Characterization and management of gastrointestinal (GI) adverse events (AEs) with zanidatamab + chemotherapy (CT) ± tislelizumab in first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): Analysis from HERIZON-GEA-01

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Characterization and management of gastrointestinal (GI) adverse events (AEs) with zanidatamab + chemotherapy (CT) ± tislelizumab in first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): Analysis from HERIZON-GEA-01

Background: In HERIZON-GEA-01, replacing 1L trastuzumab (tras) + CT with zanidatamab + CT ± tislelizumab significantly improved progression-free survival and, with tislelizumab, yielded a statistically significant overall survival benefit in HER2+ mGEA. The safety profile was manageable; diarrhea was the most common AE. Here we further characterize GI AEs and diarrhea management.

Methods: Eligible patients (pts) with previously untreated HER2+ mGEA 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. CT could be discontinued per physician preference after cycle 6. Tras dose reductions were not permitted. Prophylaxis for diarrhea (loperamide 4 mg orally BID) was mandatory in zanidatamab-containing arms for the first 7 days of cycle 1.

Results: Median treatment duration was 43.1 wk with zanidatamab + tislelizumab + CT, 31.0 with zanidatamab + CT, and 30.0 with tras + CT. Median number of CT cycles was 6, 6, and 7, respectively. Diarrhea was the most common GI AE in all arms; other GI AEs were generally similar across arms. Among pts who experienced diarrhea, most had first onset in cycle 1 (76% in ≤3 wk) with median duration <2.5 wk (**Table**). Few pts had their first onset of diarrhea occur after cycle 6 when pts could discontinue CT. HER2-targeted therapy discontinuations (4.1%, 1.3%, 0.3%, respectively) and dose reductions (9.9%, 10.8%, NA) or delays (13.6%, 13.4%, 7.6%) due to diarrhea were infrequent. Diarrhea was more often managed with CT dose reduction (21.8%, 23.6%, 14.2%, respectively). Immune-mediated colitis occurred in 2.7% of pts with zanidatamab + tislelizumab + CT. Additional incidence and management data will be presented.

Conclusions: In zanidatamab-treated pts, most diarrhea events were grade 1/2, and first-onset events tended to occur in cycle 1 and resolved in <3 wk. Diarrhea rarely led to zanidatamab discontinuation. The safety of zanidatamab-containing regimens appears favorable given the survival benefits; diarrhea should be managed with prophylactic loperamide and CT dose modifications as needed.

Diarrhea	**Zanidatamab + Tislelizumab + CT n = 294**	**Zanidatamab + CT n = 305**	**Tras + CT n = 302**
Any-grade, n (%)	244 (83.0)	241 (79.0)[a]	161 (53.3)
Grade 1	79 (26.9)	80 (26.2)	84 (27.8)
Grade 2	92 (31.3)	99 (32.5)	38 (12.6)
Grade ≥3	73 (24.8)	61 (20.0)	39 (12.9)
Time to first onset, n (%), wk			
≤3	188 (77.0)	192 (79.7)	108 (67.1)
>3 to ≤6	25 (10.2)	27 (11.2)	22 (13.7)
>6 to ≤9	7 (2.9)	14 (5.8)	11 (6.8)
>9 to ≤12	4 (1.6)	4 (1.7)	2 (1.2)
>12 to ≤18	8 (3.3)	3 (1.2)	7 (4.3)
>18	12 (4.9)	1 (0.4)	11 (6.8)
Duration of first onset, median (95% CI), wk	2.0 (1.6, 2.6)	2.4 (1.9, 2.9)	1.4 (1.0, 2.1)

[a]Grade missing for 1 pt.