2026 ASCO® ANNUAL MEETING

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

HERIZON GEA-301

- **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**

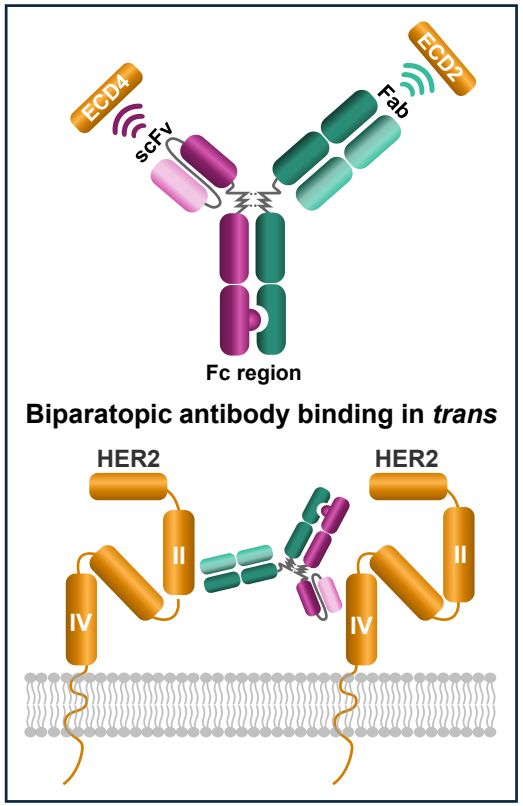
- **The PFS and OS benefits** were consistent across patients with **PD-L1–positive and PD-L1–negative** disease **by both TAP score and CPS**

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

1L, first line; CPS, combined positive score; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; mGEA, advanced or metastatic gastroesophageal adenocarcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, tumor area positivity.

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 tumors[1-3]
- 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 action[5]
  - 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-301

HERIZON-GEA-01 (NCT05152147)

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

Key Eligibility Criteria

- Age ≥18 years
- Unresectable, locally advanced, recurrent or metastatic GEA
- HER2 IHC 3+ or IHC 2+/ISH+ per central testing
- ECOG PS 0 or 1
- No prior treatment for locally advanced or metastatic disease
- No prior HER2-targeted agents or immunotherapy in any setting

R 1:1:1

N = 914

Arm A: Trastuzumab + chemotherapy[a]

Arm B: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W + chemotherapy[a]

Arm C: Zanidatamab 1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W + tislelizumab[b] + chemotherapy[a]

Prophylaxis to prevent IRR and diarrhea was mandatory in the zanidatamab-containing arms

CT/MRI[c] Q6W

Dual Primary Endpoints

- PFS (per BICR)
- OS

Treatment until disease progression/death/unacceptable toxicity
Chemotherapy could be discontinued after 6 cycles

PD-L1 expression was assessed retrospectively by the VENTANA SP263 assay[d]

TAP score (%)	CPS
Prespecified analyses (TAP ≥1% vs <1%)	**Exploratory analyses**

$$\frac{\text{Area occupied by PD-L1–stained tumor cells and immune cells}}{\text{Tumor area}} \times 100\%$$

$$\frac{\text{\# of PD-L1–stained tumor cells and immune cells}}{\text{Total \# of viable tumor cells}} \times 100$$

[a]Physician'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.
[b]Tislelizumab 200 mg was administered IV Q3W. [c]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks. [d]TAP 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	
	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)
Geographic region				
Asia	96 (51.3)	56 (62.2)	101 (53.7)	55 (56.1)
EU/North America	61 (32.6)	21 (23.3)	60 (31.9)	26 (26.5)
Rest of the world	30 (16.0)	13 (14.4)	27 (14.4)	17 (17.3)
ECOG PS[a]				
0	76 (40.6)	38 (42.2)	75 (39.9)	40 (40.8)
1	111 (59.4)	51 (56.7)	113 (60.1)	58 (59.2)
Choice of chemotherapy backbone				
CAPOX	164 (87.7)	87 (96.7)	170 (90.4)	93 (94.9)
FP	23 (12.3)	3 (3.3)	18 (9.6)	5 (5.1)

	Zanidatamab + tislelizumab + CT		Trastuzumab + CT	
	TAP ≥1% (n = 187)	TAP <1% (n = 90)	TAP ≥1% (n = 188)	TAP <1% (n = 98)
Anatomical subtype				
Gastric	131 (70.1)	65 (72.2)	137 (72.9)	74 (75.5)
GEJ	41 (21.9)	20 (22.2)	37 (19.7)	20 (20.4)
Esophageal	15 (8.0)	5 (5.6)	14 (7.4)	4 (4.1)
HER2 IHC 3+	150 (80.2)	77 (85.6)	160 (85.1)	77 (78.6)
MSI				
MSI-high/dMMR	3 (1.6)	0	3 (1.6)	1 (1.0)
MSS/MSI-low/pMMR	110 (58.8)	38 (42.2)	102 (54.3)	50 (51.0)
Unknown	74 (39.6)	52 (57.8)	83 (44.1)	47 (48.0)
CPS[b]				
<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.
[a]One patient in the zanidatamab + tislelizumab + chemotherapy arm with TAP <1% had an ECOG PS score of 2 at baseline. [b]CPS 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.

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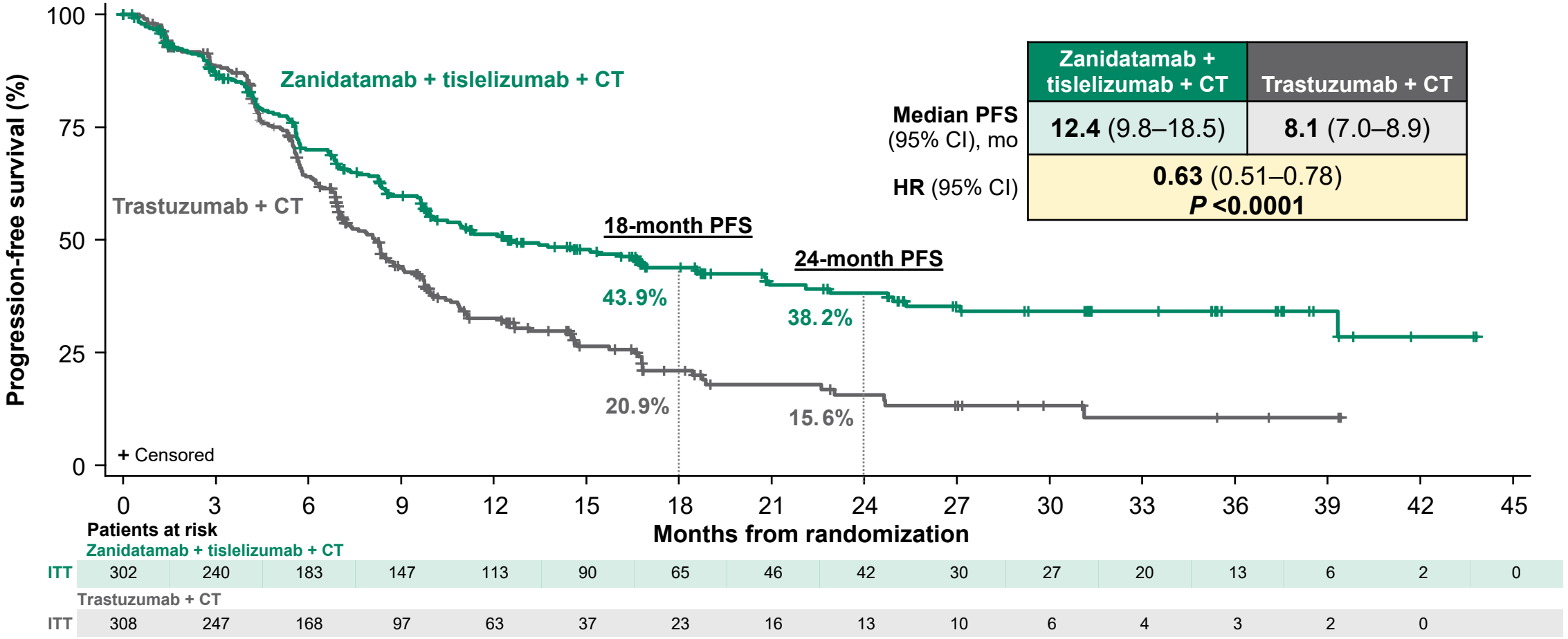
Primary Endpoint: PFS per BICR, ITT population

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



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–18.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.63** (0.51–0.78) ***P* <0.0001**	

Patients at risk

Zanidatamab + tislelizumab + CT																
ITT	302	240	183	147	113	90	65	46	42	30	27	20	13	6	2	0
Trastuzumab + CT																
ITT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

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.

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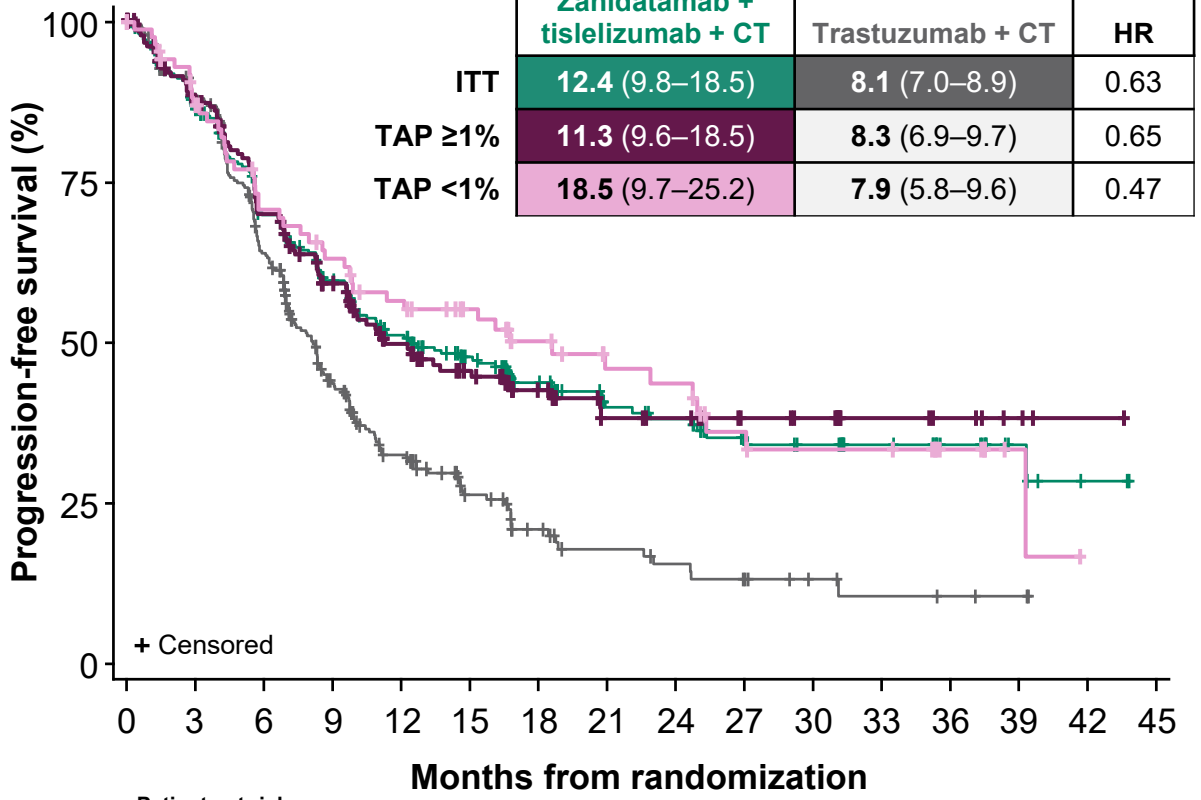
PFS per BICR by PD-L1 Subgroups (TAP and CPS)

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

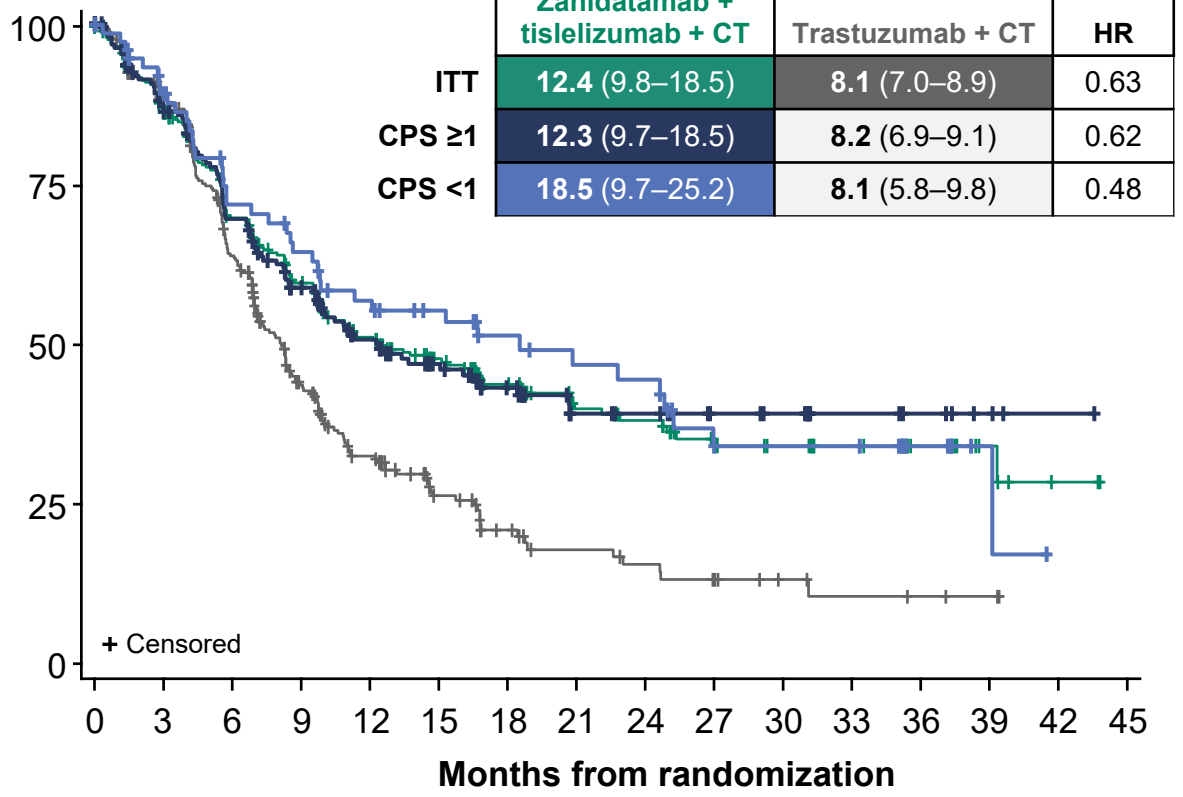


Patients at risk
Zanidatamab + tislelizumab + CT

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	

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

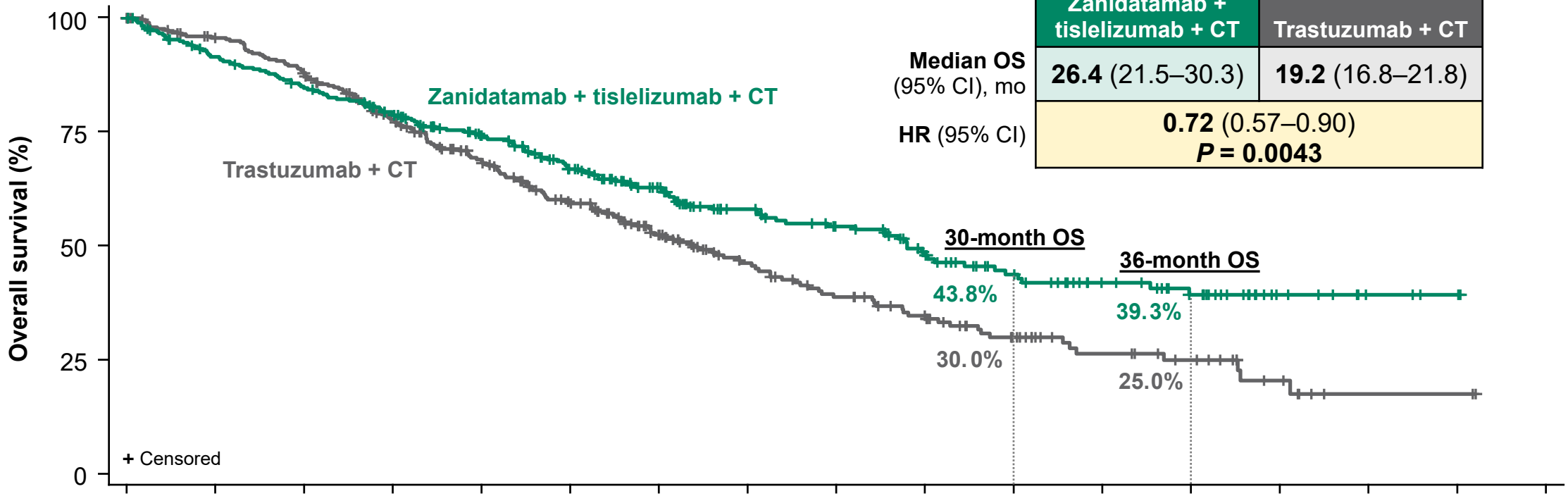
CPS ≥1	198	156	119	93	69	53	38	24	22	17	15	8	6	3	1	0
CPS <1	78	64	49	43	36	31	23	20	19	12	11	11	6	2	0	

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

	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)
HR (95% CI)	**0.72** (0.57–0.90) ***P* = 0.0043**	



Patients at risk

Zanidatamab + tislelizumab + CT																	
ITT	302	267	246	222	190	157	125	96	82	64	49	36	27	10	4	2	0
Trastuzumab + CT																	
ITT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

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.

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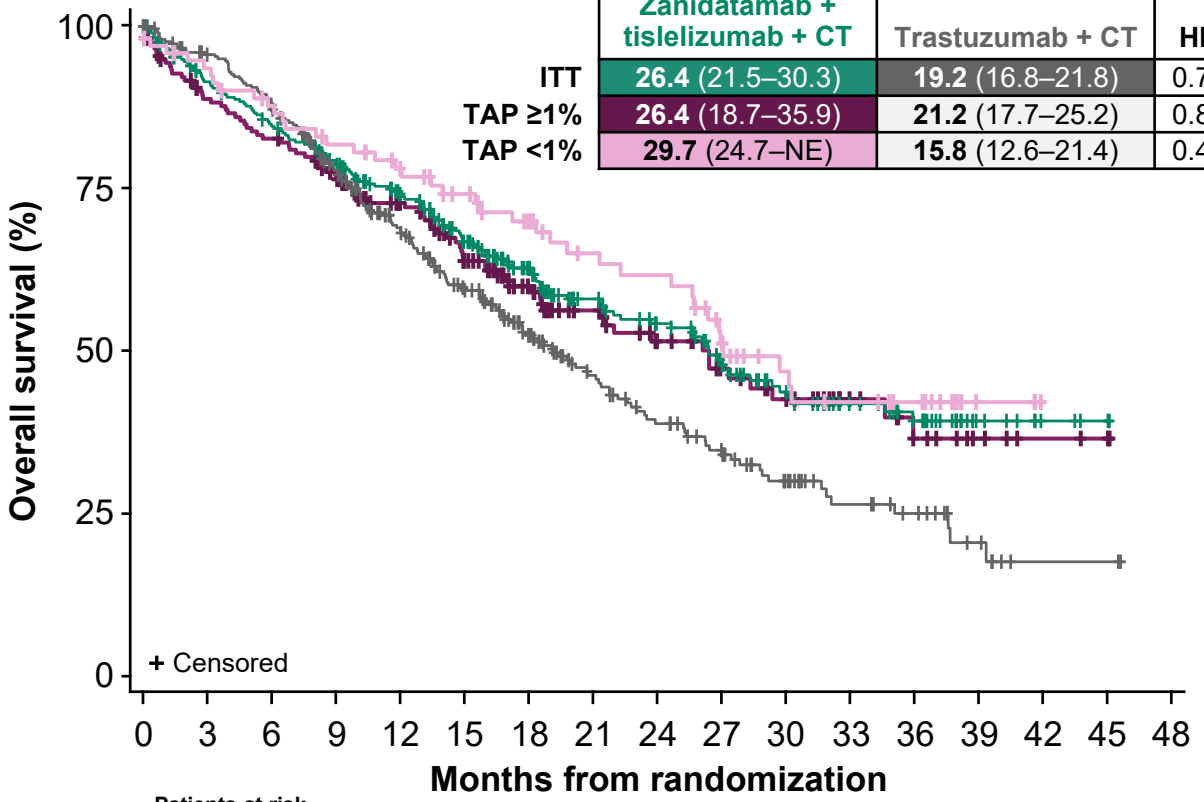
OS by PD-L1 Subgroups (TAP and CPS)

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

Median OS (95% CI), months

	Zanidatamab + tislelizumab + CT	Trastuzumab + CT	HR
ITT	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)	0.72
TAP ≥1%	**26.4** (18.7–35.9)	**21.2** (17.7–25.2)	0.82
TAP <1%	**29.7** (24.7–NE)	**15.8** (12.6–21.4)	0.49

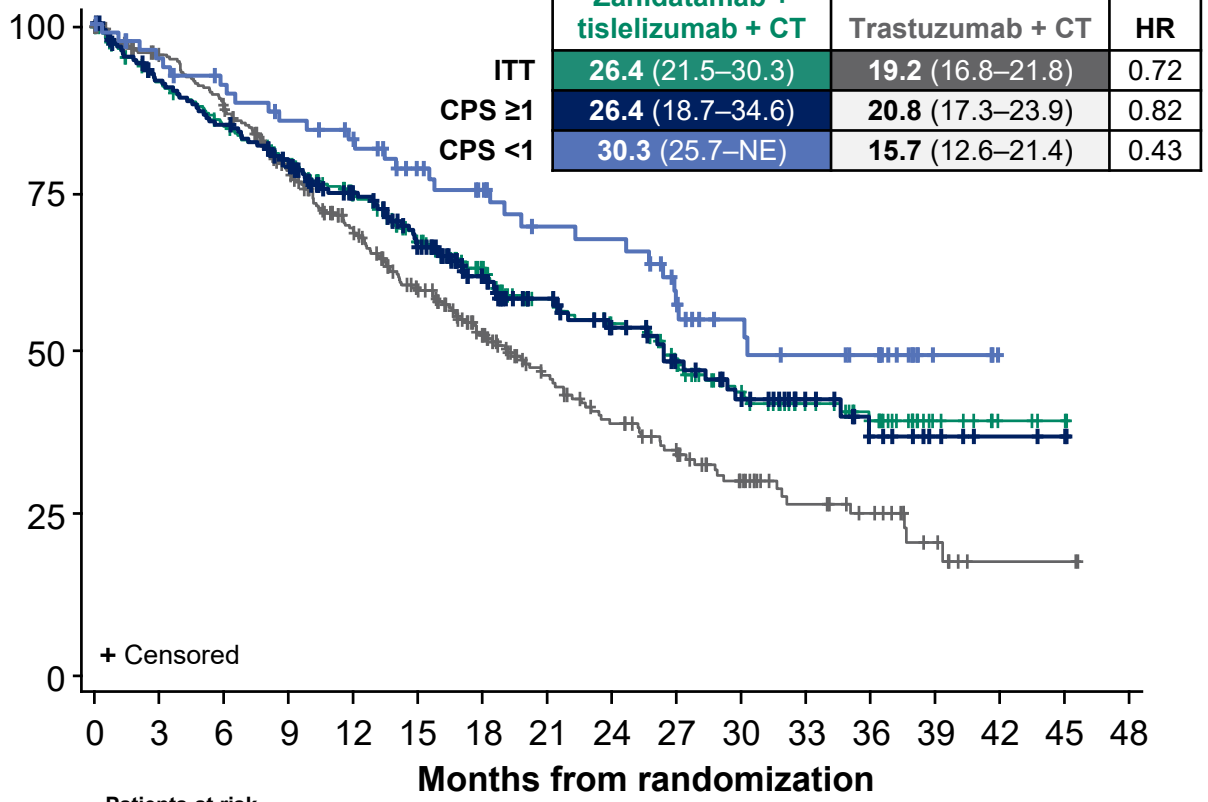


Patients at risk
Zanidatamab + tislelizumab + CT

TAP ≥1%	187	163	152	137	114	92	69	53	41	33	27	17	11	6	3	2	0
TAP <1%	90	83	76	70	64	56	48	40	38	29	21	18	15	3	0		

Median OS (95% CI), months

	Zanidatamab + tislelizumab + CT	Trastuzumab + CT	HR
ITT	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)	0.72
CPS ≥1	**26.4** (18.7–34.6)	**20.8** (17.3–23.9)	0.82
CPS <1	**30.3** (25.7–NE)	**15.7** (12.6–21.4)	0.43



Patients at risk
Zanidatamab + tislelizumab + CT

CPS ≥1	198	174	161	145	120	99	73	56	44	35	28	18	11	6	3	2	0
CPS <1	78	71	66	61	57	48	43	36	35	27	20	17	15	3	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.
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.

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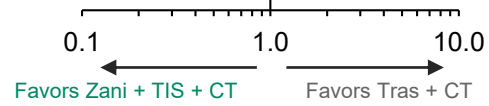
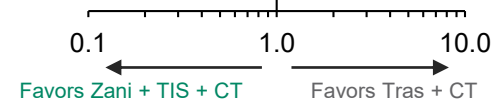
PFS and OS by PD-L1 Cutoff (TAP and CPS)

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

	PFS events/patients		Zani + TIS + CT vs Tras + CT	PFS HR (95% CI)	OS events/patients		Zani + TIS + CT vs Tras + CT	OS HR (95% CI)
	Zanidatamab + tislelizumab + CT	Trastuzumab + CT			Zanidatamab + tislelizumab + CT	Trastuzumab + CT		
All patients	**154/302**	**196/308**		**0.63 (0.51–0.78)**	**134/302**	**170/308**		**0.72 (0.57–0.90)**
TAP <1%	47/90	71/98		0.47 (0.32–0.69)	38/90	65/98		0.49 (0.33–0.74)
TAP ≥1%	91/187	114/188		0.65 (0.49–0.86)	79/187	92/188		0.82 (0.60–1.10)
TAP <5%	90/181	138/200		0.52 (0.40–0.68)	79/181	118/200		0.63 (0.47–0.84)
TAP ≥5%	48/96	47/86		0.79 (0.53–1.19)	38/96	39/86		0.80 (0.51–1.25)
TAP <10%	118/235	157/241		0.57 (0.45–0.73)	102/235	137/241		0.66 (0.51–0.85)
TAP ≥10%	20/42	28/45		0.69 (0.39–1.24)	15/42	20/45		0.80 (0.41–1.56)
CPS <1	41/78	56/80		0.48 (0.32–0.73)	30/78	53/80		0.43 (0.27–0.67)
CPS ≥1	96/198	129/206		0.62 (0.48–0.81)	86/198	104/206		0.82 (0.62–1.10)
CPS <5	75/150	123/172		0.47 (0.35–0.64)	62/150	110/172		0.50 (0.37–0.69)
CPS ≥5	62/126	62/114		0.81 (0.57–1.16)	54/126	47/114		1.08 (0.73–1.59)
CPS <10	100/194	144/210		0.55 (0.43–0.71)	85/194	126/210		0.62 (0.47–0.81)
CPS ≥10	37/82	41/76		0.71 (0.46–1.12)	31/82	31/76		0.89 (0.54–1.46)





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.

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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.
[a]Includes 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)
IRRs	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.
[a]Five 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. [b]AESIs 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

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- 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

FPO

A copy of the presentation can be accessed via the QR code

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

1L, first line; CPS, combined positive score; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; mGEA, advanced or metastatic gastroesophageal adenocarcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TAP, tumor area positivity.

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