P-26 HERIZON-GEA-01: A phase 3 study of zanidatamab in combination with chemotherapy with or without tislelizumab in first-line human epidermal growth factor receptor 2 positive (HER2+) advanced/metastatic gastroesophageal adenocarcinoma (GEA)

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Background: Gastroesophageal adenocarcinomas (GEAs), including gastric, esophageal, and gastroesophageal junction (GEJ) adenocarcinomas, are common cancers with high morbidity and mortality. In approximately 25% of GEA cases, HER2 is overexpressed/amplified. Patients with advanced/metastatic HER2+ GEA are typically treated with trastuzumab, a HER2-targeted therapy, plus chemotherapy in the first-line setting. Preliminary data suggests that the addition of an immune checkpoint inhibitor to the treatment regimen may further improve patient outcomes. Zanidatamab is a novel, bispecific HER2-targeting monoclonal antibody (mAb) that binds to two non-overlapping extracellular domains (ECD4 and ECD2) on HER2. This bispecific binding forms HER2 clusters and induces greater internalization and downregulation of cell surface HER2 compared to trastuzumab (as observed in preclinical studies). Zanidatamab also causes growth signal reduction and triggers immune-mediated antitumor activity through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). Early studies have shown that zanidatamab has a manageable safety profile with encouraging antitumor activity in HER2+ GEA, when used both as a monotherapy and in combination with chemotherapy in later-line treatment. In the first-line setting in a phase 2 study, zanidatamab plus chemotherapy demonstrated a confirmed objective response rate (ORR) of 75%, median duration of response (DOR) of 16.4 months, and median progression-free survival (PFS) of 12.0 months. Separately, the anti-programmed cell death-1 (PD1) mAb tislelizumab has demonstrated a manageable safety profile and clinical activity in multiple cancers, including gastric and GEJ adenocarcinoma. The combination of zanidatamab with chemotherapy plus tislelizumab is being studied in an ongoing phase 1b/2 study and has recently completed accrual. HERIZON-GEA-01 (NCT05152147; EudraCT#: 2021-000296-36), is a global, randomized, open-label, active-comparator, phase 3 study that will further investigate the efficacy and safety of zanidatamab in combination with chemotherapy with or without tislelizumab as first-line treatment for patients with advanced/metastatic HER2+ GEA.

Trial design: Key eligibility criteria include: age $\geq$ 18 years, untreated, unresectable locally advanced/metastatic GEA that is HER2+ (IHC3+ or IHC2+/ISH+) per central testing, ECOG PS of 0 or 1, and adequate organ function, including LVEF $>$ 50%. Enrolled patients will be assigned randomly (1:1:1) to either: trastuzumab (6 mg/kg IV Q3W) plus chemotherapy; zanidatamab (1800 mg IV [patient 2 IV Q3W and capecitabine 1000 mg/m^2 oral BID on days 1—15) or FP (cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2 continuous IV on days 1—5). The primary endpoints of the study are PFS per RECIST v1.1 assessed by blinded independent central review (BICR), and overall survival. Secondary endpoints include: BICR-assessed confirmed ORR and DOR; investigator-assessed PFS, ORR, and DOR; incidence and severity of AEs; and changes in health-related quality of life (HRQoL). 714 patients are planned to be enrolled from ~300 sites in 30+ countries across North America (not including the US), South America, Europe, Africa, Asia, and Oceania. The study is currently recruiting patients.

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Legal entity responsible for the study: Sponsor.

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P-27 Phase 2 study of pembrolizumab-based combination therapy in patients with microsatellite instability-high or mismatch repair-deficient stage IV colorectal cancer

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Background: The PD-1 inhibitor pembrolizumab has shown robust clinical activity in patients with mismatch repair-deficient or microsatellite instability-high (dMMR/MSI-H) metastatic colorectal cancer (CRC). However, given the response rate of 45% with first-line pembrolizumab monotherapy demonstrated in KEYNOTE-177, there is room for improvement. Targeting a different pathway such as CTLA-4, LAG-3, TIGIT, or ILT4 using a second checkpoint inhibitor may improve the efficacy of PD-1 inhibition. This ongoing, open-label, multicenter, multiarm, randomized, phase 2 trial (NCT04895722) will enroll patients in 2 cohorts, A and B. This study will evaluate efficacy and safety of coformulated pembrolizumab and anti—CTLA-4 quavonlimab compared with pembrolizumab monotherapy in chemotherapy-refractory stage IV dMMR/MSI-H CRC in cohort A. In cohort B, the study will evaluate the efficacy and safety of 4 pembrolizumab-based combinations (coformulated pembrolizumab with either quavonlimab, anti—LAG-3 favezelimab, or anti-TIGIT vibostolimab; anti-ILT4 antibody MK-4830 given sequentially with pembrolizumab) compared with pembrolizumab monotherapy in previously untreated stage IV dMMR/MSI-H CRC.

Trial design: This trial will enroll patients aged $\geq$18 years with histologically confirmed dMMR/MSI-H stage IV CRC that is measurable by investigator, per RECIST v1.1, and confirmed by blinded independent central review (BICR). Cohort A will include patients who experienced disease progression after the following therapies: chemotherapy (fluoropyrimidine, irinotecan, and oxaliplatin), with or without anti-VEGF antibody, and anti-EGFR antibody for patients with left-sided tumors that are RAS wild type. Cohort B will include patients who have not been previously treated for metastatic disease. Additional eligibility criteria for both cohorts include ECOG performance status 0 or 1, adequate organ function, and availability of archival or newly obtained tissue sample. Patients with autoimmune disease, active CNS metastases, and those who received systemic therapy within 4 weeks or radiotherapy within 2 weeks before intervention will be excluded. Patients in cohort A will be randomly assigned 1:1 to receive either coformulated quavonlimab 25 mg/pembrolizumab 400 mg IV Q6W or pembrolizumab 400 mg IV Q6W. Patients in cohort B will be randomly assigned 1:1:1:1:1 to receive coformulated quavonlimab 25 mg/pembrolizumab 400 mg IV Q6W, favezelimab 800 mg/pembrolizumab 200 mg IV Q3W, vibostolimab 200 mg/pembrolizumab 200 mg IV Q3W, MK-4830 800 mg + pembrolizumab 200 mg IV Q3W (given sequentially), or pembrolizumab 400 mg IV Q6W. Patients will be stratified by RAS mutation (mutant vs wild type). Treatment will continue for $\leq$2 years or until unacceptable toxicity, disease progression, confirmed CR (after $\geq$6 months of study treatment and patients have received $\geq$6 weeks of treatment after initial CR), or withdrawal from study. Disease assessment will be performed by CT or MRI at screening (within 28 days before treatment) and every 9 weeks thereafter. For both cohorts, primary end point is ORR by BICR per RECIST v1.1; secondary end points are ORR assessed by investigator, duration of response and PFS assessed by BICR and by investigator per RECIST v1.1, OS, and safety and tolerability graded per NCI CTCAE v5.0. Enrollment in this trial is ongoing.

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P-28 Real-world observational study of MVASI in metastatic colorectal cancer patients in Canada: Baseline patient characteristics

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Background: MVASI is a biosimilar to bevacizumab, a recombinant immunoglobulin G1 monoclonal antibody binding the vascular endothelial growth factor. Following comprehensive analytical characterization, MVASI was shown to be comparable to the reference product bevacizumab. It became one of the first therapeutic biosimilars approved by Health Canada for the treatment of all previously approved bevacizumab indications, including metastatic colorectal cancer (mCRC). To address Canadian healthcare stakeholders' focus on real-world evidence generation for oncology biosimilars, this study aims to characterize Canadian mCRC patients treated with MVASI and to describe the real-world safety and effectiveness of MVASI.

Methods: This retrospective observational chart review included adult patients who received ≥1 MVASI cycle as their first-line biologic treatment for mCRC. Baseline demographics and cancer characteristics were collected from medical records within six months of pre-MVASI initiation (index date). Medical history, adjuvant treatment, and CRC diagnosis data were gathered within five years of pre-index date. MVASI safety and effectiveness data collection spanned from index date to chart review date. The initial data described herein were collected approximately one-year post-MVASI availability; a second wave of data collection will include centers where MVASI has been available for approximately two years, thereby allowing for increased follow-up period.

Results: Most participants were recruited from Quebec (35/75; 46.7%) and Ontario (22/75; 29.3%). Among the 75 eligible participants, 39/75 (52.0%) were female, 38/75 (50.7%) were Caucasian, and the median age was 62 years. Most participants never smoked (32/75; 43%), followed by former (19/75; 25.3%), and current smokers (16/75; 21.3%). Among those with a recorded Eastern Cooperative Oncology Group status at baseline, most had a grade of 0 (27/62; 43.5%) or 1 (33/62; 53.2%). Normal stool habit was reported for 27/75 (36.0%) participants, while no record was available for 31/75 (41.3%) participants. Most participants with a recorded Charlson comorbidity index had a score of 6-10 (28/38; 73.7%). The most common comorbidity was cardiovascular disease (21/75; 28.0%), and the use of anti-hypertensive therapies was reported for 22/75 (29.3%) participants. At mCRC diagnosis, TNM stage in most participants was T3 (22/75; 29.3%) or T4a (26/75; 34.7%), N1 (13/75; 17.3%) or unknown N stage (14/75; 18.7%), and M1 (27/75; 36.0%) or unknown M stage (26/75; 34.7%). Most primary tumours were left-sided, involving the rectum (18/75; 24.0%) or sigmoid colon (17/75; 22.7%) and were moderately differentiated (32/75; 42.7%). RAS or BRAF mutations were reported in 42/69 (60.9%) and 14/63 (22.2%) participants, respectively. All participants had either one (40/75; 53.3%) or two-to-three metastatic sites (35/75; 46.7%) that were primarily located in the liver (48/75; 64.0%). The median time from mCRC diagnosis to MVASI initiation was 3.1 months (interquartile range (2.1, 4.2)).

Conclusions: Patients with mCRC included in the first wave were generally representative of the Canadian mCRC population treated with first-line bevacizumab. Compared with other published Canadian studies, differences in patient characteristics included a longer period of first-line therapy initiation and a higher proportion of patients with RAS mutation. It is anticipated that upcoming additional observations from this study will refine the real-world profile of this patient population.

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P-29 Overall survival and treatment patterns in patients with metastatic colorectal cancer (CRC): A retrospective chart review

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Background: Colorectal cancer (CRC) is one of the most prevalent cancers worldwide and the second most diagnosed cancer in Europe. This study aimed to describe demographic and clinical characteristics, treatment patterns, and overall survival (OS) for metastatic CRC (mCRC) patients in the UK.

Methods: This was an observational, single-centre, retrospective chart review of patients receiving systemic treatment (chemotherapy with or without targeted biologics), radiotherapy, surgery or best supportive care for mCRC at the University College London Hospital between 01 January 2011 to 31 December 2016. The index date was defined as the date of first confirmed diagnosis of mCRC.

Results: In total, 107 patients (mean age 58.8 years, male [52.3%] with Eastern Cooperative Oncology Group performance status 0/1 [70.4%]) met the eligibility criteria. The majority of patients were white (73.8%), had grade 2 or moderately differentiated tumours (59.8%) and had not undergone prior resection (86.0%). The most commonly received first- and second-line therapies included FOLFOX and FOLFIRI chemotherapy regimens with or without targeted biologicals e.g., bevacizumab or cetuximab. Later lines of therapy included re-challenge with pervious chemotherapy regimens, trifluridine—tipiracil chemotherapy or a switch to palliative non-systemic therapies, e.g., surgery, radiotherapy or best supportive care. The mean time from diagnosis to initiation of first-line therapy was 53.1 days (SD: 97.1 days). The median OS for the entire cohort (from index date) was 20.2 months; one-, two- and four-year OS were 70.8%, 41.6% and 13.4%, respectively. Median OS was 17.6, 14.0, 10.5, 10.1, and 8.3 months when stratified by initiation of first-, second-, third-, fourth-, and fifth-line therapy, and the corresponding one-year OS were 64.6%, 56.0%, 42.2%, 35.5%, and 19.2%, respectively.

Conclusions: In this real-world cohort, patients diagnosed with mCRC survive on average less than two years with limited therapeutic options, particularly following first- and second-line therapy. This highlights the need for novel treatments to improve survival in this patient population.

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