LBA292 **Oral Abstract Session**

Zolbetuximab + mFOLFOX6 as first-line (1L) treatment for patients (pts) withclaudin-18.2+ (CLDN18.2+) / HER2− locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary results from phase 3 SPOTLIGHT study

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Background: 1L treatment for pts with HER2−, mG/GEJ adenocarcinoma is typically chemotherapy and immunotherapy; an unmet need still exists. CLDN18.2 is expressed in normal gastric mucosa cells and retained in mG/GEJ tumor cells. In the FAST study, zolbetuximab, which targets CLDN18.2, prolonged survival of pts with LA unresectable or mG/GEJ adenocarcinoma when combined with chemotherapy. SPOTLIGHT (NCT03504397) is a phase 3 global, double-blind study comparing zolbetuximab + folinic acid, 5-FU, and oxaliplatin (mFOLFOX6) vs placebo + mFOLFOX6 as 1L treatment for pts with CLDN18.2+/ HER2−, LA unresectable or mG/GEJ adenocarcinoma. **Methods:** Previously untreated pts with CLDN18.2+ (moderate-to-strong membrane staining in ≥75% tumor cells by IHC)/HER2− LA unresectable or mG/GEJ adenocarcinoma were randomized 1:1 to zolbetuximab IV 800 mg/m^2 (cycle [C] 1, day [D] 1) followed by 600 mg/m^2 (C1D22, and every 3 weeks in later cycles) + mFOLFOX6 IV (D1, 15, 29) for four 42-day cycles vs placebo + mFOLFOX6; pts without PD continued for >4 cycles with zolbetuximab or placebo, + folinic acid and 5-FU at investigator's discretion until PD or discontinuation criteria were met. The primary endpoint (EP) was PFS per RECIST v1.1 by IRC. Secondary EPs included OS, ORR, and safety. Differences in efficacy between treatment arms were tested by stratified log rank tests; OS was tested if PFS was significant. **Results:** Among 2735 pts screened, 565 pts were randomized 1:1 to zolbetuximab + mFOLFOX6 (N = 283) or placebo + mFOLFOX6 (N = 282). PFS was statistically significantly improved with zolbetuximab + mFOLFOX6 (median 10.61 vs 8.67 mo, HR 0.751, *P*=0.0066; Table). OS was also significantly improved (median 18.23 vs 15.54 mo, HR 0.750, *P*=0.0053, < 0.0135 as boundary; Table). ORR was similar between treatment arms. Most common TEAEs with zolbetuximab + mFOLFOX6 were nausea (82.4% vs 60.8% in zolbetuximab vs placebo arms), vomiting (67.4% vs 35.6%), and decreased appetite (47.0% vs 33.5%); the incidences of serious TEAEs were similar between both arms (44.8% vs 43.5%). **Conclusions:** Targeting CLDN18.2 with 1L zolbetuximab combined with mFOLFOX6 statistically significantly prolonged PFS and OS in pts with CLDN18.2+/ HER2−, LA unresectable or mG/GEJ adenocarcinoma. TEAEs were consistent with previous studies. Zolbetuximab + mFOLFOX6 may be a new option for these pts. Funding source: This study was funded by Astellas Pharma Inc. Medical writing support, conducted in accordance with Good Publication Practice (GPP 2022) and the International Committee of Medical Journal Editors (ICMJE) guidelines, was provided by Ann Ferguson, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and funded by Astellas Pharma Inc. Clinical trial information: NCT03504397. Research Sponsor: Astellas Pharma, Inc.

Table. Efficacy responses.

	Zolbetuximab + mFOLFOX6 (N = 283)	Placebo + mFOLFOX6 (N = 282)
PFS		
Events, n (%)	146 (51.6)	167 (59.2)
Median, mo (95% CI)	10.61 (8.90–12.48)	8.67 (8.21–10.28)
HR (95% CI); *P*-value (1-sided)	0.751 (0.598–0.942); 0.0066	
OS		
Deaths, n (%)	149 (52.7)	177 (62.8)
Median, mo (95% CI)	18.23 (16.43–22.90)	15.54 (13.47–16.53)
HR (95% CI); *P*-value (1-sided)	0.750 (0.601–0.936); 0.0053	

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LBA-1 RATIONALE-306: Randomized, global, placebo-controlled, double-blind phase 3 study of tislelizumab plus chemotherapy versus chemotherapy as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma (ESCC)

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Background: Tislelizumab, an anti-programmed cell death protein 1 antibody, has demonstrated a survival benefit as second-line treatment in ESCC. Here, we report interim analysis (IA) data from the phase 3 RATIONALE-306 study, which evaluated the efficacy and safety of tislelizumab plus chemotherapy vs placebo plus chemotherapy in patients with advanced or metastatic ESCC in the first-line setting.

Methods: In this randomized, double-blind, global study, adults with unresectable locally advanced or metastatic ESCC, with no prior systemic treatment for advanced disease were enrolled regardless of programmed death-ligand 1 (PD-L1) expression status. Patients were randomized (1:1) to receive tislelizumab 200 mg (Arm A) or placebo (Arm B) intravenously once every three weeks, both in combination with investigator-chosen chemotherapy (ICC; platinum [cisplatin or oxaliplatin] and fluoropyrimidine [capecitabine or 5-FU] or platinum and paclitaxel) until disease progression per RECIST v1.1, intolerable toxicity, or withdrawal. Randomization was stratified by geographic region, prior definitive therapy and ICC. The primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Hierarchical sequentially-tested secondary endpoints were progression-free survival (PFS), objective response rate (ORR) by the investigator, OS in the PD-L1 score ≥10% subgroup, and health-related quality of life. Other secondary endpoints included duration of response (DoR) by the investigator, and safety.

Results: Of 649 patients enrolled from 16 countries/4 regions (74.9% and 25.1% from Asia and non-Asian countries [Europe, Oceania, and North America]), 326 and 323 patients were randomized to Arms A and B, respectively (ITT population). At data cutoff (28/02/2022), median follow-up was 16.3 and 9.8 months in Arms A and B, respectively. The study met its primary endpoint at IA by demonstrating statistically significant improvement in OS in Arm A vs Arm B (median OS: 17.3 vs 10.6 months; HR 0.66 [95% CI 0.54, 0.80], $p<0.0001$). OS improvement was consistently observed across prespecified subgroups including ICC option, region, and PD-L1 expression status. In patients with PD-L1 score ≥10%, Arm A also demonstrated significant improvement in OS vs Arm B (median OS: 16.8 vs 10.0 months, HR 0.61 [95% CI 0.44, 0.85], p=0.0017). A significant improvement in PFS was observed in Arm A vs Arm B (median PFS: 7.3 vs 5.6 months; HR 0.62 [95% CI 0.52, 0.75], $p<0.0001$). Arm A was associated with a higher ORR (63.5% vs 42.4%, odds ratio 2.38 [95% CI 1.73, 3.27], $p<0.0001$) and more durable response (median DoR: 7.1 [95% CI 6.1, 8.1] vs 5.7 months [95% CI 4.4, 7.1]) than Arm B. Overall, similar proportions of patients in Arms A and B had ≥1 treatment-related treatment-emergent adverse event (TRAE; 96.6% and 96.3%), ≥Grade 3 TRAEs (66.7% vs 64.5%), and TRAEs leading to death (1.9% vs 1.2%), respectively. Serious TRAEs occurred in 28.7% vs 19.3%, and treatment-emergent AEs leading to discontinuation occurred in 31.8% vs 22.4% in Arms A vs B. No new safety signal for tislelizumab was observed.

Conclusions: Tislelizumab plus chemotherapy as first-line treatment demonstrated a statistically significant and clinically meaningful improvement in OS over placebo plus chemotherapy in patients with advanced or metastatic ESCC, with a manageable safety profile.

Clinical trial identification: NCT03783442.

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LBA-2 Primary analysis of MOUNTAINEER: A phase 2 study of tucatinib and trastuzumab for HER2-positive mCRC

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Background: Despite the occurrence of HER2 amplification/overexpression (HER2+) in ~3% to 5% of all patients with metastatic colorectal cancer (mCRC) and up to ~10% of patients with RAS/BRAF wild-type mCRC, there are currently no FDA- or EMA-approved HER2-directed therapies for HER2+ mCRC. Patients with mCRC who progress on early lines of chemotherapy regimens receive limited clinical benefit from current standard-of-care treatments. Tucatinib is a highly selective, HER2-directed, tyrosine kinase inhibitor. The MOUNTAINEER trial (NCT03043313) was initiated to evaluate the efficacy and safety of the investigational combination of tucatinib with trastuzumab in patients with HER2+ mCRC. Here we present results from the primary analysis of MOUNTAINEER.

Methods: MOUNTAINEER is a multi-center, open-label, randomised, phase 2 trial conducted in the US and Europe. Eligible patients had HER2+ (one or more local tests: 3+ immunohistochemistry, 2+ immunohistochemistry with amplification by in situ hybridization, or amplification by next-generation sequencing of tumor tissue) and RAS wild-type mCRC with progression on or intolerance to fluoropyrimidine, oxaliplatin, irinotecan, and an anti-VEGF antibody. Measurable disease and an ECOG performance status of 0–2 were required. Previous HER2-directed therapies were not permitted. The trial initially consisted of a single cohort (Cohort A) to be treated with tucatinib (300 mg PO BID) and trastuzumab (8 mg/kg IV then 6 mg/kg IV every 3 weeks). The trial was expanded to include patients randomised 4:3 to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C). The primary endpoint is confirmed objective response rate (ORR) per RECIST 1.1 by blinded independent central review (BICR) in Cohorts A+B. Secondary endpoints include duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety and tolerability.

Results: MOUNTAINEER enrolled 117 patients between 08Aug2017 and 22Sept2021. Data cutoff was 28Mar2022. The median age was 56.0 years (range, 24, 77), and baseline characteristics were balanced across cohorts. Eighty-six patients received at least 1 dose of study treatment in Cohorts A+B, and 30 patients received tucatinib monotherapy in Cohort C (total, 116). The overall median duration of follow-up was 16.3 months (IQR, 10.8, 28.2). In Cohorts A+B, the confirmed ORR by BICR was 38.1%

(95% CI, 27.7, 49.3). The median DOR was 12.4 months (95% CI, 8.5, 20.5). The median PFS was 8.2 months (95% CI, 4.2, 10.3), and the median OS was 24.1 months (95% CI, 20.3, 36.7). The most common adverse events (AEs) in Cohorts A+B were diarrhoea (64.0%), fatigue (44.2%), nausea (34.9%), and infusion-related reaction (20.9%); the most common AE of grade ≥3 was hypertension (7.0%). Adverse events leading to tucatinib discontinuation in Cohorts A+B occurred in 5.8% of patients and included alanine amino transferase increase (2.3%), COVID-19 pneumonia (1.2%), cholangitis (1.2%), and fatigue (1.2%). No deaths resulted from AEs.

Conclusions: In patients with chemotherapy-refractory HER2+ mCRC, tucatinib in combination with trastuzumab was well tolerated with clinically meaningful anti-tumor activity including durable responses and a median overall survival of 2 years. Tucatinib in combination with trastuzumab has the potential to become a new standard of care for patients with HER2+ mCRC.

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LBA O-9 Botensilimab, a novel innate/adaptive immune activator, plus balstilimab (anti-PD-1) for metastatic heavily pretreated microsatellite stable colorectal cancer

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Background: Botensilimab (BOT) promotes optimized T cell priming, activation and memory formation by strengthening antigen presenting cell/T cell co-engagement. As a fragment crystallizable (Fc)-enhanced next-generation anti—cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, BOT also promotes intratumoral regulatory T cell depletion via enhanced Fc gamma receptor signaling and activation on natural killer cells and macrophages. Further, BOT is specifically engineered to avoid complement binding and complement-mediated toxicities including hypophysitis. This analysis presents results from patients with microsatellite stable colorectal cancer (MSS CRC) treated with BOT + balstilimab (BAL; an anti-programmed cell death 1 [PD-1] antibody), in an expanded phase IA/B study; NCT03860272.

Methods: Patients with metastatic MSS CRC received BOT at 1 or 2 mg/kg every 6 weeks (Q6W) + BAL 3 mg/kg every 2 weeks and were evaluable with ≥1 Q6W tumor imaging assessment. Primary and secondary endpoints include incidence of adverse events (AE), objective response rate (ORR), disease control rate (DCR; patients with a best overall response of either stable disease [SD] or a complete [CR] or partial response [PR]), duration of response (DOR), progression free survival (PFS), and overall survival (OS). Enrollment is ongoing.

Results: Forty-one evaluable patients are included in this analysis. Patients were heavily pretreated and the median number of prior lines of therapy was 4 (range, 2-10) including 34% with prior immunotherapy. ORR measured 24% (10/41), DCR was 73% (30/41), and DOR ranged from 0.0+-17.0+ months. Median follow-up is 5.8 months (range, 1.6-24.4). In patients with no history of liver metastases or status post resection or ablation of liver metastases without recurrence (n=24), ORR was 42% (10/24) and DCR was 96% (23/24), with eight of ten responses ongoing. Additionally, a patient with SD by RECIST 1.1 developed an ongoing metabolic CR by PET with CEA normalization. In responders, metastatic sites included soft tissue, peritoneum, retroperitoneum, pleural effusions, bone, lungs, and lymph nodes. Of the ten responders, five had RAS mutations (4 KRAS, 1 NRAS), none had BRAF mutations, one had a TMB of ≥10 mutations/Mb (TMB=10), one was reported PD-L1 positive (50% combined positive score by IHC 22C3 pharmDx, Agilent) and none had POLE mutations. The safety profile in all 41 patients is favorable with no cases of hypophysitis. Most AEs were grade 1 or 2; grade 3 treatment-related AEs (TRAEs) occurred in 24% of patients, with no grade 4 or 5 TRAEs reported. Diarrhea/colitis was the only grade 3 TRAE occurring in more than one patient (10%). Eight patients (20%) discontinued BOT and four patients (10%) discontinued BOT + BAL due to a TRAE. Immune and genomic analyses are ongoing.

Conclusions: BOT + BAL demonstrates unprecedented activity for immunotherapy in heavily pretreated patients with metastatic MSS CRC and manageable safety, consistent with its design. The ORR and DOR, including compelling efficacy in patients without liver metastases, are informing phase 2/3 study designs.

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LBA661 **Oral Abstract Session**

NAPOLI-3: A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).

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Background: Liposomal irinotecan administered with 5-fluorouracil/leucovorin (5-FU/LV) is approved in the USA and Europe for mPDAC following progression with gemcitabine-based therapy. A phase 1/2 study (Wainberg *et al. Eur J Cancer* 2021;151:14–24; NCT02551991) demonstrated promising antitumor activity in patients with mPDAC who received first-line liposomal irinotecan 50 mg/m^2 + 5-FU 2400 mg/m^2 + LV 400 mg/m^2 + oxaliplatin 60 mg/m^2 (NALIRIFOX). Herein, we present results from NAPOLI-3 (NCT04083235), a randomized, open-label, phase 3 study investigating the efficacy and safety of NALIRIFOX compared with nab-paclitaxel + gemcitabine as first-line therapy in patients with mPDAC. **Methods:** Eligible patients with histopathologically/cytologically confirmed untreated metastatic PDAC were randomized (1:1) to receive NALIRIFOX on days 1 and 15 of a 28-day cycle or nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 (Gem+NabP) on days 1, 8 and 15 of a 28-day cycle. Randomization was stratified by ECOG performance status, geographic region and presence or absence of liver metastases. The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), overall response rate (ORR) and safety. OS was evaluated when $\geq$ 543 events were observed using a stratified log-rank test with an overall 1-sided significance level of 0.025. **Results:** Overall, 770 patients (NALIRIFOX, n = 383; Gem+NabP, n = 387) were included. Baseline characteristics were well balanced between arms. At a median follow-up of 16.1 months, 544 events had occurred. The median OS was 11.1 months in the NALIFIROX arm as compared with 9.2 months in the Gem+NabP arm (HR 0.84 [95% CI 0.71–0.99]; p = 0.04); PFS was also significantly improved (7.4 months vs 5.6 months; HR 0.70 [0.59–0.84]; p = 0.0001). Grade 3/4 treatment-emergent adverse events (TEAEs) with $\geq$ 10% frequency in patients receiving NALIRIFOX versus Gem+NabP included diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%) and neutropenia (14.1% vs 24.5%). **Conclusions:** First-line NALIRIFOX demonstrated clinically meaningful and statistically significant improvement in OS and PFS compared with Gem+NabP in treatment-naïve patients with mPDAC. The safety profile of NALIRIFOX was manageable and consistent with the profiles of the treatment components. Funding: Funded by Ipsen. Clinical trial information: NCT04083235. Research Sponsor: Ipsen.

	NALIRIFOX (n = 383)	Gem+NabP (n = 387)
Median OS (95% CI), months	11.1 (10.0–12.1)	9.2 (8.3–10.6)
OS Hazard Ratio (95% CI); p value	0.84 (0.71–0.99); p = 0.04	
Median PFS (95% CI), months	7.4 (6.0–7.7)	5.6 (5.3–5.8)
PFS Hazard Ratio (95% CI); p value	0.70 (0.59–0.84); p = 0.0001	
ORR (95% CI), %		
CR + PR	41.8% (36.8%–46.9%)	36.2% (31.4%–41.2%)