Zanidatamab + chemotherapy (CT) ± tislelizumab for first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): PD-L1 subgroup analysis from HERIZON-GEA-01

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Background: In HERIZON-GEA-01 (NCT05152147), 1L zanidatamab + CT ± tislelizumab significantly improved progression-free survival (PFS) and, with tislelizumab, yielded a statistically significant overall survival (OS) benefit in HER2+ mGEA. Here we report efficacy in PD-L1 subgroups.

Methods: Eligible patients (pts) with previously untreated HER2+ mGEA, irrespective 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. PD-L1 expression was retrospectively assessed using the VENTANA SP263 assay according to tumor area positivity (TAP) score and combined positive score (CPS). Primary endpoints were PFS (BICR) and OS; efficacy by PD-L1 status (TAP) was prespecified.

Results: With 26 mo median follow-up, PFS (HR, 0.63; *P* <0.001) and OS (HR, 0.72; *P* = 0.004) were significantly prolonged with zanidatamab + tislelizumab + CT vs tras + CT in the ITT population. In pts treated with zanidatamab + tislelizumab + CT, similarly prolonged PFS and OS were observed in PD-L1–negative and PD-L1–positive pts (**Table**); data were consistent between TAP and CPS. In PD-L1 TAP <1%

and ≥1% pts, the 18-mo PFS was 50.3% and 42.6%, respectively, and the 24-mo OS was 63.7% and 53.5% with zanidatamab + tislelizumab + CT. In the tras + CT arm, OS was prolonged in PD-L1–positive vs –negative pts. Of note, in the tras + CT arm, 15% of pts received subsequent checkpoint inhibitors and 29% received subsequent HER2-targeted therapies vs 2% and 13%, respectively, in the zanidatamab + tislelizumab + CT arm. Additional details on these subgroups will be presented at the congress.

Conclusions: In HERIZON-GEA-01, zanidatamab + tislelizumab + CT demonstrated meaningful improvements in PFS and OS in both PD-L1–positive and PD-L1–negative pts as determined by TAP or CPS. The longer OS observed with tras + CT in PD-L1–positive vs –negative pts may be at least partially explained by differences in subsequent therapies. These findings are notable as they demonstrate benefit for this regimen regardless of PD-L1 status.

	Zanidatamab + Tislelizumab + CT	**Tras + CT**
ITT		
N	302	308
mPFS (95% CI), mo	12.4 (9.8, 18.5)	8.1 (7.0, 8.9)
mOS (95% CI), mo	26.4 (21.5, 30.3)	19.2 (16.8, 21.8)
TAP <1%		
n (%)	90 (29.8)	98 (31.8)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	7.9 (5.8, 9.6)
mOS (95% CI), mo	29.7 (24.7, NE	15.8 (12.6, 21.4)
CPS <1		
n (%)	78 (25.8)	80 (26.0)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	8.1 (5.8, 9.8)
mOS (95% CI), mo	30.3 (25.7, NE)	15.7 (12.6, 21.4)
TAP ≥1%		
n (%)	187 (61.9)	188 (61.0)
mPFS (95% CI), mo	11.3 (9.6, 18.5)	8.3 (6.9, 9.7)
mOS (95% CI), mo	26.4 (18.7, 35.9)	21.2 (17.7, 25.2)
CPS ≥1		
n (%)	198 (65.6)	206 (66.9)
mPFS (95% CI), mo	12.3 (9.7, 18.5)	8.2 (6.9, 9.1)
mOS (95% CI), mo	26.4 (18.7, 34.6)	20.8 (17.3, 23.9)