing promising pathologic responses in G/GEJ cancer highlight the efficacy of neoadjuvant atezolizumab plus chemotherapy in this patient cohort and suggest promising biomarker tools to predict response to treatment. ■

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From neoadjuvant to second-line therapeutic options for RCC patients

Kidney cancer accounted for more than 400,000 newly diagnosed cases in 2020, [1]. Interestingly, after over two decades of increasing rates, the worldwide incidence of renal cell carcinoma (RCC) has shown signs of plateauing in recent years, whereas an increase of the global kidney cancer death rate was observed. Here, the widespread use of non-invasive radiological techniques allows the detection of early and small RCCs, which are potentially curable [2].

Radical nephrectomy (RN) or partial nephrectomy (PN) are the standard-of-care for localized stage I to III non-metastatic RCC [2, 3]. Patients with stage II or III tumors have a substantial risk of post-nephrectomy relapse [4]. Therapeutic options in this patient population include sunitinib - a vascular endothelial growth factor (VEGF) pathway inhibitor approved in the US, only, based on the S-TRAC trial (NCT00375674) [5] - and pembrolizumab - an anti-PD-1 immune checkpoint inhibitor (ICI) approved in the US and the EU based on the KEYNOTE-564 trial (NCT03142334) [6]. Several clinical studies are currently ongoing to identify new effective adjuvant therapies and therefore improve efficacy outcomes.

CheckMate 914: dual ICI adjuvant therapy

The combination of the anti-PD-1 antibody nivolumab (NIVO) and the anti-CTLA4 antibody ipilimumab (IPI) has already demonstrated its significant superiority over sunitinib in terms of overall survival (median OS, 47.0 vs 26.6 months; HR, 0.68; 95 % CI, 0.58-0.81; p<0.0001) and duration of response (median DoR, not-reached [NR] vs 19.7 months; HR, 0.46; 95 % CI, 0.31-0.66; p<0.0001) in the CheckMate 214 trial in patients with untreated advanced or metastatic RCC [7, 8]. In a two-part trial, the combination NIVO+IPI is being assessed as adjuvant therapy in comparison to placebo (part A) or versus nivolumab monotherapy versus placebo (part B) in patients with resected stage II/III clear cell RCC in the phase III CheckMate 914 trial (NCT03138512). At this year's ESMO conference, Motzer et al. reported on the efficacy and safety outcomes from part A of the CheckMate 914 trial [9].

Patients' eligibility criteria included an RN or PN with negative surgical margins, a predominant clear cell histology, including sarcomatoid features as well as predefined tumor/node/metastasis TNM staging (pT2a grade 3/4 - N0, M0; pT2b, PT3 or pT4 any grade – N0, M0; or pT any grade - N1 M0), no residual or distant metastases after nephrectomy as confirmed by blinded independent central review (BICR) and a good performance status (ECOG 0-1). Four to 12 weeks after surgery, eligible patients were randomized 1:1 to receive either twelve cycles of nivolumab (240 mg, intravenously [IV], every second week [Q2W]) plus four cycles of ipilimumab (1 mg/kg, IV, Q6W) or equivalent placebo (twelve cycles of placebo [IV, Q2W] plus four cycles of placebo [IV, Q6W]). Patients were stratified by pathologic TNM stage and type of nephrectomy. The primary endpoint was disease free survival (DFS) by BIRC, while OS and safety were set as secondary endpoints.

A total of 816 patients were followed-up over a median period of 37 months. Patients' median age was 58 years in the NIVO+IPI arm (n = 405) versus 57 in the placebo arm (n = 411). Most patients (93 % in each group) had a RN, and the most predominant tumor stage was pT3, G any, N0 M0 (78 % versus 77 %, respectively). The median duration of treatment was 5.1 months in both arms. The primary endpoint of DFS was not

reached in the NIVO+IPI arm versus 50.7 months with placebo (HR, 0.92; 95% CI, 0.71-1.19; p=0.5347). The 24-month DFS rate were 76.4% for NIVO+IPI and 74.0% for placebo, respectively. Due to a hierarchical testing procedure, and the fact that the DFS endpoint was no reached, no formal analysis of OS was performed. At the time of this analysis, 33 deaths were reported in the treatment arm and 28 deaths in the placebo arm.

Overall, grade ≥3 treatment-related adverse events (TRAEs) in the NIVO+IPI arm were mild and included mostly diarrhea (4%) and increased alanine transaminase (ALT, 2%) **(Figure 1)**. Four deaths (1%) were reported due to drug toxicity. In total, 23% of the patients in the combination arm versus 2% in the placebo arm received corticosteroids to manage any grade immune-related AEs (irAEs), with diarrhea/colitis being the most frequent grade ≥3 irAE (5%). Compared to placebo, more patients in the NIVO+IPI arm discontinued treatment (1% vs 29%) due to TRAEs any grade.

The combination of nivolumab plus ipilimumab did not meet the primary endpoint of DFS in patients with localized stage II/III RCC at high risk of post-nephrectomy relapse. Part B of CheckMate 914 focusing on nivolumab adjuvant monotherapy is currently ongoing.

IMmotion010 trial: adjuvant atezolizumab

The standard-of-care for patients with locoregional or oligometastatic RCC is PN or RN, with or without metastasectomy [10-12]. Atezolizumab, an anti-PD-L1 inhibitor that has already been approved in several malignant entities as adjuvant therapy, was investigated in patients with oligometastatic RCC after resection and increased risk of recurrence in the IMmotion010 phase III trial (NCT03024996). At ESMO 2022, Bex et al. presented the efficacy and safety outcomes [13].

Eligibility criteria were a resected intermediate to high-risk RCC, a predefined TNM tumor stage (pT2 grade 4, pT3a grade 3/4, pT3b/c or pT4 any grade, pTXN+ any grade, or M1 with no evidence of disease [NED]) and a clear cell or sarcomatoïd component. Patients were randomized 1:1 to receive either 16 cycles (or one year, whichever occurred first) of atezolimumab (1,200 mg, IV, Q3W) or of placebo (IV, Q3W). Patients were stratified by disease

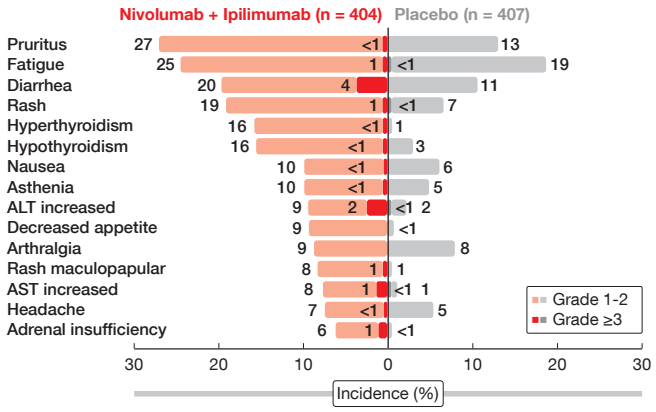

Figure 1: Treatment-related AEs in all treated patients in the phase III CheckMate 914 trial.

stage, PD-L1 expression of immune cell (IC) and geographic area. The primary endpoint was the investigator-assessed DFS in the intention-to-treat (ITT) population. Key secondary endpoints enclosed OS in the ITT population, investigator-assessed DFS in the IC1/2/3 population, independent review facility (IRF)-assessed DFS in the ITT and IC1/2/3 populations, IRF-assessed event-free survival (EFS) in the ITT population and safety.

From January 2017 to February 2019, 390 patients were enrolled in the treatment arm and 388 in the placebo arm; all of them were followed-up for more than 38.6 months. In both groups, the median age was approximately 60 years and almost 80% of the patients had a very good performance status (ECOG 0). More than 90% of the patients had a clear cell histology. The predominant tumor stage was pT2/PT3a (about 64%) and the PD-L1 IC1/2/3 attained approx. 60 % in both arms. The primary endpoint was not met, as no DFS advantage was reported with atezolizumab compared to placebo (57.2 vs 49.5 months; HR, 0.93; 95% CI, 0.75-1.15; p=0.495). This was seen in the DFS analysis of pre-specified subgroups, too, although there was a trend in favor of atezolizumab in females (HR, 0.61; 95% CI, 0.40-0.94). Additionally, no improvement was observed with atezolizumab versus placebo in terms of median OS (NE in both groups; stratified HR, 0.97; 95% CI, 0.67-1.42) or investigator-assessed DFS by PD-L1 status (PD-L1 IC expression <1% stratified HR, 1.09; 95 % CI, 0.77-1.59; PD-L1 IC expression 1% to <5% stratified HR, 0.92; 95% CI, 0.68-1.25; PD-L1 IC expression ≥5% stratified HR, 0.57; 95% CI, 0.29-1.15).

Atezolizumab was well tolerated, with a rate of grade 3-4 TRAEs of 14.1% in the treatment arm versus 4.7% in the placebo arm. The most frequent all-grade AEs were arthralgia (20% with atezolizumab vs 14.9% with placebo), pruritus (19.0% vs 12.5%) and hypothyroidism (14.4 % vs 3.1%). AEs leading to discontinuation occurred in 11.5% of the atezolizumab-treated patients versus 2.6% in the control group.

In the IMmotion010 trial, atezolizumab did not improve clinical outcomes versus placebo as adjuvant therapy in patients with locoregional or oligometastatic RCC after resection and high risk of recurrence but adverse events were manageable and in line with the known safety profile of atezolizumab.

PROSPER, ECOG-ACRIN EA8143: neoadjuvant nivolumab

Several clinical investigations are currently evaluating neoadjuvant therapies to improve the survival of RCC patients undergoing nephrectomy by priming their immune system preoperatively. Preclinical studies demonstrated promising advantages of neoadjuvant immunotherapy over adjuvant therapy in eradicating metastatic disease [14]. This was confirmed in the clinical setting, with neoadjuvant nivolumab being associated with a good pathological response in lung, melanoma and breast cancer [15]. At this year's ESMO conference Allaf et al. presented the interim analysis of a first phase III neoadjuvant study in RCC, the PROSPER, ECOG-ACRIN EA8143 trial (NCT03055013) [16].

This open-label study compared neoadjuvant nivolumab followed by adjuvant nivolumab to observation in RCC patients undergoing nephrectomy. Eligible patients

were randomized 1:1 to nivolumab or the observational arm. Inclusion criteria included a clear cell or non-clear cell histology and a minimum TNM tumor stage of ≥ T2, any N, M0 or oligo M1 (if resectable at the same time or within 12 weeks and patient rendered NED). Eligible patients in the treatment arm underwent biopsy, received one dose of nivolumab (480 mg, IV, Q4W) seven to 28 days before PN or RN, as well as nine adjuvant doses starting 4-10 weeks after surgery **(Figure 2)**. The primary endpoint was recurrence-free survival (RFS), defined as time from randomization to disease recurrence or death, whichever occurred first. The secondary endpoints included OS, RFS for clear cell RCC (ccRCC), safety and tolerability, patient-reported outcomes, and correlative science.

A total of 819 patients were enrolled in the study and analyzed after a 16-month median follow-up. At baseline, about 50 % of patients presented with cT1/T2 tumors and the other half with cT3/T4 tumors. After surgery, more than 60 % of the patients had pT3/T4 tumors, 80 % had a ccRCC and about 3 % were not disease-free. At the time of data cut-off 87.4 % of patients had started neoadjuvant nivolumab, 88.9 % patients had received surgery and 77.7 % had started an adjuvant therapy in the treatment arm compared to 93.2 % of patients who had received surgery in the observational arm. This interim analysis did not demonstrate similar RFS in both arms (HR, 0.97; 95 % CI, 0.74-1.28, one-sided p-value=0.43) and the median RFS was not reached. The OS data were still immature when this interim analysis was performed but also did not differ significantly between the study groups (HR, 1.48; 95 % CI, 0.89-2.48; one-sided p=0.93). Therefore, ECOG-ACRIN data safety monitoring committee stopped the trial due to inefficacy.

More patients in the treatment arm than in the observational arm experienced grade 3-4 TRAEs (15 % vs 4 %) with the most common TRAEs being fatigue (60.4 % with nivolumab vs 26.6 % in the control arm), pruritus (31.5 % vs 2.8 %) and rash maculopapular (31.2 % vs 1.3 %). Treatment discontinuation due to any grade TRAEs occurred in 13 % of patients who received nivolumab.

This first phase III trial investigating the antitumoral activity and safety of perioperative nivolumab failed to meet its primary endpoint in RCC patients. However, nivolumab safety data were consistent with previous historic data. Future neoadjuvant RCC trials could be planned based on the ongoing radiomic, pathomic and biomarkers analyses of this pioneer trial.

COSMIC-313: 1L cabozantinib plus dual ICI

The combination of nivolumab plus ipilimumab is a first-line standard-of-care for advanced RCC of intermediate or poor risk, as defined by the International Metastatic RCC Database Consortium (IMDC) [17]. Although this combination has demonstrated OS superiority over sunitinib, a large proportion of patients (20 %) had a progressive disease as best response. Cabozantinib - a tyrosine kinase inhibitor (TKI) directed against a broad range of targets, including the VEGF receptor - already demonstrated its efficacy and safety as monotherapy [18-20] or in combination with nivolumab in advanced RCC [21]. The combination of cabozantinib plus nivolumab plus ipilimumab has been tested in phase I trials; it proved to be efficient and to have a manageable toxicity in patients with genitourinary tumors [22] or untreated advanced RCC [23]. At this year's ESMO, Choueiri et al. reported on the COSMIC-313 phase III trial (NCT03937219), which currently evaluates this triple combination versus placebo in previously untreated patients with advanced RCC [24].

Study patients were treatment-naïve, had a clear cell histology, an IMDC intermediate or poor risk, a measurable disease as assessed by RECIST v1.1 and a minimum Karnofsky performance status ≥ 70 %. Eligible patients were randomized 1:1 to receive either cabozantinib (40 mg, per os[PO], every day [QD]) in arm A or placebo (PO, QD) in arm B plus nivolumab (3 mg/kg, IV, Q3W x 4) plus ipilimumab (1 mg/kg, IV, Q3W x 4), followed by cabozantinib (40 mg, PO, QD) plus nivolumab (3 mg/kg, IV, Q4W). The treatment was administered until loss of clinical benefit or intolerable toxicity. To note, no crossover was allowed. A tumor assessment according to RECIST v1.1 was planned every eight weeks. Patients were stratified by IMDC risk and region. The primary endpoint was PFS, as assessed by BICR per RECIST v1.1 in the PFS-ITT population (PITT). The secondary endpoint included OS in the ITT population, as well as the overall response rate (ORR), the DoR and safety.

Patients in the arm A (Cabo+Nivo+Ipi, n=428) and in the arm B (Pbo+Nivo+Ipi, n = 427) were followed-up for a median duration of 17.7 months (ITT population, n=855) or 20.2 months (PITT population, n=550). Study participants had a median age of 60 to 61 years, a predominant intermediate IMDC risk (75 %) and two or more metastatic sites (80 %) mainly located in the lung (about 70 %) or in the lymph nodes (more than 50 %). The primary endpoint was met: the median PFS demonstrated a significant advantage of the cabozantinib combination compared to the control group in the PITT population (NR vs 11.3 months; HR, 0.73; 95 % CI, 0.57-0.94; p=0.013). In the subgroup analysis, the PFS by IMDC risk suggested a greater benefit for cabozantinib-treated patients having an intermediate risk (HR,

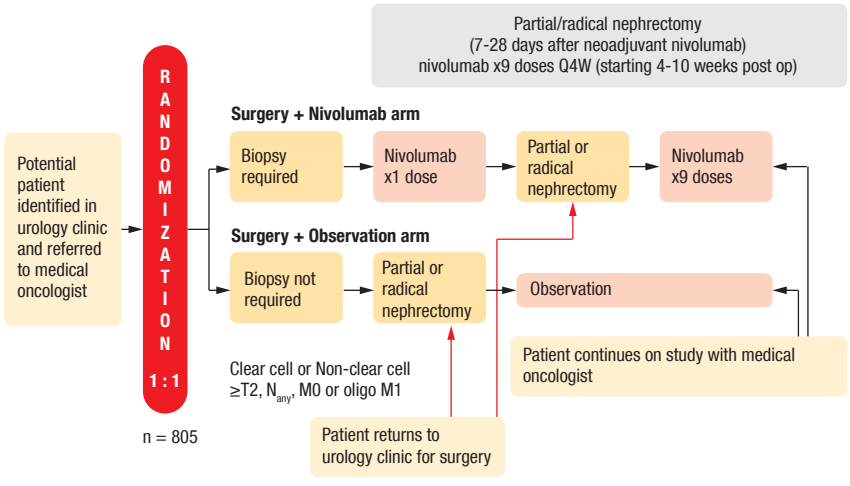

Figure 2: Design of the PROSPER, ECOG-ACRIN EA8143 phase III trial.

0.63; 95 % CI, 0.47–0.85) than those having a poor risk (HR, 1.04; 95 % CI, 0.65-1.69). At the data cut-off (January 31, 2022), the ORR in the PITT population was also improved in the Cabo+Nivo+Ipi arm with 43 % (3 % with a complete response [CR], 41 % with a partial response [PR]) compared to the Pbo+Nivo+Ipi arm with 36 % (3 % CR, 32 % PR), while the disease control rate (DCR) reached 86 % and 72 %, respectively. Compared to the control arm, a higher ORR benefit was observed in patients with an intermediate risk (45 % vs 35 %) receiving the cabozantinib-combined therapy than in those who presented with a poor risk (37 % vs 38 %).

Overall, grade 3-4 TRAEs were more frequent in the arm A than in the arm B (73 % vs 41 %), with the most common ones being increased ALT (26 % vs 6 %, respectively), increased aspartate aminotransferase (AST, 20 % vs 5 %), increased lipase (9 % vs 6 %) and hypertension (8 % vs 2 %). Three patients experienced grade 5 TRAEs within 30 days after the last dose in each arm.

The phase III COSMIC-313 trial was the first study to use a combination of two standard-of-care ICIs as control arm (nivolumab plus ipilimumab). This trial demonstrated efficacy and safety of cabozantinib plus dual ICI over placebo plus dual ICI in previously untreated patients with advanced RCC of IMDC intermediate or poor risk. Further followed-up to determine overall survival is still ongoing.

LITESPARK-003: belzutifan plus cabozantinib

Belzutifan is a highly selective small molecule designed to inhibit the hypoxia-inducing factor (HIF)-2α that is a key oncogenic driver in ccRCC, when it is constitutively activated. Belzutifan has previously shown antitumoral activity with an ORR of 25 % in heavily pretreated patients with ccRCC (NCT02974738) [25]. As cabozantinib was already approved for advanced ccRCC as monotherapy [18-20], a combined treatment targeting both the HIF-2α and VEGF pathway might improve patients' outcome in advanced ccRCC even further.

At ESMO 2022, Merchan et al. presented the interim analysis of the cohort 1 of the LITESPARK-003 phase II trial (NCT03634540) [26]. Key eligibility criteria include locally advanced or metastatic ccRCC with no prior treatment and a good performance status (ECOG 0 or 1). Tumor assessments are planned at week 9, then Q8W until month 12, and Q12W thereafter. The primary endpoint is the ORR, as assessed per RECIST v1.1by the investigator; PFS, DoR and time to response (TTR) assessed per RECIST v1.1 by investigator, OS, as well as safety and tolerability, are secondarily analyzed.

At the time of data cut-off (February 1, 2022), 35 out of 50 planned treatment-naïve patients had been enrolled with a median followed-up of 14 months. Median age was 64 years, 83 % males, 60 % of patients had a good performance status (ECOG 0) and 40 % presented with an intermediate or poor IMDC risk. Eligible patients receive belzutifan (120 mg, PO, QD) plus cabozantinib (60 mg, PO, QD).

More than half of the patients responded to the treatment (ORR, 57 % [6 % CR, 51 % PR]); DCR, 94 %). To note, the ORR was consistent across the IMDC favorable versus intermediate/poor risk categories (62 % [10 % CR, 52 % PR] vs 50 % [50 % PR]). Most patients (94 %) experienced a reduction in target lesion size **(Figure 3)**. At the time of this interim analysis, 25 patients (71 %) were still on treatment. The median TTR was 1.9 months (range, 1.7-9.2) and the median DoR was 28.6 months (range, 1.7+ to 28.6), with 78 % of responders having a DoR of at least twelve months. The median PFS was 30.3 months (95 % CI, 9.4-NR), the 1-year PFS rate was 67 % and the 1-year OS rate was 96 %.

Grade 3 TRAES were experienced by 37 % of the patients, while no grade 4 or 5 TRAEs were reported. Serious TRAEs occurred in 6 % of patients. Anemia and diarrhea (71 %, each) and fatigue (63 %) were the most frequent TRAEs any grade. One patient discontinued cabozantinib due to an AE (abdominal abscess) whereas no patient discontinued belzutifan due to an AE. Twenty-five (71 %) patients experienced belzutifan-related anemia (including two grade 3 events) and two patients (6 %) experienced belzutifan-related hypoxia (including one grade 3 event).

Moreover, at ESMO 2022, McDermott et al. presented an update from cohort 2 of LITESPARK-003 including patients with prior immunotherapy and a maximum of two regimens for locally advanced or metastatic RCC [27]. At the time of data cut-off (February 1, 2022), 10 of 52 patients were still on treatment. Median age was 63 years, 73 % males, 56 % of patients had a ECOG 1. Most patients had one prior line of anticancer therapy (56 %) with more patients being treated with immunotherapy only (54 %) compared to anti-VEGF/VEGFR therapy (46 %).

With a median follow-up of 24.6 months, belzutifan plus cabozantinib still showed a promising antitumor activity in patients with advanced ccRCC previously treated with immunotherapy (ORR, 31 % [2 % CR, 29 % PR]). To note, the ORR was consistent across the different pre-treatment groups – immunotherapy only (ORR, 32 %), immunotherapy/anti-VEGF therapy (ORR 29 %), 1 line of prior therapy (ORR, 31%) and 2 lines of prior therapy (ORR, 30 %). Most patients (87 %) experienced a reduction in target size with a median DoR of 18.6 months (range, 4.2+ to 22.8). The median PFS was 13.8

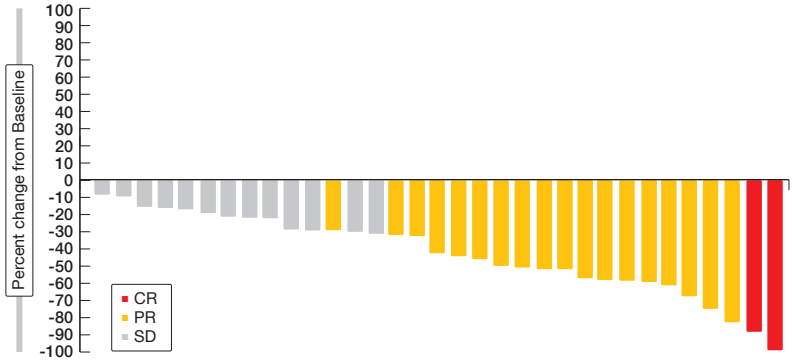

Figure 3: Best percentage change from baseline in target lesions of treatment naïve-patients in the LITESPARK-003 phase II trial. (CR, complete response; PR, partial response; SD, stable disease)

months (range, 9.2-19.4) and the 1-year PFS rate was 56 %. The median OS was 24.1 months (range, 20.0-37.4) and the 1-year OS rate was 77 %. The safety profile was consistent with individual profiles of each agent and no grad 4 TRAEs occurred. Of note, one patient died due to treatment-related respiratory failure.

The interim outcomes of the LITESPARK-003 phase II trial showed manageable safety accompanied by promising antitumor activity of belzutifan plus cabozantinib in treatment-naïve as well as previously immunotherapy-treated patients with advanced ccRCC. Thus, data from the ongoing phase III study LITESPARK-011 trial (NCT04586231) are highly awaited. ■

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Promising therapeutic strategies for colorectal cancer treatment

With more than 1.9 million new cases, colorectal cancer (CRC) accounted in 2020 for 10 % of all diagnosed cancers. CRC ranked third in terms of incidence and was the second leading cause of cancer mortality worldwide, with 935,000 estimated deaths in 2020 [1]. Over the last five years, clinical studies have shown that treatments specifically tailored to the molecular and pathological characteristics of the tumor improved overall survival. In addition, genomic profiling able to detect somatic variants represents an important asset to identify effective treatments for specific patient subsets [2]. At this year's ESMO meeting, the recent updates on CRC treatment were presented.

Neoadjuvant immune-checkpoint inhibition in dMMR CRC

Deficient mismatch repair (dMMR) occurs in approximately 10-15 % of colon cancers, with one-third of dMMR CRC being associated with the Lynch Syndrome [3]. Despite long established

standard-of-care chemotherapy, recurrence rates of stage III dMMR tumors are still 20-40 % and closely associated with a poor survival [4]. Recent studies have shown that neoadjuvant immunotherapy leads to a clinically meaningful pathological response in various malignancies – such as bladder cancer or melanoma - and was associated with excellent outcomes [5, 6]. NICHE-1 was the first study with neoadjuvant immunotherapy in non-metastatic dMMR colon cancer where all patients had a pathological response and 60 % a pathologic complete response [7].

At ESMO 2022, Chalabi et al. presented the first results of the NICHE-2 trial (NL58483.031.16, EudraCT 2016-002940-17), a non-randomized study in patients with non-metastatic, untreated dMMR colon adenocarcinoma [8]. Overall, 112 eligible patients were treated with one dose of ipilimumab (1 mg/kg) plus nivolumab (3 mg/kg) in the first cycle, then only nivolumab in the second cycle two weeks later, followed by surgery within six weeks of enrollment. The co-primary endpoints were safety, feasibility, and 3-year disease-free survival (DFS).

Among 112 patients enrolled in this study, 107 were available for the efficacy analysis; 74 % had high-risk stage III CRC, including 35 % and 28 % patients with clinical T4a and T4b tumors, respectively. In total, 98 % of patients underwent timely surgery, with a median time between first dose and surgery of 5.4 weeks, thus meeting the primary safety endpoint. Overall, 99 % of patients achieved a pathologic response, with a pathologic complete response (pCR, defined as 0 % residual viable tumor) observed in 67 % of patients, a major pathologic response (MPR, defined as ≤ 10 % residual viable tumor) in 95 % of them and a partial pathologic response (pPR, defined as 10 - 50 % of residual viable tumor) in 4 % **(Figure 1)**. The rate of pCR was higher in patients with Lynch syndrome (n = 32) than in those with sporadic tumors (n = 65) (78 % vs 58 %; p = 0.056). After a median follow-up of 13.1 months, no disease recurrence has been observed in any patient, which might predict promising upcoming results. Moreover, the treatment was well tolerated, with only 4 % grade ≥ 3 immune-related adverse events. Further results on 3-year DFS are expected in 2023.

These initial results from the NICHE-2 trial demonstrated that neoadjuvant immunotherapy consisting of ipilimumab plus nivolumab has the potential to become a new standard-of-care in dMMR colon cancer.

Update on KRYSTAL-1: adagrasib ± cetuximab in *KRAS*^{G12C}-mutated CRC

KRAS^{G12C} mutations, which are reported in approximately 3 % of CRC tumors, are associated with a poor prognosis [9]. They are a negative predictor of cetuximab – an anti-EGFR monoclonal antibody - efficacy, and late treatment options are limited [10]. Adagrasib, an irreversible and selective KRAS^{G12C} inhibitor, has been optimized with favorable pharmacokinetic properties, including a long half-life (23 h), extensive tissue distribution, dose-dependent pharmacokinetics, and central nervous system (CNS) penetration [11, 12]. Thus, the combination of cetuximab with adagrasib may enhance the inhibition of KRAS-dependent signaling or overcome adaptive feedback and provide a more durable efficacy.

KRYSTAL-1 (NCT03785249) is a phase Ib/II multicohort study evaluating adagrasib as monotherapy or in combinations with cetuximab across patients with advanced solid tumors harboring a *KRAS*^{G12C} mutation [13]. In the CRC cohort, eligible patients received either adagrasib (600 mg, orally, twice daily [BID]) plus cetuximab (400 mg/m², followed by 250 mg/m² once weekly [QW] or 500 mg/m² every other week [Q2W]) in phase Ib or adagrasib monotherapy in phase II. Primary study endpoints included safety, recommended phase II dose and pharmacokinetics in phase Ib and overall response rate (ORR) according to RECIST v1.1 in phase II.

At ESMO 2022, Klempner et al. reported updated results from CRC cohorts (phase Ib and II), with a median follow-up of 17.5 and 20.1 months, respectively [14]. As of June 16, 2022, 44 patients received adagrasib monotherapy and 32 patients received adagrasib plus cetuximab. Baseline characteristics were balanced between both cohorts, with a median of three prior lines of systemic therapy each. Forty-three patients with adagrasib monotherapy and 28 patients on combination therapy were evaluable for efficacy. At the time of data cut-off, a clinical benefit was observed for the combination therapy, in terms of confirmed ORR (46 % for adagrasib plus cetuximab vs 19 % for adagrasib) **(Figure 2)**, disease control rate (DCR, 100 % vs 86 %), median duration of response (DoR, 7.6 vs 4.3 months), progression-free survival (PFS, 6.9 vs 5.6 months) and median overall survival (OS, 13.4 vs 19.8 months), with a 1-year survival rate of 69 % versus 61 %, respectively. Tumor shrinkage of any extent was observed in 93 % of patients treated with the combined therapy versus 79 % of those who were administered adagrasib monotherapy.

Adagrasib had a manageable toxicity, as grade ≥3 TRAEs were experienced by 30 % of patients in the monotherapy arm (mostly anemia [9 %] and diarrhea [7 %]) and by 9 % of patients in the combination arm (diarrhea, dermatitis acneiform and stomatitis, 3 % each). No serious TRAEs were observed.

So far, the KRYSTAL-1 trial showed an encouraging clinical activity of adagrasib both as monotherapy and in combination with cetuximab particularly in heavily pretreated patients with *KRAS*^{G12C}-mutated CRC. This therapeutic combination is being currently evaluated in the phase III KRYSTAL-10 trial (NCT04793958) in the second line (2L) setting of this patient population.

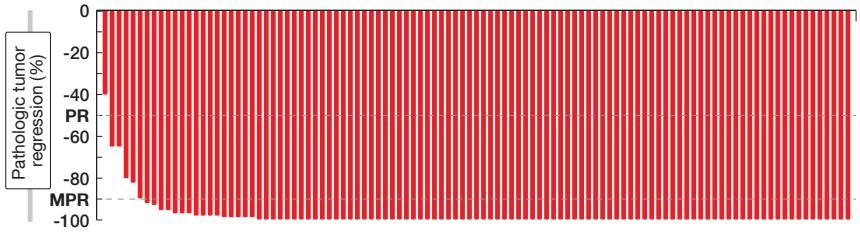

Figure 1: Pathologic response in the NICHE-2 trial. *PR, pathologic response; MPR, major pathologic response*

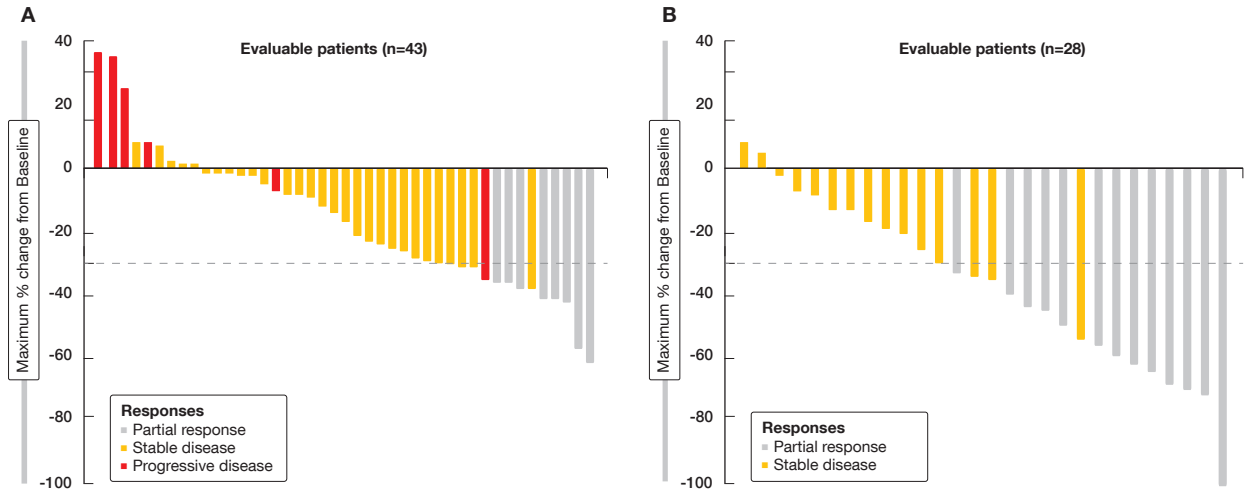

Figure 2: Waterfall plots of best tumor change from baseline with adagrasib monotherapy **(A)** or adagrasib plus cetuximab **(B)** in the KRYSTAL-1 trial.

CodeBreaK 101: sotorasib plus panitumumab

In the phase II CodeBreaK 100 trial (NCT03600883), sotorasib - a *KRAS*^{G12C} inhibitor - monotherapy was previously shown to elicit modest benefit in heavily pretreated patients with *KRAS*^{G12C}-mutated CRC [15]. Unfortunately, resistance to sotorasib may occur as a feedback reactivation of the RAS-MAPK pathway and accumulation of activated EGFR [16, 17]. Initial data from the phase I CodeBreaK 101 trial (NCT04185883) have shown that sotorasib combined with the EGFR antibody panitumumab appears to inhibit tumor growth to a better extend than sotorasib monotherapy in patients with chemorefractory *KRAS*^{G12C}-mutated metastatic CRC (mCRC) [18, 19]. Safety and efficacy data of the combination therapy from the fully enrolled dose expansion cohort (n = 40) were presented by Kuboki et al. at ESMO 2022 [20].

Inclusion criteria in the CodeBreaK 101 study comprised *KRAS*^{G12C} inhibitor-naïve patients who were diagnosed with *KRAS*^{G12C}-mutated mCRC through molecular testing, at least one prior treatment for advanced disease, and a progression on or after fluoropyrimidine, oxaliplatin, irinotecan, or an anti-angiogenic agent. Patients in the dose-expansion cohort received 960 mg of sotorasib (960 mg, orally, daily) and panitumumab (6 mg/kg, intravenous [IV], every second week [Q2W]). Primary endpoints enclosed safety and tolerability, while secondary endpoints included ORR, DCR, DoR, time to response (TTR), PFS per RECIST v1.1, OS, and pharmacokinetics.

Overall, 40 patients with a median age of 58 years were enrolled in this study. Most patients were heavily pretreated, with a median of two prior lines of therapy. A confirmed ORR of 30 % (95 % CI, 16.6-46.5), was obtained, with all responders (n = 12) showing a partial response. A stable disease (SD) was determined in 25 patients (63 %), the DCR reached 93 % (95 % CI, 79.6-98.4). Moreover, tumor shrinkage of the target lesions according to RECIST v1.1 was observed in 87.5 % of patients. The median duration of treatment was 5.9 months, with 25 % of patients remaining on treatment at data cut-off (June 24, 2022). After a median follow-up of eleven months, the median DOR reached 4.4 months (range, 2.8-7.4) and the median PFS was 5.7 months (95 % CI, 4.2-7.6). Of note, the 9-month PFS rate attained 12.3 % (95 % CI, 3.4-27.2). The median OS was not reached at the time of analysis, but the 9-month OS rate attained 82.5 % (95 % CI, 61.8-92.6).

The combination was very well tolerated, with TRAEs of grade 3 occurring in 23 % of patients and no grade 4 or fatal TRAEs. No patient had to discontinue either drug due to TRAEs. Dose interruptions or reductions due to TRAEs, were related to sotorasib treatment in 15 % of patients and associated with panitumumab therapy in 25 %.

This updated analysis of the CodeBreak 101 dose expansion cohort provides further evidence that sotorasib plus panitumumab is safe and tolerable in chemorefractory patients with *KRAS*^{G12C}-mutated mCRC. Compared to previously reported sotorasib monotherapy outcomes, the threefold higher response obtained with the sotorasib plus panitumumab supports further development of this new therapeutic approach. Thus, the currently ongoing global phase III CodeBreaK 300 trial (NCT05198934) is evaluating sotorasib plus panitumumab versus standard therapy of the investigator's choice for the treatment of *KRAS*^{G12C}-mutated mCRC.

FRESCO-2: fruquintinib in refractory mCRC

The vascular endothelial growth factor (VEGF) signaling pathway is a key mediator of angiogenesis, which is involved in tumor growth and metastasis [21]. Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor (TKI) of VEGF receptor (VEGFR) 1, 2, and 3 [22]. In the phase III FRESCO trial (NCT02314819), fruquintinib already demonstrated efficacy and safety in Chinese patients with mCRC in the third-line setting and beyond (3L+), which led to its approval in China in 2018 [23]. To better reflect current global treatment practice, the phase III FRESCO-2 study (NCT04322539) evaluated the antitumoral activity and tolerability of fruquintinib in heavily pretreated mCRC patients from the United States, Europe, Japan, and Australia. The results of the FRESCO-2 trial were presented by Dasari et al. at ESMO 2022 [24].

The study design of the FRESCO-2 trial required eligible patients to have previously received a fluoropyrimi-

dine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and an anti-EGFR therapy for RAS wild-type, as well as a prior treatment with an immune checkpoint inhibitor (ICI) or BRAF inhibitor if indicated. They also had to have progression on or intolerance to TAS-102 and/or regorafenib. Patients were randomized 2:1 to receive either fruquintinib (5 mg orally, once daily [QD] for three weeks, followed by one week off) or placebo until progression or unacceptable toxicity. All patients were additionally administered best supportive care. The primary endpoint was OS, while PFS, ORR, DCR, and safety were secondarily analyzed.

Overall, 691 patients (fruquintinib, n = 461; placebo, n = 230) were randomized between September 2020 and December 2021 in this study. Patients were heavily pretreated, with a median of five prior lines of treatment in both arms. After a median follow-up of 11.3 months for fruquintinib and 11.2 months for placebo (data cut-off of June 24, 2022), the study met its primary endpoint in terms of median OS improvement (7.4 months in the fruquintinib arm vs 4.8 months with placebo; HR, 0.662; 95 % CI, 0.549-0.800; p < 0.001), and therefore a 33.8 % risk reduction of death **(Figure 3)**. The median PFS was also in favor of fruquintinib (3.7 months vs 1.8 months, respectively; HR, 0.321; 95 % CI, 0.267-0.386; p < 0.001); this PFS-improvement was consistent across the pre-specified subgroups. The DCR was significantly higher in the fruquintinib arm compared to placebo (55.5 % vs 16.1 % with an adjusted difference of 39.4 % (95 % CI, 32.8-46.0; 2-sided p < 0.001) and the ORR reached 1.5 % versus 0 % (2-sided p = 0.059), respectively.

In terms of safety profile, more grade ≥ 3 treatment-related adverse events (TEAEs) were reported by patients who received fruquintinib compared to placebo (62.7 % vs. 50.4 %), most frequently hypertension (13.6 % vs 0.9 %), asthenia (7.7 % vs 3.5 %) and hand-foot syndrome (6.4 % vs 5.3 %). In both arms, the proportion of any serious TEAEs was similar (37.5 % vs 38.3 %).

The FRESCO-2 trial met its primary endpoint, OS, and its key secondary endpoint, PFS, overall showing that fruquintinib therapy resulted in a significant and clinically meaningful improvement in patients with refractory mCRC. The results are consistent with those of the prior FRESCO trial and support fruquintinib as a new treatment option in this patient population.

ERMES trial: maintenance therapy with cetuximab ± FOLFIRI

Cetuximab, a highly selective antibody against EGFR, has previously demonstrated its efficacy and safety in combination with FOLFIRI (leucovorin, fluorouracil [5-FU] and irinotecan) as first-line treatment in EGFR-expressing, RAS-wt mCRC [25]. Although maintenance therapy following anti-*EGFR* based treatment is controversial and evidence lies on three phase II studies (MACRO 2, VALENTINO, PANAMA), the phase III EREMES trial (NCT02484833) is currently investigating whether a maintenance with cetuximab monotherapy after FOLFIRI plus cetuximab induction is a valid choice in RAS/BRAF-wt mCRC. Initial results were presented by Armando Orlandi at this year's ESMO meeting [26].

In the ERMES study, it was investigated whether cetuximab alone (arm B, given until progression or cumulative toxicity) after eight cycles of FOLFIRI plus cetuximab results in a non-inferiority when compared with continuous FOLFIRI plus cetuximab (arm A, given until progression or cumulative toxicity) in untreated RAS/BRAF-wt mCRC patients who were randomized 1:1. Co-primary endpoints of this study were PFS for the modified per-protocol (mPP) population (treated beyond cycle 8) per blinded independent central review (BICR) and safety in term of incidence of G3-4 AE. Secondary endpoints included PFS in the modified intention-to-treat (mITT) population (who received at least one cycle of treatment), OS in the mPP and mITT populations, ORR, and quality of life [27].

A total of 606 patients were randomized between May 2015 and March 2020; a drop-out rate of 40 % left the mPP population at only 337 patients (arm B, n = 183; arm A, n =154;). With a median follow-up of 22.3 months, the median PFS of the mPP population failed to demonstrate a non-inferiority for maintenance therapy with cetuximab monotherapy (arm B, 10.0 months vs arm A, 12.2 months; HR, 1.30; 95 % CI, 1.03-1.64; p = 0.43). To note, in the mPP population, the median PFS of patients with right-sided primary tumor location showed a significant benefit of continuous FOLFIRI plus cetuximab (arm B, 8.29 months vs arm A, 11.73 months; HR, 2.07; 95 % CI, 1.20-3.57; p = 0.007). In the mITT population, median PFS was 9.01 months versus 10.72 months, respectively (HR, 1.1; 95 % CI, 0.92-1.31; p = 0.305). The median OS was 36.64 months in arm B versus 30.76 months in arm A in the mPP population (HR, 0.81; 95 % CI, 0.80-1.09; p = 0.157), and 31.09 months vs 25.36 months in the mITT population (HR, 0.9; 95 % CI, 0.72-1.12; p = 0.327). In the mPP population, the ORR was higher in arm B (71.6 %; 95 % CI, 64.5-78.0, including 8.8 % of patients with a CR) compared to arm A (67.5 %; 95 % CI, 59.5-74.9, including 10.5 % of patients with a CR).

Grade 3-4 adverse events - the co-primary endpoint - occurred in 39.9 % of patients in arm B and 44.2 % of patients in arm A in the whole treatment period. The most frequent grade 3-4 AEs were skin disorders (18.0 % in arm B vs 20.1 % in arm A), a decreased neutrophil count (9.8 % vs 14.9 %) and diarrhea (8.2 % vs 11.0 %).

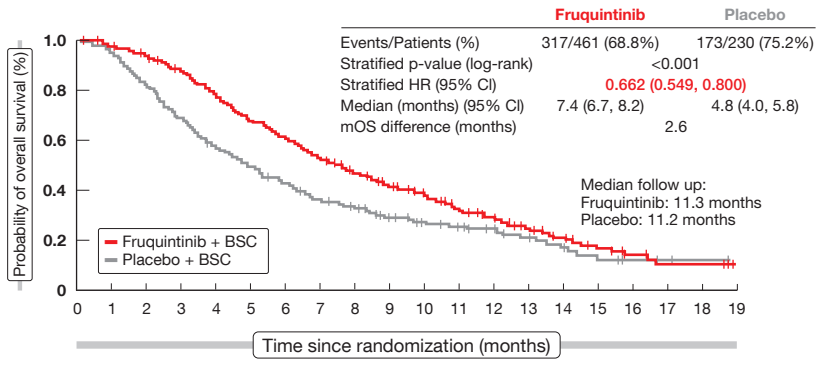

Figure 3: Overall survival according to treatment received in der FRESCO-2 study (ITT population).

The EREMES trial failed to demonstrate non-inferiority of the maintenance therapy with cetuximab monotherapy, but the results may have been negatively influenced by the unexpectedly high dropout rate. Nevertheless, the OS analysis of the mPP and mITT populations showed promising results still supporting the hypothesis of a de-escalation therapy with cetuximab monotherapy as an option for selected RAS/BRAF-wt CRC patients. In this way, the pre-planned translational research on tissue sample and liquid biopsies with NGS is ongoing.

Resistance alterations in BRAF V600E-mutated mCRC

The *BRAF* V600E mutation is associated with a poor prognosis for patients with mCRC and the inhibition of BRAF alone has limited efficacy due to the pathway reactivation through EGFR signaling. In this context, the BEACON trial (NCT02928224), evaluating the triple combination of encorafenib (a BRAF inhibitor) plus binimetinib (a MEK inhibitor) plus cetuximab (a EGRF inhibitor), demonstrated an improved OS compared to doublet therapy (encorafenib + cetuximab) or standard chemotherapy (FOLFIRI + cetuximab or irinotecan + cetuximab) in patients with previously treated *BRAF* V600E-mutated mCRC [28]. To identify genomic alterations possibly mediating treatment resistance, plasma samples were collected from study participants at baseline and at the end of the treatment (EOT). Circulating tumor DNA (ctDNA) was analyzed by genomic profiling using GuardantOMNITM. Somatic alterations, including non-synonymous mutations, amplifications, and rearrangement, as well as other patient-level genomic alterations, were evaluated to characterize acquired alterations [29]. At ESMO 2022, Kopetz et al. presented the results of this genomic post-hoc analysis [30].

To investigate mechanisms of resistance, paired baseline and EOT samples were evaluated from 320 out of the 665 patients (48.1%) enrolled in the BEACON trial. The most frequently acquired resistant alterations in both, the triplet therapy (encorafenib + binimetinib + cetuximab) and the doublet therapy (encorafenib + cetuximab), were mutations in KRAS (40.2% and 44.6%), NRAS (25.0% and 36.6%) and amplification of MET (19.6% and 17.0%) compared with the control arm (FOLFIRI plus cetuximab or irinotecan plus cetuximab, [0%, 3.2% and 0%], respectively). MAP2K1 (MEK1) mutations were observed in more doublet-treated patients than triplet-treated patients (16.1% vs 3.6%; $p<0.01$). At least one of the above-mentioned mutations, and/or MET, KRAS, BRAF, and IGFR1 per patient, was found in patients treated with triplet-, doublet-, or control-treated patients (62.5%, 63.4 , 7.4 %, respectively).

This post-hoc analysis of the BEACON trial showed that in patients with previously treated *BRAF* V600E-mutated mCRC, MAPK pathway reactivation is a common mechanism of resistance following inhibition of BRAF and EGFR ± MEK inhibition. Moreover, enhanced receptor signaling was more prevalent in the triplet arm, whereas acquired mutations in RAS-MEK signaling were more prevalent in the doublet arm. ■

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Novel early clinical approaches in solid tumors

CLDN6 CAR-T cell therapy - Encouraging results

Chimeric antigen receptor (CAR)-T cells have proven to be effective in the clinic for patients with malignant B-cell tumors but their application for solid tumors is challenging [1]. BNT211 is a novel therapeutic approach which comprises two components: CAR-T cells targeting the Claudin 6 (CLDN6) and a CLDN6-encoding CAR-T cell amplifying RNA vaccine (CARVac) [2]. On June 23, 2022, BNT211 has received priority medicine (PRIME) designation by the European Medicines Agency (EMA) for the third- or later-line treatment of testicular germ cell tumors [3]. The PRIME status was based on positive preliminary data from the ongoing BNT211-01 phase I/II study (NCT04503278) [4]. Updated data from this study were presented at ESMO 2022 [2].

The trial followed a 3+3 dose escalation design with bifurcation **(Figure 1)**. Patients with an ECOG performance status of 0 or 1, CLDN6-positive tumors (≥50% of tumor cells CLDN6-high [II/III+]) and no other treatment option were eligible. In part I of the phase I dose escalation study, patients received a dose of 1x107 CLDN6 CAR-T cells (dose level [DL] 1; n=3) or 1x108 CAR-T cells (DL 2, n=6) as monotherapy. In part two of the phase I trial, four patients received the DL 1 of the CAR-T cells plus CARVac and nine patients received DL 2 plus CARVac. Apheresis and CAR-T cell manufacturing were performed at Day -18 or earlier. Patients underwent lymphodepletion on Day -5 to Day -3. CAR-T cell infusion was done on Day 1 and dose-limiting toxicity (DLT) was then assessed for 28 days. Patients who also received the vaccine were administered the first dose on Day 4; the first five CARVac treatments occurred every three weeks (Q3W) according to a one intra-patient dose escalation schemata, followed by a treatment every six weeks thereafter. Of the nine patients who received DL 2 plus CARVac, one patient had 50% lymphodepletion and two patients had no lymphodepletion.

The updated data read-out (data cut-off dates: June 15, 2022, for safety and August 16, 2022, for efficacy) included 22 patients (21 evaluable for efficacy) with a median age of 46 years, most patients being male (n=15). This heavily pretreated population received a median of four (range, 3-9) prior lines of therapy. All patients showed a robust dose-dependent CAR-T cell expansion. A long-term persistence of CAR-T cells was detected for more than 100 days post CAR-T cell infusion, with a few patients showing a persistence for ≥200 days. Efficacy assessment showed a best overall response rate (ORR) of 33% (7/21) and a disease control rate (DCR) of 67% (14/21), with one patient having a complete response (CR), six patients with a partial response (PR) and seven patients with a stable disease (SD). Testicular cancer patients showed particularly encouraging responses at DL 2 (ORR 57%, DCR 85%; n=7).

DLTs were observed in two patients, including one treated at DL2 monotherapy (prolonged pancytopenia after lymphodepletion) and one at DL2 plus CARVac (hemophagocytic lymphohistiocytosis before start of CARVac). A total of 13 patients experienced treatment-emergent adverse effects (TEAEs) of grade 3 or higher suspected to be related to the investigational agents. These TRAEs consisted mainly of lymphodepletion or asymptomatic elevations of lipase and transaminases. Cytokine release syndrome (CRS) was observed in ten patients (45%) and associated with high interleukin-6 (IL-6) levels. All instances of CRS were grade 3 or less and manageable with tocilizumab, if needed. The only reported case of grade 1 immune effector cell-associated neurotoxicity syndrome quickly resolved. A total of eight patients died due to disease progression.

The new dataset from the BNT211-01 study underscored the promising previously reported results obtained with the combination of CLDN6 CAR-T cells and CARVac. Moreover, the process of CLDN6 CAR T-cell generation was switched to an automated process and the recommended phase II dose escalation is still ongoing.

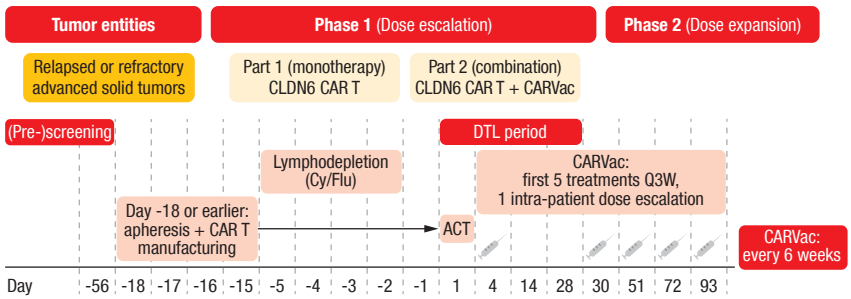

Figure 1: BNT211-01 trial design

GDFATHER-1 trial of visugromab

Growth and differentiation factor 15 (GDF-15), a TGF-β superfamily member, has been associated not only with anorexia but more importantly also with potent local immunosuppression under physiological and pathophysiological conditions [5]. GDF-15 is overexpressed by several solid tumors, associated with the resistance to anti-PD1/PD-L1 treatments and high levels have been linked to a limited survival of the affected patients. Once secreted by the tumor, GDF-15 prevents T-cell migration into the tumor and suppresses T-cell function as well as the adaptive immune response in the tumor microenvironment [6, 7]. The first-in-human trial GDFATHER-1 (NCT04725474) investigated the GDF-15 neutralizing antibody visugromab - formerly known as CTL-002 - combined to an anti-PD1 immune checkpoint inhibitor (ICI) in patients with relapsed or refractory tumors; the final results were presented at this year's ESMO meeting [7].

Eligible patients with an advanced-stage mixed solid tumor in last-line treatment (including those relapsed/refractory to prior anti-PD1/PD-L1 therapy) received escalating doses of visu-

gromab intravenously (IV) (0.3-20 mg/kg, Q2W) in this 3+3 phase I trial in a "monotherapy-followed-by-combination"- design: visugromab was first given as monotherapy and thereafter combined with the anti-PD-1 ICI nivolumab. Biopsies were taken consecutively at Day 0, 14 (monotherapy) and 28 (combination). The analysis of the tumor material showed increased CD4+ and CD8+ T-cells in most of the patients.

At enrollment, patients already received a median of 4.3 prior lines of treatment. The number of Ki67+ and GranzymeB (GrzB)+ T-cells was increased 2-fold in 55 % and 50 % of evaluable patients, respectively, demonstrating a proof-of-mechanism of this study design. Regarding clinical activity, the ORR according to RECIST v1.1 reached 17 % for DL 3-5, with six of 18 patients (33.3 %) experiencing a significant clinical benefit. Three of those patients (50 %), who received up to six lines of prior therapy, achieved a confirmed PR with up to twelve months duration (one patient was still on treatment at the time of analysis). The other three patients had a long-term disease stabilization (SD), with one moving to a PR after local irradiation of a single progressive lesion. The tumor regression rate for DL 3-5 and DL 4-5 were 22 % and 25 %, respectively. Additionally, two potential predictive biomarkers were identified and will be further investigated in a biomarker-selected cohort.

Regarding safety, the combination of visugromab and nivolumab showed an excellent tolerability, with no DLT and grade ≥4 AEs. The pharmacodynamic analysis confirmed the complete neutralization of GDF-15.

In conclusion, visugromab monotherapy followed by a combination with nivolumab has demonstrated a clinically meaningful tumor response, as well as an excellent safety and tolerability in last-line anti-PD1/PD-L1 relapsed/refractory solid tumor patients. To validate those primarily encouraging results, visugromab is currently in phase II development with signal-finding studies in five indications, a predictive biomarker-selected cohort and in the neoadjuvant setting.

BI 907828: an MDM2-p53 antagonist

The tumor suppressor protein p53 is activated upon various stress signals and mediates downstream cellular responses, including amongst others cell-cycle arrest, DNA repair, senescence, and apoptosis [8]. MDM2 is a negative regulator of p53; of note, the auto-regulatory feedback loop between MDM2 and p53 is essential to keep a low p53 level and to limit aberrant p53 activity [8, 9]. Approximately 5-7 % of tumors present with MDM2 amplifications [10]. By binding to free MDM2, the BI 907828 acts as a highly potent, orally available antagonist of the interaction between MDM2 and p53 thereby restoring p53 function [11] . Preclinical data in TP53 wild-type, MDM2-amplified dedifferentiated liposarcoma (DDLPS) patient derived xenograft models have already shown the antitumoral activity of BI907828 [11]. Preliminary data of the ongoing phase Ib (dose expansion) study (NCT03449381) were presented at ESMO 2022 [12].

Currently, patients with TP53 wild-type (wt), MDM2-amplified advanced solid tumors are recruited to cohort I (sarcomas, any line) or cohort II (NSCLC, gastric-, urothelial-, pancreatic- and biliary tract-cancers, 2nd and later lines). As of July 2022, 107 patients have received BI907828 orally across all dose levels; among them, 39 patients had DDLPS, 16 patients had well-differentiated liposarcoma (WDLPS), and four patients had biliary tract cancer. These heavily pretreated patients (median of 2 prior treatment lines; range, 0-11) had a median age of 57 years, were predominantly male (55.1 %), Caucasian (70.1 %) and had a very good performance status (ECOG 0, 58.9 %).

The maximum tolerated dose of BI 907828 was 60 mg Q3W; the recommended dose for expansion was selected as 45 mg, Q3W. BI907828 showed a long half-life of around 30 to 60 hours; a linear correlation between the target engagement biomarker GDF-15 and patient exposure was detected, too (70-fold increase of GDF-15 over baseline). Among the 94 evaluable patients included in the efficacy analysis, 79 achieved at least a stable disease (DCR, 84.0 %). In total, twelve patients had a confirmed PR, most of them were MDM2-amplified (ORR, 12.8 %) **(Figure 2)**. Overall, all 16 WDLPS-patients achieved at least a stable disease (DCR, 100 %), with nine patients receiving study treatment for at least nine months. Of the 36 DDLPS-patients, 32 achieved at least stable disease (DCR, 88.9 %) and the preliminary median PFS was 8.1 % (13 patients are still on treatment).

Nausea (in 74.1 % of patients) was the most common treatment-related adverse event (TRAE) any grade, thus, antiemetic prophylaxis or treatment was implemented. The most frequent grade ≥3 TRAEs experienced by patients receiving the recommended dose of 45 mg were neutropenia (20.3 %), thrombocytopenia (18.6 %) and anemia (10.2 %).

In this phase Ib study, the MDM2-p53 antagonist BI907828 demonstrated a manageable safety profile and encouraging preliminary antitumor activity in patients with solid tumors. The efficacy was particularly promising in patients with MDM2-amplified DDLPS, WDLPS, and biliary tract cancer. An ongoing phase II/III study (Brightline-1, NCT05218499) is currently investigating the safety and efficacy of BI 907828 compared to doxorubicin as first-line treatment for patients with advanced DDLPS.

Antitumor activity of B7-H3 DXd antibody-drug conjugate

The B7 homologue 3 (B7-H3) - a transmembrane protein belonging to the B7 family - is frequently overexpressed in many tumors and associated with a poor prognosis [13-15]. DS-7300 is an antibody-drug conjugate (ADC) comprising

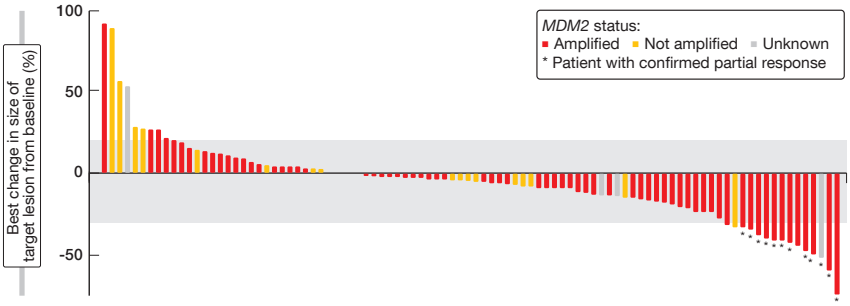

Figure 2: Waterfall-plot indicating the best change in size of target lesions from baseline

a humanized anti-B7-H3 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker [16]. Part I of the phase I/II DS7300-A-J101 study (NCT04145622) previously showed that DS-7300 was well tolerated with early signs of antitumor activity [17]. At ESMO 2022, extended follow-up data for a larger cohort of patients with selected tumor types were presented [18].

As of June 30, 2022, 147 pretreated patients received DS-7300 (IV, Q3W) at doses of 4.8 mg/kg to 16.0 mg/kg in the dose escalation part I of this study. In part II (dose expansion), 66 eligible patients with advanced/unresectable or metastatic solid tumors (unselected for B7-H3 expression) divided into three cohorts (cohort 1, patients with esophageal squamous cell cancer [ESCC]; cohort 2, patients with metastatic castration-resistant prostate cancer [mCRPC]; cohort 3, patients with squamous non-small cell lung cancer [sqNSCLC]) received the DS-7300 recommended dose of 12.0 mg/kg (IV, Q3W) as monotherapy. The key primary endpoint was DLTs, serious AEs (SAEs), TEAEs and AE of interest (AESI) in the dose escalation of the study, while ORR according to RECIST v1.1, duration of response (DoR), DCR, PFS and overall survival (OS) were analyzed in the dose expansion part.

In total, 35 patients (24 %) were still on treatment at the time those results were presented, including SCLC (40 %), mCRPC (23 %), ESCC (15 %), and sqNSCLC (56 %). Most patients showed a durable disease and tumor shrinkage across all tumor types and doses analyzed **(Figure 3)**. Responses were observed in 32 % (95 % CI, 24-41).

For the SCLC subset, after a median follow-up of 4.9 months, a response was seen in 58 % (95 % CI, 33-80), the median time to response (TTR) was 1.2 months (95 % CI, NA-1.4), and the median DoR was 5.5 months (95 % CI, 2.8-NR). With respect to the mCRPC subgroup, after a median follow-up of 9.3 months, a response was measured in 33 % (95 % CI, 21-47) with 18 patients (33 %) achieving a PR; in this subgroup, the median DoR was 4.4 months (95 % CI, 2.7-NR), while seven responders remained on treatment. In the ESCC subset, after a median follow-up of 7.7 months, a response was detected in 23 % (95 % CI, 8-45) and half of the patients with post-baseline scans showed a tumor shrinkage; the median DoR was 2.8 months (95 % CI, 2.6-NR), with two responders still on treatment. After a median follow-up of 1.7 months for the sqNSCLC subset, a response was seen in 40 % (95 % CI, 5-85), with four out of five patients (80 %) having a post-baseline reduction in target lesions; the median DoR in this subgroup was 4.3 months (95 % CI, 3.1-NR) and one responder remained on treatment.

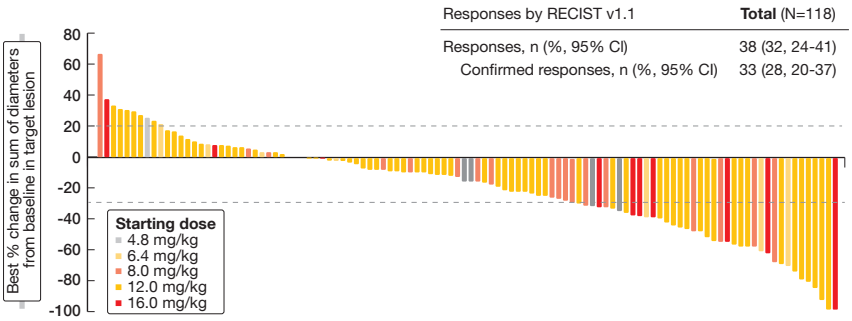

Figure 3: Waterfall-Plot indicating the best percentage of change from baseline for target lesions.

Regarding safety, the most common grade ≥ 3 TEAEs were anemia (19 %), neutropenia (4 %), nausea (3 %), pneumonia (3 %), and a decreased neutrophil count (3 %). A total of nine patients experienced interstitial lung disease (ILD) or pneumonitis, of which seven were allocated as drug-related ILD (grade 1, n = 2; grade 2, n = 4; grade 5, n = 1), and two ILD or pneumonitis events were pending adjudication.

The investigational B7-H3–directed DXd-ADC DS-7300 continues to show an encouraging antitumoral activity in heavily pretreated patients in several cancer types, including SCLC, mCRPC, ESCC, and sqNSCLC. No new safety signals were detected. These data further supported clinical development of DS-7300, including a phase II dose-optimization study in SCLC (NCT05280470), the design and current status of which was presented at ESMO 2022, too [19].

Phase I trial of IMC-F106C in selected advanced solid tumors

Immune-mobilizing monoclonal T-cell receptors against cancer (ImmTAC) are a new class of T-cell–redirecting bispecific fusion proteins that use an engineered high-affinity T-cell receptor to target any protein, including intracellular antigens, that is presented as a peptide–HLA complex on the surface of target cells. ImmTAC molecules previously showed an OS benefit in uveal melanoma (HR, 0.51) [20]. The investigational agent IMC-F106C was designed for the treatment of tumors positive for the tumor-associated antigen PRAME. This first-in-human trial evaluates the safety and efficacy of IMC-F106C in adult patients who have the appropriate HLA-A2 tissue marker and whose cancer is positive for PRAME [21]. At ESMO 2022, results from the phase I dose escalation study (NCT04262466) of IMC-F106C in patients with selected advanced solid tumors were discussed [22].

Patients with advanced solid tumors positive for HLA-A*02:01 according to central testing and PRAME as confirmed by immunohistochemistry (IHC) received IMC-F106C weekly (IV) with intra-patient dose escalation (0.3 to 320 µg) over the first three weeks. Tumor assessment took place every nine weeks. The primary endpoint was to determine the expansion dose, while the preliminary antitumor activity, pharmacokinetic and pharmacodynamic markers were analyzed secondarily.

Pharmacologically, IMC-F106C showed a strong and consistent pharmacodynamic activity at 20 µg or higher; indeed, in peripheral blood, strong interferon gamma (IFNγ) induction and high T-cell trafficking (22-fold increase) were detected. Median PRAME H-score in the efficacy population was high (90 %). Responses to IMC-F106C were observed in multiple tumor types: three out of six (50 %) uveal melanoma patients, two out of six (33 %) cutaneous melanoma patients and two out of four (50 %) serous ovarian patients showed a partial response (one of them unconfirmed). Most patients had a durable tumor response or disease stabilization, with six out of the seven observed partial responses still ongoing at the time of data presentation at ESMO 2022 and two patients showing an

ongoing PR for more than seven months. Patients with lower PRAME expression seemed to progress earlier, whereas high PRAME expression was associated with response and benefit. Moreover, out of 20 patients with available circulating tumor DNA (ctDNA), four achieved a PR with a tumor reduction greater of 50 %, including three with a clearance.

In relation to safety, IMC-F106F was well tolerated. The most reported AEs (all grades) were pyrexia (56 %) and cytokine release syndrome (49 %), the most frequent grade ≥3 AE being lymphopenia (15 %). No treatment-related discontinuation or grade 5 AE were reported.

IMC-F106C showed durable responses across multiple tumor types with a manageable safety profile. The dose escalation continues, while combinations with chemotherapy and checkpoint inhibitors are planned.

ACTIVATE trial: etigilimab combined to nivolumab

TIGIT is an inhibitory immunoreceptor that is upregulated by immune cells, like activated T-cells and natural killer (NK) cells, as well as regulatory T-cells in several cancer entities [23]. Etigilimab (MPH313) is a FCγR competent, humanized anti-TIGIT IgG1 monoclonal antibody that inhibits its interaction with PVR (poliovirus receptor) and therefore inhibits downstream signaling. In an early clinical trial (phase Ia/b), etigilimab showed an acceptable safety profile and antitumor activity either as monotherapy or in combination with nivolumab [24]. At this year's ESMO meeting, an interim biomarker analysis of the ACTIVATE study (NCT04761198) combining etigilimab (etig) with the anti-PD1 nivolumab (nivo) was presented [25].

In this open-label phase Ib/II basket study, the efficacy, safety, tolerability, and pharmacokinetics/pharmacodynamics of etig plus nivo have been evaluated in selected locally advanced or metastatic solid tumors. This study included a biomarker monitoring to follow the activation of immunological modulators by flow cytometry from peripheral blood; additionally, plasma samples were also analyzed for cytokine changes and ctDNA. At baseline, tissue samples (FFPE) were collected to determine PD-L1 expression by cIHC or multiplex immune-fluorescence (F-IHC) and mRNA seq.

No objective responses were observed in PVR low and TIGIT negative tumors patients. On the contrary, patients showing a TIGIT-high tumor expression had a clinical benefit (58 % in TIGIT-high patients vs 33 % in TIGIT-low patients) and ORR (33 % vs 10 %, respectively). Moreover, in patients with a clinical benefit, a robust target engagement was observed though increases in proliferating CD4 and CD8 effector memory populations, as well as NK cells and PD-1-positive T-cells. Furthermore, an increase in IFNγ was observed in NK cells and CD4 EM T-cells as well as an elevation of the IL-2 production in CD4 EM T cells. Tissue biomarker (PVR, CD226/CD8) expression at baseline was associated with tumor shrinkage (2 patients with a CR and 5 patients with a PR). A decrease of ctDNA at five to six weeks post-treatment correlated with an objective response.

These interim biomarker data from Etig plus nivo combination therapy brought evidence of a dual TIGIT/PD-1 blockade and was associated with increased levels of proliferating and cytokine producing T-cells in circulation. Furthermore, ctDNA reductions correlated with clinical response. Altogether, these preclinical data support further evaluation of PVR, TIGIT and CD226 as potential biomarkers for this therapeutic combination. ■

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Expert interviews at ESMO 2022

Stacey A. Cohen explains if ctDNA can detect MRD and predict recurrence in patients with colon cancer in a real-world setting, if it should be used in daily clinical practice or as a surveillance biomarker in stage II ctDNA-negative colon cancer patients. Moreover, she depicts how the treatment of patients with colon cancer might change in the foreseeable future.

A congress digest specifically dedicated to lung cancer is availbable, too. Check out the ESMO lung cancer report including interviews with highly esteemed experts.

Marina Garassino comments on checkpoint inhibition in lung cancer patients with oncogenic drivers, highlights novel developing therapies in EGFR-mutant NSCLC patients with resistance to TKIs, summarizes the most relevant findings presented at ESMO 2022 in terms of the management of patients with previously untreated, metastatic non-squamous and squamous NSCLC without EGFR/ALK alterations as well as patients with extensive-stage small-cell lung cancer; and finally discusses how artificial intelligence can be used to predict the efficacy of immunotherapy in lung cancer patients.

Noemi Reguart outlines if EGFR-directed treatment in the setting of advanced NSCLC should be based on T790M monitoring in clinical practice, outlines recent insights gained in the negative CANOPY-A trail using the anti-IL-1β antibody canakinumab after resection of early-stage NSCLC and summarizes the current treatment landscape in Europe with respect to small-cell lung cancer.

Gérard Zalcman discusses recent findings regarding the duration of immune checkpoint inhibitor treatment in patients with NSCLC, expectations of checkpoint inhibitor therapy in the setting of unresectable malignant pleural mesothelioma and how the treatment of patients with malignant pleural mesothelioma might be further optimized based on molecular findings.

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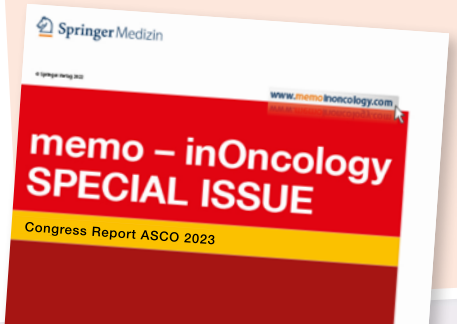

Forthcoming Special Issue

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 multidisciplinary approach to cancer treatment and care. Again, lung cancer will be at the heart of this special issue.

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