

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

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Key Takeaway Points

- **Zanidatamab + tislelizumab + CT demonstrated a clinically meaningful and statistically superior prolongation of PFS and OS vs trastuzumab + CT, with a >4-month prolongation of median PFS and a >7-month prolongation of median OS**

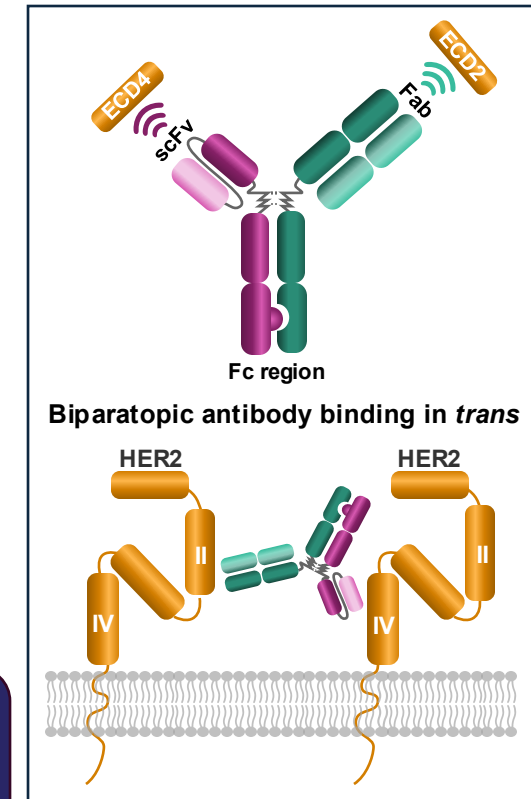
- **The PFS and OS benefits were consistent across patients with PD-L1–positive and PD-L1–negative disease by both TAP score and CPS**

HERIZON-GEA-01 supports zanidatamab in combination with tislelizumab and chemotherapy as a new 1L standard of care in HER2-positive mGEA, regardless of PD-L1 status

Background

- For patients with mGEA, the addition of immunotherapy to 1L standard of care improves survival irrespective of HER2 status, but the benefit is limited to patients with PD-L1–positive tumors¹⁻³
- In the **primary analysis of PFS** and **first interim analysis of OS** from the phase 3 **HERIZON-GEA-01** trial, **zanidatamab + chemotherapy, ± tislelizumab**, significantly **prolonged PFS**, and **+ tislelizumab**, yielded a **significant OS benefit vs trastuzumab + chemotherapy in 1L HER2-positive mGEA**⁴
- **Zanidatamab** is a **HER2-directed bispecific antibody** that binds to the **HER2 ECD 2 and 4** in a **trans configuration**, facilitating the formation of **distinct HER2 clusters** on the cell surface. It has several key mechanisms of action⁵
 - Increasing **HER2 internalization**
 - Reducing **phosphorylation of EGFR, HER2, and HER3** and blocking **downstream signaling**
 - Inducing immune-mediated effects (**CDC, ADCC, and ADCP**)
- **Tislelizumab** is a **high-affinity immune checkpoint inhibitor targeting PD-1** and is specifically engineered to **minimize Fcγ receptor binding on macrophages**^{6,7}

Here we report efficacy from **HERIZON-GEA-01 by PD-L1 status (assessed by both TAP and CPS)** for **zanidatamab + tislelizumab + chemotherapy vs trastuzumab + chemotherapy**

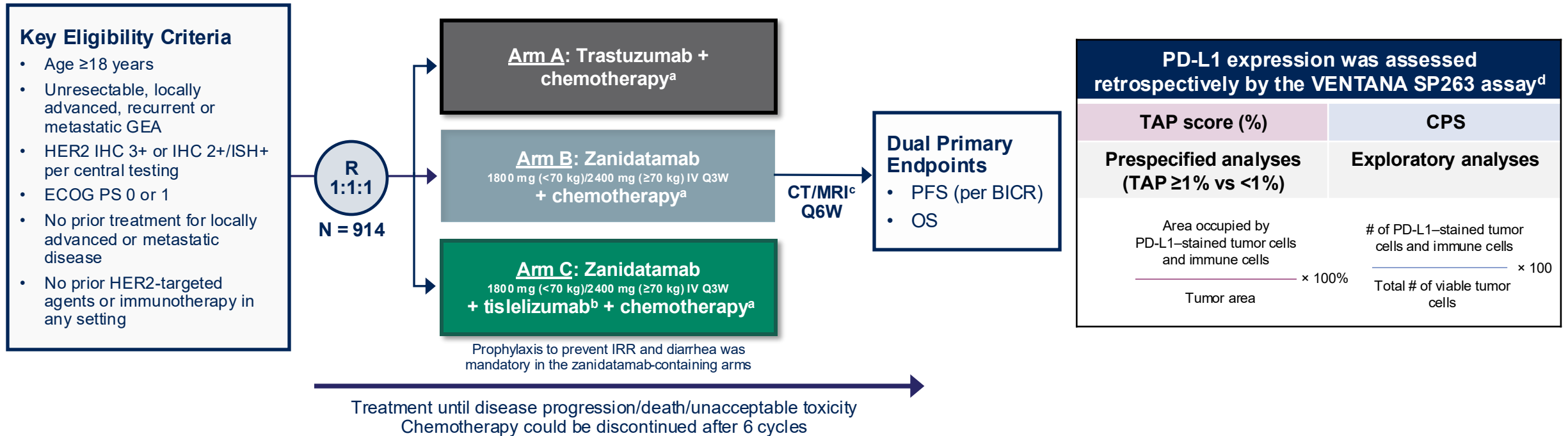


1L, first-line; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; CPS, combined positive score; ECD, extracellular domain; EGFR, epidermal growth factor receptor; Fab, fragment antigen binding; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; mGEA, advanced or metastatic gastroesophageal adenocarcinoma; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; scFv, single-chain variable fragment; TAP, tumor area positivity.

1. Janjigian YY, et al. *Lancet*. 2023;402(10418):2197-208. 2. Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. 3. Qiu MZ, et al. *BMJ*. 2024;385:e078876. 4. Elimova E, et al. *J Clin Oncol*. 2026;44:LBA285. 5. Weisser NE, et al. *Nat Commun*. 2023;14(1):1394. 6. Hong Y, et al. *FEBS Open Bio*. 2021;11(3):782-92. 7. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67(7):1079-90.

HERIZON-GEA-01 (NCT05152147)

Global phase 3 trial of zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2-positive mGEA



^aPhysician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met.

^bTislelizumab 200 mg was administered IV Q3W. ^cCT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks. ^dTAP score and CPS were assessed using the same stained samples.

BICR, blinded independent central review; CPS, combined positive score; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridization; IV, intravenously; mGEA, advanced or metastatic GEA; MRI, magnetic resonance imaging; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization; TAP, tumor area positivity.

Baseline Demographics and Disease Characteristics

Although PD-L1 status was not a stratification factor, demographics and clinical characteristics were well balanced across PD-L1 subgroups. Concordance between PD-L1 status by TAP and CPS was high

	Zanidatamab + tislelizumab + CT		Trastuzumab + CT			Zanidatamab + tislelizumab + CT		Trastuzumab + CT	
	TAP ≥1% (n = 187)	TAP <1% (n = 90)	TAP ≥1% (n = 188)	TAP <1% (n = 98)		TAP ≥1% (n = 187)	TAP <1% (n = 90)	TAP ≥1% (n = 188)	TAP <1% (n = 98)
Age , median (range), years	63.0 (22–81)	63.0 (37–81)	64.5 (29–84)	62.0 (29–82)					
Male sex	150 (80.2)	75 (83.3)	142 (75.5)	78 (79.6)	Anatomical subtype				
Geographic region					Gastric	131 (70.1)	65 (72.2)	137 (72.9)	74 (75.5)
Asia	96 (51.3)	56 (62.2)	101 (53.7)	55 (56.1)	GEJ	41 (21.9)	20 (22.2)	37 (19.7)	20 (20.4)
EU/North America	61 (32.6)	21 (23.3)	60 (31.9)	26 (26.5)	Esophageal	15 (8.0)	5 (5.6)	14 (7.4)	4 (4.1)
Rest of the world	30 (16.0)	13 (14.4)	27 (14.4)	17 (17.3)	HER2 IHC 3+	150 (80.2)	77 (85.6)	160 (85.1)	77 (78.6)
ECOG PS^a					MSI				
0	76 (40.6)	38 (42.2)	75 (39.9)	40 (40.8)	MSI-high/dMMR	3 (1.6)	0	3 (1.6)	1 (1.0)
1	111 (59.4)	51 (56.7)	113 (60.1)	58 (59.2)	MSS/MSI-low/pMMR	110 (58.8)	38 (42.2)	102 (54.3)	50 (51.0)
Choice of chemotherapy backbone					Unknown	74 (39.6)	52 (57.8)	83 (44.1)	47 (48.0)
CAPOX	164 (87.7)	87 (96.7)	170 (90.4)	93 (94.9)	CPS^b				
FP	23 (12.3)	3 (3.3)	18 (9.6)	5 (5.1)	<1	2 (1.1)	76 (84.4)	0	80 (81.6)
					≥1	184 (98.4)	14 (15.6)	188 (100)	18 (18.4)

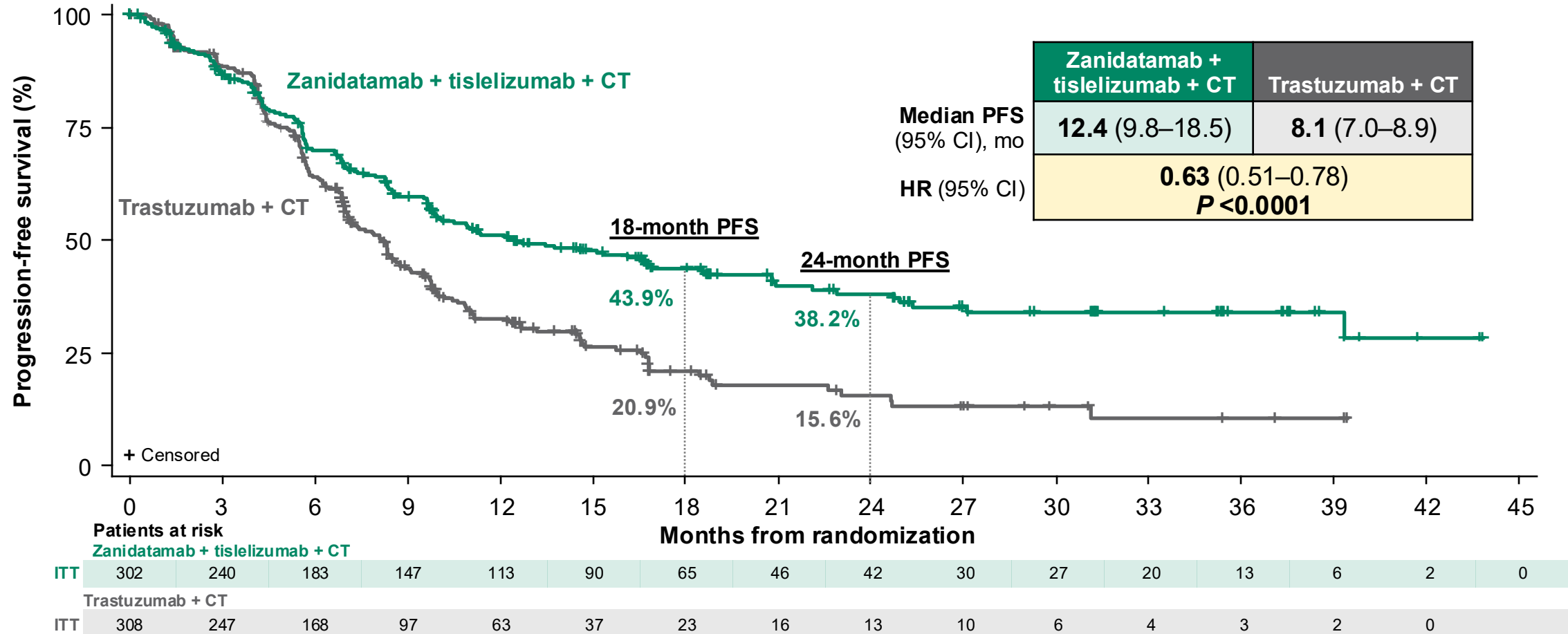
Concordance of 93.3% for PD-L1 status (across all patients) by TAP score ≥1% vs <1% compared with CPS ≥1 vs <1

All data are shown as n (%) unless otherwise indicated.

^aOne patient in the zanidatamab + tislelizumab + chemotherapy arm with TAP <1% had an ECOG PS score of 2 at baseline. ^bCPS was missing from one patient in the zanidatamab + tislelizumab + chemotherapy arm with TAP ≥1%. CAPOX, capecitabine and oxaliplatin; CPS, combined positive score; CT, chemotherapy; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; FP, 5-fluorouracil (5-FU) plus cisplatin; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITT, intent-to-treat; MSI, microsatellite instability; MSS, microsatellite stable; PD-L1, programmed death-ligand 1; pMMR, proficient mismatch repair; TAP, tumor area positivity.

Primary Endpoint: PFS per BICR, ITT population

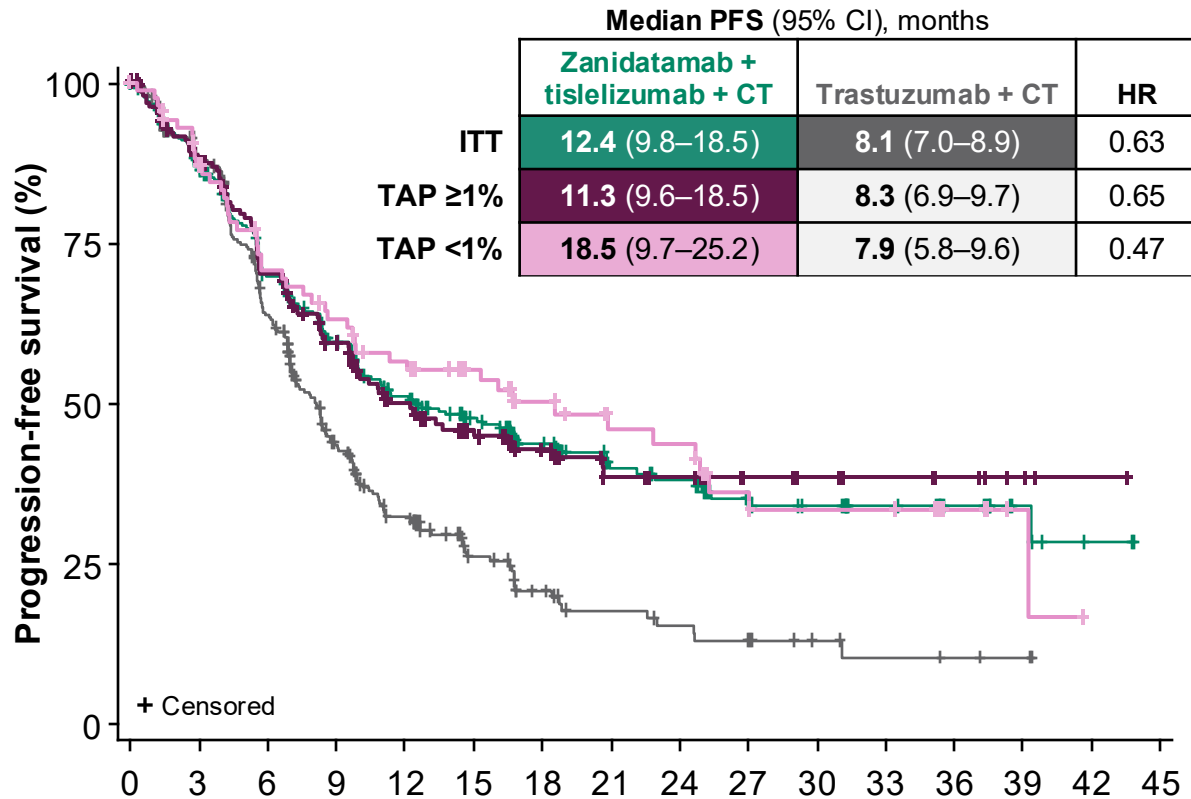
Statistically significant and clinically meaningful improvement in PFS with zanidatamab + tislelizumab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



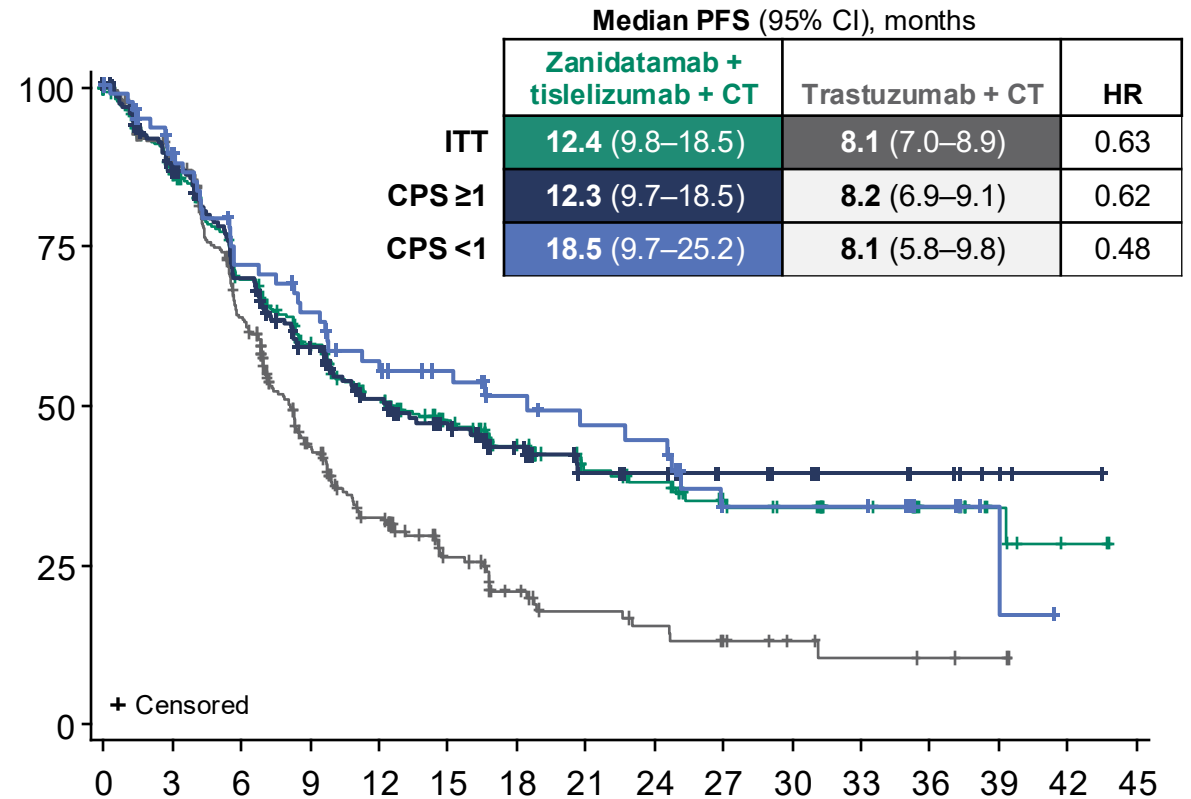
Data cutoff: October 1, 2025. Data previously presented in Elimova E, et al. *J Clin Oncol*. 2026;44:LBA285.
BICR. blinded independent central review; CT. chemotherapy; HR. hazard ratio; ITT. intent-to-treat; PFS. progression-free survival.

PFS per BICR by PD-L1 Subgroups (TAP and CPS)

PFS improvements with zanidatamab + tislelizumab + CT vs trastuzumab + CT were independent of PD-L1 status



	Median PFS (95% CI), months		
	Zanidatamab + tislelizumab + CT	Trastuzumab + CT	HR
ITT	12.4 (9.8–18.5)	8.1 (7.0–8.9)	0.63
TAP ≥1%	11.3 (9.6–18.5)	8.3 (6.9–9.7)	0.65
TAP <1%	18.5 (9.7–25.2)	7.9 (5.8–9.6)	0.47



	Median PFS (95% CI), months		
	Zanidatamab + tislelizumab + CT	Trastuzumab + CT	HR
ITT	12.4 (9.8–18.5)	8.1 (7.0–8.9)	0.63
CPS ≥1	12.3 (9.7–18.5)	8.2 (6.9–9.1)	0.62
CPS <1	18.5 (9.7–25.2)	8.1 (5.8–9.8)	0.48

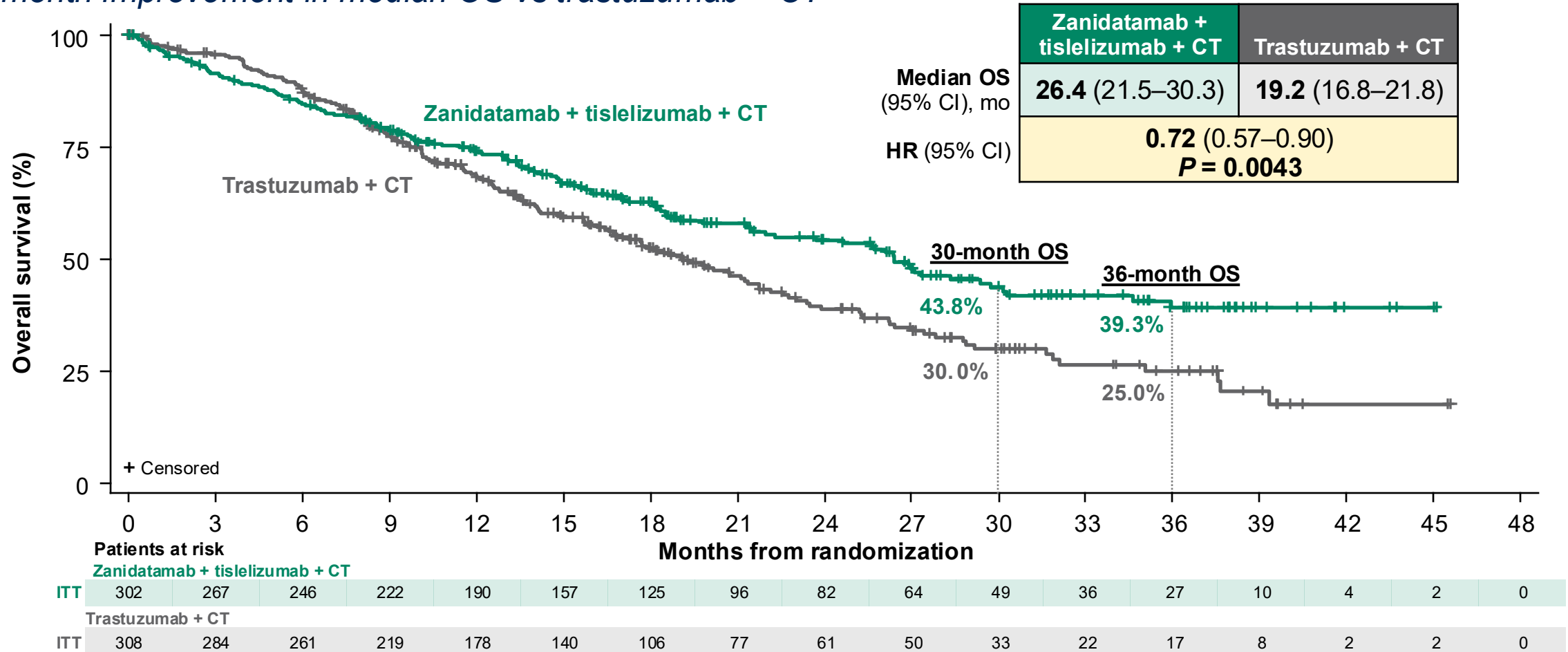
	Patients at risk															
	Zanidatamab + tislelizumab + CT															
TAP ≥1%	187	149	113	88	63	49	35	24	22	17	15	8	6	3	1	0
TAP <1%	90	72	56	49	42	35	26	20	19	12	11	11	6	2	0	

	Patients at risk															
	Zanidatamab + tislelizumab + CT															
CPS ≥1	198	156	119	93	69	53	38	24	22	17	15	8	6	3	1	0
CPS <1	78	64	49	43	36	31	23	20	19	12	11	11	6	2	0	

Data cutoff: October 1, 2025. The widths of the confidence intervals for the PD-L1 subgroups were not adjusted for multiplicity and cannot be used to infer treatment effects. BICR, blinded independent central review; CPS, combined positive score; CT, chemotherapy; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, tumor area positivity.

Primary Endpoint: OS, ITT population

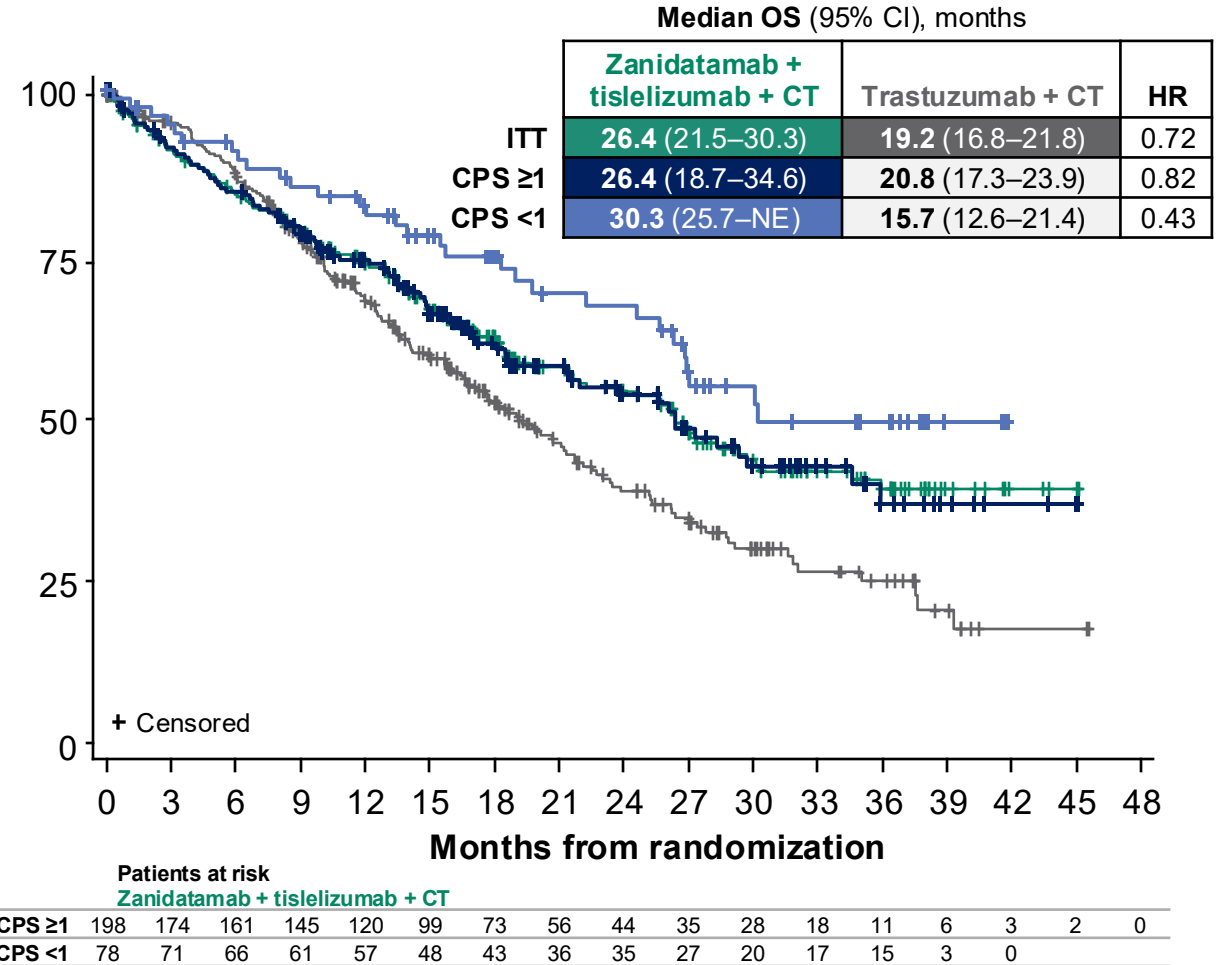
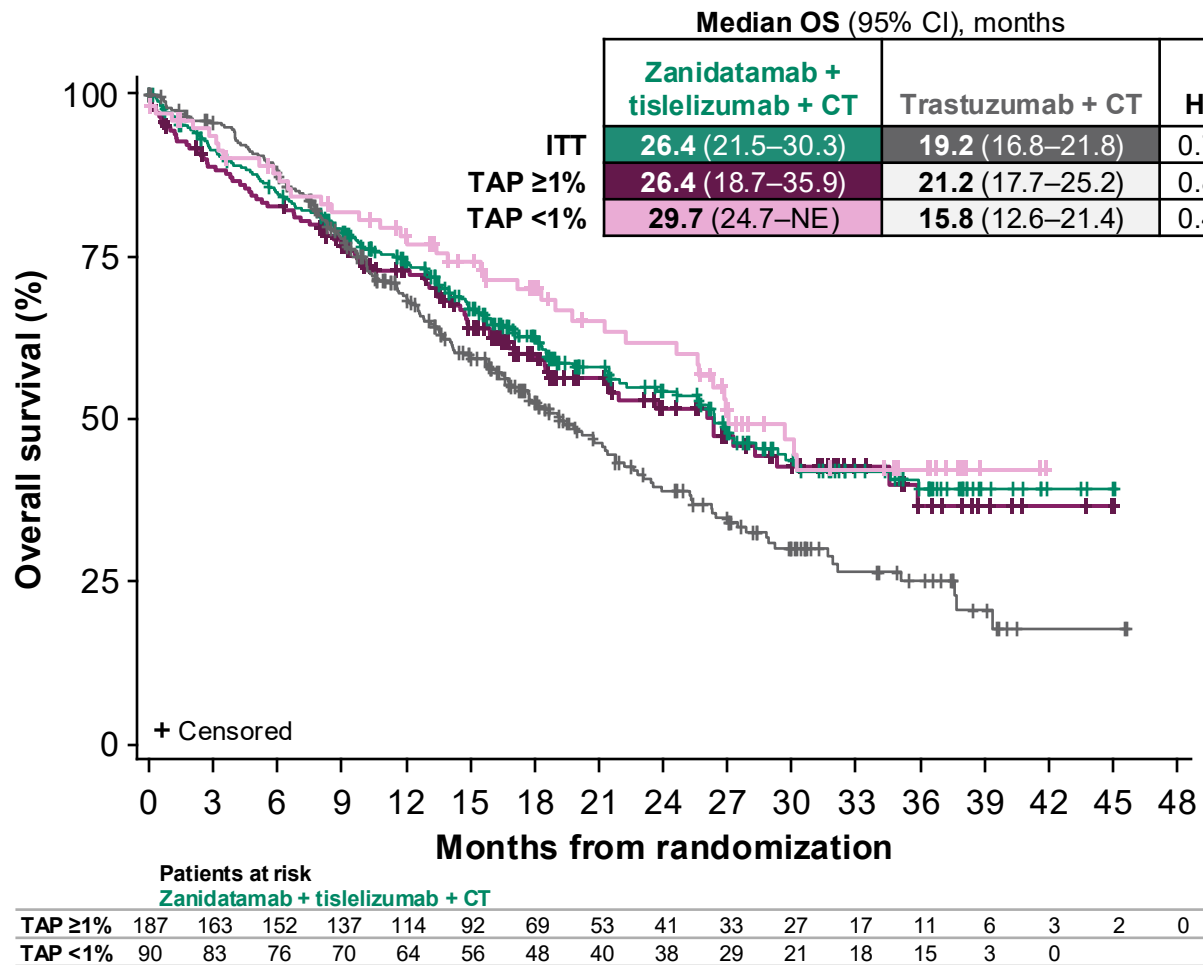
Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT



Data cutoff: October 1, 2025. Data previously presented in Elimova E, et al. *J Clin Oncol*. 2026;44:LBA285. CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

OS by PD-L1 Subgroups (TAP and CPS)

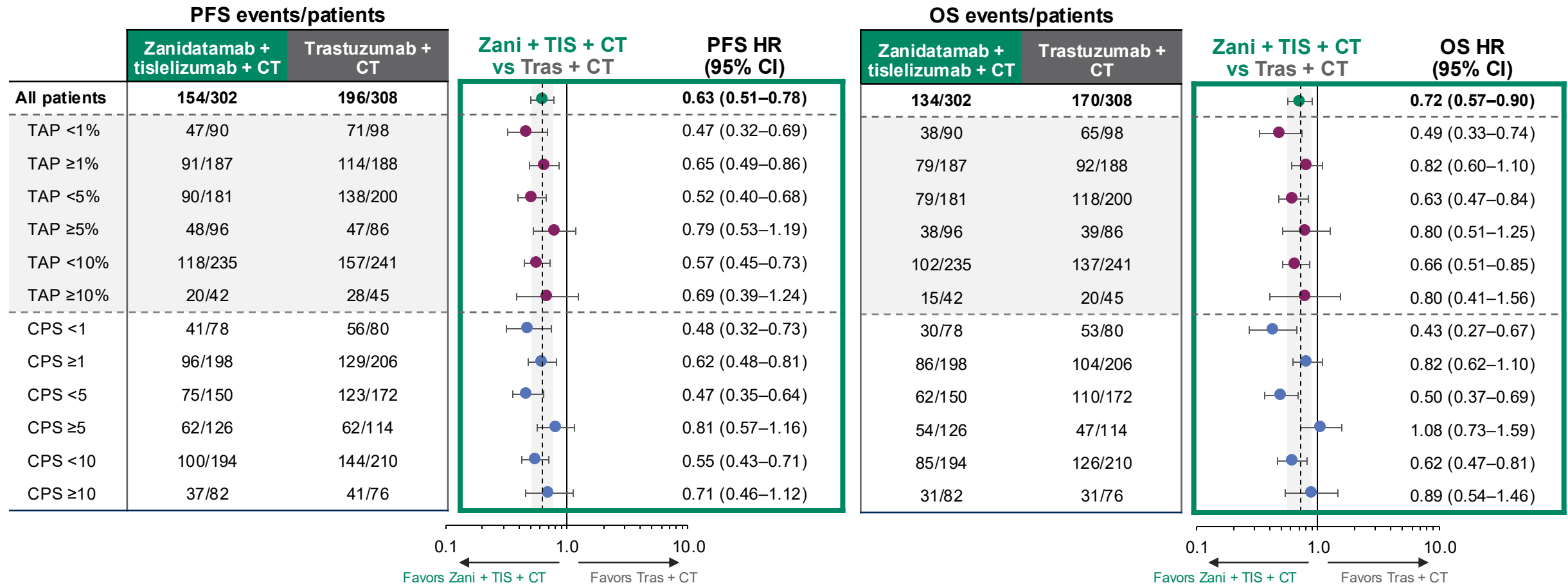
OS improvements with zanidatamab + tislelizumab + CT vs trastuzumab + CT were independent of PD-L1 status



Data cutoff: October 1, 2025. The widths of the confidence intervals for the PD-L1 subgroups were not adjusted for multiplicity and cannot be used to infer treatment effects.
CPS, combined positive score; CT, chemotherapy; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

PFS and OS by PD-L1 Cutoff (TAP and CPS)

Improvements in PFS and OS were observed with zanidatamab + tislelizumab + CT vs trastuzumab + CT across most PD-L1 TAP scores and CPS ranges



Data cutoff: October 1, 2025. The widths of the CIs for the PD-L1 subgroups were not adjusted for multiplicity and cannot be used to infer treatment effects. CPS, combined positive score; CT, chemotherapy; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Subsequent Therapies by PD-L1 Subgroups

OS in the trastuzumab + chemotherapy arm may be impacted by increased use of subsequent therapies

	Zanidatamab + tislelizumab + CT		Trastuzumab + CT	
	TAP ≥1% (n = 187)	TAP <1% (n = 90)	TAP ≥1% (n = 188)	TAP <1% (n = 98)
Any subsequent therapy, n (%)	61 (32.6)	27 (30.0)	105 (55.9)	57 (58.2)
Chemotherapy	50 (26.7)	27 (30.0)	81 (43.1)	50 (51.0)
Immune checkpoint inhibitor	5 (2.7)	1 (1.1)	22 (11.7)	22 (22.4)
HER2-targeted therapy^a	25 (13.4)	8 (8.9)	55 (29.3)	29 (29.6)
Other	28 (15.0)	12 (13.3)	46 (24.5)	20 (20.4)

Data cutoff: October 1, 2025.

^aIncludes trastuzumab, HER2 ADCs, disitamab vedotin, trastuzumab deruxtecan, trastuzumab emtansine, or investigational compounds.
ADC, antibody-drug conjugate; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; OS, overall survival; TAP, tumor area positivity.

Safety Summary

Safety profile was manageable, with diarrhea the most common AE of grade ≥ 3 or higher across groups

	Zanidatamab + tislelizumab + CT (n = 294) ^a	Trastuzumab + CT (n = 302)
Duration of treatment , median (IQR), weeks	43.1 (56.7)	30.0 (32.2)
Any-grade TEAE , n (%)	293 (99.7)	297 (98.3)
Treatment-related TEAE , n (%)	289 (98.3)	291 (96.4)
Grade ≥ 3	211 (71.8)	180 (59.6)
Serious TEAEs , n (%)	172 (58.5)	128 (42.4)
Treatment-related	121 (41.2)	61 (20.2)
TEAEs leading to death , n (%)	28 (9.5)	22 (7.3)
Treatment-related	7 (2.4)	4 (1.3)
Discontinuation due to treatment-related TEAEs , n (%)		
Any component	125 (42.5)	88 (29.1)
Zanidatamab or trastuzumab	35 (11.9)	7 (2.3)
Tislelizumab	42 (14.3)	—
AESIs^b , n (%)	102 (34.7)	56 (18.5)
IRR ^s	74 (25.2)	40 (13.2)
Noninfectious pulmonary toxicities	20 (6.8)	3 (1.0)
Left ventricular dysfunction	26 (8.8)	13 (4.3)
Immune-mediated AES^b , n (%)	111 (37.8)	31 (10.3)
Treatment-related diarrhea	240 (81.6)	146 (48.3)
Grade ≥ 3	72 (24.5)	39 (12.9)

Data cutoff: October 1, 2025. Data previously presented in Elimova E, et al. *J Clin Oncol*. 2026;44:LBA285.

^aFive patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm. ^bAESIs for zanidatamab were IRRs, noninfectious pulmonary toxicities, and left ventricular dysfunction; AESIs for tislelizumab were IRRs and immune-mediated AEs. AESIs for zanidatamab and tislelizumab were reported in all treatment groups, even if the study agent was not administered in that group. AE, adverse event; AESI, AE of special interest; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; IRR; infusion-related reaction; TEAE, treatment-emergent AE.

Discussion

- Zanidatamab + tislelizumab + CT demonstrated a **clinically meaningful and statistically superior prolongation of PFS and OS** vs trastuzumab + CT, with a >4-month prolongation of median PFS and a >7-month prolongation of median OS
- PFS and OS benefits with zanidatamab + tislelizumab + CT were **consistent in patients with PD-L1–positive and PD-L1–negative disease** determined by TAP score and CPS and across PD-L1 cutoffs
 - Patients in the trastuzumab + chemotherapy arm received more subsequent therapies than patients in the other arms, possibly prolonging OS
- There was a **high concordance between TAP score and CPS**
- The safety profile for zanidatamab + tislelizumab + chemotherapy was manageable



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The results support zanidatamab + tislelizumab + chemotherapy as a new 1L standard of care in HER2-positive mGEA, regardless of PD-L1 status

Acknowledgments

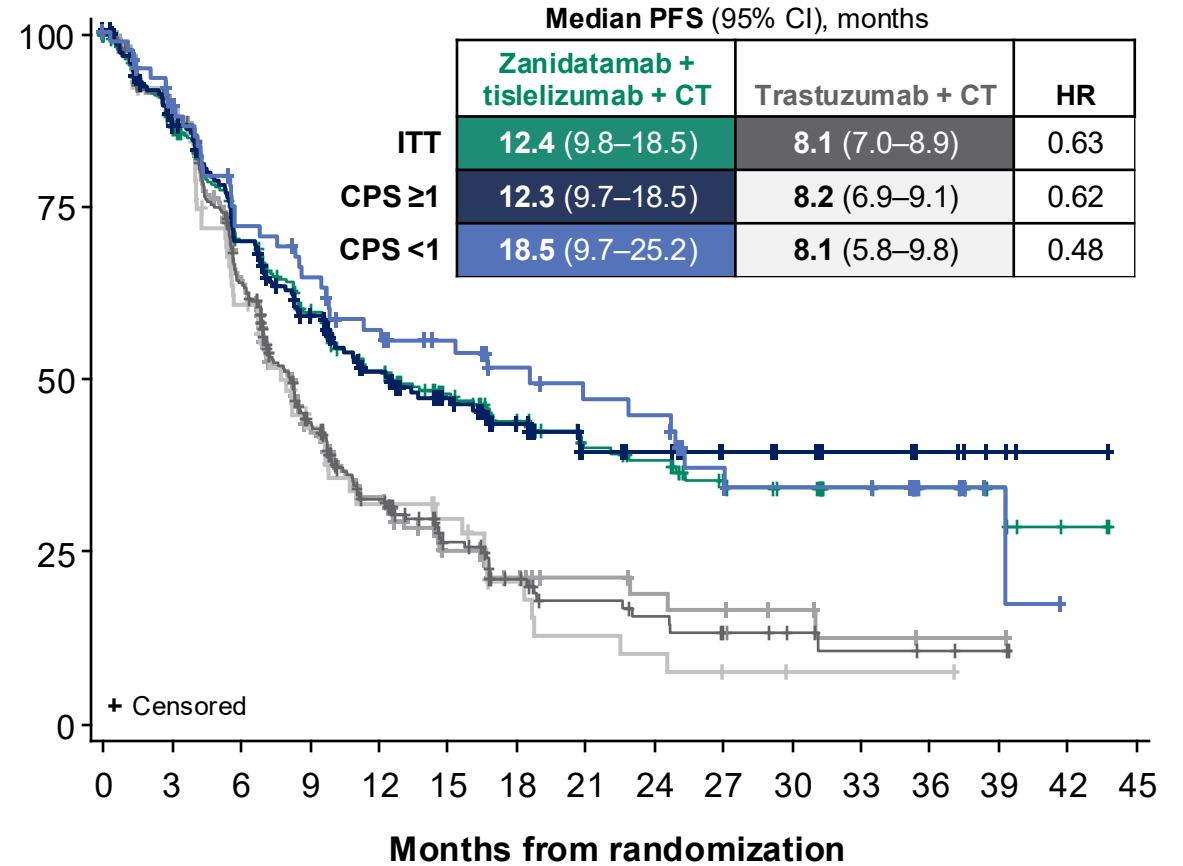
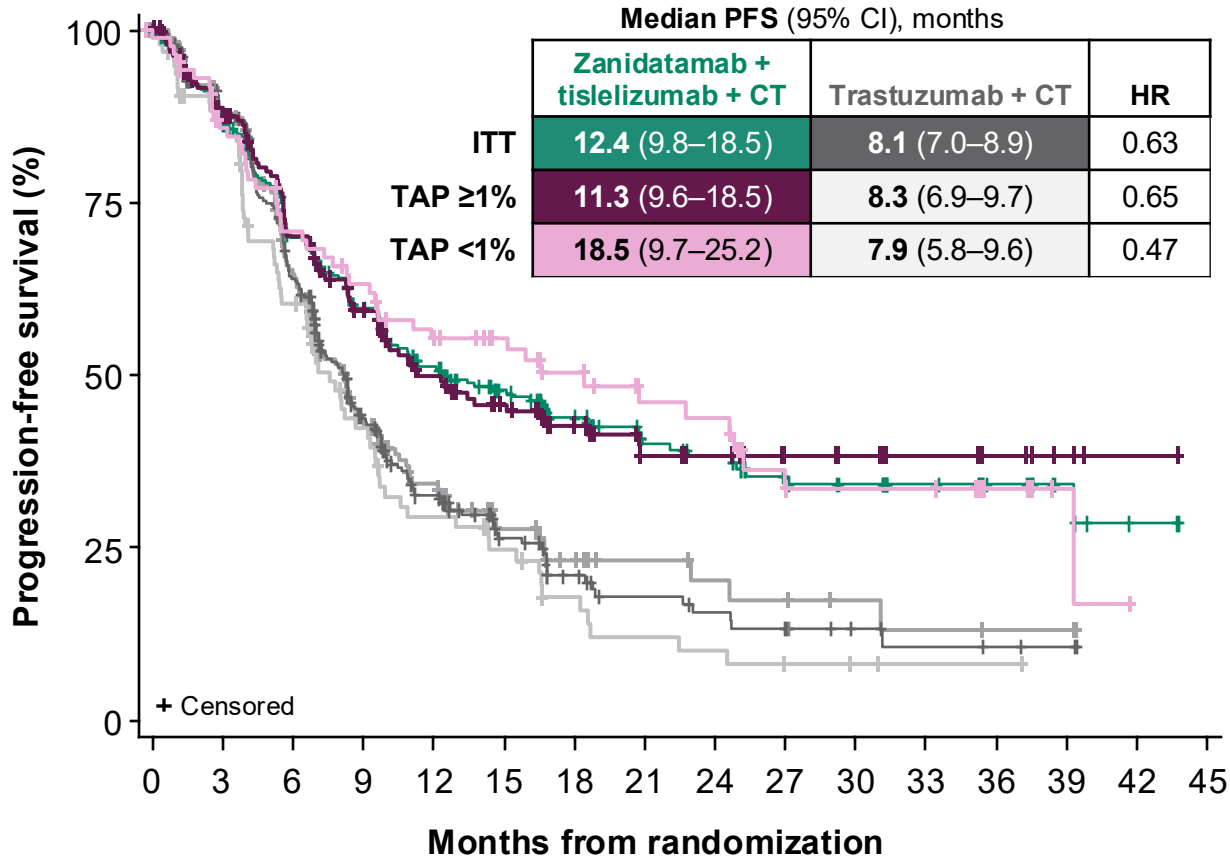
The authors would like to thank all the patients and their families as well as all the investigators, clinical trial researchers, personnel, and staff who contributed to or participated in the trial

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Supplemental Slides

PFS by PD-L1 Subgroups (TAP and CPS)

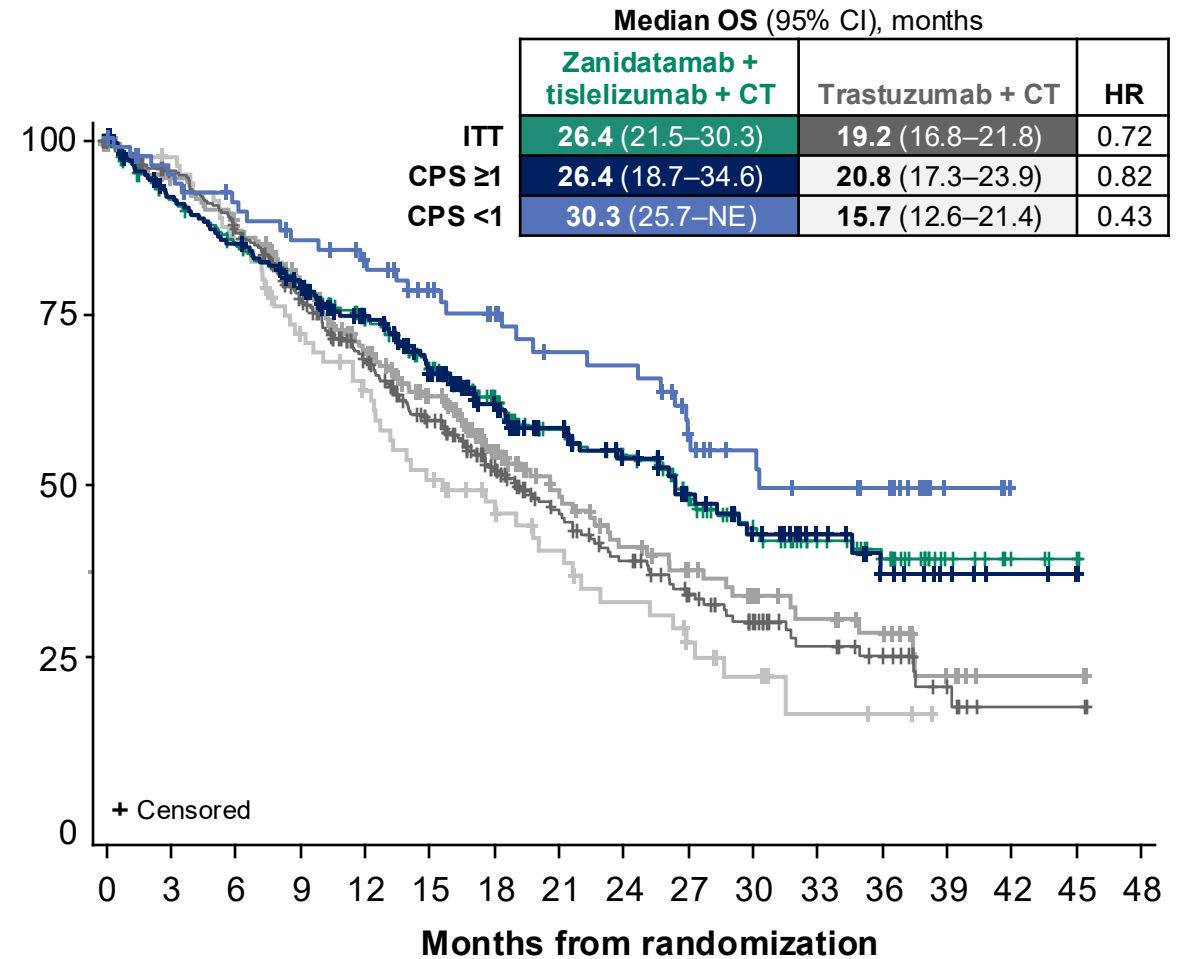
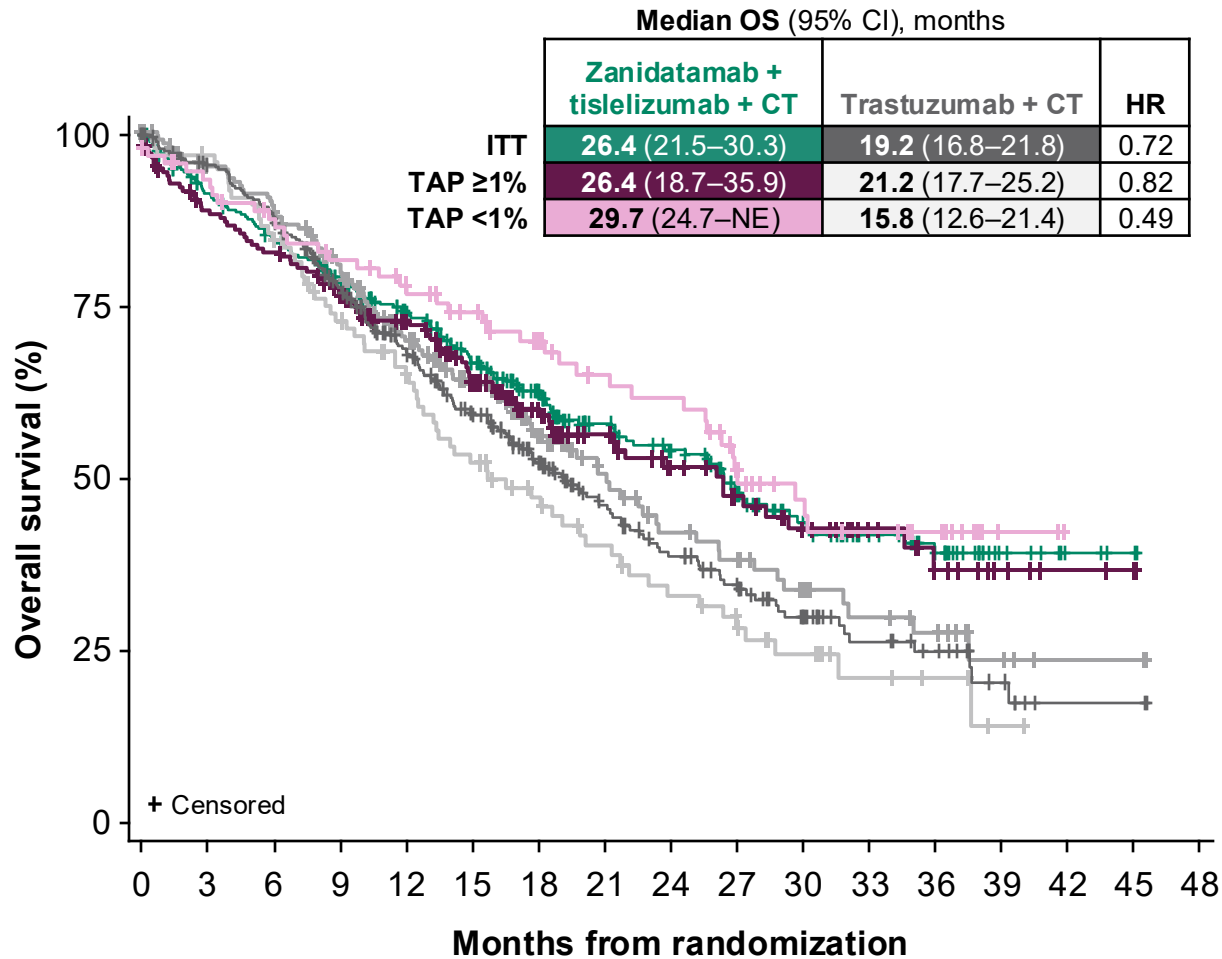
PFS improvements with zanidatamab + tislelizumab + CT vs trastuzumab + CT were independent of PD-L1 status



Data cutoff: October 1, 2025. The widths of the CIs for the PD-L1 subgroups were not adjusted for multiplicity and cannot be used to infer treatment effects.
 BICR, blinded independent central review; CPS, combined positive score; CT, chemotherapy; ITT, intent-to-treat; NE, not estimable; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, tumor area positivity.

OS by PD-L1 Subgroups (TAP and CPS)

OS improvements with zanidatamab + tislelizumab + CT vs trastuzumab + CT were independent of PD-L1 status



Data cutoff: October 1, 2025. The widths of the CIs for the PD-L1 subgroups were not adjusted for multiplicity and cannot be used to infer treatment effects. CT, chemotherapy; CPS, combined positive score; ITT, intent-to-treat; NE, not estimable; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

Concordance Between TAP score and CPS

High concordance was observed between PD-L1 status as assessed by TAP score and by CPS

	Concordance
TAP ≥1% vs CPS ≥1 TAP <1% vs CPS <1	93.3% (791/848)
TAP ≥5% vs CPS ≥5 TAP <5% vs CPS <5	88.6% (751/848)
TAP ≥10% vs CPS ≥10 TAP <10% vs CPS <10	88.0% (746/848)

Concordance is shown as the overall percent agreement between PD-L1 status by TAP score vs CPS among all patients in the ITT population. Missing: 7.8% (66/848)
 CPS, combined positive score; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

Lay Summary

Why did we perform this research?

- Current treatments for people with advanced or metastatic gastroesophageal adenocarcinoma (or mGEA, including certain cancers of the stomach, the esophagus, and the area where the two meet) only provide limited benefits to patients
- Some of these tumors have too much of a protein called HER2. When this happens, the cancer is called “HER2-positive”
- Some tumors also have higher levels of a protein called PD-L1, which attaches to a protein called PD-1 and helps cancer cells avoid being detected by the body’s immune system
 - Some treatments only work well for people whose tumors express PD-L1 and do not work as well for tumors that are PD-L1–negative

How did we perform this research?

- This study examined whether zanidatamab, a medicine that targets the HER2 protein, could help patients with previously untreated HER2-positive mGEA when combined with tislelizumab (which targets PD-1) and standard chemotherapy
- The researchers compared this combination to trastuzumab, a standard medicine for targeting HER2 in mGEA, plus standard chemotherapy
- This study included people with HER2-positive mGEA whose tumors were either PD-L1–positive or PD-L1–negative
- The researchers measured PD-L1 in two different ways
 - Tumor area positivity (or TAP) score measures the percentage of the tumor area that shows PD-L1 expression
 - Combined positive score (or CPS) measures the number of tumor cells and certain immune cells in the tumor area that express PD-L1

What were the results of this research?

- Patients with HER2-positive mGEA who received zanidatamab plus tislelizumab and chemotherapy lived longer without their tumors growing and overall than those who received trastuzumab and chemotherapy, no matter whether their tumors expressed PD-L1 or not
 - The results were similar whether PD-L1 was measured using TAP score or CPS
- The side effects that patients experienced were manageable