HERIZON-GEA-01: Phase 3 study of zanidatamab (ZANI) + chemotherapy (chemo) ± tislelizumab (TIS) in first-line (1L) human epidermal growth factor receptor 2 positive (HER2+) locally advanced (LA)/metastatic gastroesophageal adenocarcinoma (GEA)

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Abstract body:

Background: GEAs have high morbidity and mortality. In ~25% of GEAs, HER2 is overexpressed/amplified. Patients (pts) with LA/metastatic HER2+ GEA usually receive anti-HER2 monoclonal antibody (mAb) trastuzumab (TRAS) + chemo in the 1L setting. Preliminary data suggest that addition of an immune checkpoint inhibitor to the treatment regimen may improve patient outcomes. ZANI is a novel, bispecific anti-HER2 mAb that binds two non-overlapping HER2 extracellular domains (ECD4 and ECD2). This bispecific binding forms HER2 clusters, inducing greater internalization and downregulation of cell-surface HER2 vs TRAS (in preclinical studies). ZANI 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 ZANI ± chemo has a manageable safety profile with encouraging antitumor activity in later-line HER2+ GEA treatment. In a 1L phase (ph)2 study, ZANI + chemo demonstrated a confirmed ORR of 75%, median DoR of 16.4 months, and median PFS of 12.0 months in HER2+ GEA. Separately, the anti-PD-1 mAb TIS has shown a manageable safety profile and clinical activity in multiple cancers, including GEA. ZANI + chemo + TIS is being studied in an ongoing ph1b/2 study that has completed accrual. HERIZON-GEA-01 (NCT05152147; EudraCT#: 2021-000296-36) is a global, randomized, open-label, active-comparator, ph3 study to investigate the efficacy and safety of ZANI + chemo ± TIS as 1L treatment for pts with LA/metastatic HER2+ GEA.

Methods: Pts ≥18 years old with untreated, unresectable LA/metastatic GEA that is HER2+ (IHC3+ or IHC2+/ISH+) by central testing, ECOG PS 0/1, and adequate organ function, including LVEF >50%, will be enrolled. Eligible pts will be randomized (1:1:1) to: TRAS (6 mg/kg IV Q3W) + chemo; ZANI (1800 mg [pts <70 kg] or 2400 mg [≥70 kg] IV Q3W) + chemo; or ZANI + chemo + TIS (200 mg IV Q3W). In all arms, chemo will be the investigator (INV)'s choice of CAPOX

(oxaliplatin 130 mg/m^2 IV Q3W and capecitabine 1000 mg/m^2 oral BID, days [D]1-15) or FP (cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2 continuous IV, D1-5). Primary endpoints are PFS (per blinded independent central review [BICR]; RECIST v1.1) and overall survival. Secondary endpoints include: BICR-assessed confirmed ORR and DoR; INV-assessed PFS, ORR, and DoR; incidence and severity of AEs; and changes in HRQoL. Overall, 714 pts will be randomized from ~300 sites in 30+ countries; this study is currently recruiting.