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 Advanced/Metastatic Gastroesophageal Adenocarcinoma

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Topic: Gastrointestinal

Objective: 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, human epidermal growth factor receptor 2 (HER2) is overexpressed/amplified. Patients with advanced/metastatic HER2 positive (HER2+) GEA are typically treated with trastuzumab, a HER2-targeted therapy, plus chemotherapy in the first-line setting. Preliminary data suggest 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, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity. 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 (PD-1) 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.

Methods: 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.

Key eligibility criteria include: aged ≥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 left ventricular ejection fraction >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 <70 kg] or 2400 mg IV [≥70 kg] Q3W) plus chemotherapy; or zanidatamab plus chemotherapy plus tislelizumab (200 mg Q3W). In all treatment arms, chemotherapy will be the investigator's choice of either CAPOX (oxaliplatin 130 mg/m^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 adverse events; and changes in health-related quality of life. Seven hundred fourteen 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.

Results: N/A

Conclusions: N/A