Zanidatamab + chemotherapy (CT) ± tislelizumab for first-line (1L) HER2-positive (HER2+) locally advanced, unresectable, or metastatic gastroesophageal adenocarcinoma (mGEA): Primary analysis from HERIZON-GEA-01.

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ABSTRACT

Background: HERIZON-GEA-01 (NCT05152147) is a global, open-label, phase 3 trial of zanidatamab (dual HER2-targeted bispecific antibody) + CT ± tislelizumab (anti–PD-1) vs trastuzumab (tras) + CT in 1L HER2+ mGEA.

Methods: Eligible patients (pts) with previously untreated HER2+ mGEA, regardless of PD-L1 status, were randomized (1:1:1) to zanidatamab (1800 mg [<70 kg] / 2400 mg [≥70 kg] IV Q3W) + tislelizumab (200 mg IV Q3W) + capecitabine/oxaliplatin (CAPOX) or 5-FU/cisplatin (FP); zanidatamab + CAPOX or FP; or tras + CAPOX or FP. Dual primary endpoints were progression-free survival (PFS) by blinded independent central review and overall survival (OS).

Results: 914 pts were randomized (Dec 2021 to Feb 2025). Demographics and baseline disease characteristics were balanced. At data cutoff (Oct 2025), median follow-up was 26

mo. Compared with tras + CT, PFS was significantly prolonged in zanidatamab-containing arms (Table). A statistically significant OS benefit was observed with zanidatamab + tislelizumab + CT (Table). OS for zanidatamab + CT was not significant at the first interim analysis, although a strong trend favoring zanidatamab + CT was observed. Improvements in PFS and OS occurred across major subgroups, including by region and PD-L1 TAP score. Grade ≥3 treatment-related AEs (TRAEs) occurred in 71.8% of pts with zanidatamab + tislelizumab + CT, 59.0% with zanidatamab + CT, and 59.6% with tras + CT. Grade ≥3 TRAEs occurring in >10% of pts in either zanidatamab-containing arm were diarrhea, hypokalemia, and anemia; the tras + CT arm were diarrhea, anemia, neutrophil count decreased, and platelet count decreased. HER2-targeted therapy was discontinued for related AEs in 11.9% of pts with zanidatamab + tislelizumab + CT, 8.5% with zanidatamab + CT, and 2.3% with tras + CT.

Conclusion: Both zanidatamab-containing regimens demonstrated a clinically meaningful and statistically significant prolongation of PFS (mPFS >12 mo) vs tras + CT. Zanidatamab + tislelizumab + CT also provided a statistically significant and clinically meaningful OS benefit (mOS >26 mo). The trial is ongoing with additional OS analyses planned for zanidatamab + CT. No new safety signals were observed for zanidatamab or tislelizumab. These results support zanidatamab as a new standard in HER2-targeting agents, potentially replacing tras, as well as the use of tislelizumab in 1L HER2+ mGEA.

Table

	Tras + CT (n=308)	**Zanidatamab + CT (n=304)**	**Zanidatamab + Tislelizumab + CT (n=302)**
mPFS (95% CI), mo	8.1 (7.0, 8.9)	12.4 (9.8, 14.5)	12.4 (9.8, 18.5)
Hazard ratio (95% CI)	-	0.65 (0.52-0.81); *P* < 0.0001	0.63 (0.51, 0.78); *P* < 0.0001
18-mo PFS, %	20.9	38.0	43.9
mOS (95% CI), mo	19.2 (16.8, 21.8)	24.4 (20.4, 30.0)	26.4 (21.5, 30.3)
Hazard ratio (95% CI)	-	0.80 (0.64, 1.01) [Interim] *P* = 0.0564	0.72 (0.57, 0.90) *P* = 0.0043
24-mo OS, %	38.8	50.3	54.3