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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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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