

Zanidatamab + chemotherapy $\pm$ tislelizumab for first-line HER2-positive advanced/metastatic gastro-oesophageal adenocarcinoma: second interim analysis from HERIZON-GEA-01

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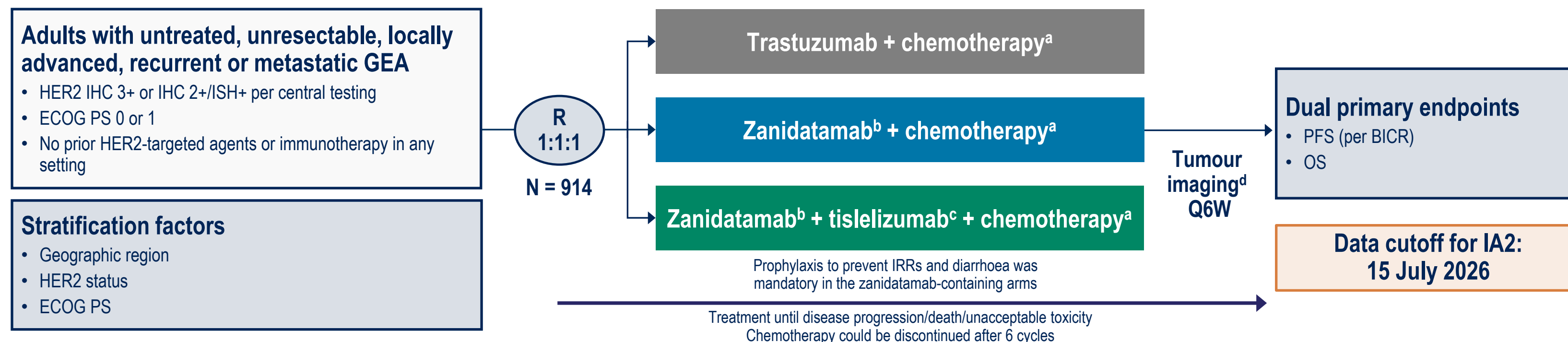
Declaration of Interests

Kohei Shitara reports consulting fees from AbbVie, ALX Oncology, Amgen, Arcus Biosciences, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CMIC, Daiichi Sankyo, eChinaHealth, Elevation Oncology, Gilead Sciences, Guardant Health Japan, Healios, Leap Therapeutics, Merck, Novartis, Oncolys BioPharma, Ono Pharmaceutical, Phanes Therapeutics, Revolution Medicines, Sanofi, Scandion Oncology, Suzuhou Lingyuhui Network Technology, Takeda, and Zymeworks; honoraria from Astellas Pharma; and research funding (all to institution) from AbbVie, Amgen, Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, ICON, Incyte, Medpace Japan, Merck, Ono Pharmaceutical, PPD-SNBL, PRA Health Sciences, Syneos Health, Taiho Pharmaceutical, and Toray Industries.

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Background

- **Zanidatamab** is a **bispecific HER2-directed antibody** that binds to **HER2 ECD 2 and 4** in a *trans* configuration, **facilitating crosslinking** associated with the **formation of distinct HER2 clusters** on the cell surface. It has several key mechanisms of action¹:
 - Increasing HER2 internalisation; reducing phosphorylation of EGFR, HER2, and HER3 and blocking downstream signalling; and inducing immune-mediated effects (CDC, ADCC, and ADCP)
- **Tislelizumab** is a high-affinity **ICI targeting PD-1** and is specifically engineered to minimise Fcγ receptor binding on macrophages



Here we report results from the planned second interim analysis of OS (IA2) from HERIZON-GEA-01

^aPhysician's choice of CAPOX (capecitabine plus oxaliplatin) or FP (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. ^bZanidatamab 1800 mg (<70 kg) or 2400 mg (≥70 kg) was administered IV Q3W. ^cTislelizumab 200 mg was administered IV Q3W. ^dComputed tomography/magnetic resonance imaging scans were performed Q6W for the first 54 weeks, then every 9 weeks.

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BICR, blinded independent central review; CDC, complement-dependent cytotoxicity; ECD, extracellular domain; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; Fcγ, fragment crystallisable-gamma; GEA, gastro-oesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; IA2, planned second interim analysis of OS; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridisation; IV, intravenously; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomisation.

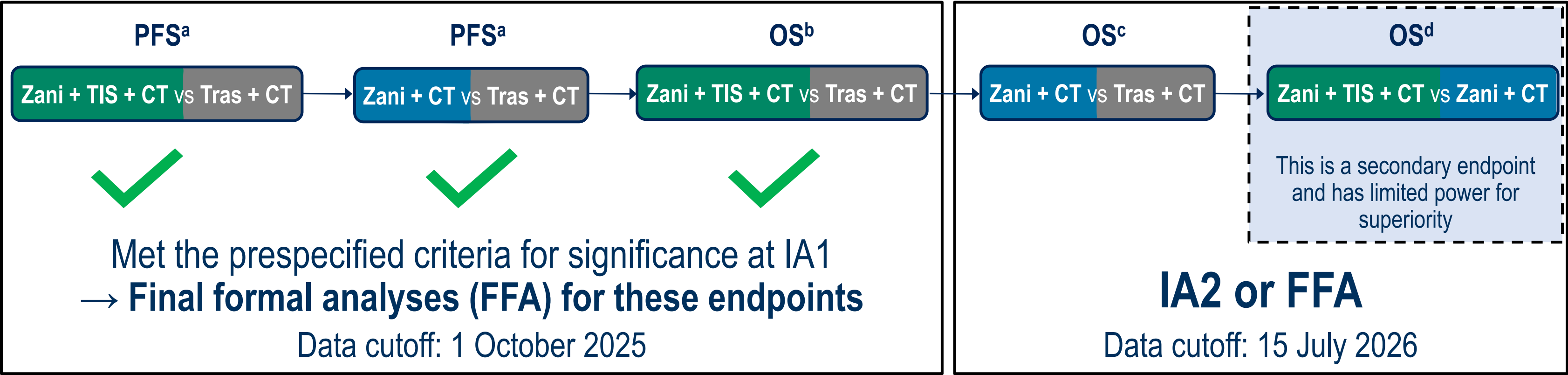
1. Weisser NE, et al. *Nat Commun.* 2023;14(1):1394.

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Dual primary endpoints (PFS and OS): Analysed in the ITT population using log-rank tests (overall 2-sided $\alpha = 0.05$)

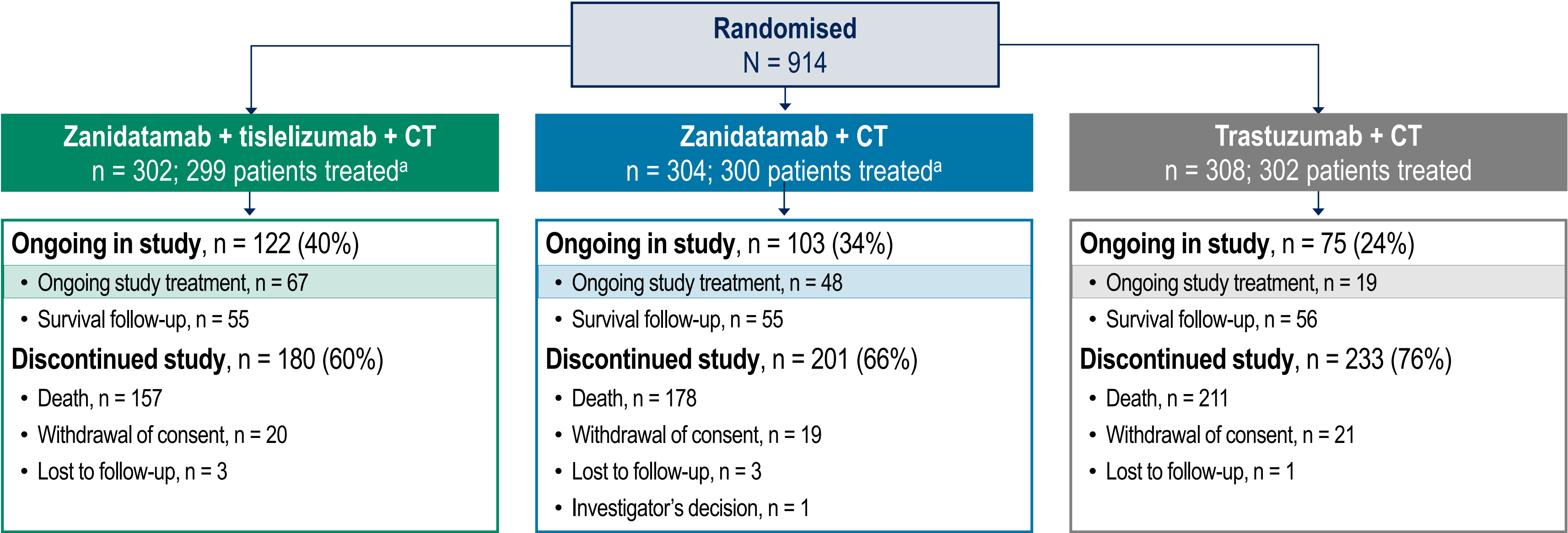
Fixed-Sequence Testing Procedure



^aFor the primary analysis of PFS, the critical 2-sided alpha was 0.05. ^bFor IA1, the critical 2-sided alpha was 0.0135. ^cThe critical 2-sided alpha was 0.0279. ^dThe critical 2-sided alpha was 0.0242.
CT, chemotherapy; FFA, final formal analysis, IA1; first interim analysis of OS; IA2, planned second interim analysis of OS; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Patient Disposition

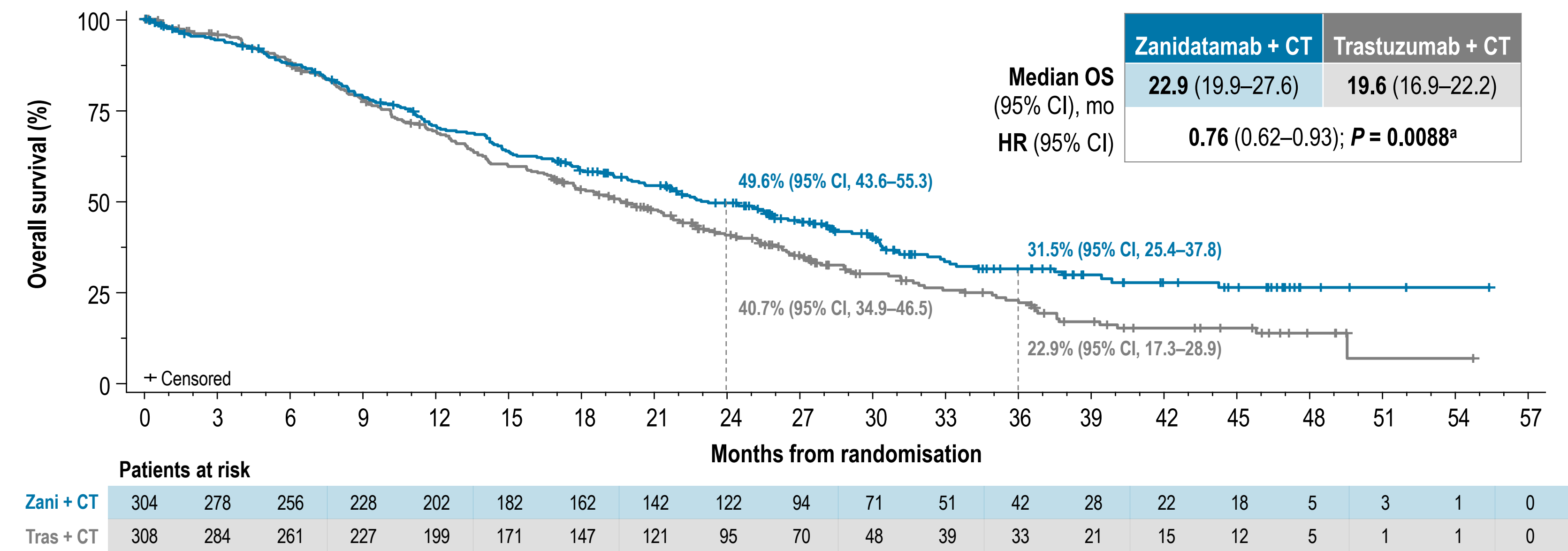
Median follow-up was 35.3 months at IA2, 9.4 months longer than at IA1



Data cutoff: 15 July 2026. ^aTreated includes all randomised patients who received any amount of any study treatment and does not necessarily reflect the safety analysis set. Five patients assigned to the zanidatamab-tislelizumab-CT arm did not receive tislelizumab and are included in the safety analysis set for the zanidatamab-CT arm.
 CT, chemotherapy; IA1, first interim analysis of overall survival; IA2, planned second interim analysis of overall survival.

Zanidatamab + CT: OS in the ITT Population

Zanidatamab + CT demonstrated a statistically significant and clinically meaningful improvement in OS vs trastuzumab + CT (FFA criteria met)

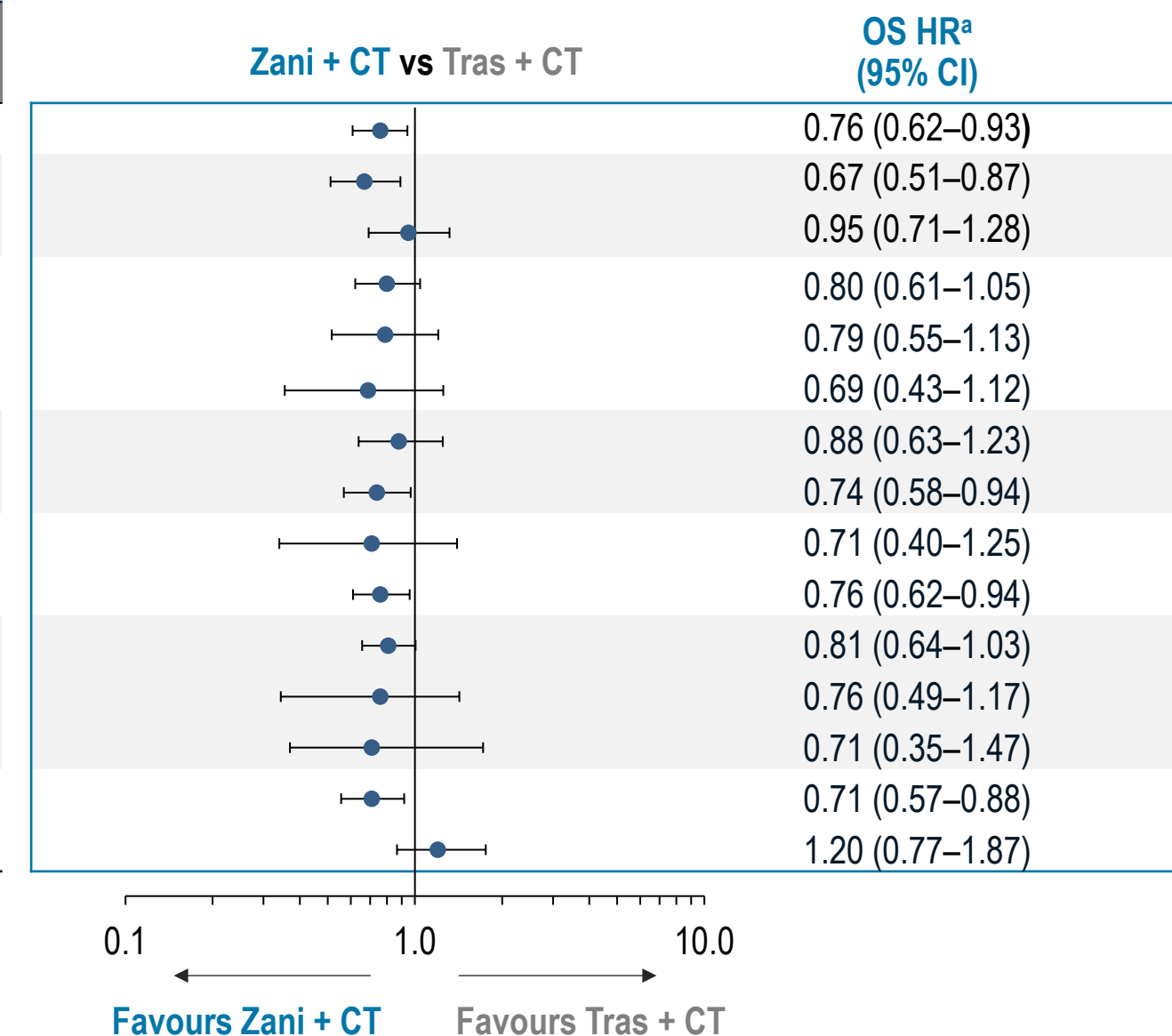


Data cutoff: 15 July 2026. ^aThe critical 2-sided alpha was 0.0279.
CT, chemotherapy; FFA, final formal analysis; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Tras, trastuzumab; Zani, zanidatamab.

Zanidatamab + CT vs Trastuzumab + CT: OS in Key Prespecified Subgroups

Improvements in OS with zanidatamab + CT vs trastuzumab + CT occurred across most prespecified subgroups

Subgroup	Category	Events/Patients	
		Zanidatamab + CT	Trastuzumab + CT
All patients		182/304	212/308
Age	<65 years	98/174	116/162
	≥65 years	84/130	96/146
Geographic region	Asia	96/163	111/165
	EU/NA	54/91	65/93
	ROW	32/50	36/50
ECOG PS	0	68/134	67/120
	1	114/170	145/188
Prior gastrectomy	Yes	18/43	34/56
	No	164/261	178/252
Anatomical subtype	Gastric	125/204	155/226
	GEJ	38/61	45/60
	Oesophageal	19/39	12/22
HER2 status	IHC 3+	141/251	172/255
	IHC 2+/ISH+	39/51	39/52



Data cutoff: 15 July 2026. ^aThe widths of the CIs were not adjusted for multiplicity and cannot be used to infer treatment effects.

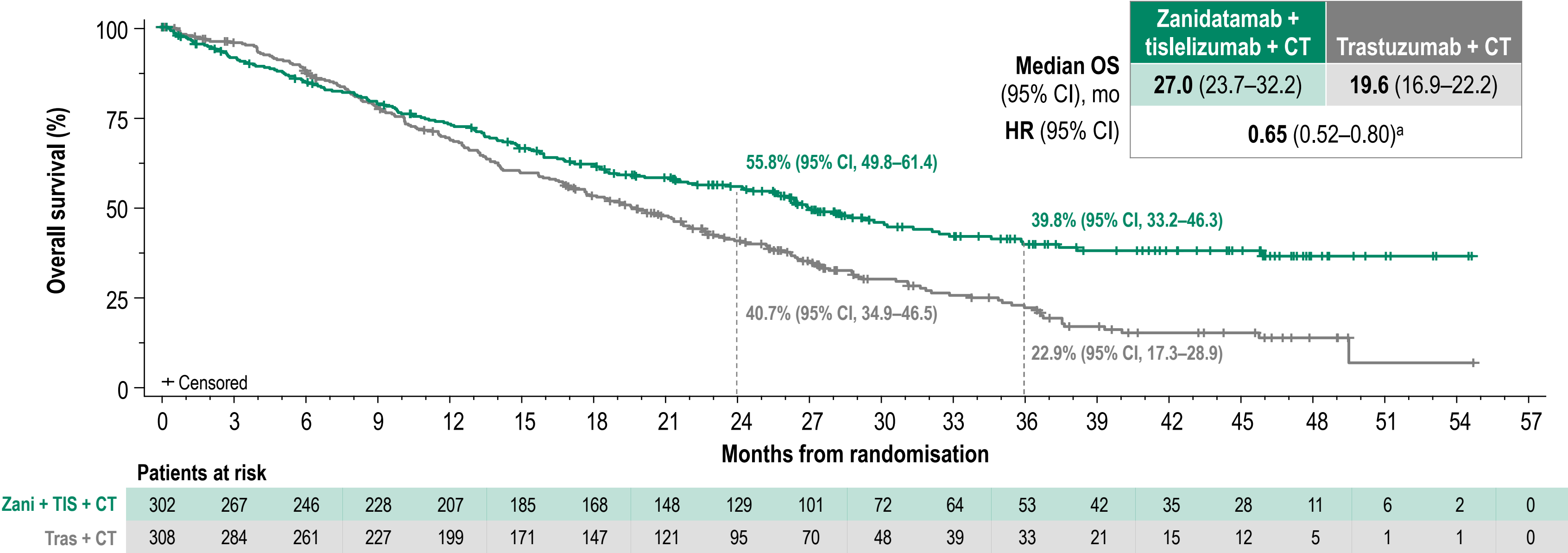
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, European Union; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridisation; NA, North America; OS, overall survival; ROW, rest of the world; Tras, trastuzumab; Zani, zanidatamab.

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Zanidatamab + Tislelizumab + CT: OS in the ITT Population

Zanidatamab + tislelizumab + CT continued to demonstrate an OS benefit vs trastuzumab + CT, with an **improved HR from IA1**

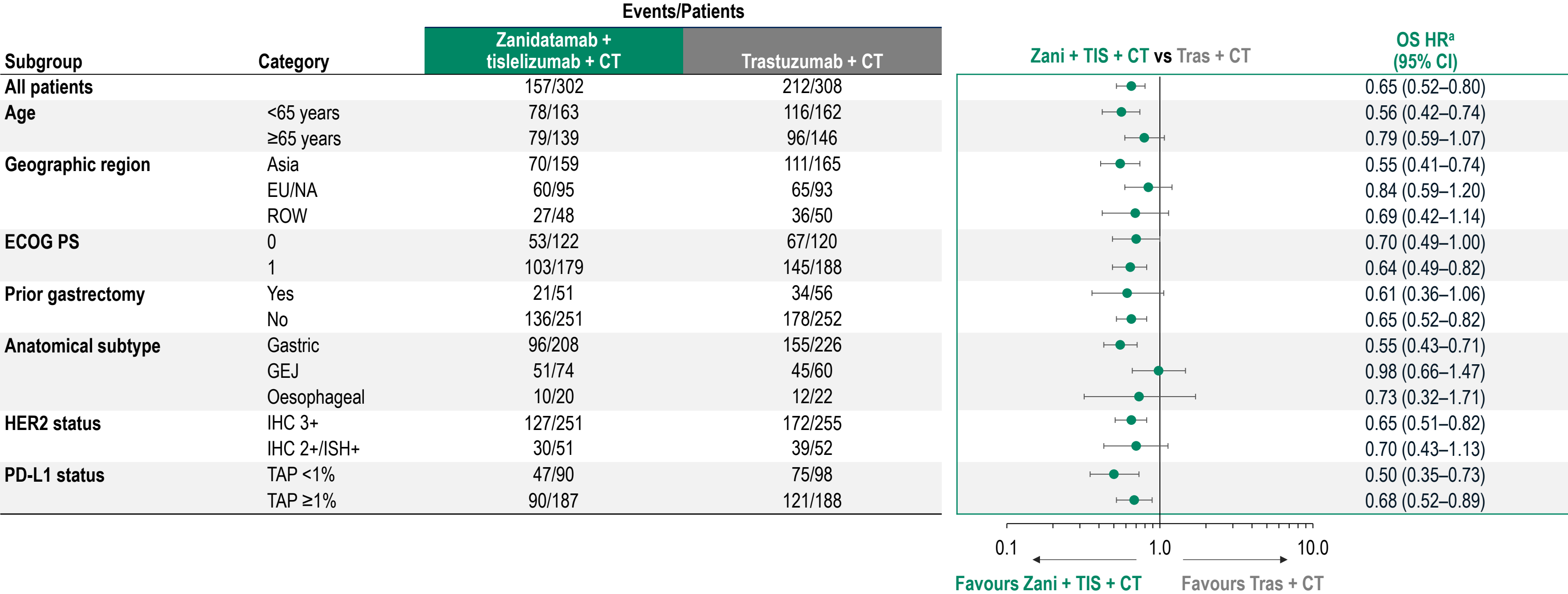


Data cutoff: 15 July 2026. ^aAnalysis was descriptive, as prespecified criteria for significance were previously met.
CT, chemotherapy; HR, hazard ratio; IA1, first interim analysis of OS; ITT, intent-to-treat; OS, overall survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Zanidatamab + Tislelizumab + CT vs Trastuzumab + CT: OS in Key Prespecified Subgroups



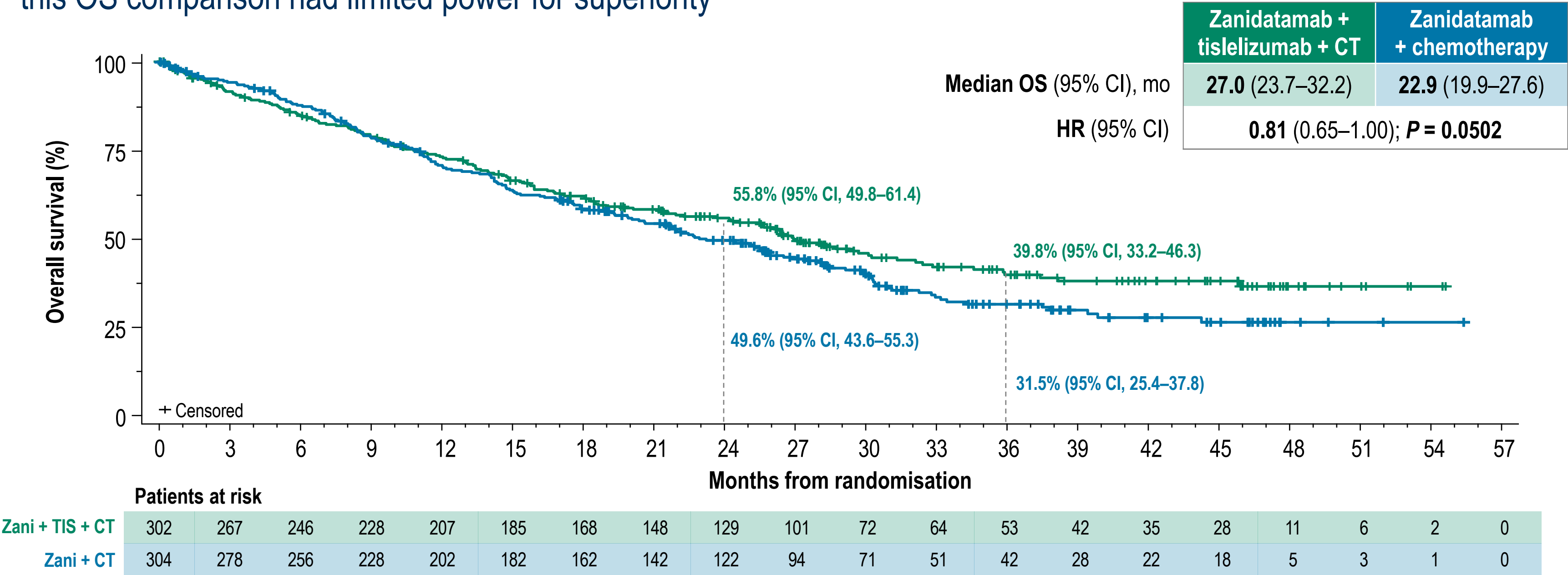
The OS benefit with zanidatamab + tislelizumab + CT vs trastuzumab + CT was generally consistent across prespecified subgroups, **including in patients with PD-L1–negative disease**



Data cutoff: 15 July 2026. ^aThe widths of the CIs were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EU, European Union; GEJ, gastro-oesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridisation; NA, North America; OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of the world; TAP, tumour area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Zanidatamab + Tislelizumab + CT vs Zanidatamab + CT: OS in the ITT Population

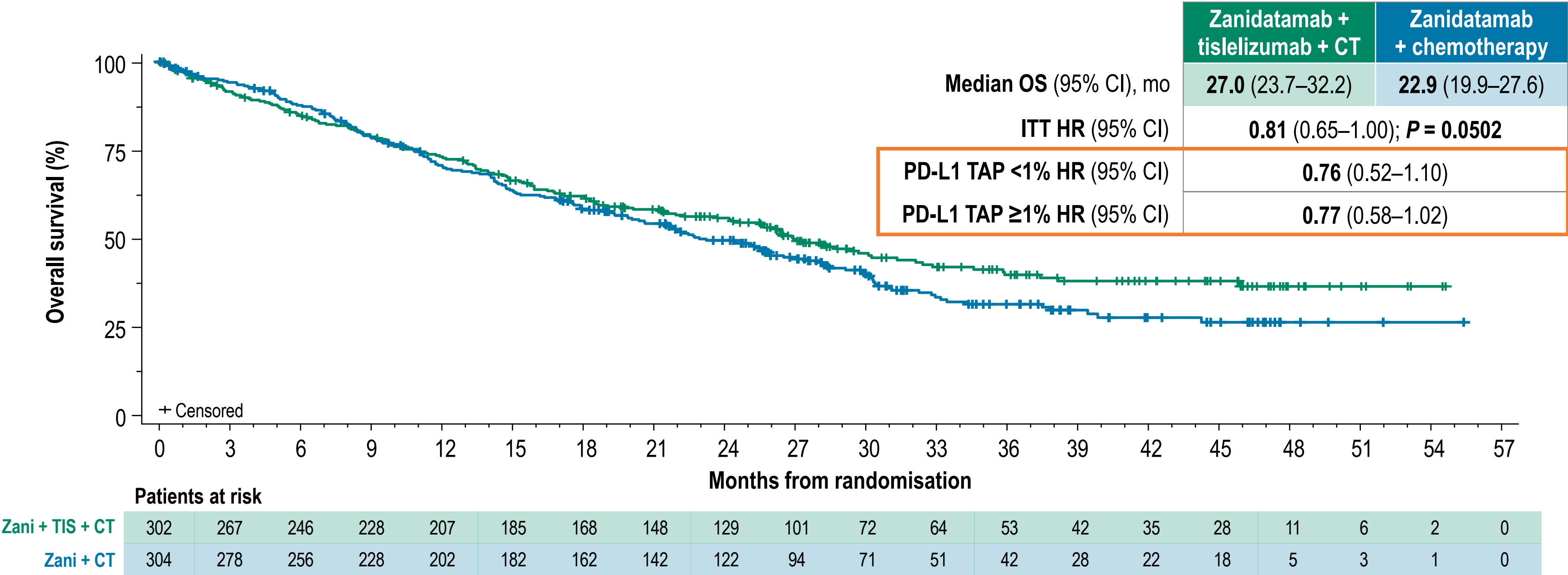
Median OS was 4 months longer with zanidatamab + tislelizumab + CT compared with zanidatamab + CT; however, this OS comparison had limited power for superiority



Data cutoff: 15 July 2026.
CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; TIS, tislelizumab; Zani, zanidatamab.

Zanidatamab + Tislelizumab + CT vs Zanidatamab + CT: OS in the ITT Population

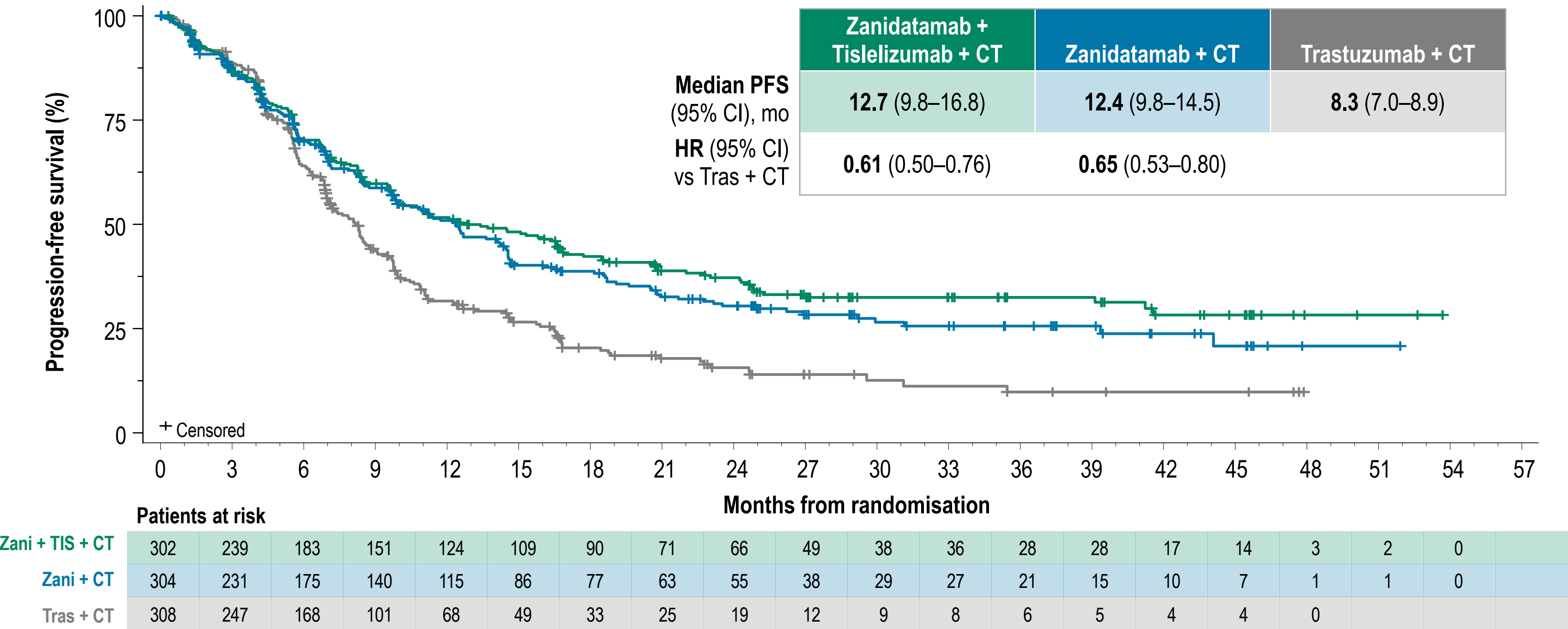
A consistent trend toward improved OS was observed irrespective of PD-L1 status



Data cutoff: 15 July 2026.
CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; TAP, tumour area positivity; TIS, tislelizumab; Zani, zanidatamab.

Progression-Free Survival in the ITT Population

PFS was consistent with the primary analysis (IA1)



Data cutoff: 15 July 2026.
CT, chemotherapy; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Safety Summary

The AE profile remained consistent with IA1, and no unexpected safety signals were observed

	Zanidatamab + tislelizumab + CT (n = 294) ^a	Zanidatamab + CT (n = 305) ^a	Trastuzumab + CT (n = 302)
Duration of treatment, weeks			
Mean (SD)	64.1 (58.0)	52.6 (52.6)	42.3 (39.2)
Median (IQR)	46.6 (17.6–101.4)	31.1 (14.3–74.7)	30.0 (18.1–54.1)
Duration of zanidatamab or trastuzumab treatment, weeks			
Mean (SD)	60.2 (57.4)	51.0 (52.9)	40.8 (39.4)
Median (IQR)	40.5 (14.4–97.1)	30.1 (12.1–72.7)	28.2 (16.3–52.1)
Any-grade TEAE, n (%)	293 (99.7)	301 (98.7)	297 (98.3)
TRAE, n (%)	289 (98.3)	296 (97.0)	291 (96.4)
Grade ≥3	213 (72.4)	180 (59.0)	181 (59.9)
Serious TEAEs, n (%)	176 (59.9)	155 (50.8)	131 (43.4)
Treatment-related	124 (42.2)	87 (28.5)	62 (20.5)
TEAEs leading to death, n (%)	30 (10.2)	26 (8.5)	22 (7.3)
Treatment-related	7 (2.4)	1 (0.3)	4 (1.3)
Discontinuation due to TRAEs, n (%)			
Any component	132 (44.9)	107 (35.1)	88 (29.1)
Zanidatamab or trastuzumab ^b	35 (11.9)	28 (9.2)	7 (2.3)
Tislelizumab ^c	49 (16.7)	—	—
Any-grade diarrhoea, n (%)	244 (83.0)	241 (79.0)	161 (53.3)
Grade ≥3	74 (25.2)	61 (20.0)	39 (12.9)
AESIs^d, n (%)	103 (35.0)	94 (30.8)	56 (18.5)
IRRs	74 (25.2)	77 (25.2)	40 (13.2)
Noninfectious pulmonary toxicities	22 (7.5)	5 (1.6)	4 (1.3)
Left ventricular dysfunction	27 (9.2)	20 (6.6)	13 (4.3)
Immune-mediated AEs^d, n (%)	118 (40.1)	44 (14.4)	32 (10.6)

- **Diarrhoea occurred primarily in cycles 1 and 2, and the incidence was consistent with IA1**

Data cutoff: 15 July 2026. ^aFive patients who were assigned to the zanidatamab + tislelizumab + CT arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab + CT arm. ^bZanidatamab- or trastuzumab-related TEAEs that led to discontinuation of zanidatamab or trastuzumab. ^cTislelizumab-related TEAEs that led to discontinuation of tislelizumab. ^dAESIs for zanidatamab were IRRs, non-infectious pulmonary toxicities, and left ventricular dysfunction; AESIs for tislelizumab were IRRs and immune-mediated AEs. Immune-mediated AEs are excluded from AESIs and reported separately. AESIs for zanidatamab and tislelizumab are 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; IA1, first interim analysis of OS; IQR, interquartile range; IRR, infusion-related reaction; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Summary and Conclusions

Zanidatamab Demonstrated Superiority Over Trastuzumab

- At this FFA, zanidatamab + CT demonstrated a statistically significant and clinically meaningful **improvement in OS (HR, 0.76)** vs trastuzumab + CT
- All primary endpoints have been met, showing PFS and OS benefits for both zanidatamab-containing regimens

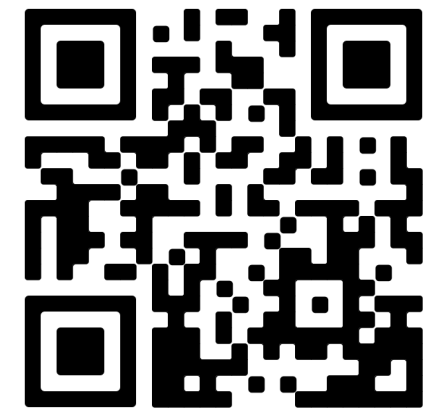
Sustained Long-Term Survival With Zanidatamab + Tislelizumab + CT

- With longer follow-up, zanidatamab + tislelizumab + CT sustained a robust OS benefit over trastuzumab + CT, with an **improved HR vs IA1** (HR, 0.65 vs 0.72)¹ and a **40% 3-year OS rate** vs 23% with trastuzumab + CT
- Adding tislelizumab to zanidatamab + CT provided a meaningful trend toward further OS benefit irrespective of PD-L1 status

Long-Term Safety and Tolerability

- The safety profiles remained manageable with **no new safety signals**, supporting the tolerability of prolonged treatment

These results solidify zanidatamab with chemotherapy ± tislelizumab as the new standard of care in 1L HER2-positive mGEA, replacing trastuzumab-based regimens



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1L, first-line; CT, chemotherapy; FFA, final formal analysis; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IA1, first interim analysis of OS; mGEA, advanced or metastatic gastro-oesophageal adenocarcinoma; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

1. Shitara K, et al. *N Engl J Med*. 2026;394:2002-14.

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