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Zanidatamab (zani) + chemotherapy (CT) ± tislelizumab (TIS) for first-line (1L) HER2-positive (HER2+) advanced/metastatic gastroesophageal adenocarcinoma (mGEA): Second interim analysis (IA) from HERIZON-GEA-01

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Background

In the primary analysis of progression-free survival (PFS) and first IA (IA1) of overall survival (OS) of the phase 3 HERIZON-GEA-01 trial (NCT05152147), zani + CT ± TIS significantly prolonged PFS and, with TIS, provided a significant OS benefit (HR 0.72) vs trastuzumab (tras) + CT (Shitara, et al. *NEJM*. 2026), supporting the US approval of these regimens in 1L HER2+ mGEA. Here, we present the planned second IA of OS (IA2).

Methods

Patients (pts) with untreated HER2+ mGEA were randomized 1:1:1 to zani (1800 mg [<70 kg]/2400 mg [≥ 70 kg] IV every 3 weeks [Q3W]) + CT (capecitabine/oxaliplatin or 5-FU/cisplatin) ± TIS (200 mg IV Q3W) or tras + CT. PFS (by blinded independent central review) and OS were primary endpoints. At IA2, formal OS comparisons were tested in sequence: zani + CT vs tras + CT, then zani + CT + TIS vs zani + CT.

Results

914 pts were randomized. With a median follow-up of 35.3 mo (data cutoff: 15 July 2026; 9.4 mo longer than IA1), zani + CT significantly improved OS vs tras + CT (HR 0.76 [95% CI: 0.62–0.93]; $P = 0.0088$; median OS, 22.9 mo [95% CI: 19.9–27.6] vs 19.6 mo [95% CI: 16.9–22.2]). A 4-mo longer median OS was observed with zani + TIS + CT (27.0 mo [95% CI: 23.7–32.2]) vs zani + CT (HR 0.81 [95% CI: 0.65–1.00]), although the difference was not statistically significant ($P = 0.0502$). The OS benefit of zani + TIS + CT vs tras + CT observed at IA1 (HR 0.72) was sustained at IA2 with an improved HR (0.65 [95% CI: 0.52–0.80]). Estimated 36-mo OS was 39.8% for zani + CT + TIS, 31.5% for zani + CT, and 22.9% for tras + CT. Median duration of treatment was 46.6 (40.5 for zani) wks with zani + CT + TIS, 31.1 (30.1 for zani) wks with zani + CT, and 30.0 (28.2 for tras) wks with tras + CT. The safety profiles were consistent with IA1.

Conclusions

At IA2, zani + CT led to a statistically significant and clinically meaningful OS improvement vs tras + CT. With longer follow-up, zani + CT + TIS showed improved OS benefit over tras + CT and there was a meaningful trend for OS improvement vs zani + CT. Unchanged safety profiles support the tolerability of prolonged treatment. These results continue to support zani combined with CT ± TIS as a new HER2-directed 1L standard of care in HER2+ mGEA.

Clinical trial identification

NCT05152147.

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Legal entity responsible for the study

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Disclosure

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