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Preface

Dear Colleagues,

After 2 years of the COVID-19 pandemic, the Annual Meeting of the American Society of Clinical Oncology (ASCO), was held in Chicago, USA, and virtually from 3rd–7th June 2022. As always, the very much-anticipated event brought leading experts from across the globe together to learn and discuss the groundbreaking updates and scientific advancements which were covered in more than 2,000 abstracts, along with 85 livestream sessions, and more than 2,500 poster presentations.

This memo inOncology issue promises to make for stimulating reading by offering a summary of studies investigating new agents or combinations in multiple solid tumor entities including recurrent or metastatic nasopharyngeal cancer where vast energy has been invested in developing not only effective 1L treatment options but also investigating new agents or combinations with immune checkpoint inhibitors for patients who have failed two or more lines of systemic therapy.

Moreover, innovative combinations in esophageal squamous cell carcinoma outlined in this report yield promising efficacy and safety, especially for those patients with advanced or metastatic disease whose overall survival was limited until now to less than a year after standard 1L chemotherapy.

Since the prevalence of gastric and gastrointestinal junction cancer (G/GEJC) increased in the last years, we are also dedicating a chapter to updated analyses and novel therapeutic options including an autologous chimeric antigen receptor (CAR) T-cell therapy that suggests promising efficacy and a manageable safety profile in previously treated patients. Eager awaited are results from ongoing studies with bemarituzumab, a first-in-class monoclonal antibody against FGFR2b having potential to inhibit tumor proliferation, to change the tumor microenvironment, sensitizing it to PD-1 inhibitors, and to enhance the antibody-dependent cellular cytotoxicity.

Future treatment strategies in advanced or metastatic colorectal cancer (mCRC) especially in *RAS* and *BRAF* wild-type but also in *KRAS*-mutated mCRC are depicted, supporting e.g. panitumumab plus mFOLFOX6 as 1L therapy in patients with *RAS*-WT and left-sided mCRC. Here, CAR-T cell therapies start to find their way into the armamentarium of treatment options, too.

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Last but not least, this issue gives up-to-date clinical insights in advanced unresectable or metastatic hepatocellular carcinoma with special interest on quality of life, an outcome becoming more and more important and relevant to explore.

Once again, this year's meeting under the motto "Advancing Equitable Cancer Care Through Innovation" ensured that, based on the intensive exchange of healthcare professionals who stay at the cutting edge of research, we are getting closer to a practice that will further improve the landscape of care for patients with cancer all over the world.

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Novel agents or combinations in recurrent or metastatic nasopharyngeal cancer

Nasopharyngeal cancer (NPC) is a rare malignancy with an incidence of approximately 133,000 annually worldwide, resulting in about 80,000 deaths per year [1]. Whereas early-stage and locally advanced NPC have a good prognosis, treatment of recurrent or metastatic nasopharyngeal cancer is a challenging; it is thus associated with a poor prognosis, especially in patients who have failed two or more lines of systemic therapy, with a median progression-free survival (mPFS) of seven months and median overall survival (mOS) of 22 months [2].

Tislelizumab as first-line treatment option

Tislelizumab is a humanized monoclonal antibody directed against programmed cell death protein 1 (PD-1), engineered to minimize binding to the Fc receptors for IgG (FcγR) on macrophages to evade antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and potential anti PD-1 resistance [3, 4]. Recent phase 2 and 3 studies have shown that tislelizumab was efficacious in the management of multiple solid tumor entities [5-8].

RATIONALE-309 is a randomized, double-blind phase 3 study (NCT03924986) which analyzed 263 patients with recurrent or metastatic NPC; those patients were randomly assigned 1:1 to receive tislelizumab (200 mg intravenously [IV]) or placebo on Day 1, plus gemcitabine (1 g/m², IV, Day 1, Day 8), plus cisplatin (80 mg/m², Day 1) every three weeks (Q3W) for 4–6 cycles, followed by tislelizumab or placebo Q3W until disease progression, unacceptable toxicity, or withdrawal. Patients in the placebo arm could crossover to tislelizumab monotherapy if disease progression was

confirmed by the independent review committee (IRC) and the investigator considered it clinically beneficial. IRC-assessed PFS was the primary endpoint and IRC-assessed objective response rate (ORR), as well as duration of response (DoR), OS, investigator assessed PFS, time to second objective disease progression (PFS2) and safety were the secondary endpoints.

The results of RATIONALE-309 trial were consistent with interim data [9] and demonstrated a clinically meaningful improvement for tislelizumab plus chemotherapy versus placebo plus chemotherapy (mPFS, 9.6 vs. 7.4 months; HR, 0.50; 95 % CI, 0.37-0.68) after a median follow-up of 15.5 months **(Figure 1)** [10]. To note, the PFS benefit observed was independent of PD-L1 expression, as an improvement in PFS for tislelizumab plus chemotherapy versus placebo plus chemotherapy was observed in all subgroups (< or ≥ 1 % and < or ≥ 10 %). Additionally, a numerical OS benefit was observed in the investigational arm with mOS not yet reached in the tislelizumab combination arm and 23 months for the chemotherapy plus placebo arm (HR, 0.60; 95 % CI, 0.35-1.01). For patients treated with tislelizumab plus chemotherapy, median PFS2 was not yet reached compared to 13.9 months for those treated with placebo plus chemotherapy (HR, 0.38; 95 % CI, 0.25-0.58). Moreover, gene expression profiling identified three gene expression clusters (cold, medium, hot) as potential biomarkers for efficacy. A hot tumor immune profile, characterized by the highest expression of immune cells in the tumor microenvironment (including dendritic cells) was associated with a greater PFS advantage versus cold tumors for tislelizumab plus chemotherapy. The safety profile of tislelizumab plus chemotherapy was manageable and as expected based on previously reported interim analysis. The following treatment emergent adverse events (TEAEs) grade ≥3 were experienced by at least 20 % of patients: decrease in white blood cell count, anemia, decrease in neutrophil count, neutropenia, decrease in platelet count, and leukopenia.

In this study, the combination of tislelizumab and chemotherapy provides a consistent, clinically meaningful improvement in PFS, accompanied by PFS2 and OS benefits, compared with placebo plus chemotherapy. Thus, the authors concluded that this combined therapy has the potential to become a new standard-of-care 1L treatment for patients with recurrent or metastatic NPC.

Anti-angiogenic therapy: synergistic activity with immune checkpoint inhibitors

In patients with recurrent or metastatic immune checkpoint inhibitor (ICI)-resistant nasopharyngeal cancer, ICI given in combination with an antiangiogenic therapy might lead to a potential synergistic effect [11]. Camrelizumab – a programmed cell death 1 (PD-1) inhibitor – has been investigated as treatment of various malignancies and has demonstrated a significantly improved OS or PFS when administered in combination with chemotherapy in phase 3 trials among patients with advanced or metastatic esophageal squamous cell carcinoma [12] or NPC [13]. Famitinib – a receptor tyrosine kinase inhibitor – showed a prolonged PFS in refractory patients with metastatic colorectal cancer when administered as monotherapy [14], and a potent and enduring antitumor activity when combined with camrelizumab in patients with advanced or metastatic renal cell carcinoma [15].

An open-label, multi-center, phase II basket trial (NCT04346381) evaluated the use of camrelizumab plus famitinib for the treatment of recurrent or metastatic, ICI-resistant NPC [16]. Patients who met inclusion criteria - histologically confirmed recurrent or metastatic NPC (non-keratinizing carcinoma, WHO type II-III), who had been treated with platinum-based chemotherapy and ICIs (≤2 lines of systemic treatment) – were enrolled to receive camrelizumab (200 mg intravenously [IV] Q3W) and famitinib (20 mg orally, once daily). The primary endpoint was the ORR according to RECIST v1.1, while the DoR, disease control rate (DCR), time to response (TTR), PFS, OS and safety were secondarily analyzed.

Data reported at ASCO 2022 showed that of the 15 patients enrolled in this study, twelve (80 %) had received a prior 1L therapy and three (20 %) patients a second-line treatment. All patients were pretreated with anti-PD-1/PD-L1 immunotherapies (toripalimab, n = 9; tislelizumab, n = 4; sintilimab, n = 1; pembrolizumab, n = 1). After a median follow-up of 6.3 months, the ORR reached 33.3 % (95 % CI, 11.8-61.6), five patients had a confirmed partial response (PR), seven patients a stable disease (SD), two patients a progressive disease (PD) and one was not evaluated. The DCR was 80.0 % (95 % CI, 51.9-95.7), the median DoR was 4.2 months (95 % CI, 2.1-not reached [NR]), the median PFS was 6.3 months (95 % CI, 4.1-NR), while the median OS has not been reached.

The most common grade ≥3 treatment emergent adverse events (TEAEs) were a decreased platelet count, a decreased neutrophil count and a palmar-plantar erythrodysaesthesia syndrome (13.3 % each). In total, eleven patients had to interrupt, and one patient had to discontinue the treatment due to TRAEs. Moreover, five patients had serious TRAEs (grade 2 platelet count decreased, grade 2 pharyngeal necrosis, grade 2 pulmonary tuberculosis, grade 3 left ventricular dysfunction, grade 3 pharyngeal hemorrhage; 1 patient each).

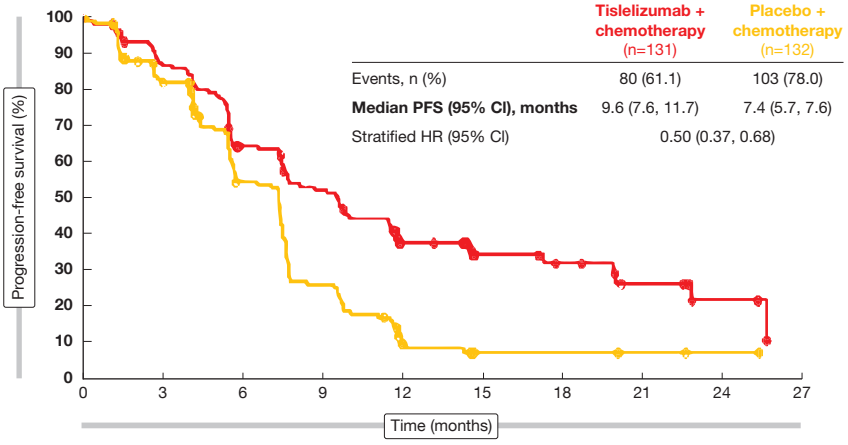


Figure 1: Updated PFS analysis of tislelizumab plus chemotherapy versus placebo plus chemotherapy.

In summary, the combination of camrelizumab plus famitinib, due to the encouraging antitumor activity, may be a novel efficient and safe alternative therapeutic approach for difficult to treat NPC and support further investigation.

Camrelizumab combined to apatinib

Apatinib is a VEGFR2 tyrosine kinase inhibitor, which has been shown to optimize the tumor immunosuppressive microenvironment and therefore to potentiate the antitumor effect of anti-PD-1/PD-L1 blockade in lung cancer [17]. Previous data demonstrated that apatinib has also proven clinical efficacy in recurrent or metastatic NPC [17, 18]. Moreover, apatinib combined with camrelizumab showed promising synergistic efficacy and manageable safety in patients with advanced HCC [19].

In the phase 2 study, 26 patients with recurrent or metastatic NPC were enrolled (between January 2011 and September 2021) to receive either apatinib (250 mg, orally once daily) plus camrelizumab (200 mg, IV, Q2W) until disease progression or unacceptable toxicity [20]. The median age was 49 years (range, 33-67), most of them were male (84.6 %), the most frequent sites of metastasis were the bone (53.8 %), the lung or the liver (38.5 % each).

After a median follow up of eight months, the ORR according to RECIST version 1.1. – the primary endpoint – reached 38.5 % (10/26) - with ten patients having a PR (38.5 %). The DCR was 61.5 % (16/26), the mPFS six months and mOS was not reached yet. TEAEs were in line with those expected: six patients had grade 3 or 4 TEAEs, including anemia (7.7 %), as well as stomatitis, headache, pneumonia and myocarditis (3.8 % each).

TABLE 1 **Primary and secondary outcome measures.**

Efficacy variable, n (%)	
Complete response (CR)	0 (0)
Partial response (PR)	10 (38.5)
Stable disease (SD)	6 (23.1)
Progressive disease (PD)	10 (38.5)
Objective response rate (ORR)	10 (38.5)
Disease control rate (DCR)	16 (61.5)

The authors concluded that camrelizumab plus apatinib had promising antitumor activity and manageable toxicities in this patient population. Hence, larger randomized trails are warranted to further evaluate this new combinational therapy.

Anlotinib: inhibition of tumor angiogenesis

A novel oral tyrosine kinase inhibitor, anlotinib, has been developed to inhibit tumor angiogenesis and proliferation by targeting vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptors (PDGFR), and c-kit [21]. Anlotinib has already shown encouraging efficacy, as well as a manageable and tolerable safety profile, in a broad range of malignancies, including advanced non-small cell lung cancer [22] or sarcoma [23].

A recent prospective, single arm, phase 2 study (NCT03906058) assessed the efficacy and safety of the single agent anlotinib in patients with recurrent or metastatic NPC [24] with anlotinib being administered orally at 12 mg daily from Day 1 to Day 14 Q3W until disease progression or intolerable toxicity. Eligible patients were aged 18-70 years, had to present with a histologically confirmed recurrent or metastatic NPC, and at least one measurable lesion as well as at least two failed lines of prior systemic treatments (including chemotherapy, targeted therapy, or immunotherapy). Confirmed DCR was the primary endpoint and tumor response (confirmed ORR according to RECIST v1.1), PFS, OS and safety according to NCI-CTCAE v5.0 were the secondary endpoints.

Among 39 patients (84.6 % male) were enrolled in this study from April 2019 to March 2021; the mean age was 46.7 years (range, 20-64), 61.5 % of patients had liver metastasis, 74.4 % had previously received two lines of systemic treatments and 48.7 % had a prior anti-PD-1 immunotherapy. Anlotinib was given for a median of four cycles (range, 0.5-20). Of the 36 patients evaluated, the ORR was 22.2 % and the DCR 77.8 %, with a PR in eight patients and a SD in 20 patients. The mPFS was 5.7 months (95 % CI: 4.7-6.7) and the mOS was 23.9 months (95 % CI: 5.3-42.5).

TRAEs were manageable, with hand foot mouth syndrome (HFS) any grade occurring in 24 patients (61.5 %). Grade 3 or 4 TRAEs included hypertension (54 %), hand-foot skin reaction (23 %), mucositis (21 %), liver dysfunction (5 %) and pneumonia (3 %).

This initial data support anlotinib as a new monotherapy for patients with recurrent or metastatic NPC due to the observed survival benefit in this heavily treated population.

First-in-class bintrafusp alfa in previously treated patients

To improve the poor prognosis of patients with recurrent or metastatic NPC who progressed after platinum-based chemotherapy, the clinical activity and safety of bintrafusp alfa – a first-in-class bifunctional fusion protein that blocks PD-L1 and neutralizes TGF-α- was investigated. Bintrafusp alfa recently showed its ability to induce polyclonal neoadjuvant-specific T-cell responses in tumors in head and neck cancer [25].

A single arm, prospective phase 2 study (NCT04396886) evaluated the antitumoral activity of bintrafusp alfa in patients with heavily pretreated recurrent or metastatic NPC. Overall, 43 patients with recurrence at distant sites and not eligible for curative treatment were screened and 38 were enrolled in this trial [26]. NPC patients with histologically confirmed NPC, who had at least one prior line of platinum-based chemotherapy for recurrent disease, were subsequently treated with bintrafusp alfa (1200 mg, Q2W) until disease progression. Investigators set out to measure ORR as the primary endpoint, while survival and toxicity were the secondarily analyzed endpoints.

After a median follow-up of 14.9 months (range, 1.6 – 23.3), the confirmed ORR was 23.7 % (95 % CI, 12.4-38.8) including one patient with a CR and eight patients with a PR. In total, the median treatment duration was 1.8 months (range, 0.5-14.3 months). To note, eight patients (21.1 %) received bintrafusp alfa for more than six months and two patients (5.3 %) for more than twelve months. At Week 4, ORR was higher in patients with decreased EBV-DNA levels (40 vs. 6.3 %, p = 0.02), whereas high exosomal PD-L1 levels seemed to be predictive of worse ORR (5.3 vs. 41.7 %, p = 0.012). No associations were shown between clinical outcome and tissue PD-L1 expression or plasma TGF-β clearance. The 1-year OS

rate reached 57.5 % (95 % CI, 40.2-71.5) and the 1-year PFS rate was 23 % (95 % CI, 10.1-39.4).

Grade ≥ 3 treatment-related adverse events (TRAEs) were observed in 16 patients and most commonly included anemia (23.7 %) and secondary malignancies (10.5 %).

The authors concluded that bintrafusp alfa has promising antitumor activity in heavily pretreated recurrent or metastatic NPC patients.

SHR-1701: Expanding the clinical benefit of immune checkpoint inhibitors

The antitumor activity of ICIs in recurrent or metastatic NPC was only seen in a subset of patients [13]. In an attempt to expand the clinical benefit of ICIs to more patients, ICIs were combined to agents that block immunosuppressive pathways, like TGF-β, and investigated in advanced solid tumors [27, 28]. The purpose of the NCT04282070 study was to evaluate the efficacy and safety of SHR-1701 – a bifunctional fusion protein composed of a monoclonal antibody against PD-L1 fused to the extracellular domain of the TGF-β receptor II – in patients with recurrent or metastatic NPC.

The ongoing multicenter, open-label, phase 1b study evaluates the safety and efficacy of SHR-1701 (30 mg/kg, Day 1) monotherapy, or in combination with cisplatin (80 mg/m², Day 1) and gemcitabine (1000 mg/m², Day 1 and Day 8), or in combination with albumin-paclitaxel (260 mg/m², Day 1) in 3-week cycles in patients with recurrent or metastatic NPC until confirmed progression, unaccepted toxicity or patient withdrawal [29]. The primary endpoint for this study was safety. This study reports on an analysis of patients who failed previous platinum-based chemotherapy (Arm 1) or both platinum-based chemotherapy and anti-PD-1/PD-L1 antibody treatment (Arm 2). All NPC patients included in the analysis had stage IVb disease and metastatic lesions. The primary endpoint concerned safety, while the secondary endpoints included ORR, DoR, DCR, PFS and OS.

Among the 56 eligible patients who were enrolled (Arm 1, n = 30; Arm 2, n = 24), 51.8 % (Arm 1, n = 13; Arm 2, n=16) had received ≥ 2 prior lines of therapy. Grade ≥ 3 TRAEs occurred in ten patients (18.5 %), the most frequent being anemia (7.4 %) and hemoptysis (3.7 %). Only two patients (3.7 %) discontinued study treatment due to TRAEs (peripheral nerve injury and epistaxis, 1 patient each), ten patients (18.5 %) had dose delay because of AEs and Five patients (9.3 %) experienced grade ≥ 3 investigator reported immune related AEs (irAEs). Moreover, one death from unknown cause, not assessable SHR-1701, was reported.

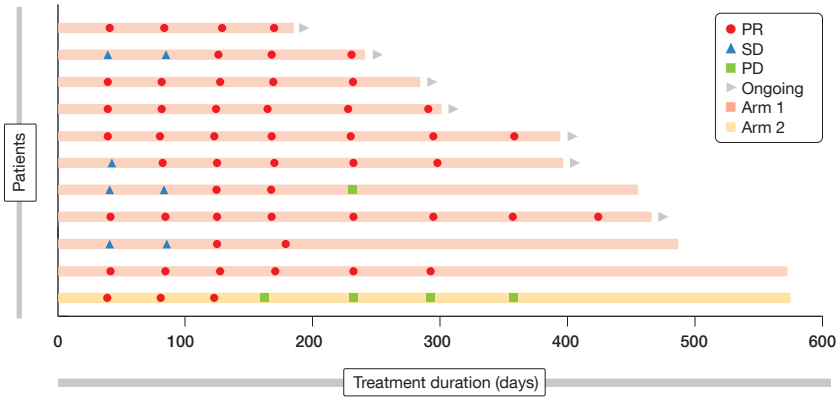


Figure 2: Treatment duration and response.

At data cutoff, the ORR reached 33.3 % (95 % CI, 17.3-52.8) in Arm 1 and 4.2 % (95 % CI, 0.1-21.1) in Arm 2, while the DCR was 53.3 % (95 % CI, 34.3-71.7) and 25.0 % (95 % CI, 9.8-46.7), respectively. Response was still ongoing in nine patients (Arm 1) and none in Arm 2 **(Figure 2)**. The median DoR was not reached (Arm 1) or 4.1 months (Arm 2), while the median PFS reached 5.3 months (95 % CI, 1.3-not reached) in Arm 1 and 1.4 months (95 % CI, 1.3-2.7) in Arm 2. The median OS was not reached in both arms, but the 12-month OS rate was 79.9 % (95 % CI, 53.2-92.3) and 71.9 % (95 % CI, 47.6-86.4), respectively.

Overall, SHR-1701 showed a tolerable safety profile combined with good efficacy, leading the authors to conclude that it is a promising new antitumor treatment for patients with recurrent or metastatic NPC who have failed prior platinum-based chemotherapy.

Dual immune checkpoint blockade for advanced NPC

Combination of anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody and anti-programmed cell death 1 (PD-1) antibody is suggested to have a synergistic anti-tumor effect [30]. QL1706, a novel dual immune checkpoint blockade contains a mixture of anti-PD-1 IgG4 and anti-CTLA4 IgG1 antibodies produced by a single cell line. In the phase 1a dose escalation and expansion study (NCT04296994), patients received intravenous QL1706 at 0.3, 1.0, 3.0, 5.0, 7.5, or 10.0 mg/kg Q3W for dose escalation in an accelerated 3+3 design, whereas the dose expansion cohorts received selected doses. The aim was to define the safety, tolerability, and recommended phase 2 dose of QL1706. In phase 1b (NCT05171790), patients with advanced solid tumors were given intravenous QL1706 (5.0 mg/kg, Q3W), according to the data obtained in phase 1a, to evaluate the preliminary efficacy. Pooled analyses were conducted in the NPC cohorts receiving QL1706 (5 mg/kg). Additionally, dynamic changes of plasma EBV DNA level from baseline were determined in a part of patients during the studies [31].

As of Dec 31, 2021, a total of 110 patients with NPC were included of whom 79 (71.8 %) patients had ≥ two prior treatment lines and 48 (43.6 %) patients received previous immunotherapy. After a median follow-up of 7.7 months, confirmed overall response was reached in 27 patients (24.5 %; 95 % CI, 16.8-33.7). In immunotherapy-naive patients with one and ≥ 2 prior lines of treatment, ORR were 39.1 % (9/23) and 38.5 % (15/39), respectively. Three of 48 (6.3 %) immunotherapy-treated patients had partial response. Disease control was observed in 54 (49.1 %; 95 % CI, 39.4-58.8) patients. Median DoR reached 11.7 months (95 % CI 8.1-not estimable). Median PFS was 2.0 months (95 % CI 1.4-2.9) and overall survival data were immature. Patients with ≥ 50 % decrease in EBV DNA level on Day 43 had significantly better ORR

than those with < 50 % decrease (67 % [8/12] versus 12 % [2/17]; p = 0.0045). TRAEs were reported in 85 (77.3 %) patients. In total, 14 patients (12.7 %) experienced grade ≥ 3 TRAEs. The most common TRAEs were rash, hypothyroidism (25 [22.7 %], each), and pruritus (22 [20 %]). TRAEs leading to dose interruptions occurred in 10 (9.1 %) patients. No TRAE leading to dose discontinuation or death was reported. The immune-related TRAEs and serious TRAEs were observed in 51 (46.4 %) and eight patients (7.3 %), respectively.

Based on the impressive anti-tumor effects of QL1706 on advanced NPC, accompanied by acceptable tolerability and manageable toxicity, further investigation of QL1706 in NPC is continuing. ■

REFERENCES

1 Global Cancer Observatory. Cancer Today. Lyon France International Agency for Research on Cancer. Last assessed on June 20, 2022; Available from: https://gco.iarc.fr/today/data/factsheets/cancers/4-Nasopharynx-fact-sheet.pdf.
2 Zhang, L, et al., Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2016; 388(10054): 1883-1892.
3 Zhang, T, et al., The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother 2018; 67(7): 1079-1090.
4 Dahan, R, et al., FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis. Cancer Cell 2015; 28(3): 285-95.
5 Ye, D, et al., Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer Sci 2021; 112(1): 305-313.
6 Shen, L, et al., Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer 2020; 8(1).
7 Lu, S, et al., Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. J Thorac Oncol 2021; 16(9): 1512-1522.
8 Wang, J, et al., Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol 2021; 7(5): 709-717.
9 Yang, Y, et al., 121O RATIONALE 309: A randomized, global, double-blind, phase III trial of tislelizumab (TIS) vs placebo, plus gemcitabine + cisplatin (GP), as first-line treatment for recurrent/metastatic nasopharyngeal cancer (RM-NPC). Annals of Oncology 2021; 32: S1430.
10 Zhang, L, et al., RATIONALE-309: Updated progression-free survival (PFS), PFS after next line of treatment, and overall survival from a phase 3 double-blind trial of tislelizumab versus placebo, plus chemotherapy, as first-line treatment for recurrent/metastatic nasopharyngeal cancer. J Clin Oncol 2022; 40(suppl 36; Abs 384950).
11 Song, Y, et al., Anti-angiogenic Agents in Combination With Immune Checkpoint Inhibitors: A Promising Strategy for Cancer Treatment. Front Immunol 2020; 11: 1956.
12 Luo, H, et al., Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. Jama 2021; 326(10): 916-925.
13 Yang, Y, et al., Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2021; 22(8): 1162-1174.
14 Xu, RH, et al., Famitinib versus placebo in the treatment of refractory metastatic colorectal cancer: a multicenter, randomized, double-blinded, placebo-controlled, phase II clinical trial. Chin J Cancer 2017; 36(1): 97.
15 Qu, YY, et al., Camrelizumab plus Famitinib in Patients with Advanced or Metastatic Renal Cell Carcinoma: Data from an Open-label, Multicenter Phase II Basket Study. Clin Cancer Res 2021; 27(21): 5838-5846.
16 Chen, M-Y, et al., Camrelizumab plus famitinib in patients with recurrent or metastatic nasopharyngeal carcinoma: Data from an open-label, multicenter phase II basket study. J Clin Oncol 2022; 40(suppl 16; Abs e18031).
17 Zhao, S, et al., Low-Dose Apatinib Optimizes Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer. Cancer Immunol Res 2019; 7(4): 630-643.
18 Ruan, X, et al., Apatinib for the treatment of metastatic or locoregionally recurrent nasopharyngeal carcinoma after failure of chemotherapy: A multicenter, single-arm, prospective phase 2 study. Cancer 2021; 127(17): 3163-3171.
19 Xu, J, et al., Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): A Nonrandomized, Open-label, Phase II Trial. Clin Cancer Res 2021; 27(4): 1003-1011.
20 Mo, Y, et al., Camrelizumab plus apatinib in patients with recurrent and/or metastatic nasopharyngeal carcinoma: A single-arm, multicenter, phase 2 trail. J Clin Oncol 2022; 40(suppl 16; Abs e18025).
21 Gao, Y, et al., Anlotinib as a molecular targeted therapy for tumors. Oncol Lett 2020; 20(2): 1001-1014.
22 Zha, B, et al., Efficacy and safety of anlotinib as a third-line treatment of advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials. Oncol Lett 2022; 24(1): 229.
23 Yao, W, et al., Long-Term Efficacy and Safety of Anlotinib as a Monotherapy and Combined Therapy for Advanced Sarcoma. Onco Targets Ther 2022; 15: 669-679.
24 Cai, Q, et al., Anlotinib for patients with recurrent or metastatic nasopharyngeal carcinoma: A phase II study. J Clin Oncol 2022; 40(suppl 16; Abs e18020).
25 Redman, JM, et al., Enhanced neoepitope-specific immunity following neoadjuvant PD-L1 and TGF-b blockade in HPV-unrelated head and neck cancer. J Clin Invest 2022.
26 Chiang, C, et al., Antitumor activity of bintrafusp alfa in previously treated patients with recurrent or metastatic nasopharyngeal cancer (NPC): A single arm, prospective phase II trial. J Clin Oncol 2022; 40(suppl 16; Abst e18029).
27 Lan, Y, et al., Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-β. Sci Transl Med 2018; 10(424).
28 Strauss, J, et al., Phase I Trial of M7824 (MSB0011359C), a Bifunctional Fusion Protein Targeting PD-L1 and TGFβ, in Advanced Solid Tumors. Clin Cancer Res 2018; 24(6): 1287-1295.
29 Yang, Y, et al., A phase Ib study of SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with recurrent or metastatic nasopharyngeal carcinoma (RM-NPC). J Clin Oncol 2022; 40(suppl16; Abst 6024).
30 Rotte A., Combination of CTLA-4 and PD-1 blockers for treatment of cancer. J Exp Clin Cancer Res. 2019;38(1):255.
31 Zhao, H, et al., Efficacy and safety of QL1706, a novel dual immune checkpoint blockade containing a mixture of anti-PD1 IgG4 and anti-CTLA4 IgG1 antibodies, for advanced nasopharyngeal carcinoma (NPC): Pooled cohort data from phase 1a/1b trials. J Clin Oncol 2022; 40(suppl16; Abst 6034).

Innovative combinations in esophageal squamous cell carcinoma

Each year, esophageal cancer (EC) is responsible for more than half a million deaths worldwide. Among them, esophageal squamous cell carcinoma (ESCC) accounts for the vast majority (~ 85 %) of EC incidences [1, 2]. At diagnosis, 70 % of ESCC is unresectable [3] and the 5-year survival rate is limited (30 % - 40 %) [4]. Patients with advanced or metastatic ESCC have a poor prognosis; their overall survival (OS) after standard first-line chemotherapy is limited to less than a year [5, 6] and other treatment options are scarce.

Expanded analysis of the CheckMate 648 study

On one hand, PD-L1 overexpression has been shown to be significantly associated with poor clinical outcome in ESCC patients [7], whereas on the other

hand, the combination of chemotherapy with an immune checkpoint inhibitor (ICI) has demonstrated synergistic antitumoral activity [8]. In the CheckMate 648 study, nivolumab (NIVO) plus chemotherapy and NIVO plus ipilimumab (IPI) showed a significant better OS and a longer duration of response (DoR) compared to chemotherapy alone in therapy-naïve ESCC patients with PD-L1 expression ≥ 1 %, as well as in all randomized patients [9]. The expanded efficacy and safety analyses of Checkmate 648 were presented at this year's ASCO meeting [10].

CheckMate 648 (NCT03143153) is a global, randomized, open-label phase III study, which investigates the efficacy and safety of nivolumab (anti-PD-1) as first-line therapy in patients with unresectable, advanced, recurrent, or metastatic ESCC. A total of 970 eligible patients were randomized following a 3-arm design (1:1:1) to receive either nivolumab (240 mg, every 2nd week [Q2W] plus chemotherapy (CT, fluorouracil + cisplatin, Q4W), or nivolumab (3 mg/kg, Q2W) plus the anti-CTLA-4 ICI ipilimumab (1 mg/kg, Q6W), or chemotherapy alone until disease progression, discontinuation due to toxicity or withdrawal. The co-primary endpoints were OS and progression-free survival (PFS) according to a blinded independent central review (BICR) in patients whose tumor cells expressed ≥1 % PD-L1. The secondary endpoints included OS and PFS in all randomized patients, as well as objective response rate (ORR), time to second objective disease progression (PFS2), duration of response (DoR) and safety.

After a minimum of 12.9 months follow-up, the combination nivolumab plus chemotherapy showed a significant superior OS compared to chemotherapy alone (15.4 vs 9.2 months; unstratified HR=0.55) in patients with tumor cells PD-L1 ≥ 1 % or in all randomized patients (13.2 vs 10.7 months; unstratified HR=0.74). A PFS2 benefit (11.0 vs 7.9 months; HR=0.64; 95 % CI, 0.54-0.77) was also observed in all randomized patients. The ORR was higher in patients with tumor cell PD-L1 ≥ 1 % (53 % vs 20 %) or in all randomized patients (47 % vs 27 %) in the combination arm compared to the chemotherapy alone. Additionally, among all analyzed patient groups, a larger number of responders who received NIVO plus chemotherapy versus chemotherapy had a DoR of at least twelve months. The best percentage reduction from baseline in target lesion with NIVO plus chemotherapy is shown in **Figure 1A**.

Superior OS with NIVO plus IPI versus chemo was observed in patients with tumor cell PD-L1 ≥ 1 % (13.7 vs 9.2 months; unstratified HR=0.63) with no further enrichment in higher tumor cell PD-L1 expression subgroups; or in all randomized patients (12.7 vs 10.7 months; unstratified HR= 0.78) or related to the PFS2 (9.7 vs 7.9 months; HR=0.74) in all patients. Deep responses were observed with NIVO plus IPI compared to the chemotherapy, especially in patients with tumor cell PD-L1 ≥ 1 % (ORR, 35 % vs 20 %), while the DoR reached 11.8 versus 5.7 months, respectively (11.1 vs 7.1 months in all randomized patients). **Figure 1B** shows the best response in target lesion in this study arm.

No new safety signals were identified with both combinations (NIVO + chemotherapy or NIVO + IPI). Grade 3 and 4 treatment-related adverse events (TRAEs) with potential immunologic etiology occurred in ≤ 2 % of patients treated with NIVO plus chemotherapy and in ≤ 6 % of those who received NIVO plus IPI, with the majority of non-endocrine TRAEs being resolved in most patients following established adverse event management.

The authors concluded that these results further support NIVO plus chemotherapy and NIVO plus IPI as new 1L standard-of-care therapies for patients with advanced ESCC, especially for those having PD-L1 positive tumors.

NXCEL1311 phase III study with nimotuzumab versus placebo

As approximately half of ESCC patients overexpress the epidermal growth factor receptor (EGFR), the antitumoral activity of nimotuzumab - an novel anti-EGFR monoclonal antibody – has been investigated in several clinical studies; these trials confirmed the antiproliferative, antiangiogenic and proapoptotic activity of nimotuzumab which enhances the sensitivity of certain solid tumors to chemotherapy and radiotherapy [11-13].

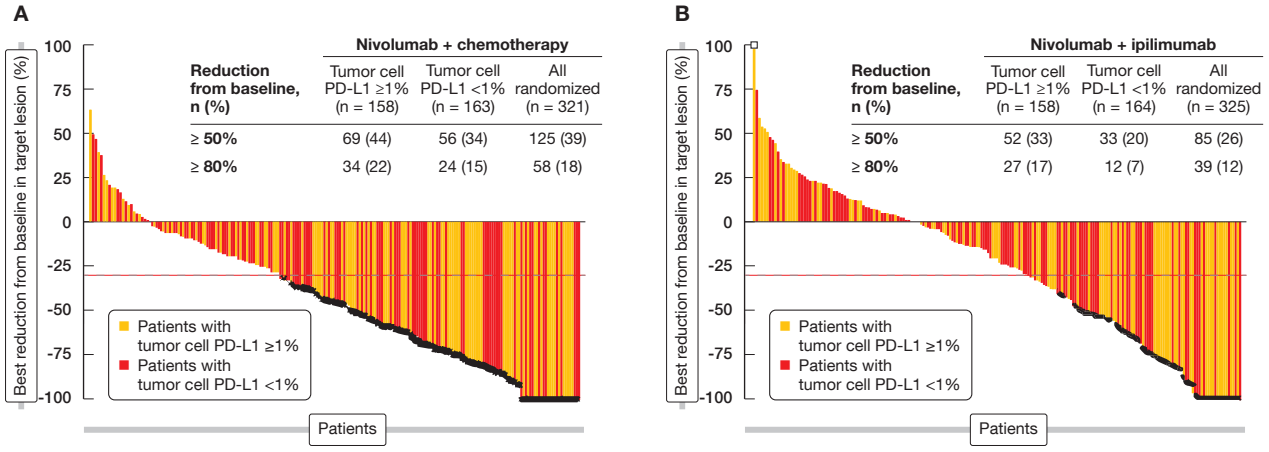


Figure 1: Target lesion reduction in CheckMate 648 study **(A)** Nivolumab plus chemotherapy **(B)** Nivolumab plus ipilimumab. *Best reduction is maximum reduction in sum of diameters of target lesions. Horizontal reference line indicates the 30 % reduction consistent with a response per RECIST v1.1. Asterix symbol represents responders. Square symbol represents percent change truncated to 100 %.*

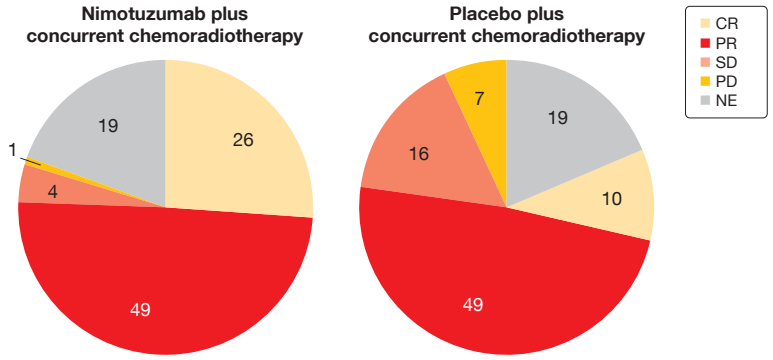


Figure 2: Response rate in both study arms of the phase III NXCEL1311 study.

A currently ongoing, prospective, randomized, double-blind, multicenter, phase III study (NXCEL1311, NCT02409186) is investigating the efficacy and safety of nimotuzumab plus concurrent chemoradiotherapy (Nimo+CCRT) versus placebo plus chemoradiotherapy (Placebo+CCRT) in unresectable, locally advanced ESCC. In total, 200 eligible patients were randomized (1:1) to receive either nimotuzumab (400 mg, IV, D1, weekly) or placebo, both in combination with concurrent chemotherapy (paclitaxel [45 mg/m², IV, D1, weekly], cisplatin [20 mg/m², IV, D1, weekly]) for seven weeks and radiotherapy [3DCRT/IMRT: 59.4 Gy/33 times]). The OS was the primary endpoint, whereas PFS, ORR, disease control rate (DCR) and quality of life (QoL) were secondary endpoints.

At ASCO 2022 meeting, the response rate (interim analysis) was presented [14]. Of the 80 evaluable patients in the Nimo+CCRT arm 26 patients achieved a complete response (CR) compared to 10 out of 82 evaluable patients in the Placebo+CCRT arm (CR-rate, 32.5 % vs 12.2 %; p=0.002); 49 patients had a partial response (PR) in both groups, while four patients reached a stable disease (SD) in the Nimo+CCRT arm (versus 16 patients in the Placebo+CCRT arm) **(Figure 2)**. The ORR was significantly higher in the investigational group: 93.8 % in Nimo+CCRT arm versus 72.0 % in Placebo+CCRT arm (p<0.001). The DCR reached 98.8 % compared to 91.5 % (p=0.064), respectively. A single factor logistic regression evaluation showed that none of the factors analyzed (age, sex, target lesion number and BMI) did affect the efficacy outcome parameters (ORR, CR and DCR).

Overall, the incidence of grade ≥3 adverse drug reactions (ADRs) with Nimo+CCRT was comparable to those observed in the Placebo+CCRT arm (11.0 % vs 10.9 %; p>0.05); the most frequent grade ≥3 ADRs being leucopenia, bone marrow inhibition, fever, infectious pneumonia, nausea, neutropenia, and nutritional anemia.

The interim-analysis demonstrated promising efficacy and safety; a follow-up of five years is planned to finally analyze the effect on OS.

Rationale 302: 2L tislelizumab versus chemotherapy

Tislelizumab - an IgG4 monoclonal antibody against PD-1 – has been designed to overcome resistance to anti-PD-1 therapy [15]. Its efficacy has been previously shown in multiple malignancies, including ESCC [16]. The primary analysis of the study data of the global phase III study RATIONALE 302 (NCT03430843) has already been presented at the ASCO 2021 meeting [17]; this trial investigated the efficacy and safety of tislelizumab compared to chemotherapy in patients with histologically confirmed unresectable advanced or metastatic ESCC, who progressed during or after a prior systemic therapy. The study met its primary endpoint as tislelizumab showed a statistically significant OS benefit compared to chemotherapy in the intent-to-treat population (ITT) (8.6 vs 6.3 months; HR=0.70; 95 % CI, 0.57-0.85; p=0.0001). At this year's ASCO meeting, the outcomes of the Asia subgroup (China, Taiwan, Japan, and Korea) of the RATIONALE 302 trial have been reported [18].

Following disease progression after first-line systemic therapy, eligible Asian patients (404 out of 512 patients, 79 %) randomized 1:1 to receive tislelizumab (n=201; 200 mg, IV, Q3W) or chemotherapy (n=203) (paclitaxel, docetaxel, or irinotecan) until disease progression, intolerable toxicity, or withdrawal. The OS in all randomized patients was the primary endpoint, whereas the key secondary endpoints comprised OS in patients with PD-L1 Tumor Area Positivity Score ≥ 10 %; other secondary endpoints included PFS, ORR, DoR, health-related quality of life and safety.

After a median follow-up of 6.9 months, tislelizumab showed a significant improvement in OS compared to chemotherapy (8.5 vs 6.3 months; HR=0.73; 95 % CI, 0.59-0.90) in the Asia subgroup, while the median PFS reached 1.5 months with tislelizumab versus 1.7 months in the comparator arm (HR=0.81; 95 % CI, 0.64-1.02). Tislelizumab-treated patients had a higher ORR (20.4 % vs 9.4 %) and a longer DoR (7.4 vs 4.0 months; HR=0.42; 95 % CI, 0.21-0.84) versus chemotherapy.

Fewer TRAEs (74.1 % vs 95. 3 %), grade ≥3 TRAEs (19.4 % vs 57.1 %), serious TRAEs (15.4 % vs 20.9 %) and a similar proportion of grade 5 TRAEs (2.5 % vs 2.6 %) were reported with tislelizumab compared to chemotherapy.

The Asia subgroup results obtained with tislelizumab are consistent with the outcomes in the overall population; thus, tislelizumab is an efficient and safe second-line therapy option for patients with unresectable advanced or metastatic ESCC.

Rationale 302: health-related quality of life

In the RATIONALE 302 study described above, the impact on health-related quality of life (HRQoL) was additionally evaluated by using the global health status/quality of life (GHS/QoL) questionnaire for measuring physical functioning, the EORTC QLQ-C30 for fatigue scores and the EORTC QLQ-OES18 for dysphagia, reflux, eating, and pain scores from screening visit through Cycle 6 or until treatment discontinuation (whichever occurred first) [19].

At Cycle 4 and Cycle 6, patients who were administered tislelizumab showed stable GHS/QoL and fatigue scores, as well as less decline in physical functioning compared to those who received chemotherapy (Cycle 4, -4.0 vs -6.6; Cycle 6, -4.6 vs -8.9, respectively)

TABLE 1 **Health-related quality of life outcomes in the RATIONALE 302 study.**

		Tislelizumab (N=256)		ICC (N=256)	
		Cycle 4	Cycle 6	Cycle 4	Cycle 6
QLQ-C30	GHS/QoL	0.0 (-2.5, 2.4)	-0.8 (-3.5, 2.0)	-5.8 (-8.8, -2.8)	-8.9 (-12.8, -4.9)
	Physical functioning	-4.0 (-6.3, -1.8)	-4.6 (-7.1, -2.1)	-6.6 (-9.3, -4.0)	-8.9 (-12.1, -5.6)
	Fatigue	3.5 (0.4, 6.6)	1.0 (-2.1, 4.2)	11.3 (7.5, 15.1)	6.4 (2.0, 10.9)
QLQ-OES18	Dysphagia	2.7 (-1.7, 7.1)	1.6 (-3.5, 6.6)	7. 7 (2.2, 13.2)	1.9 (-5.5, 9.2)
	Reflux	-2.3 (-4.6, -0.1)	-1.8 (-4.7, 1.2)	1.8 (-1.1, 4.7)	-1.1 (-5.4, 3.2)
	Eating	0.0 (-2.8, 2.8)	-0.5 (-3.6, 2.6)	2. 7 (-0.8, 6.2)	4.7 (0.3, 9.1)
	Pain	-1.6 (-3.4, 0.2)	-1.4 (-3.9, 1.0)	-1.1 (-3.6, 1.3)	0.2 (-3.6, 4.1)

ICC, investigator-chosen chemotherapy.
Least-square mean change (95 % CI) from baseline to Cycle 4 and Cycle 6.

(Table 1). Patients treated with tislelizumab experienced less OES18 symptoms (except for pain) relative to baseline compared to those who received chemotherapy. The time to deterioration (TTD) for the GHS/QoL score – analyzed using the Kaplan-Meier method – showed that patients in the tislelizumab versus chemotherapy group had a lower risk for dysphagia worsening (HR=0.76; 95 % CI, 0.53-1.07; p=0.0562).

These data highlighted a longer maintenance of HRQoL for patients treated with tislelizumab compared to those who received chemotherapy. Taken together with the clinical outcomes of the RATIONALE 302 study, tislelizumab has great potential as new second-line treatment option for patients with advanced or metastatic ESCC.

Camrelizumab combined with fluorouracil as first-line therapy

In the treatment of ESCC, ICIs given as monotherapy did not show substantive improvements in terms of ORR and OS in patients with advanced ESCC [20]. As first-line therapy of ESCC, different combinations of ICIs with chemotherapy led to positive outcomes in several clinical trials (KEYNOTE-590, Checkmate-648, ORIENT-15 or ESCORT-1st) [21]. More than half of all ESCC cases worldwide are observed in China [22]; therefore, it is of interest to evaluate antitumoral activity and safety of such ICI/chemotherapy combination in the Chinese population.

Thus, a multicenter, open-label, prospective cohort study (ChiCTR2000037942) has been performed in China between May 2020 to February 2022 to evaluate the efficacy and safety of camrelizumab (anti-PD-1) combined with either fluorouracil or taxol/platinum [23]. In total, 40 patients with locally progressed and advanced ESCC have been enrolled in this trial to receive six cycles of camrelizumab plus chemotherapy (11 patients received fluorouracil/platinum and 29 taxol/platinum), followed by camrelizumab monotherapy.

After analysis of the first 33 patients (82.5 %), with a median treatment time of 5.8 months, the ORR reached 72.7 % and the DCR 97.0 %. No statistically significant difference was observed between both chemotherapy regimens in terms of ORR (55.6 % with fluorouracil/platinum vs 79.2 % with taxol/platinum; p=0.1779) or DCR (88.9 % vs 100 %, respectively; p=0.1005). Partial response was seen in 24 patients (19 with fluorouracil/platinum, 5 with taxol/platinum) and eight patients had a SD (5 vs 3 patients, respectively). At the time of this analysis, the median PFS has not been reached.

The most frequent grade 3 or 4 toxicities were thrombocytopenia, neutropenia, and leukopenia (2.5 % each). The most common immune-related AEs were reactive cutaneous capillary endothelial proliferation (12.5 %) and hypothyroidism (7.5 %). No new significant AEs were reported.

The authors concluded that camrelizumab plus chemotherapy is a promising regimen with good tolerability in the first-line treatment of ESCC.

1L lenvatinib plus pembrolizumab plus chemotherapy in ESCC

In the KEYNOTE-590, the benefit of pembrolizumab plus chemotherapy (5-fluorouracil [5-FU] + cisplatin) over chemotherapy alone has previously been shown as 1L treatment for unresectable locally advanced, recurrent, or metastatic esophageal cancer [24]. Lenvatinib is a multiple tyrosine kinase inhibitor against vascular endothelial growth factor receptor 1 (VEGFR1), VEGFR2 and VEGFR3. In combination with pembrolizumab, lenvatinib already showed promising antitumoral activity in advanced solid tumors [25-27].

The LEAP-014 trial (NCT04949256) is a randomized, 2-part, open-label, phase III study that aims to investigate the effi-

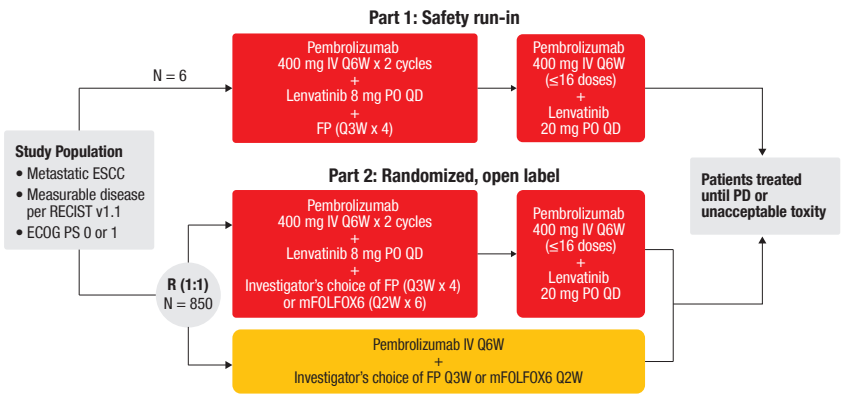


Figure 3: Study design of the LEAP-014 trial.

cacy and safety of upfront lenvatinib plus pembrolizumab plus chemotherapy versus pembrolizumab plus chemotherapy in patients with metastatic ESCC [28]. The primary endpoint in part-1 of the study **(Figure 3)** is safety per NCI CTCAE v5.0 and tolerability (dose-limiting toxicity, DLT), whereas the dual primary endpoint in part-2 consists of OS and PFS by BICR per RECIST v1.1; the secondary endpoints include ORR by BICR per RECIST v1.1, DoR, and HRQoL.

In part-1 (safety run-in) of the study, six patients will receive an induction with intravenous pembrolizumab (400 mg, Q6W) for 2 cycles plus oral lenvatinib (8 mg, QD) plus intravenous chemotherapy (5-FU, 4000 mg/m² on Day 1-Day 5, plus cisplatin, 80 mg/m2) for four cycles, then pembrolizumab (400 mg, Q6W for ≤16 doses) plus lenvatinib (20 mg, QD) for consolidation and are then closely monitored for 21 days after the first dose of study intervention for DLTs. In part-2 (main study), approximatively 850 adult patients with a histologically or cytologically confirmed metastatic ESCC, a measurable disease according to RECIST v1.1 and a good performance status (ECOG PS, 0 or 1) will be randomized (1:1) to receive either pembrolizumab plus lenvatinib plus chemotherapy (5-FU + cisplatin, IV, Q3W for 4 cycles or mFOLFOX6, Q2W for 6 cycles) followed by consolidation with pembrolizumab plus lenvatinib (arm A) or pembrolizumab plus chemotherapy (arm B), illustrated in **Figure 3**. The randomization will be stratified by PD-L1 combined positive score (≥10 vs < 10), region (East Asia vs North America and Western Europe vs rest of world), and chemotherapy backbone (5-FU plus cisplatin vs mFOLFOX6). The patients will be treated until progressive disease or unacceptable toxicity. This study is currently enrolling patients. ■

REFERENCES

1 Arnold, M, et al., Global burden of oesophageal and gastric cancer by histology and subsite in 2018. Gut 2020; 69(9): 1564-1571.
2 Sung, H, et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209-249.
3 Arnold, M, et al., Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology 2020; 159(1): 335-349.e15.
4 Murphy, AG, et al., State of the art management of metastatic gastroesophageal cancer. Ann Transl Med 2015; 3(16): 236.
5 Hiramoto, S, et al., A retrospective analysis of 5-fluorouracil plus cisplatin as first-line chemotherapy in the recent treatment strategy for patients with metastatic or recurrent esophageal squamous cell carcinoma. Int J Clin Oncol 2018; 23(3): 466-472.
6 Moehler, M, et al., Cisplatin and 5-fluorouracil with or without epidermal growth factor receptor inhibition panitumumab for patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer: a prospective, open-label, randomised phase III AIO/EORTC trial (POWER). Ann Oncol 2020; 31(2): 228-235.
7 Wang, Q, et al., PD-L1 Expression On tumor Cells Was Associated With Unfavorable Prognosis In Esophageal Squamous Cell Carcinoma. J Cancer 2018; 9(12): 2224-2231.
8 Baba, Y, et al., Tumor immune microenvironment and immune checkpoint inhibitors in esophageal squamous cell carcinoma. Cancer Sci 2020; 111(9): 3132-3141.
9 Doki, Y, et al., Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med 2022; 386(5): 449-462.
10 Chau, I, et al., Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): Expanded efficacy and safety analyses from CheckMate 648. J Clin Oncol 2022; 40(suppl 16; Abstr 4035).
11 Crombet-Ramos, T, et al., Antiproliferative, antiangiogenic and proapoptotic activity of h-R3: A humanized anti-EGFR antibody. Int J Cancer 2002; 101(6): 567-575.
12 You, B, et al., A dose-escalation phase I trial of nimotuzumab, an antibody against the epidermal growth factor receptor, in patients with advanced solid malignancies. Invest New Drugs 2011; 29(5): 996-1003.
13 Zhao, L, et al., Nimotuzumab promotes radiosensitivity of EGFR-overexpression esophageal squamous cell carcinoma cells by upregulating IGFBP-3. J Transl Med 2012; 10: 249.
14 Meng, X, et al., Nimotuzumab plus concurrent chemo-radiotherapy versus chemo-radiotherapy in unresectable locally advanced esophageal squamous cell carcinoma (ESCC): Interim analysis from a prospective, randomized-controlled, double-blinded, multicenter, and phase III clinical trial (NXCEL1311 Study). J Clin Oncol 2022; 40(suppl 16; Abstr 4016).
15 Zhang, T, et al., The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer Immunol Immunother 2018; 67(7): 1079-1090.
16 Shen, L, et al., Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer 2020; 8(1): e000437.
17 Shen, L, et al., RATIONALE 302: Randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. J Clin Oncol 2021; 39(suppl 15; abstr 4012).
18 Zhao, K, et al., Randomized, phase 3 study of second-line tislelizumab vs chemotherapy in advanced or metastatic esophageal squamous cell carcinoma, RATIONALE 302: Asia subgroup. J Clin Oncol 2022; 40(suppl 16; Abstr e16107).
19 Van Cutsem, E, et al., Tislelizumab versus chemotherapy as second-line treatment for advanced or metastatic esophageal squamous cell carcinoma (ESCC, RATIONALE 302): Impact on health-related quality of life (HRQoL). J Clin Oncol 2022; 40(suppl 16; Abstr 16095).
20 Kato, K, et al., Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20(11): 1506-1517.
21 Thuss-Patience, P, et al., Immunotherapy in Squamous Cell Cancer of the Esophagus. Curr Oncol 2022; 29(4): 2461-2471.
22 Hou, H, et al., Survival of Esophageal Cancer in China: A Pooled Analysis on Hospital-Based Studies From 2000 to 2018. Front Oncol 2019; 9: 548.
23 Zhao, J, et al., Camrelizumab in combination with fluorouracil or taxol plus platinum chemotherapy as first-line treatment of esophageal squamous cell carcinoma: A multicenter, open-label, prospective cohort study. J Clin Oncol 2022; 40(suppl 16; Abstr e16084).
24 Sun, JM, et al., Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021; 398(10302): 759-771.
25 Finn, RS, et al., Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. J Clin Oncol 2020; 38(26): 2960-2970.
26 Makker, V, et al., Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022; 386(5): 437-448.
27 Motzer, R, et al., Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med 2021; 384(14): 1289-1300.
28 Sun, J, et al., First-line lenvatinib plus pembrolizumab plus chemotherapy in esophageal squamous cell carcinoma: LEAP-014 trial in progress. J Clin Oncol 2022; 40(suppl 16; Abstr TPS4167).

An update and future directions in advanced gastric or gastrointestinal junction cancer (G/GEJC)

With more than 1 million newly diagnosed cases in 2020, gastric cancer (GC) is the fifth most frequent cancer; it was also the third leading cause of cancer-related death worldwide [1]. Gastroesophageal junction (GEJ) cancer concerns a form of gastric cancer developing around the digestive tract where esophagus and stomach connect; in the last years, the prevalence of GEJ constantly increased [2].

Zanidatamab combined with tislelizumab and chemotherapy

Around 15% to 25% of gastric cancers express the human epidermal growth factor receptor 2 (HER2-positive) [3, 4]. Zanidatamab is a novel bispecific antibody targeting two non-overlapping extracellular domains of HER2; it previously showed an encouraging antitumoral activity and a manageable safety profile, either as monotherapy in HER2-positive biliary tract cancer [5], with chemotherapy in HER2-positive breast cancer [6] and in G/GEJ adenocarcinoma [7].

The ongoing open-label, multicenter Phase 1b/2 study (NCT04276493) evaluates different doses of zanidatamab (Cohort A: 30 mg/kg or Cohort B: 1800 mg/2400 mg) combined with chemotherapy (CAPOX [capecitabine 1000 mg/m² plus oxaliplatin 130 mg/m²], every third week [Q3W]) and tislelizumab (200 mg, intravenously [IV]; a humanized IgG4 anti–PD-1 monoclonal antibody) as first-line treatment of unresectable, locally advanced, recurrent, or metastatic HER2-positive G/GEJ adenocarcinoma [8]. The treatment is continued until disease progression, intolerable toxicity or in case any other discontinuation criteria are met. Safety and objective response rate (ORR) are the co-primary endpoints; duration of response (DoR), progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) are secondarily analyzed.

So far, 33 eligible patients (Cohort A: 19, Cohort B: 14) have been randomized to this study. At the data cut-off (January 5th, 2022), 20 patients (60.6%) were still on treatment. **Figure 1** shows the best percentage change in target lesions. Confirmed ORR was 75.8% (95% CI, 57.7-88.9) with one patient showing a complete response (CR), 24 patients a partial response (PR) and eight patients a stable response (SD). The DCR was 100% (95% CI, 89.4-100), and the median PFS was 10.9 months (95% CI, 8.2-non-estimable), with 36.4% of patients having PFS events.

Concerning the safety, 20 patients (60.6%) experienced at least one grade ≥3 treatment-related adverse event (TRAE), the most common being diarrhea (24.2%) and increased lipase (9.1%). Nine patients (27.3%) had immune-mediated AEs (imAEs), seven of them (21.2%) being grade ≥3 imAEs. Three patients had to discontinue tislelizumab due to imAEs; which included pneumonitis and immune hepatitis.

The authors concluded that zanidatamab combined with tislelizumab and CAPOX chemotherapy showed a tolerable safety profile and efficacy as first-line therapy for patients with HER2-positive G/GEJC. Based on these results, a randomized, global phase 3 study (HERIZON-GEA-01) has been initiated to investigate zanidatamab and chemotherapy with or without tislelizumab for first-line treatment of locally advanced, unresectable, or metastatic HER2-positive gastroesophageal adenocarcinoma.

CT041: CAR T-cell therapy

In solid tumors, chimeric antigen receptor (CAR) T-cell therapy remains limited compared to its success in hematologic malignancies. Nevertheless, CT041, an autologous CAR T-cell product candidate against protein Claudin18.2 (CLDN18.2) previously showed promising antitumoral activity and a tolerable toxicity in a phase 1 study in pre-treated gastrointestinal cancers [9].

An open-label, multicenter phase 1b/2 study (NCT04581473) investigated in Part 1 (dose-escalation/dose-expansion) the safety, tolerability as well as recommended phase 2 dose of CT041 in adults with pathologically diagnosed advanced G/GEJ adenocarcinoma [10]. Before each CT041 infusion, lymphodepletion treatment with fludarabine, cyclophosphamide and nab-paclitaxel was administered to each patient. Key eligibility criteria included patients who were 18 to 75 years old, were refractory to or intolerant of at least two prior lines of treatment, had a confirmed positive expression of CLDN18.2 by immunohistochemistry (IHC) staining (2+/3+ in ≥40% of tumor cells) and at least one measurable lesion per RECIST v1.1.

From November 2020 to May 2021, 14 eligible patients with G/GEJC were enrolled and received one cycle of bridging chemotherapy, of whom 13 received FOLFIRI and one patient

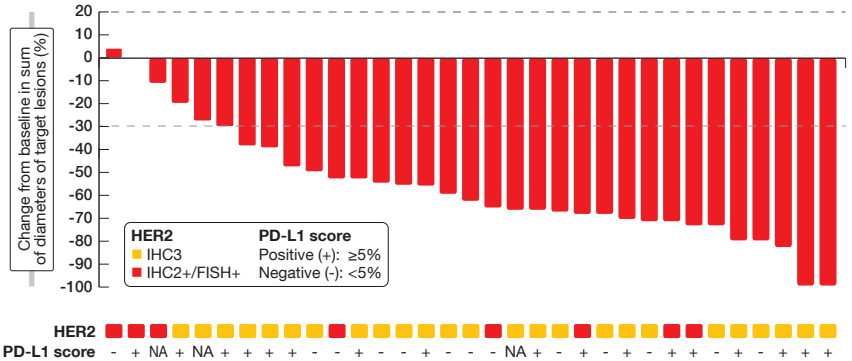


Figure 1: Waterfall plot of best change in target lesion size.

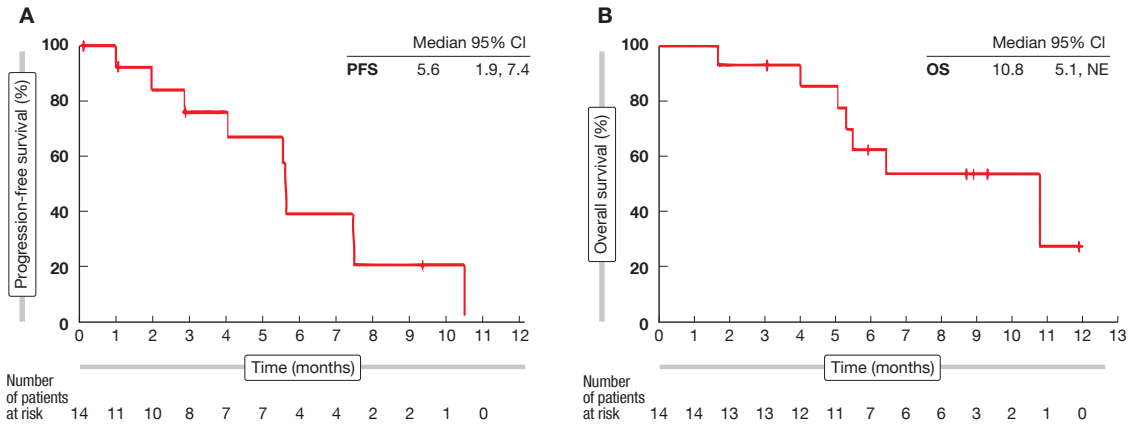


Figure 2: Median progression-free survival **(A)** and median overall survival **(B)** after administration of CT041.

received 5-FU plus intraperitoneal nab-paclitaxel. All patients had at least one infusion of CT041 (11 patients received 2.5 x 108 and 3 patients received 3.75 x 108 cells, respectively) whereas seven patients received two infusions (6 in the low dose and 1 in the high dose group), with a median interval between the two infusion of 132 days.

The median persistence time of these CAR T-Cells after the first/second CT041 infusion was 27 days (range, 14-189) and 26 days (range, 5-68), respectively. Most frequently observed grade ≥3 TREAs were lymphopenia related to the lymphodepletion. Otherwise, three serious TRAEs were reported in two patients, while no patients had dose-limiting toxicities (DLTs) or AE leading to death. All patients experienced light or moderate (grade 1 or 2) cytokine release syndrome after the first infusion and six out of seven patients (85.7%) after the second infusion (median onset time of 2 days and 1 day, respectively). The median recovery time was seven days (range, 1-22). After a median follow-up of 8.8 months (range, 3.0-13.6), eight out of 14 patients (57.1%) had a PR and three patients (21.4%) showed stable disease after the first CT041 infusion. The ORR reached 57.1% (95% CI, 28.9-82.3), the DCR was 78.6% (95% CI, 49.2-95.3), the median PFS **(Figure 2A)** was 5.6 months (95% CI, 1.9-7.4) and the median OS 10.8 months (95% CI, 5.1-non reached) **(Figure 2B)**.

This preliminary data of CT041 suggests a manageable safety and tolerability profile, as well as a promising efficacy in previously treated patients with advanced G/GEJ adenocarcinoma. A phase 2 study is currently ongoing.

IBI110 in combination with sintilimab

Efficacy and safety of the anti-PD-1 inhibitor sintilimab have been demonstrated in several malignant entities [11], both in advanced disease like recently shown in esophageal squamous cell carcinoma [12], and in the neoadjuvant setting [13]. In gastric cancer, sintilimab plus XELOX (capecitabine plus oxaliplatin) has demonstrated efficacy after neoadjuvant chemotherapy [14], while lymphocyte-activation gene 3 (LAG-3) – an immune checkpoint receptor protein – controls T-cell response, activation, and growth [15]. Thus, a dual inhibition with anti-PD-1 and anti-LAG-3 might act synergistically against tumoral cells [16]. Indeed, IBI110 – an anti-LAG-3 monoclonal antibody – plus sintilimab has previously shown preliminary efficacy in advanced solid tumors [17].

At this year ASCO meeting, a phase 1b study (NCT04085185) investigated the safety and efficacy of IBI101 (200 mg, IV, Q3W) plus sintilimab (200 mg, IV, Q3W) plus XELOX as first-line treatment in patients with unresectable, locally advanced, or recurrent/metastatic HER2-negative G/GEJ adenocarcinoma [18]. The primary endpoints included safety, tolerability, and efficacy of the combined therapy.

At the data cut-off date (January 22, 2022), 18 eligible patients have already been enrolled in this study. With a median follow-up of four weeks (range, 0-20) and a median exposure of combination therapy of 9.4 weeks (range, 3-24), the most common grade ≥3 TRAEs included decreased neutrophil count, decreased platelet count, abnormal hepatic function (n = 2; 11.1% each). ImAEs occurred in seven patients (38.9%), the most frequent one being increased amylase (n = 2, 11.1%).

Among the 15 evaluable patients, the ORR reached 60%, including nine patients with a PR, and the DCR was 100%. The median DoR and the median PFS were not mature at the data cut-off date, as 17 patients were still on treatment.

The authors concluded that, although this triple combination seemed to be well tolerated, longer follow-up is needed to analyze the clinical benefit.

Camrelizumab plus FLOT as neoadjuvant therapy

In patients with locally advanced G/GEJC, both docetaxel-based neoadjuvant chemotherapy and immunotherapy have already shown promising efficacy in gastric cancer [19, 20]. A randomized study (ChiCTR2000030610) evaluated the safety and efficacy of camrelizumab - an anti-PD-1 immune checkpoint inhibitor - plus chemotherapy versus chemotherapy alone as neoadjuvant therapy for patients with resectable locally advanced GC/GEJC [21].

Eligible patients who underwent gastrectomy with D2 lymph node dissection received fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) in Arm A and FLOT plus camrelizumab (200 mg, IV, Q3W) in Arm B. The primary endpoint was pathologic complete response (pCR) and R0 resection rate, while the secondary endpoints comprised the ORR, PFS, OS and safety.

Although 61 patients had been recruited in this study between mid-Janu-

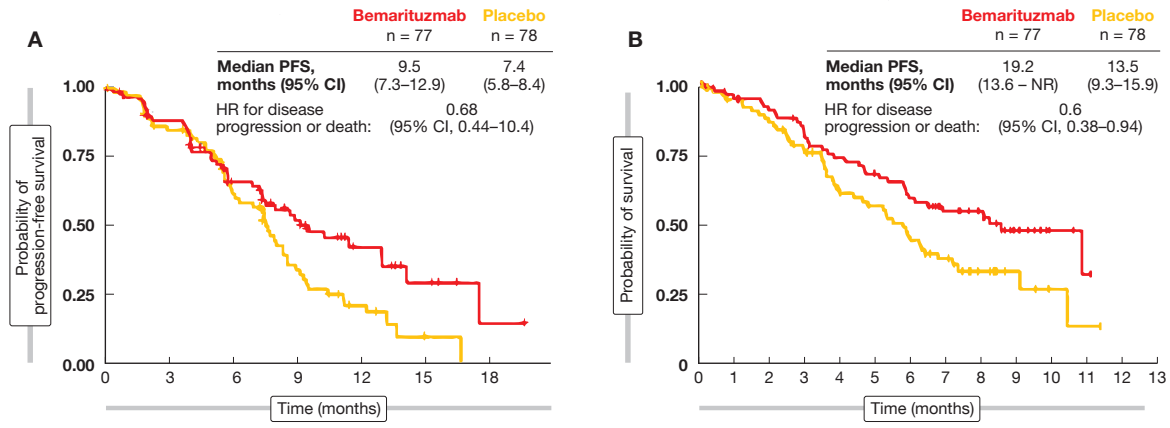


Figure 3: Improvement in progression-free survival (data cut-off, September 2020) **(A)** and overall survival (data cut-off, February 2021) **(B)**.

ary 2020 and mid-January 2022, the data presented at ASCO 2022 were related to 47 analyzed patients only (Arm A, n = 26; Arm B, n = 21). The median age was 63 years in both arms. The patients in Arm B showed a higher R0 resection rate than in Arm A (100.0% in Arm B vs 90.5% in Arm A); a similar outcome was reflected in the pCR (11.5% vs 4.8%, respectively) and the proportion of postoperative stage ypN0 (46% vs 24%, respectively).

No serious intraoperative complications, or immune-related adverse events (irAEs) were observed during perioperation. TRAEs – mostly neutropenia and leucopenia – were manageable and no treatment-related death occurred.

In the neoadjuvant setting, camrelizumab plus FLOT showed a promising efficacy, low complications, and manageable safety profile in patients with locally advanced resectable G/GEJ adenocarcinoma.

FORTITUDE-101: bemarituzumab plus mFOLFOX6

Overall, 80% to 85% of patients with advanced GEJ cancer do not express HER2; in those HER2-negative GEJC patients, prior clinical trials reached a limited median OS of 12 to 14 months [22-24]. Around 30% of HER2-negative G/GEJ adenocarcinoma express the fibroblast growth factor receptor 2b (FGFR2b) [25]. Bemarituzumab is a first-in-class monoclonal antibody that is binding specifically FGFR2b to inhibit tumor proliferation and it has the potential to enhance the antibody-dependent cellular cytotoxicity (ADCC) [26-27]. In the phase 2 FIGHT study, bemarituzumab plus 5-fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) already demonstrated a median PFS (9.5 vs 7.4 months; HR: 0.68; 95% CI, 0.44-10.4) and OS (19.2 vs 13.5 months; HR: 0.6; 95% CI, 0.38-0.94) benefit in this patient group [26], see **Figure 3**.

Moreover, a phase 3 study will investigate the combination of bemarituzumab plus mFOLFOX6 versus mFOLFOX6 in patients with FGFR2b overexpressing advanced gastric or GEJ cancer [28]. The FORTITUDE-101 study (NCT05052801) is currently enrolling patients according to the following inclusion criteria: adults, histologically confirmed G/GEJ adenocarcinoma, FGFR2b overexpression as determined by centrally performed IHC testing, unresectable, locally advanced, or metastatic disease, evaluable disease per RECIST v1.1 and no contraindication to receive mFOLFOX6 chemotherapy. The 516 patients will be randomized 1:1 and patients will receive either bemarituzumab (15 mg/kg, Q2W + additional 7.5 mg/kg on Cycle 1 Day 8) and mFOLFOX6 (Q2W) or mFOLFOX6 alone. Patients will receive treatment until disease progression, unacceptable toxicity, withdrawal of consent or death (whichever occurs first). The stratification will occur according to the geographic region (US/European Union vs Asia vs rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), as well as tumor cell and PD-1 status (Combined Positive Score [CPS] ≥5 vs <5 or indeterminate).

TABLE 1 **Ongoing bemarituzumab trials**

Study/Phase	Indications*	Key Overview
FORTITUDE-101 Phase 3 Study (NCT05052801)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 vs mFOLFOX6 alone** **Primary outcome:** Efficacy assessed by OS **Secondary outcomes:** Efficacy assessed by PFS and OR; safety and tolerability
FORTITUDE-102 Phase 1 b/3 Study (NCT05111626)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + mFOLFOX6 + nivolumab (Part 2: comparison with mFOLFOX6 + nivolumab alone)** **Part 1 (phase 1b):** DLTs, TEAEs, clinically significant changes **Part 2 (phase 3):** Efficacy assessed by OS, PFS, OR
FORTITUDE-103 Phase 1 Study (NCT05322577)	Untreated advanced gastric and GEJ cancer	**Bemarituzumab + CAPOX, SOX, CAPOX + nivolumab, or SOX + nivolumab** **Primary outcomes:** Safety and tolerability assessed by DLTs, TEA Es **Secondary outcomes:** Efficacy assessed by OR, DOR, PFS, OS, and pharmacokinetics
FORTITUDE-201 Phase 1 b/3 Study (NCT05267470)	Squamous-cell non-small-cell lung cancer	**Bemarituzumab + docetaxel (Part 3: bemarituzumab monotherapy)** **Part 1:** Dose exploration assessed by DLTs and TEAEs **Part 2:** Part 1 identified dose safety assessed by TEAEs **Part 3:** Safety assessed by TEAEs
FORTITUDE-301 Phase 1 b/2 Study (NCT05325866)	Solid tumors	**Bemarituzumab monotherapy** **Part 1:** Dose exploration assessed by DLTs, TEA Es **Part 2:** Part 1 identified dose efficacy assessed by OR

* in FGFR2b overexpressed tumors.

The primary endpoint is OS, while the secondary endpoints enclose PFS assessed locally per RECIST v1.1, ORR, DoR, DCR, TEAEs, clinically significant changes, pharmacokinetics, QoL and anti-bemarituzumab antibody formation.

FORTITUDE-102: bemarituzumab plus mFOLFOX6 plus nivolumab

Preclinical studies previously showed that bemarituzumab can change the tumor microenvironment to sensitize tumors to PD-1 inhibitors [26, 29]. A phase 1b/3 study currently evaluates the efficacy and safety of bemarituzumab plus mFOLFOX6 plus nivolumab versus mFOLFOX6 plus nivolumab in patients with previously untreated FGFR2b overexpressing advanced G/GEJ cancer [30]. The FORTITUDE-102 trial (NCT05111626) presents a similar design than the previously described FORTITUDE-101 study, except that it is a 2-part study, that in Part 1 elucidates the recommended dose to be used in the Part 2. Eligible patients should not present any contraindication to receive nivolumab. The co-primary endpoints of Part 1 are overall safety, tolerability, and pharmacokinetics; in Part 2 of this trial, the primary endpoint is OS. In this study, the stratification occurs according to FGFR2b IHC 2+/3+ staining in ≥10% of tumor cells vs FGFR2b IHC 2+/3+ in <10%.

In Part 2, FORTITUDE-102 aims to enroll approximately 682 patients. An overview of all currently ongoing bemarituzumab studies is presented in **Table 1**. ■

REFERENCES

1 GLOBOCAN 2020, last accessed Juli 2022, https://gco.iarc.fr/today/fact-sheets-cancers
2 Rawla P et al., Epidemiology of gastric cancer: global trends, risk factors and prevention. Przeglad gastroenterologiczny 2019; 14(1): 26-38.
3 Kahraman S et Yalcin S., Recent Advances in Systemic Treatments for HER-2 Positive Advanced Gastric Cancer. Onco Targets Ther 2021; 14: 4149-4162.
4 Nakamura Y et al., Biomarker Targeted Therapies for Advanced-Stage Gastric and Gastro-Oesophageal Junction Cancers: An Emerging Paradigm. Nat Rev Clin Oncol 2021; 18: 473–487.
5 Meric-Bernstam F et al., Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. J Clin Oncol 2021; 39(suppl 3; Abstr 299).
6 Bedard PL et al., Zanidatamab (ZW25), a HER2-targeted Bispecific Antibody, in Combination with Chemotherapy (chemo) for HER2-positive Breast Cancer (BC): Results from a Phase 1 Trial. Cancer Res 2022; 82(suppl 4; P2-13-07).
7 Ku G et al., Phase (Ph) II study of zanidatamab + chemotherapy (chemo) in first-line (1L) HER2 expressing gastroesophageal adenocarcinoma (GEA). Annals of Oncology (2021) 32 (suppl_5): S1040-S1075.
8 Lee K-W et al., Zanidatamab (zani), a HER2-targeted bispecific antibody, in combination with chemotherapy (chemo) and tislelizumab (TIS) as first-line (1L) therapy for patients (pts) with advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma (G/GEJC): Preliminary results from a phase 1b/2 study. J Clin Oncol 2022; 40(suppl 16; Abstr 4032).
9 Qi C et al., Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. Nat Med 2022; 8(6): 1189-1198.
10 Qi C et al., Safety, tolerability, and preliminary efficacy results in patients with advanced gastric/gastroesophageal junction adenocarcinoma from a phase Ib/II study of CLDN18.2 CAR T-cell therapy (CT041). J Clin Oncol 2022; 40(suppl 16; Abstr 4017).
11 Zhang L et al., Sintilimab: A Promising Anti-Tumor PD-1 Antibody. Front Oncol 2020; 10: 594558.
12 Lu Z et al., Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double blind, phase 3 trial. Bmj 2022; 77: e068714.
13 Gao S, et al., Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. J Thorac Oncol 2020; 15(5): 816-826.
14 Ding P et al., Combined systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI) predicts chemotherapy response and prognosis in locally advanced gastric cancer patients receiving neoadjuvant chemotherapy with PD-1 antibody sintilimab and XELOX: a prospective study. BMC Gastroenterol 2022; 22(1): 121.
15 Maruhashi T et al., LAG-3: from molecular functions to clinical applications. J Immunother Cancer 2020; 8(2): e001014.
16 Jiang H et al., PD-L1/LAG-3 bispecific antibody enhances tumor-specific immunity. Oncoimmunology 2021; 10(1): 1943180.
17 Zhou C et al., Phase Ia/Ib dose-escalation study of IBI110 (anti-LAG-3 mAb) as a single agent and in combination with sintilimab (anti-PD-1 mAb) in patients (pts) with advanced solid tumors. J Clin Oncol 2021; 39(suppl 15; Abstr 2589).
18 Mao C et al., Efficacy and safety of IBI110 in combination with sintilimab in first-line advanced HER2-negative gastric cancer or gastroesophageal junction cancer: Preliminary results from a phase Ib study. J Clin Oncol 2022; 40(suppl 16; Abstr e16097).
19 Kang YK et al., PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer. J Clin Oncol 2021;39(26): 2903-2913.
20 Joshi SS et al., Current treatment and recent progress in gastric cancer. CA Cancer J Clin 2021; 71(3): 264-279.
21 Lui Z et al., Efficacy and safety of camrelizumab combined with FLOT versus FLOT alone as neoadjuvant therapy in patients with resectable locally advanced gastric and gastroesophageal junction adenocarcinoma who received D2 radical gastrectomy: Data update. J clin Oncol 2022; 40(suppl 16; Abstr e16044).
22 Janjigian YY et al., First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet 2021; 398(10294): 27-40.
23 Fuchs CS et al., Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20(3): 420-435.
24 Lordick F et al., Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 2013; 14(6): 490-499.
25 Wainberg ZA et al., Randomized double-blind placebo-controlled phase 2 study of bemarituzumab combined with modified FOLFOX6 (mFOLFOX6) in first-line (1L) treatment of advanced gastric/gastroesophageal junction adenocarcinoma (FIGHT). J Clin Oncol 2021; 39(suppl 3; abstr 160).
26 Xiang H et al., Preclinical characterization of bemarituzumab, an anti-FGFR2b antibody for the treatment of cancer. MAbs 2021; 13(1): 1981202.
27 Catenacci DVT et al., Patients with advanced FGFR2b-positive, HER2-negative gastric and gastro-oesophageal cancer may derive a progression-free survival gain from the addition of bemarituzumab to FOLFOX6 chemotherapy. J Clin Oncol 2021; 39(suppl 15; abstr 4010).
28 Smyth E et al., Trial in progress: Phase 3 study of bemarituzumab + mFOLFOX6 versus placebo + mFOLFOX6 in previously untreated advanced gastric or gastroesophageal junction (GEJ) cancer with FGFR2b overexpression (FORTITUDE-101). J Clin Oncol 2022; 40(suppl 16; Abstr TPS4164).
29 Power J et al., FPA144, a therapeutic monoclonal antibody targeting the FGFR2b receptor, promotes antibody dependent cell-mediated cytotoxicity and stimulates sensitivity to PD-1 in the 4T1 syngeneic tumor model. Cancer Research 2016; 76(suppl 14; Abstr 1407).
30 Wainberg ZA et al., Trial in progress: Phase 1b/3 study of bemarituzumab + mFOLFOX6 + nivolumab versus mFOLFOX6 + nivolumab in previously untreated advanced gastric and gastroesophageal junction (GEJ) cancer with FGFR2b overexpression (FORTITUDE- 102). J Clin Oncol 2022; 40(suppl 16; Abstr TPS4165).

New therapeutic options being currently investigated in advanced or metastatic colorectal cancer

Anti-EGFR antibody therapy in *RAS* and *BRAF* wild-type metastatic colorectal cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States, and it is the fourth most frequent cancer diagnosis [1]. A current treatment option for *RAS* and *BRAF* wild-type (WT) metastatic colorectal cancer (mCRC) is the chemotherapy doublet (FOLFOX/FOLFIRI) with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) [2, 3]. Early promising results have been reported in several trials that investigated the combination of intensified upfront chemotherapy regimens with an anti-EGFR agent, although high rates of gastrointestinal toxicities requiring dose modifications were observed [4, 5]. The VOLFI study (NCT01328171), a phase 2 randomized trial, demonstrated that the association of panitumumab with a modified schedule of FOLFOXIRI led to a higher objective response rate (ORR) than FOLFOXIRI alone (87% vs 61%, p=0.004) in previously untreated *RAS*-WT mCRC patients; however, no significant progression-free survival (PFS) difference was seen [6].

To assess the added value of an intensified first-line chemotherapy combined with panitumumab, a study was performed in a selected population of mCRC patients (*RAS*- and *BRAF*-WT) [6, 7]. The prospective, open-label, phase 3 trial TRIPLETE (NCT03231722) enrolled previously untreated patients with unresectable *RAS*- and *BRAF*-WT mCRC and randomized them to receive mFOLFOX6/pan (arm A) or mFOLFOXIRI (irinotecan 150 mg/m^2, oxaliplatin 85 mg/m^2, L-leucovorin (LV) 200 mg/m^2, 5-fluoruracil (5FU) 2,400 mg/m^2 48 h infusion)/pan (arm B) up to twelve cycles, followed by 5FU/LV/pan until disease progression. Given an objective response rate (ORR) of 60% in arm A, an attempt was made to detect an increase of at least 15% in arm B. The primary endpoint in this trial was the ORR according to RECIST v1.1.

In total, 435 patients were enrolled in 67 Italian sites during the study period (Sept 2017-Sept 2021). Characteristics of the patients enrolled in this study were (arm A/B): median age 59/59 years, ECOG PS 0 80%/84%, synchronous metastases 88%/87%, prior adjuvant chemotherapy 2%/6%, resected primary tumor 43%/51%, liver-only disease 37%/39%. The primary endpoint (ORR) for this study was not met, as no significant difference was observed between both arms (76% vs 73%; OR, 0.87; 95% CI, 0.56-1.34; p=0.526). Considering the secondary endpoints, neither the R0 resection rate (29% vs 25%; OR, 0.81; 95% CI, 0.53-1.23; p=0.317), nor the median PFS (12.3 vs 12.7 months; HR, 0.88; 95% CI, 0.70-1.11; p=0.277), showed any benefit for one study arm above the other **(Figure 1)**.

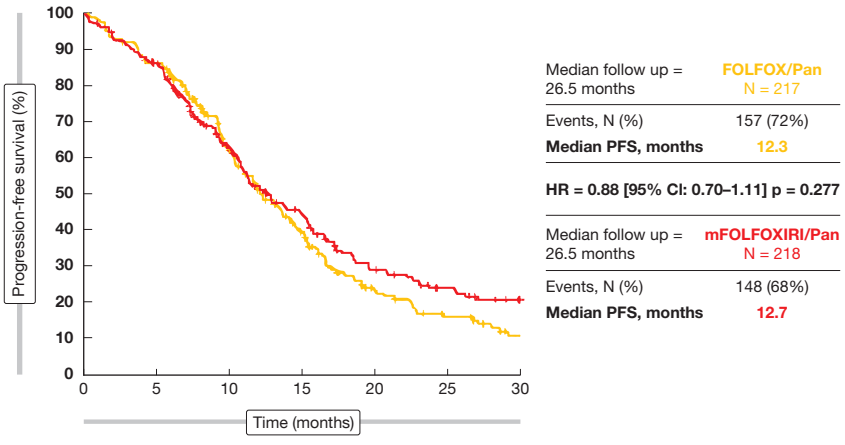


Figure 1: Progression-free survival in both arms of the TRIPLETE trial.

The main reported grade 3 and 4 adverse events (AEs) were skin rash (29%/19%, arm A/B), neutropenia (20%/32%), diarrhea (7%/23%) or stomatitis (7%/7%).

In *RAS*- and *BRAF*-WT mCRC patients, the intensification of the upfront chemotherapy backbone with mFOLFOXIRI was not associated with an improved response as compared to mFOLFOX6 when both regimens were combined with panitumumab.

Panitumumab plus mFOLFOX6 as 1L therapy in *RAS*-WT mCRC

The combination of an anti-EGFR or anti-VEGF antibody to the standard chemotherapy regimen has been shown to improve the overall survival (OS) of patients with advanced unresectable mCRC [8, 9]. However, so far comparative trials brought inconclusive outcomes [10, 11]. Panitumumab (PAN) is a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFR), approved in the USA and Europe for the treatment of *RAS* wild-type mCRC [12].

At ASCO 2022, Yoshino et al. presented results of the open-label, multicenter, phase 3 PARADIGM study (NCT02394795) which investigated the efficacy and safety of PAN plus mFOLFOX6 or bevacizumab (BEV) plus mFOLFOX6 in chemotherapy-naive patients with *RAS*-WT [13]. Eligible patients presented with an unresectable disease, had no previous chemotherapy, a good performance status (ECOG 0-1), at least one evaluable lesion, an adequate organ function and a life expectancy of at least 3 months. In total, 823 patients were randomized 1:1 to PAN plus mFOLFOX6 or BEV plus mFOLFOX6. In both study groups, around two-third of the patients had metastases in the liver. In the overall population, most patients (60%-67%) had a prior primary tumor resection.

After a median follow-up of 61 months, the median OS in the left-sided population

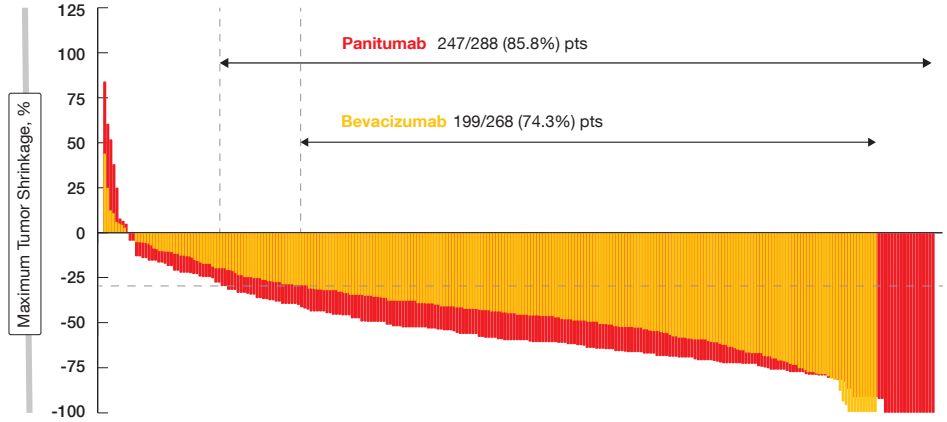


Figure 2: Depth of response in the left-sided population of the PARADIGM trial (Horizontal dotted line at 30% indicates response per RECIST v1.1).

- the primary endpoint - was in favor of the investigational arm with PAN (37.9 vs 34.3 months; HR, 0.82; 95% CI, 0.68-0.99; p=0.031). Concerning the secondary endpoints, the PFS in the left-sided population attained 13.7 months with PAN plus mFOLFOX6 compared with 13.2 months in the comparator arm (stratified HR, 0.98; 95 % CI, 0.82-1.17). The response rate was 80.2% in the PAN arm versus 68.6% in the bevacizumab arm. Tumor shrinkage of more than 30%, indicating response per RECIST v1.1, was reported in 85.8% of patients in the PAN arm versus 74.3% in the BEV arm, with a median depth of response of 59% versus 44%, respectively **(Figure 2)**. The disease control rate (DCR) was very similar in both arms (97.4% in the PAN arm vs 96.5% in the BEV arm). The median duration of response (mDoR) was 13.1 vs 11.2 months, while the curative resection (R0) rate attained 18.3% in the investigational arm versus 11.6% in the control arm. Clinical outcomes obtained for left-sided mCRC were comparable with the data presented for the overall population.

In total, grade ≥3 AEs occurred in 71.8% of patients in the PAN arm versus 64.9% in the BEV arm. SAEs related to the study treatment were experienced by 17.8% and 10.8% of patients in both study arms. In 23.8% of the PAN-treated patients and 18.4% of the BEV-treated patients, those AEs led to discontinuation of the treatment. The most common grade ≥3 AEs observed in the investigational/control arm were decreased neutrophil count (32%/35%), acne-like dermatitis (17%/0%) or peripheral sensory neuropathy (9%/10%). No new safety signals were reported.

The authors concluded that these clinical outcomes are supporting the use of panitumumab plus mFOLFOX6 as first-line therapy in patients with *RAS*-WT and left-sided mCRC.

Novel coupled CAR T-cell therapy for mCRC

Although chimeric antigen receptor (CAR-T) therapy has proven efficacy in hematologic malignancies [14], there has been limited success in solid tumors [15]. The first clinical candidate from the CoupledCar® solid tumor platform has been introduced - GCC19CART. It has been designed to overcome the limitations of conventional CAR-T cells therapy by pairing solid tumor CAR-T cells with CD19 targeting CAR-T cells to amplify proliferation and activation of the solid tumor CAR-T component. Anti-CD19 CAR T-cell therapy demonstrated its efficacy in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma [16]. Metastatic lesions of 70%-80% of subjects with CRCs are associated with guanylate cyclase-C (GCC). GCC19CART specifically targets GCC; recently, a phase 1 investigator-initiated dose escalation trial in patients with relapsed or refractory mCRC began in China [17].

In total, 21 subjects have been enrolled in this phase 1 study (ChiCTR2100053828) after positive screening for GCC expression by immunohistochemistry. All eligible subjects underwent leukapheresis, a single dose of lymphodepleting chemotherapy (fludarabine 30mg/m^2, cyclophosphamide 300mg/m^2) three days prior to infusion. Then a single infusion of GCC19CART at one of two preassigned doses (1x10^6 or 2x10^6 CAR T-cells/kg) was administered. Efficacy in this trial was determined with computed tomography (CT) or PET/CT according to RECIST v1.1 or PERCIST v1.0.

Overall, 13 subjects received the lower CAR T-cells dose and 8 subjects the higher dose. All 21 subjects had a one-month post-infusion imaging study available for review. The primary endpoint - combined ORR for both dose levels - was 28.6% (15.4% for dose level 1, 50% for dose level 2); two patients had a partial response (PR), while three more patients showed a partial metabolic response (PMR) in PET/CT scans with either stable disease or progressive disease for dose level 1 whereas 4 subjects demonstrated a PR and two a PMR with SD for dose level 2 **(Figure 3)**. Combined safety data (dose 1 and dose 2) revealed that the most common grade ≥3 AEs were decreased lymphocyte count (85.7%), diarrhea (42.9%), decreased platelet count (28.6%) and decreased neutrophil count (23.8%).

This phase 1 study demonstrated that GCC19CART had a meaningful dose-dependent antitumoral activity and a tolerable safety profile in patients with relapsed or refractory metastatic CRC.

RGX-202-01 in second line advanced *KRAS*-mutated CRC

The activating *KRAS* mutation is found in 40%-45% of patients with CRC tumors [18]. RGX-202-01, a first-in-class oral inhibitor of the SLC6A8/CKB pathway, is currently being investigated in refractory CRC patients with *KRAS*-mutated CRC [19, 20]. RGX-202-01 does not just demonstrate single agent activity, it also exhibits synergistic activity with 5-FU in preclinical animal models, leading to a therapeutic combination of RGX-202-01

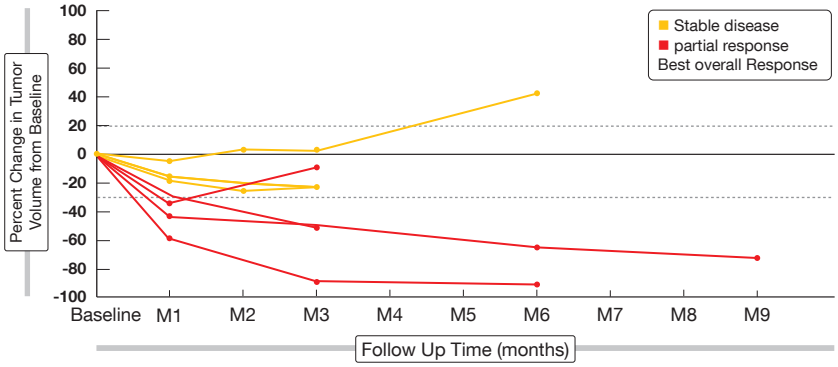


Figure 3: Change in tumor volume over time at a dose of $2x10^6$ CAR T-cells/kg.

with 5-FU containing regimens such as FOLFIRI [21, 22]. Currently, FOLFIRI plus BEV is the most used second line treatment for mCRC in the United States, (ORR, 5%-15%; median PFS, 5-6 months; median OS, 12-18 months).

Currently, a phase 1b study (NCT03597581) is underway to evaluate the safety, PK/PD, and efficacy of RGX-202-01 in combination with the standard of care (SOC) FOLFIRI plus BEV in second-line CRC. In total, 19 patients with advanced or metastatic CRC who had a measurable disease according to RECIST v1.1 were analyzed (8 patients in the dose escalation and 11 patients in the dose expansion). Patients in the dose escalation cohorts received either 2,400 mg or 3,000 mg of RGX-202-01 orally (twice daily (BID) on days 1-28 of each 28-day cycle) combined FOLFIRI plus with BEV (IV 5 mg/kg) followed by irinotecan (180 mg/m^2 IV) concurrently with folinic acid (400 mg/m^2), followed by 5-FU (2,400 mg/m^2 IV over 46 h, on days 1 and 15 of each 28-day cycle). Patients enrolled so far in the dose expansion phase received 3,000 mg of RGX-202-01 BID on days 1-28 of each 28-day cycle plus combined with FOLFIRI plus BEV.

Preliminary efficacy showed that patients with *KRAS*-mutated tumors experienced a durable clinical benefit with an ORR of 50% **(Figure 4)** and a median PFS of 11.8 months at the data cut-off date. The ORR and median PFS observed to date in patients with *KRAS* mutant tumors were superior to those with SOC FOLFIRI plus BEV alone. In this ongoing clinical trial, initial safety data demonstrated that there were no dose-limiting toxicities (DLTs) at the 2,400 mg or 3,000 mg BID dose. Grade 3 treatment-emergent AEs (TEAEs) were observed in 25% of patients, the most frequent being fatigue, hypertension, and rectal pain (25% each) at the 2,400 mg BID dose, as well as neutropenia, abdominal pain, or intestinal obstruction (13% each) at the 3,000 mg BID dose. Two patients experienced grade 4 TEAEs (sepsis and neutropenia) at the highest dose administered.

In this early phase clinical trial, the addition of RGX-202-01 to FOLFIRI plus BEV already provided a promising anti-tumoral activity and a favorable safety profile in *KRAS*-mutated advanced or metastatic CRC patients.

Maintenance for patients with newly diagnosed CRC

There has been little to no advancement in the management of metastatic microsatellite stable colorectal cancer (MSS-CRC) in the past decade and available chemotherapy treatments are associated with cytotoxicity [23]. Recently, checkpoint inhibitors (CPIs) have shown benefit to a small subset of patients deficient in mismatch repair dMMR/microsatellite instabilityhi, whereas this advantage was not seen in MSS-CRC patients. The lack of neoantigen specific T-cells and immune infiltration associated with MSS-CRC may lead to the absence of clinical benefit from CPIs. To expand the number of patients with mCRC who may benefit from an immunotherapy even further, an individualized neoantigen vaccine that induces CD8 T-cells capable of tumor lysis is currently under development. Previously reported data from a Phase 1/2 study evaluating neoantigen vaccines in combination with CPIs in patients with previously treated mCRC demonstrated a molecular response (MR) rate (≥50% reduction in circulating tumor DNA [ctDNA] relative to baseline levels) in 4/9 (44%) patients: this outcome correlated with improvement in overall survival (OS) compared to those not showing a MR.

The randomized, open-label, multicenter phase 2/3 GO-010 study (NCT05141721) aims to evaluate the efficacy and safety of 2 neoantigen-containing vectors (GRT-C901-adenoviral vector plus GRT-R902-self-amplifying mRNA vector) as prime/boost combined with CPIs (add-on to fluoropyrimidine/bevacizumab [BEV] following first-line therapy with fluoropyrimidine/oxaliplatin [FOLFOX]/BEV) in patients with mCRC [24]. The primary objective of the phase 2 study is to assess the antitumor activity based on MR, whereas the phase 3 study aims to assess antitumor activity based

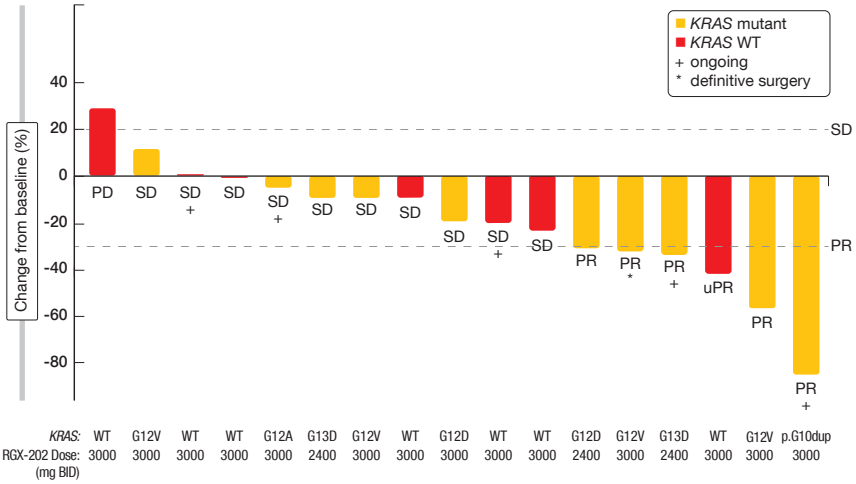


Figure 4: Best response according to RECIST v1.1 in all evaluable patients (n=17). One patient discontinued due to grade 2 allergic reaction, and another because of poor compliance.

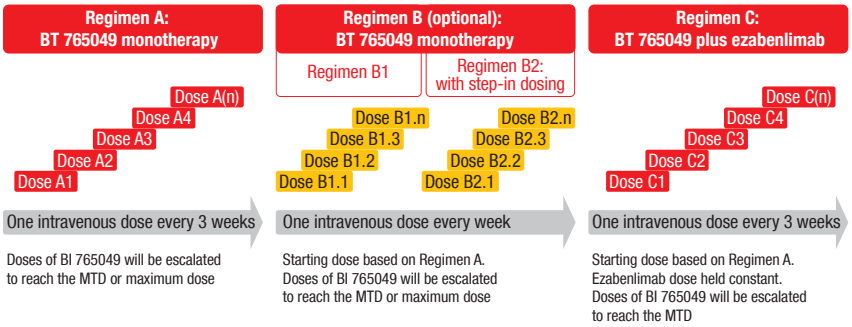


Figure 5: Study design of the first-in-human phase I dose-escalation trial of B7-H6/CD3 T-cell engager BI 765049 ± ezabenlimab in patients with advanced solid tumors expressing B7-H6.

on PFS per iRECIST. Patients will be randomized 1:1 with up to 90 patients being recruited in phase 2 and up to 226 in the phase 3 trial. This study will be conducted in two stages, vaccine production and study treatment, respectively. In the vaccine production phase, where patients receive up to 24 weeks FOLFOX/BEV (induction phase), neoantigen prediction will be performed using a tumor biopsy and Gritstone's EDGETM neoantigen prediction model. In the study treatment phase, patients in the control arm will continue with maintenance therapy (fluoropyrimidine/BEV), whereas patients in the vaccine arm will add the vaccine regimen (a total of 6 intramuscular injections of GRT-C901/GRT-R902 plus 30 mg ipilimumab subcutaneously [SC] co-administered only with the first dose of the cancer vaccines), as well as atezolizumab (1680 mg, intravenously [IV], once every 4 weeks [q4w] for up to 2 years) to the maintenance therapy. The vaccine will be evaluated using imaging, ctDNA, safety, immunogenicity, and exploratory biomarker analysis. Clinical benefit will be assessed in the 1L maintenance setting, using a real-time non-invasive ctDNA monitoring system as novel biomarker for tumor response. The key outcome will be to evaluate the correlation of ctDNA reduction with the improvement in clinical outcomes such as the immune-based PFS (iPFS).

Dose escalation trial in patients with advanced solid tumors expressing B7-H6

Several solid tumor types express B7-H6, a member of the B7 family of immune receptors, whereas little to no expression of B7-H6 is seen in normal tissue [25, 26]. A novel immunoglobin G-like bi-specific T-cell engager - BI 765049 - has been developed to simultaneously bind to B7-H6 tumor cells and CD-3 on T-cells; this binding results in cytotoxic synapse formation local activation and proliferation of T-cells, as well as cytokine secretion, converting a non-inflamed (cold) tumor environment into an inflamed (hot) tumor environment. Previously published preclinical studies have demonstrated that monotherapy with BI 765049 induced a dose-dependent anti-tumor activity in humanized in vivo CRC models, as well as an infiltration of T-cells [27]. BI 765049 is currently under clinical investigation in a Phase 1 trial as monotherapy or in combination with the PD-1 inhibitor ezabenlimab in patients with CRC or other B7-H6 positive tumors in several indications (non-small cell lung cancer [NSCLC], as well as head and neck squamous cell- [HNSCC], hepatocellular-, pancreatic-, gastric- or colorectal [CRC] carcinoma) [28].

The first open-label dose-escalation trial (NCT04752215) of BI 765049 +/- ezabenlimab already started in January 2022 to recruit adult patients with confirmed, advanced, unresectable and/or metastatic CRC, or patients with confirmed B7-H6-positive NSCLC, HNSCC, hepatocellular-, gastric-, or pancreatic carcinoma. Moreover, eligible patients should have at least 1 evaluable lesion (according to RECIST v1.1 outside of the central nervous system), adequate liver, bone marrow and renal functions, as well as a good performance status (ECOG 0/1). The co-primary endpoints of the study are the determination of the maximum tolerated dose (MTD) and the recommended dose for expansion based on the number of patients with DLTs during the MTD evaluation period. The secondary endpoints include pharmacokinetic parameters after first and multiple doses in all regimens, as well as ORR based on RECIST v1.1. The study is designed to assess up to four intravenous drug regimens **(Figure 5)**. Eligible patients receive the treatment for a maximum duration of 36 months or until confirmation of progressive disease, unacceptable toxicity, or other withdrawal reason. The enrollment goal is approximately 120 patients. ■

REFERENCES

1 Siegel, RL, et al., Cancer statistics, 2020. CA Cancer J Clin 2020; 70(1): 7-30.
2 NCCN guidelines for colon cancer. 2021 June 13, 2022]; version 2.2021:[
3 Yoshino, T, et al., Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol 2018; 29(1): 44-70.
4 Cremolini, C, et al., Activity and Safety of Cetuximab Plus Modified FOLFOXIRI Followed by Maintenance With Cetuximab or Bevacizumab for RAS and BRAF Wild-type Metastatic Colorectal Cancer: A Randomized Phase 2 Clinical Trial. JAMA Oncol 2018; 4(4): 529-536.
5 Ychou, M, et al., Chemotherapy (doublet or triplet) plus targeted therapy by RAS status as conversion therapy in colorectal cancer patients with initially unresectable liver-only metastases. The UNICANCER PRODIGE-14 randomised clinical trial. Br J Cancer 2022; 126(9): 1264-1270.
6 Modest, DP, et al., FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109). J Clin Oncol 2019; 37(35): 3401-3411.
7 Cremolini, C, et al., Modified FOLFOXIRI plus panitumumab (mFOLFOXIRI/PAN) versus mFOLFOX6/PAN as initial treatment of patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer (mCRC): Results of the phase III randomized TRIPLETE study by GONO. J Clin Oncol 2022; 40(suppl 16; abstr LBA3505).
8 Heinemann, V, et al., FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15(10): 1065-75.
9 Venook, AP, et al., Effect of First-Line Chemotherapy Combined With Cetuximab or Bevacizumab on Overall Survival in Patients With KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. Jama 2017; 317(23): 2392-2401.
10 Arnold, D, et al., Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017; 28(8): 1713-1729.
11 Stintzing, S, et al., FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol 2016; 17(10): 1426-1434.
12 Vectibix SmPC. 2022; Available from: https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf.
13 Yoshino, T, et al., Panitumumab (PAN) plus mFOLFOX6 versus bevacizumab (BEV) plus mFOLFOX6 as first-line treatment in patients with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Results from the phase 3 PARADIGM trial. J Clin Oncol 2022; 40(suppl 17; abstr LBA1).
14 Sterner, RC, et al., CAR-T cell therapy: current limitations and potential strategies. Blood Cancer J 2021; 11(4): 69.

15 Bell, M, et al., CAR T cell therapy for solid tumors: Fatal attraction requires adhesion. Med (N Y) 2022; 3(6): 353-354.
16 Abramson, JS, Anti-CD19 CAR T-Cell Therapy for B-Cell Non-Hodgkin Lymphoma. Transfus Med Rev 2020; 34(1): 29-33.
17 Cui, J, A phase 1 dose-escalation study of GCC19 CART a novel coupled CAR therapy for subjects with metastatic colorectal cancer. J Clin Oncol 2022; 40(suppl 16; Abstr 3582).
18 Jones, RP, et al., Specific mutations in KRAS codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer. Br J Cancer 2017; 116(7): 923-929.
19 Hendifar, AE, Phase 1b study of RGX-202-01, a first-in-class oral inhibitor of the SLC6A8/CKB pathway, in combination with FOLFIRI and bevacizumab (BEV) in second-line advanced colorectal cancer (CRC). J Clin Oncol 2022; 40(suppl 16; Abstr 3579).
20 Loo, JM, et al., Extracellular metabolic energetics can promote cancer progression. Cell 2015; 160(3): 393-406.
21 Kurth, I, et al., Therapeutic targeting of SLC6A8 creatine transporter suppresses colon cancer progression and modulates human creatine levels. Sci Adv 2021; 7(41): eabi7511.
22 Bendell, JC, Phase I monotherapy dose escalation of RGX-202, a first-in-class oral inhibitor of the SLC6a8/CKB pathway, in patients with advanced gastrointestinal (GI) solid tumors. J Clin Oncol 2020; 38(suppl 15; Abstr 3504).
23 Biller, LH, et al., Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. Jama 2021; 325(7): 669-685.
24 Hecht, JR, Phase 2/3, randomized, open-label study of an individualized neoantigen vaccine (selfamplifying mRNA and adenoviral vectors) plus immune checkpoint blockade as maintenance for patients with newly diagnosed metastatic colorectal cancer (GRANITE). J Clin Oncol 2022; 40(suppl 16; abstr TPS3635).
25 Boehringer Ingelheim, data on file. 2022.
26 Brandt, CS, et al., The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans. J Exp Med 2009; 206(7): 1495-503.
27 Hipp, S. ACCR Annual Meeting 2021; Abstr 53.
28 Falchook, G, et al., A first-in-human phase I dose-escalation trial of the B7-H6/CD3 T-cell engager BI 765049 ± ezabenlimab (BI 754091) in patients with advanced solid tumors expressing B7-H6. J Clin Oncol 2022; 40(suppl 16; abstr TPS3175).

New clinical insights in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) affected approximately 905,000 new diagnosed cases worldwide in 2020 and showed a high mortality rate [1]. Current first-line treatment for advanced HCC includes atezolizumab plus bevacizumab [2], as well as the tyrosine kinase inhibitors sorafenib [3, 4] and lenvatinib [5].

Pembrolizumab monotherapy: updated analysis of the KEYNOTE-224 trial

Previously reported data of the KEYNOTE-224 single-arm, non-randomized, multicenter, open-label, phase II study (NCT02702414) in advanced HCC have shown that pembrolizumab monotherapy has a durable antitumor activity and a manageable safety profile in sorafenib-pretreated (cohort 1) and treatment-naive (cohort 2) patients. At this year's ASCO meeting, the 3-year follow-up data of cohort 2 were presented [6].

Previously untreated HCC patients enrolled in cohort 2 of the KEYNOTE-224 study presented with the following eligibility criteria: histologically, cytologically, or radiologically confirmed advanced HCC; Barcelona Clinic Liver Cancer (BCLC) stage C or B not amenable or refractory to locoregional therapy, and not amenable to curative treatment; Child-Pugh liver function class A; measurable disease per RECIST v1.1 by blinded independent central review (BICR); and ECOG PS 0 or 1. Pembrolizumab (200 mg) was given intravenously (IV) every three weeks (Q3W) for ≤35 cycles (approximately 2 years). The primary endpoint of the study was the objective response rate (ORR), while the duration of response (DoR), the disease control rate (DCR), the time to progression (TTP), the progression-free survival (PFS), the overall survival (OS), the safety and the tolerability were assessed secondarily.

The median follow-up of this new analysis - defined as the time from first dose to data cut-off (October 1, 2021) - was 35 months. All 51 patients recruited in this study received at least one dose of pembrolizumab. The ORR was 16% (95% CI, 7-29), including eight patients with a partial response (PR); to note, the ORR was independent of a viral or non-viral etiology of HCC. The DCR reached 57% (95% CI, 42-71). The median DOR was not reached (NR; range, 3-24+) at the time of this analysis but 58% of responders were estimated to have a response duration of more than 18 months. The median time to progression was four months (95% CI, 3-9), the median PFS was four months (95% CI, 2-8) and the estimated 24-month PFS was 15% **(Figure 1)**. The median OS reached 17 months (95% CI, 8-23) and the estimated OS rate at 24-month was 34%.

In total, 55% of patients experienced treatment-related adverse events (TRAEs)

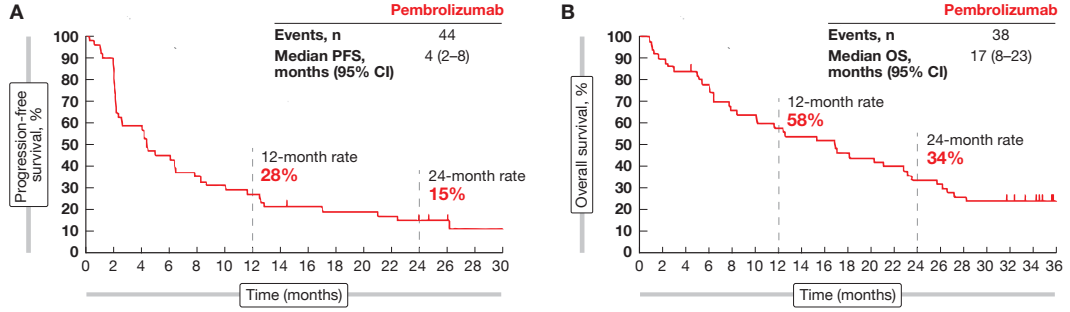


Figure 1: Progression-free survival **(A)** and overall survival **(B)** in the KEYNOTE-224 study (updated analysis).

of any grade and 16 % of grade 3 to 5. The most common grade ≥ 3 TRAEs observed were myalgia and abdominal pain (2 % each).

According to the updated results from cohort 2 of the KEYNOTE-224 study, pembrolizumab monotherapy continued to demonstrate a durable antitumor activity, a promising OS, and a manageable safety profile in patients with advanced HCC without prior systemic therapy.

Combined therapy in advanced unresectable or metastatic HCC

In an open-label, single-arm, multicenter, phase II study (NCT04542837) combining KN046 – a bispecific antibody targeting both anti-PD-1/PD-L1 and CTLA-4/B7 immune checkpoint pathways - and lenvatinib – a small-molecule tyrosine kinase inhibitor - showed good efficacy and a tolerability as treatment of advanced unresectable or metastatic HCC [7]. The data set has recently been updated, as more patients enrolled in the study with a longer follow-up duration [8].

In this phase II trial recruited patients with unresectable or metastatic HCC wo had a BCLC stage B or C not suitable for curative surgery or local therapy, received lenvatinib orally (12 mg/day for a body weight [BW] ≥ 60 kg or 8 mg/day for a BW < 60 kg) and KN046 (5 mg, IV, on Day 1 of a 21-day cycle) until disease progression, intolerable toxicity or 2-year treatment.

The co-primary endpoints - safety and ORR by RECIST v1.1 per investigators - were met. In total, 55 enrolled patients received a combination of KN046 and lenvatinib with a median duration of 25 weeks; the ORR reached 51.9 % (95 % CI, 37.6 - 66.0) and the DCR was 86.5 % (95 % CI, 74.2-94.4). The median PFS was 9.3 months (95 % CI, 7.0 – not estimable [NE]).

TRAEs were recorded in 98.2 % of patients with decreased platelet count (7.3 % of patients) and increased aspartate aminotransferase (3.6 %) being the most frequent grade ≥ 3 TRAEs.

The novel combined therapy, KN046 plus lenvatinib, demonstrated a clinical benefit in ORR and PFS, as well as a manageable safety profile as first-line treatment of advanced unresectable or metastatic HCC.

RATIONALE-208: Novel option in advanced HCC…

Patients with advanced HCC present an unmet medical need beyond the first-line treatment. Tislelizumab (TIS) is a novel anti-PD-1 antibody that has been successfully investigated as monotherapy or in combination with chemotherapy in various malignancies, like locally advanced or metastatic esophageal squamous cell carcinoma [9], non-small cell lung cancer [10] or previously treated advanced HCC [11]. TIS has been engineered to limit antibody-dependent cellular phagocytosis (ADCP), a potential mechanism of resistance to anti-PD-1 therapies [12, 13]. As first-line treatment for advanced HCC, sorafenib (SOR) or lenvatinib (LEN) continue to be an important part of the clinical armamentarium, even considering recent approval of new immune-oncology-based combinations (e.g., atezolizumab and bevacizumab). In the open-label, multicenter, phase II RATIONALE-208 study (NCT03419897), tislelizumab was clinically active and generally well tolerated in patients with previously treated advanced HCC [14]. A descriptive-only secondary analysis of patients with advanced HCC who had been previously treated with at least one prior line of systemic therapy (SOR/LEN) and had received at least one dose of TIS (200 mg, IV, Q3W) was presented at ASCO 2022 meeting [14]. Clinical activity was evaluated by an independent review committee (IRC) through ORR, DoR, PFS and OS.

After a median follow-up of 12.5 months for patients previously treated with SOR/LEN, IRC-confirmed ORR was 13.6 % (95 % CI, 9.5 - 18.7), including two patients (0.9 %) with a complete response (CR) and 30 patients (12.8 %) with a PR. Overall, 55.3 % of the patients (95 % CI, 48.7 – 61.8) achieved disease control, while the median DoR was not reached at the time of the analysis. The median PFS by IRC was 2.7 months (95 % CI, 1.6 – 2.8) and the median OS was 13.5 months (95 % CI, 10.9 – 15.8) in all treated patients.

Safety data in this study indicated that tislelizumab was generally well tolerated in patients previously treated with SOR/LEN. Overall, 49.4 % of patients had grade ≥ 3 TEAEs, the most common being increased aspartate aminotransferase (AST) (26.0 %), alanine aminotransferase (ALT) (19.6 %), increased blood bilirubin (18.3 %), decreased appetite (16.6 %) and asthenia (16.6 %). Immune-related AEs were experienced by twelve patients (5.1 %), the most frequently reported being hypothyroidism (6.8 %) and hyperthyroidism (2.6 %). Hepatic-related immune-mediated TEAEs reported in ≥ 1 % of patients included increased AST in 4 patients, and increased ALT as well as hepatitis in 3 patients each.

Tislelizumab was clinically active and well tolerated in patients with advanced HCC who have received prior systemic treatment with SOR/LEN. TIS represents an effective second- or third-line therapeutic option.

…and evaluation of hepatitis B virus DNA during tislelizumab treatment

Whether or not TIS treatment is associated with an increase in hepatitis B virus (HBV) DNA, as well as the clinical significance of HBV DNA elevations, during or after tislelizumab treatment is currently being explored in the ongoing phase II RATIONALE-208 trial (NCT03419897) [14].

So far, all 249 patients enrolled in this study had at least one prior systemic therapy for advanced HCC; all patients received TIS (200 mg, IV, Q3W). Approximately half of the recruited patients (n = 128) had a history of HBV infection. Patients with inactive, chronic, or active HBV were eligible if HBV DNA levels were less than 500 IU/mL at screening (patients with detectable hepatitis B surface antigen [HBsAg] or detectable HBV DNA were required to be managed per treatment guidelines). HBV DNA testing was conducted every four cycles if HBV DNA was detectable at screening, or when clinically indicated. The ORR assessed by an IRC in patients with a history of HBV infection was consistent with the ORR observed in the overall population (12.5 % vs 13.3 %, respectively). First results demonstrated that among the 114 patients who were HBsAg positive at baseline (BL), 36 had detectable HBV DNA at BL, and 32 had detectable HBV DNA and HBsAg at BL. In seven patients, clinically significant increased HBV DNA levels were observed compared to BL, independently of the time of TIS initiation. All seven patients were HBsAg positive at BL, had been receiving antiviral treatment for at least 3 months before the first dose of TIS, six of them showed increased ALT

levels compared to BL during the study and four of them had at least a 3-fold increase in ALT, observed concurrently or soon after HBV DNA increases.

IRC-assessed best overall response (BOR) was a PR for one patient, as well as increased HBV DNA and progressive disease for the remaining six patients. HBV-related TEAEs were reported in six of the seven treated patients (grade 3 TEAE of hepatitis B, n = 2; grade 2 TEAE of HBV reactivation, n = 2; increased HBV DNA, with one grade 1 and one grade 3 event, n = 2). All HBV-related TEAEs were non-serious and did not result in discontinuation of TIS.

In this preliminary trial, the clinically significant increases in HBV DNA from BL were reported in a small number of patients; therefore, this does not suggest that TIS is associated with increased HBV DNA. Additionally, HBV DNA increases did not impact the treatment, as tumor responses in these patients were consistent with the overall population and HBV-related TEAEs were manageable. The effect of TIS in patients with HBV infection will be further evaluated in a currently ongoing phase III trial (NCT03412773).

AdvanTIG-206: Dual targeting with anti-TIGIT and anti-PD-1 antibodies

Atezolizumab plus bevacizumab represents the new standard of care in systemic front-line treatment of patients with advanced HCC [16]. However, novel options are needed to further improve overall survival and quality of life in this patient population. In preclinical studies, dual combination with anti-TIGIT and anti-PD-1 has shown synergistic inhibition of tumor growth [17]. Moreover, BAT1706,a biosimilar of bevacizumab - an anti-VEGF antibody - has been described to improve OS rate in HCC [18].

AdvanTIG-206 is a randomized, multicenter, open-label, phase II (NCT04948697) study set out to explore triple targeting of tumors with an anti-TIGIT (ociperlimab, 900 mg, IV, Q3W), an anti-PD-1 (tislelizumab, 200 mg, IV, Q3W) and an anti-VEGF (BAT1706, 15 mg/kg, IV, Q3W) [19]. Eligible patients will be randomized 2:1 either in Arm A to receive the triple therapy or in Arm B for the dual combination of tislelizumab and BAT1706. Eligible patients must have a histologically confirmed HCC (BLCL stage C or stage B that is not amenable to curative treatment), at least one measurable lesion, an ECOG PS of 0 or 1 and no prior systemic therapy. All patients will be treated until loss of clinical benefit or unacceptable toxicity assessed by the investigator.

The primary endpoint is the ORR as evaluated by the investigator according to RECIST v1.1. The DoR, the TTR, the DCR, the clinical benefit rate (CBR), the PFS, the OS, as well as the safety and the tolerability are the secondary endpoints. The aim of this study is to enroll approximately 90 patients with unresectable HCC.

Evaluation of low dose apatinib

Recently, apatinib – a tyrosine kinase inhibitor - has shown promising antitumoral activity in the management of second- or later line of therapy in patients with advanced HCC [20]. At this year's ASCO meeting, a study analyzing the efficacy and safety of low dose apatinib in patients with advanced HCC was presented [21].

Among the 178 patients with advanced HCC enrolled in this real-world study (Chi82170369), 174 received a low dose of oral apatinib (250 mg daily) until disease progression, while four patients were administered a higher dose (500 mg daily). Moreover, 25 patients were also treated with immunotherapy and 103 patients received additional transarterial chemoembolization (TACE) at least once. The endpoints analyzed were tumor response, PFS, OS and safety.

During the 24-month follow-up period, the ORR reached 15.7 % (all patients showing a PR) and the DCR was 73.6 %. **(Figure 2)**. Among the 28 patients with a PR, 27 received apatinib as first- or second-line therapy. Moreover, 21 had a combined treatment with immunotherapy or TACE, indicating early application of apatinib and combination treatment could provide better efficacy. The median OS was 16.0 months and the median PFS was 7.0 months, respectively. A multivariable analysis confirmed that third-line therapy (HR = 3.21; 95 % CI, 1.54 – 6.68; p = 0.002) and portal vein tumor thrombus (HR = 1.75; 95 % CI, 1.13 – 2.70; p = 0.011) were significantly associated with a worse PFS. On the contrary, apatinib combined with immunotherapy (HR = 0.52; 95 % CI, 0.32 – 0.83; p= 0.008) or TACE (HR = 0.27; 95 % CI, 0.18 – 0.40; p< 0.001) were independently associated with a better PFS.

Low dose apatinib was safe in HCC patients, with the most common adverse events being hypertension (29.2 %), fatigue (16.9 %), hand and foot syndrome (16.3 %) and vomiting (14.0 %). Very few grade ≥ 3 AEs were observed; they included decreased platelet, diarrhea, and bradycardia (1 patient each, 0.6 %).

The efficacy outcomes observed in this real-world analysis were significantly better with apatinib compared to clinical data obtained with sorafenib or lenvatinib. Therefore, low dose apatinib could provide a new treatment option for advanced HCC, with early application of ap-

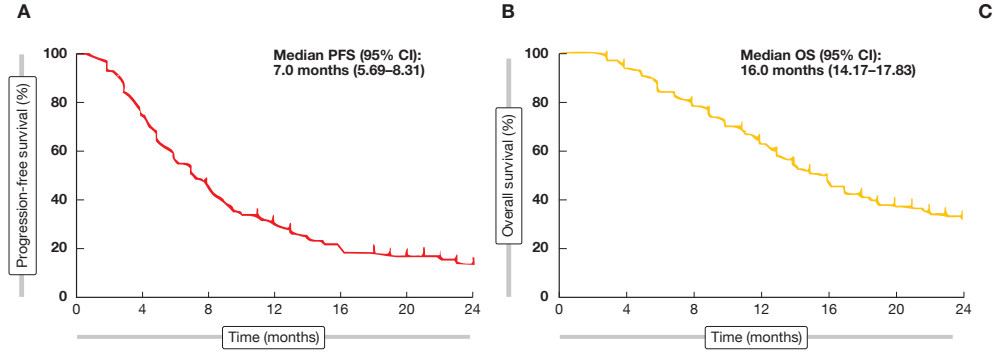


Figure 2: Progression-free survival **(A)**, overall survival **(B)** and response rate **(C)** for all patients treated with apatinib.

atinib and combination treatment potentially providing an even better efficacy.

Sequential treatment with chemoembolization plus radiotherapy followed by immunotherapy

So far, HCC has successfully been managed by the means of therapeutic synergy between loco-regional therapies and checkpoint inhibitors [22, 23]. Avelumab is an immune checkpoint inhibitor that has shown clinical efficacy in several malignancies, including advanced renal cell carcinoma [24], advanced or metastatic urothelial carcinoma [25] and advanced HCC [26].

START-FIT is a single arm, phase II study (NCT03817736) that evaluated the safety and efficacy of sequential transarterial chemoembolization (TACE) and stereotactic body radiotherapy (SBRT), followed by avelumab, in patients with locally advanced HCC [27]. Eligible patients were not candidates for curative resections with locally advanced HCC of at least 5 cm, less than three tumor nodules and child-Pugh A5-B7 liver function. The primary endpoint was the percentage of patients amenable to curable surgery, while the secondary endpoints included ORR according to modified RECIST v1.1, OS and TRAEs. Patients enrolled in this study received a single episode of TACE followed by 5-fraction SBRT (28 days afterwards), followed by avelumab (10 mg/kg, 14 days afterwards and Q2W thereafter).

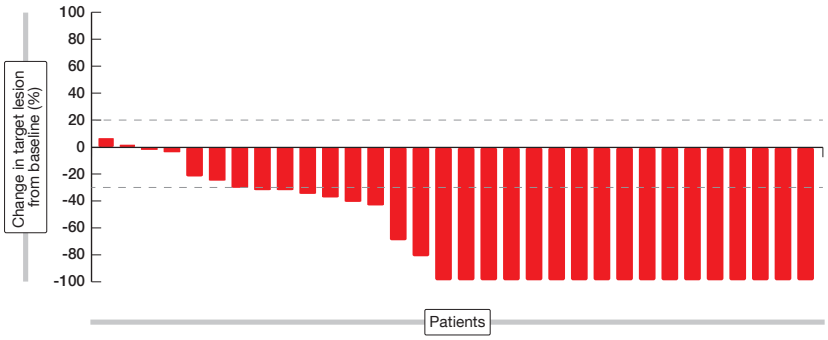


Figure 3: Waterfall plot, change in sum of longest diameter of target lesions from baseline (%).

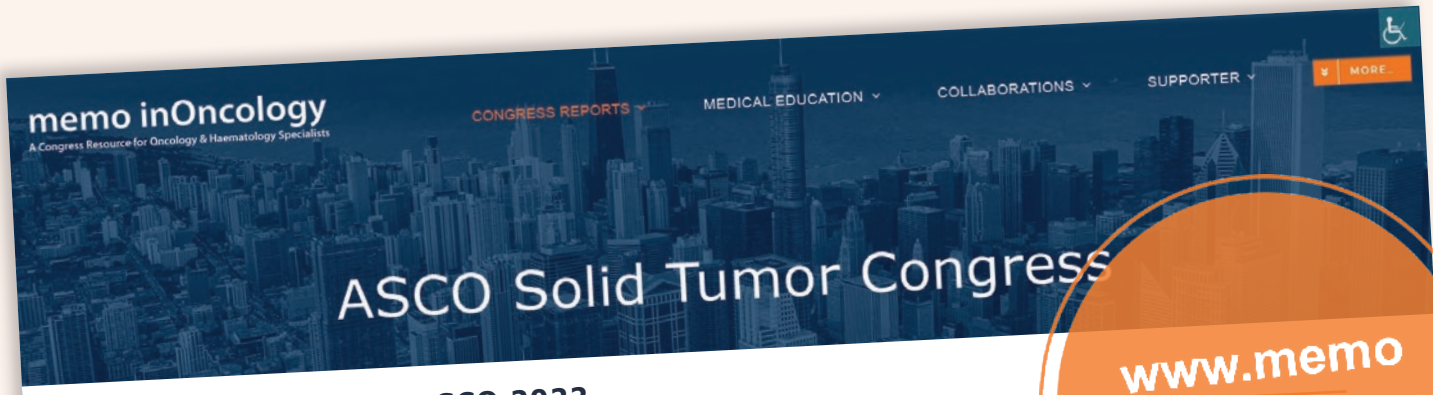
Among the 33 enrolled patients, the median age was 68 years (range, 51 – 81) with only one female patient being recruited. After a median follow-up of 17.2 months, the ORR reached 62.5 % (95 % CI, 45.3 - 77.1), including a CR rate of 43.8 % and a PR rate of 18.8 %. The median OS was 30.3 months (95 % CI, 22.7 - 37.8) and the median PFS was 20.7 months (95 % CI, 14.6 - 26.8). The outcome of this combined treatment on the size of the tumor lesions is shown in **Figure 3**.

In total, ten patients (30.3 %) experienced grade ≥ 3 TRAEs, the most common being a transient increase in ALT/AST (12.1 %) and an increased bilirubin level after TACE (6 %). Five patients (15.2 %) had grade ≥ 3 irAEs (hepatitis, n = 3; dermatitis, n = 2).

In total, only 9 % of the enrolled patients were downstaged to receive curative therapy; the combination of loco-regional treatment and immunotherapy resulted in an unexpected high cure rate of 43 % and a high overall survival rate in patients with locally advanced unresectable HCC. ■

REFERENCES

1 Sung H et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209-249.
2 Finn RS et al., IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020; 382(20): 1894-1905.
3 Cheng AL et al., Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10(1): 25-34.
4 Llovet JM et al., SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359(4): 378-390.
5 Kudo M et al., Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018; 391(10126): 1163-1173.
6 Borbath Y et al., Pembrolizumab monotherapy for previously untreated advanced hepatocellular carcinoma (aHCC): 3-year follow-up of the phase 2 KEYNOTE-224 study. J Clin Oncol 2022; 40(suppl 16; Abstr 4109).
7 Xing B et al., KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) in combination with lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Preliminary efficacy and safety results of a prospective phase II trial. Ann Oncol 2021; 32(suppl 5; S822/938P).
8 Xing B et al., A phase II study combining KN046 (an anti-PD-L1/CTLA-4 bispecific antibody) and lenvatinib in the treatment for advanced unresectable or metastatic hepatocellular carcinoma (HCC): Updated efficacy and safety results. J Clin Oncol 2022; 40(suppl 16; Abstr 4115).
9 Van Cutsem EK et al., Tislelizumab versus chemotherapy as second-line treatment of advanced or metastatic esophageal squamous cell carcinoma (RATIONALE 302): impact on health-related quality of life. ESMO Open 2022; 7(4):100517.
10 Lu S et al., Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. J Thorac Oncol 2021; 16(9):1512-1522.
11 Ren Z et al., Tislelizumab monotherapy for patients with previously treated advanced hepatocellular carcinoma (HCC): RATIONALE-208 Chinese subpopulation. An Oncol 2022; 33(suppl 4:S255/P-25).
12 Zhang T et al., The binding of an anti-PD-1 antibody to FcγRs has a profound impact on its biological functions. Cancer Immunol Immunotherapy 2018; 67(7):1079-1090.
13 Dahah R et al., FcγRs Modulate the Anti-tumor Activity of Antibodies Targeting the PD-1/PD-L1 Axis Cancer Cell 2015; 28:285-295.
14 Edeline J et al., Clinical outcomes associated with tislelizumab in patients (pts) with advanced hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (SOR) or lenvatinib (LEN) in RATIONALE-208. J Clin Oncol 2022; 40(suppl 16; Abstr 4072).
15 Bruix J et al., Update on Medical Treatment for Advanced Hepatocellular Carcinoma. Lancet 2018; 389;58-88
16 Finn RS et al., Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382(20):1894-1905.
17 Ostroumov D et al., Transcriptome Profiling Identifies TIGIT as a Marker of T-Cell Exhaustion in Liver Cancer. Hepatology 2021; 73:1399-1418.
18 Siegel, AB et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J. Clin. Oncol 2008; 26:2992-2998.
19 Fan J et al., AdvanTIG-206: Anti-TIGIT monoclonal antibody (mAb) ociperlimab (BGB-A1217;OCI) plus anti-programmed cell death protein-1 (PD-1) mAb tislelizumab (TIS) plus BAT1706 versus TIS plus BAT1706 as first-line (1L) treatment for advanced hepatocellular carcinoma (HCC). J Clin Oncol 2022; 40(suppl 16; Abstr TPS4172).
20 Qin S et al., Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol 2021; 6(7):559-568.
21 Meng L et al., Efficacy and safety of low-dose apatinib in advanced hepatocellular carcinoma. J Clin Oncol 2022; 40(suppl 16; Abstr 4104).
22 Llovet JM et al., Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2021; 18(5):293-313.
23 Lee YH et al., Combinational Immunotherapy for Hepatocellular Carcinoma: Radiotherapy, Immune Checkpoint Blockade and Beyond. Front Immunol 2020; 11:568759.
24 Choueiri TK et al., Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. Ann Oncol 2020; 31(8):1030-1039.
25 Powles T et al., Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med 2020; 383(13):1218-1230.
26 Kudo M et al., Avelumab in Combination with Axitinib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma: Results from the Phase 1b VEGF Liver 100 Trial. Liver Cancer 2021; 10(3):249-259.
27 Chiang CL et al., Sequential trans-arterial chemoembolization and stereotactic body radiotherapy followed by immunotherapy (START-FIT) for locally advanced hepatocellular carcinoma: A single-arm, phase II trial. J Clin Oncol 2022; 40(suppl 16; Abstr 4091).



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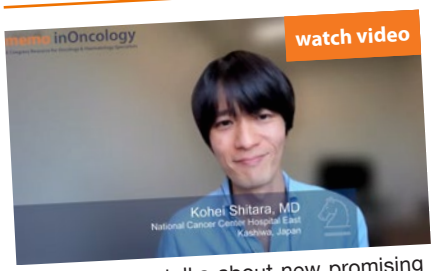
Expert interviews at ASCO 2022



Kohei Shitara talks about new promising agents in the treatment of advanced HER2-positive gastric/gastroesophageal junction adenocarcinoma and how existing drugs can blend into these new regimens. He overviews the current state of prognostic and predictive biomarkers in gastric cancer and gives an outlook on new biomarkers that are on the rise to guide therapy while finally summarizing his personal medical and scientific highlights at this year's ASCO meeting.

Anna Spreafico depicts her personal highlights regarding immunotherapy plus chemotherapy or intensity-modulated radiotherapy for people with locally advanced nasopharyngeal cancer (NPC) at this year's ASCO meeting, discusses if longitudinal plasma EBV DNA monitoring should be incorporated into the guidance of personalized disease management and future clinical trials, highlights the most promising agents explored in the 1L treatment of recurrent/metastatic NPC and overviews how the prognosis of those patients will evolve in the years to come.

Ian Chau summarizes the notable efficacy and safety data obtained with nivolumab plus chemotherapy or ipilimumab versus chemo as 1L treatment for advanced ESCC in the CheckMate 648 trial and explains the role of EGFR inhibitors in the treatment of ESCC, especially in combination with radiation. He focuses on the treatment paradigm in advanced/metastatic ESCC and how it might change in the near future while also explaining the barriers to implementing precision oncology in the setting of ESCC.

Julien Edeline highlights which clinical trials examining combination approaches are anticipated to expand the treatment armamentarium for treatment-naïve patients with unresectable HCC and which new agents are promising in the second- and third-line treatment of advanced HCC. He gives an outlook on how the prognosis of patients with advanced HCC will evolve in the years to come while focusing on the quality of life in HCC as well as the impact of systemic treatment on it.

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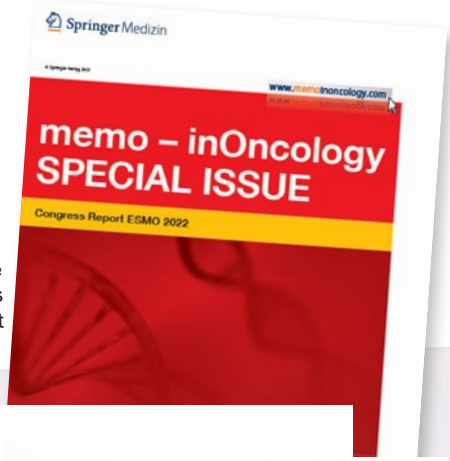

Forthcoming Special Issue

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

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