

Zanidatamab + chemotherapy ± tislelizumab for first-line HER2-positive locally advanced, unresectable, or metastatic gastroesophageal adenocarcinoma: Primary analysis from HERIZON-GEA-01

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Key Takeaway Points

HERIZON-GEA-01 supports zanidatamab as a new standard in HER2-targeting agents, potentially replacing trastuzumab, as well as the use of tislelizumab in 1L HER2+ mGEA

Progression-Free Survival and Overall Survival

- **Statistically significant ~35% reduction** in the risk of disease progression or death for **both zanidatamab + tislelizumab + CT and zanidatamab + CT** vs trastuzumab + CT (**>4-month improvement in median PFS**)
- **Statistically significant 28% reduction** in the risk of death for **zanidatamab + tislelizumab + CT** vs trastuzumab + CT (**>7-month improvement in median OS**)
- There was a **strong trend toward statistical significance for OS favoring zanidatamab + CT** vs trastuzumab + CT (**5-month improvement in median OS**)
- The PFS and OS benefits were generally observed across key prespecified subgroups, including in patients with PD-L1 TAP scores <1% and ≥1%

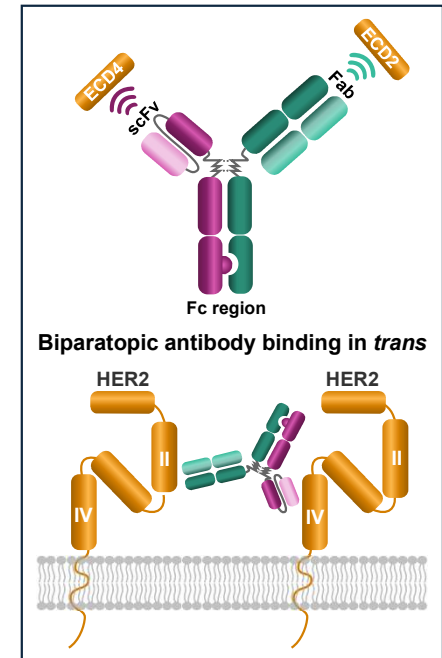
Safety Profile

- The safety profile was consistent with the known profiles of each individual treatment

1L, first-line; 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

- Outcomes with current SoC for 1L HER2+ mGEA remain modest, with an mPFS of <1 year and mOS of <2 years¹⁻⁷
- **Zanidatamab** is a **dual HER2-targeted bispecific IgG1-like antibody** that binds to **extracellular domains 2 and 4 on HER2** in a **trans configuration**⁸
 - This **biparatopic binding** enables zanidatamab to **crosslink neighboring HER2 proteins, leading to receptor clustering**
 - In preclinical studies, zanidatamab **enhanced HER2 internalization, reduced downstream signaling**, and promoted **immune-mediated cytotoxicity (CDC, ADCC, ADCP)**
- **Tislelizumab** is a **high-affinity immune checkpoint inhibitor targeting PD-1** and is specifically engineered to minimize Fcγ receptor binding on macrophages^{9,10}
- **Promising efficacy and a tolerable safety profile** were observed with zanidatamab + chemotherapy ± tislelizumab across **independent phase 2 trials in 1L HER2+ mGEA**^{11,12}



1L, first-line; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; ECD, extracellular domain; Fab, fragment antigen binding; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; mGEA, advanced or metastatic gastroesophageal adenocarcinoma; mOS, median overall survival; mPFS, median progression-free survival; PD-1, programmed cell death protein 1; SoC, standard of care; scFv, single-chain variable fragment.

1. Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-64. 2. Lordick F, et al. *Ann Oncol*. 2022;33(10):1005-20. 3. US Food and Drug Administration. FDA approved pembrolizumab for HER2 positive gastric or gastroesophageal junction adenocarcinoma expressing PD-L1 (CPS ≥1). Accessed October 14, 2025. <http://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-her2-positive-gastric-or-gastroesophageal-junction-adenocarcinoma>. 4. Bang YJ, et al. *Lancet*. 2010;376(9742):687-97. 5. Janjigian YY, et al. *N Engl J Med*. 2024;391(14):1360-2. 6. Janjigian YY, et al. *Lancet*. 2023;402(10418):2197-208. 7. Meric-Bernstam F, et al. *Nat Commun*. 2025;16(1):4293. 8. Weisser NE, et al. *Nat Commun*. 2023;14(1):1394. 9. Hong Y, et al. *FEBS Open Bio*. 2021;11(3):782-92. 10. Zhang T, et al. *Cancer Immunol Immunother*. 2018;67(7):1079-90. 11. Elimova E, et al. *Lancet Oncol*. 2025;26(7):847-59. 12. Lee KW, et al. *Clin Cancer Res*. 2025. <http://doi.org/10.1158/1078-0432.CCR-24-4295>.

HERIZON-GEA-01 Study Design

Global phase 3 trial of zanidatamab + chemotherapy \pm tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ 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

Stratification Factors

- Geographic region
- HER2 status
- ECOG PS

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

CT/MRI^c
Q6W

Dual Primary Endpoints

- PFS (per BICR)
- OS

Select Secondary Endpoints

- cORR (per BICR)
- Frequency and severity of AEs

ClinicalTrials.gov: NCT05152147

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

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

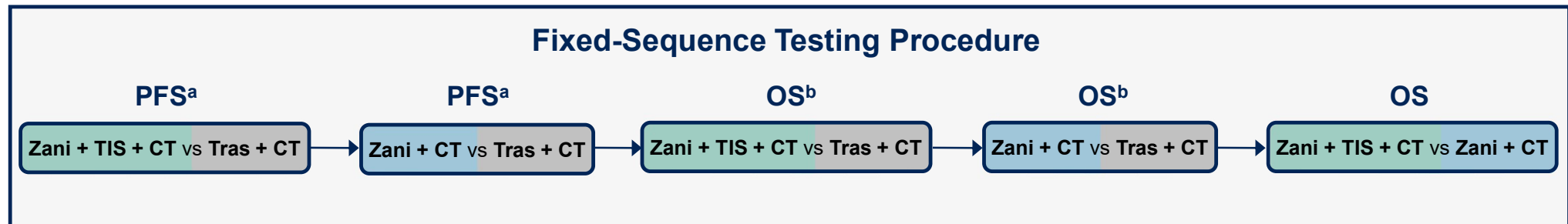
^aPhysician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met.

^bTislelizumab 200 mg was administered IV Q3W. ^cCT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks.

AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; 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; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

Statistical Design

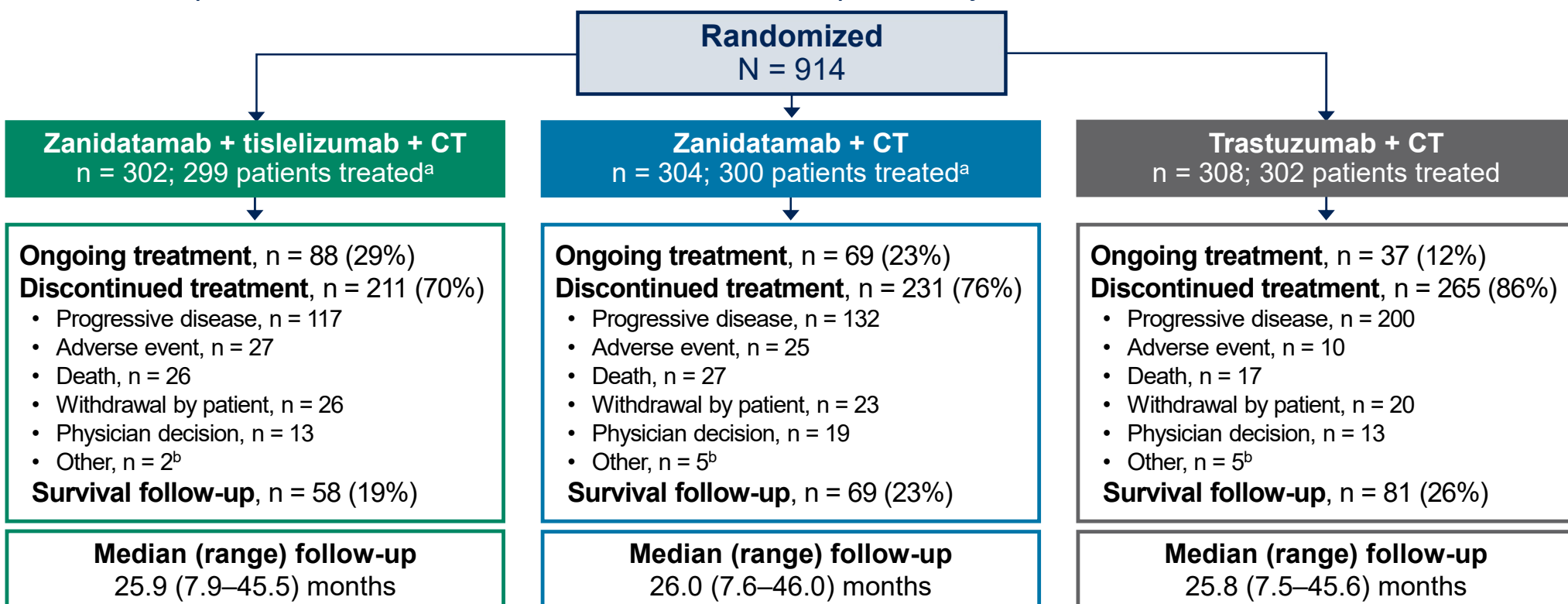
- **Dual primary endpoints (PFS and OS): Analyzed in the intent-to-treat population using log-rank tests with a 2-sided $\alpha = 0.05$**
 - **Primary PFS analysis:** After target event count was reached and patients had ≥ 7 months of follow-up
 - **First interim OS analysis:** Performed at the time of data cutoff for the primary PFS analysis



^aFor the primary analysis of PFS, the 2-sided alpha was 0.05. ^bFor the first interim analysis of OS, the 2-sided alpha was 0.020.
CT, chemotherapy; OS, overall survival; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Patient Disposition

A total of 914 patients were randomized, and median follow-up was >2 years



^aTreated includes all randomized 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-chemotherapy arm did not receive tislelizumab and are included in the safety analysis set for the zanidatamab-chemotherapy arm. ^bIncludes protocol violations and "other" reasons. CT, chemotherapy.

Baseline Demographics and Disease Characteristics

Demographics and clinical characteristics were balanced across all 3 treatment arms

	Zanidatamab + tislelizumab + CT (n = 302)	Zanidatamab + CT (n = 304)	Trastuzumab + CT (n = 308)		Zanidatamab + tislelizumab + CT (n = 302)	Zanidatamab + CT (n = 304)	Trastuzumab + CT (n = 308)
Age , median (range), years	63.0 (22–81)	62.5 (25–87)	64.0 (21–84)	Anatomical subtype			
Male sex	244 (80.8)	244 (80.3)	238 (77.3)	Gastric	208 (68.9)	204 (67.1)	226 (73.4)
Geographic region				GEJ	74 (24.5)	61 (20.1)	60 (19.5)
Asia	159 (52.6)	163 (53.6)	165 (53.6)	Esophageal	20 (6.6)	39 (12.8)	22 (7.1)
EU/North America	95 (31.5)	91 (29.9)	93 (30.2)	HER2 IHC 3+	251 (83.1)	251 (82.6)	255 (82.8)
Rest of the world	48 (15.9)	50 (16.4)	50 (16.2)	PD-L1 status^b			
ECOG PS^a				TAP score <1%	90 (29.8)	108 (35.5)	98 (31.8)
0	121 (40.1)	134 (44.1)	120 (39.0)	TAP score ≥1%	187 (61.9)	178 (58.6)	188 (61.0)
1	180 (59.6)	170 (55.9)	188 (61.0)	Choice of chemotherapy backbone			
Disease status				CAPOX	273 (90.4)	276 (90.8)	282 (91.6)
Metastatic	284 (94.0)	295 (97.0)	299 (97.1)	FP	29 (9.6)	28 (9.2)	26 (8.4)
Unresectable locally advanced	18 (6.0)	9 (3.0)	9 (2.9)				

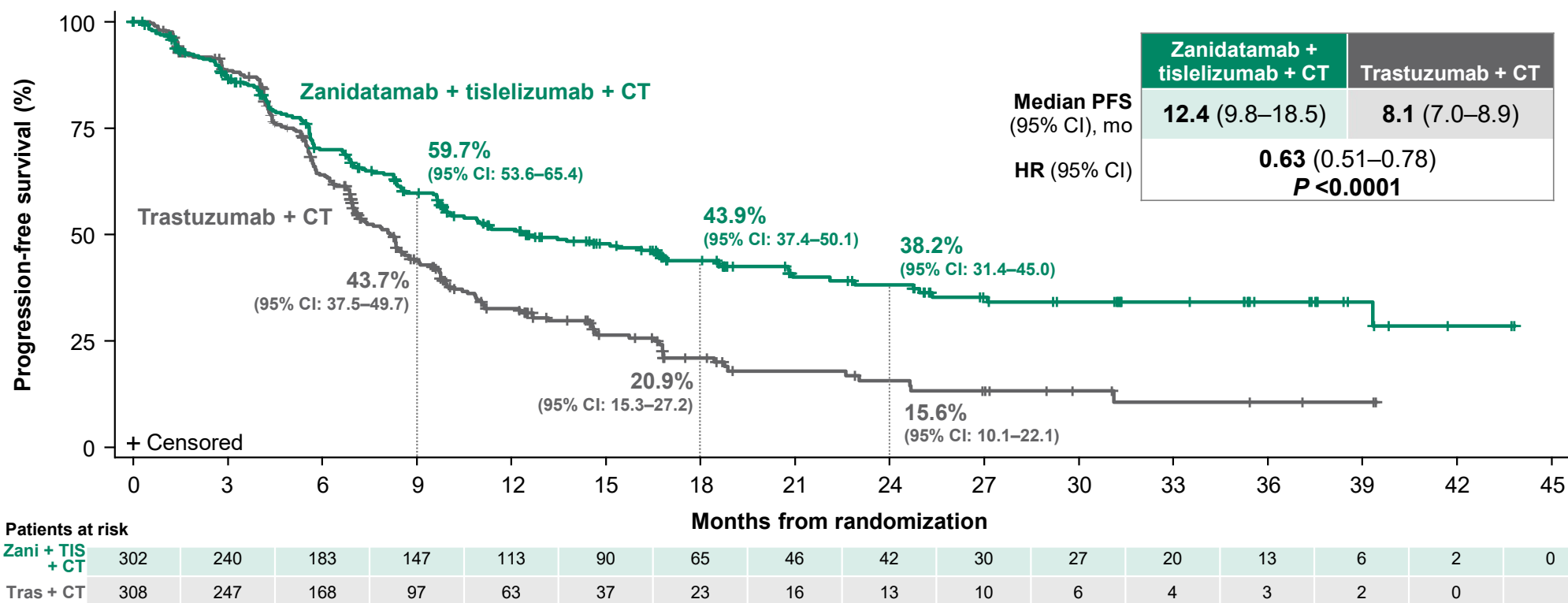
All data are shown as n (%) unless otherwise indicated.

^aOne patient in the zanidatamab-tislelizumab-chemotherapy arm had an ECOG PS score of 2 at baseline. ^bPD-L1 status was missing for 7.1% (n = 65) of patients across arms.

CAPOX, capecitabine and oxaliplatin; CT, chemotherapy; 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; PD-L1, programmed death-ligand 1; TAP, tumor area positivity.

Primary Endpoint: PFS per BICR

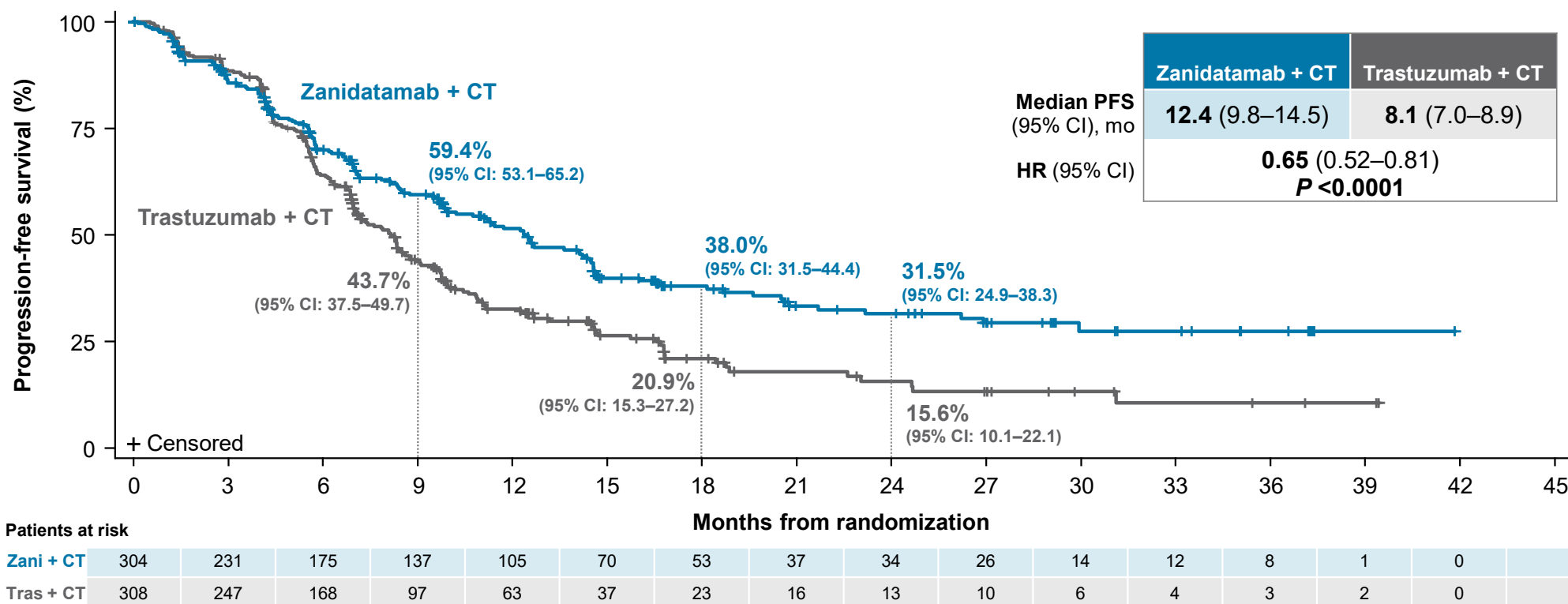
Statistically significant and clinically meaningful improvement in PFS with zanidatamab + tislelizumab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: PFS per BICR

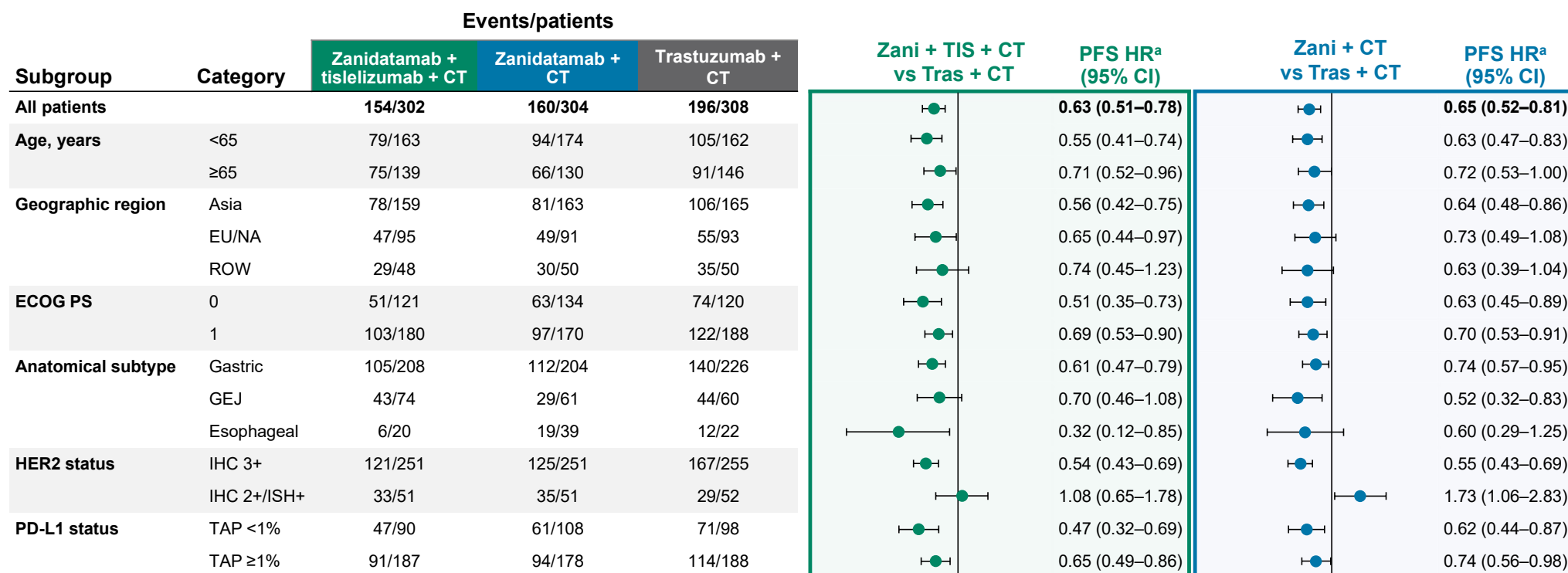
Statistically significant and clinically meaningful improvement in PFS with zanidatamab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; Tras, trastuzumab; Zani, zanidatamab.

PFS in Key Prespecified Subgroups

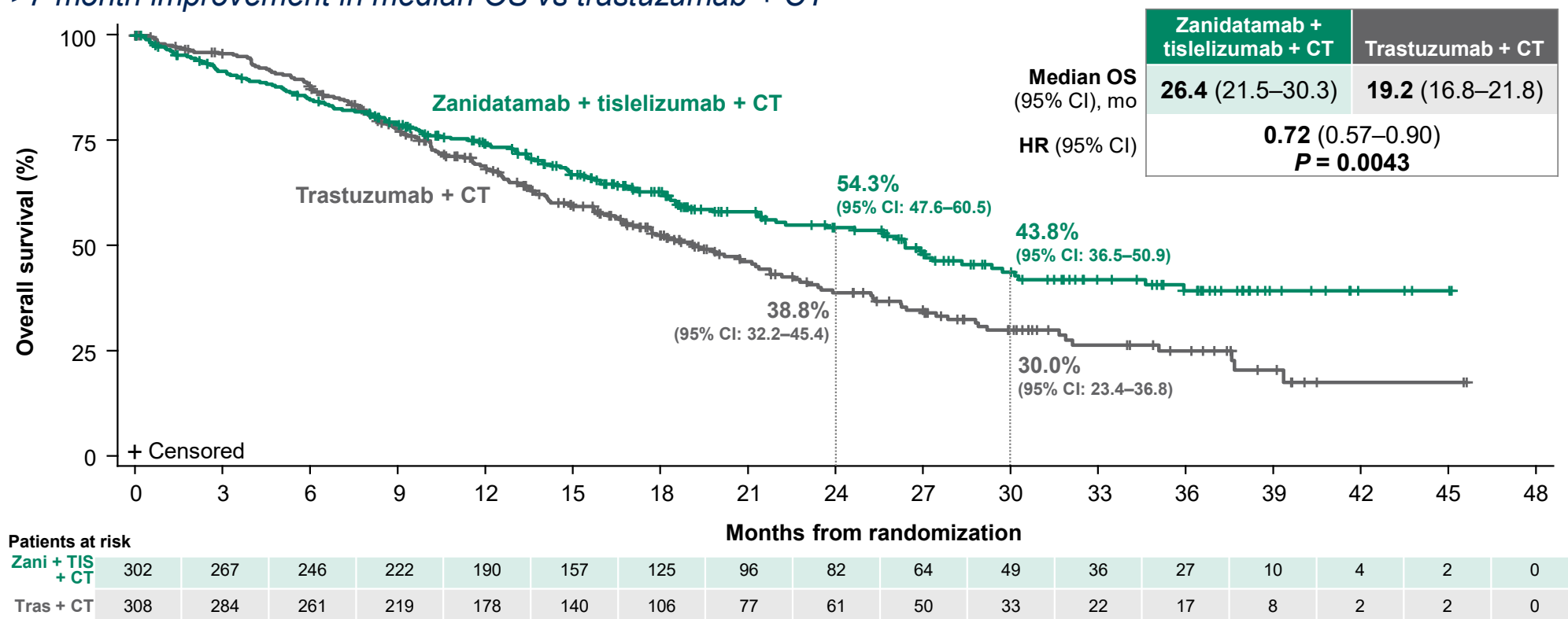
Improvements in PFS were generally consistent across major prespecified subgroups



^aThe widths of the confidence intervals 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, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry;
ISH, in situ hybridization; NA, North America; PD-L1, programmed death-ligand 1; PFS, progression-free survival;
ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: Overall Survival

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



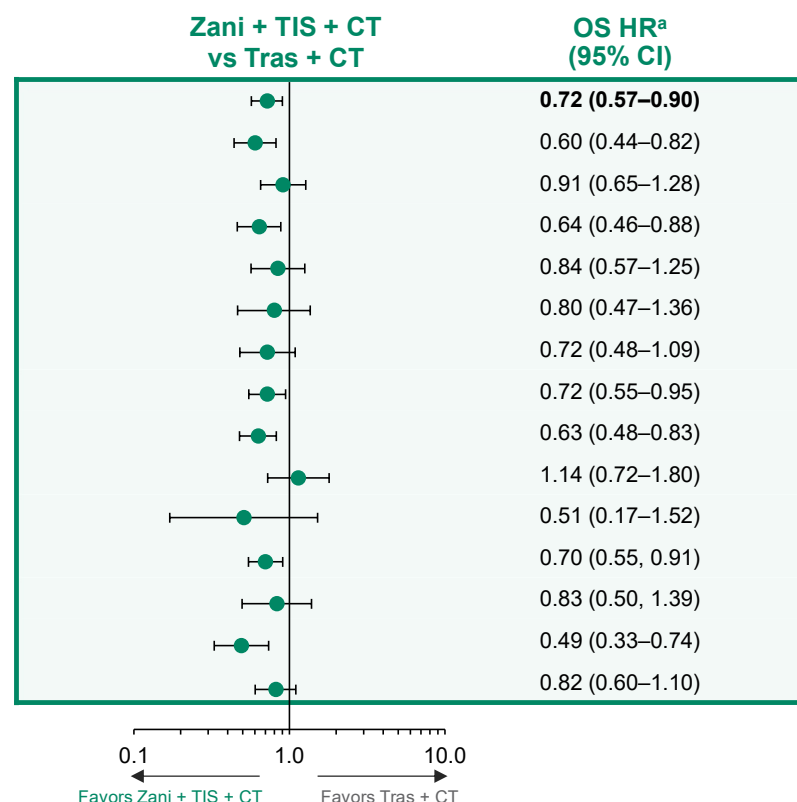
CT, chemotherapy; HR, hazard ratio; OS, overall survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

OS in Key Prespecified Subgroups

Improvements in OS occurred across major prespecified subgroups, including regions and PD-L1 TAP scores

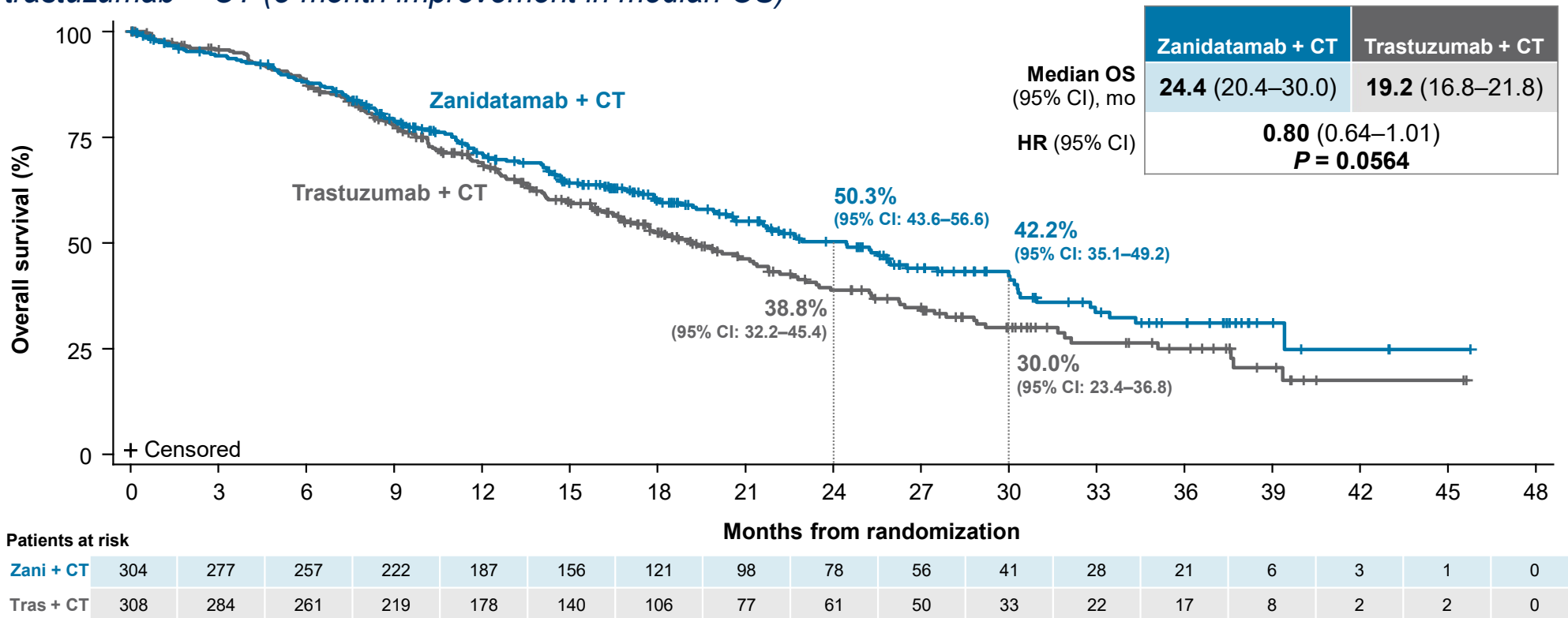
Subgroup	Category	Events/patients	
		Zanidatamab + tislelizumab + CT	Trastuzumab + CT
All patients		134/302	170/308
Age, years	<65	68/163	99/162
	≥65	66/139	71/146
Geographic region	Asia	63/159	89/165
	EU/NA	46/95	52/93
	ROW	25/48	29/50
ECOG PS	0	41/121	52/120
	1	92/180	118/188
Anatomical subtype	Gastric	87/208	127/226
	GEJ	42/74	33/60
	Esophageal	5/20	10/22
HER2 status	IHC 3+	106/251	138/255
	IHC 2+/ISH+	28/51	31/52
PD-L1 status	TAP <1%	38/90	65/98
	TAP ≥1%	79/187	92/188

^aThe widths of the confidence intervals 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, gastroesophageal junction;
 HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America;
 OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab;
 Zani, zanidatamab.



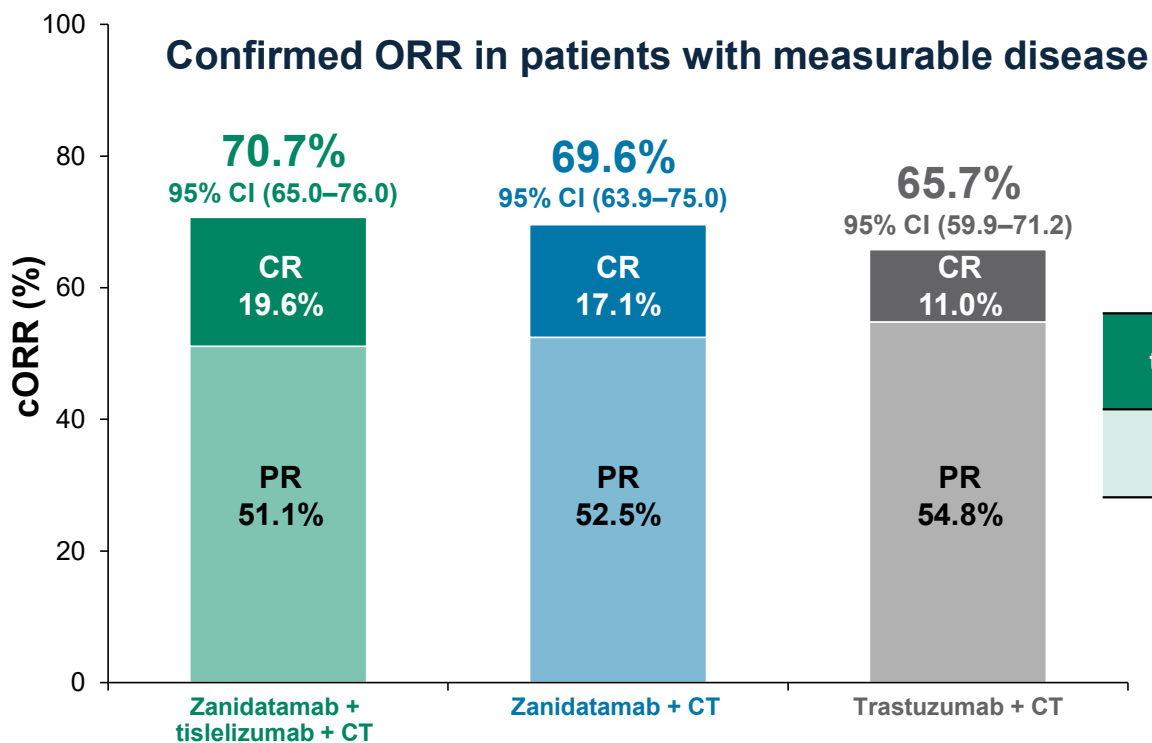
Primary Endpoint: Overall Survival

At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



Key Secondary Endpoint: Antitumor Activity

Responses were deeper and more durable in the zanidatamab-containing arms vs the trastuzumab + CT arm



Median DOR (95% CI), mo		
Zanidatamab + tislelizumab + CT (n = 195)	Zanidatamab + CT (n = 186)	Trastuzumab + CT (n = 198)
20.7 (12.6–37.7)	14.3 (11.5–21.9)	8.3 (6.7–9.8)

cORR was defined as the proportion of patients achieving a best overall response of CR or PR, as determined by BICR using RECIST v1.1, with the response confirmed at a subsequent visit ≥28 days after the initial assessment. DOR was assessed among patients with measurable disease at baseline who achieved a confirmed objective response by BICR per RECIST v1.1. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects. BICR, blinded independent central review; cORR, confirmed ORR; CR, complete response; CT, chemotherapy; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Safety Summary

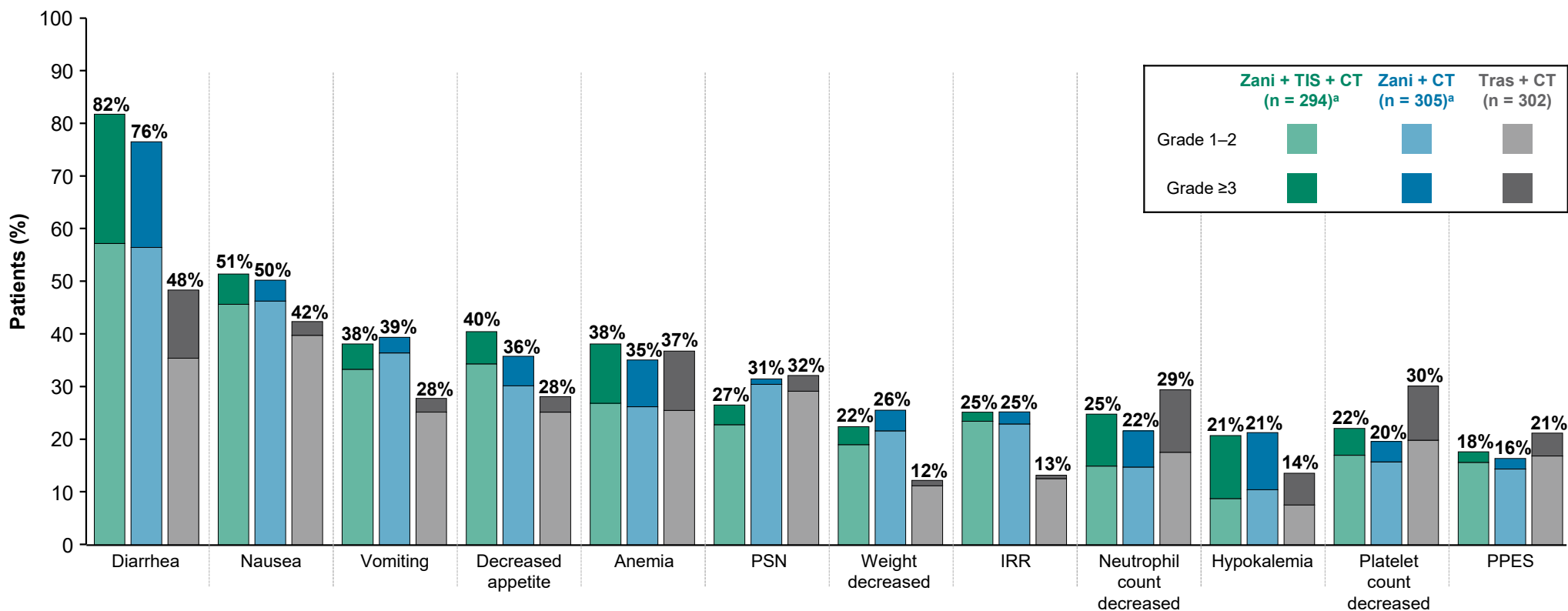
The safety profile was generally manageable, and no unexpected safety signals were identified

	Zanidatamab + tislelizumab + CT (n = 294) ^a	Zanidatamab + CT (n = 305) ^a	Trastuzumab + CT (n = 302)
Duration of treatment , median (IQR), weeks	43.1 (56.7)	31.0 (53.8)	30.0 (32.2)
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	211 (71.8)	180 (59.0)	180 (59.6)
Serious TEAEs , n (%)	172 (58.5)	150 (49.2)	128 (42.4)
Treatment-related	121 (41.2)	86 (28.2)	61 (20.2)
TEAEs leading to death , n (%)	28 (9.5)	25 (8.2)	22 (7.3)
Treatment-related	7 (2.4)	1 (0.3)	4 (1.3)
Discontinuation due to TRAEs , n (%)			
Any component	125 (42.5)	105 (34.4)	88 (29.1)
Zanidatamab or trastuzumab	35 (11.9)	26 (8.5)	7 (2.3)
Tislelizumab	42 (14.3)	—	—
AESIs^b , n (%)	102 (34.7)	93 (30.5)	56 (18.5)
IRRs	74 (25.2)	77 (25.2)	40 (13.2)
Noninfectious pulmonary toxicities	20 (6.8)	4 (1.3)	3 (1.0)
Left ventricular dysfunction	26 (8.8)	19 (6.2)	13 (4.3)
Immune-mediated AESs^b , n (%)	111 (37.8)	38 (12.5)	31 (10.3)

^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; IQR, interquartile range; IRR, infusion-related reaction; TEAE, treatment-emergent AE; TRAE, treatment-related AE.

Common TRAEs ($\geq 20\%$ of Patients in Any Arm)

Diarrhea was the most common TRAE in all treatment arms



^aFive patients who were assigned to the zanidatamab-tiselizumab-chemotherapy arm did not receive tiselizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm. CT, chemotherapy; IRR, infusion-related reaction; PPES, palmar-plantar erythrodysesthesia syndrome; PSN, peripheral sensory neuropathy; TIS, tiselizumab; TRAE, treatment-related adverse event; Tras, trastuzumab; Zani, zanidatamab.

Treatment-Emergent Diarrhea

Treatment-emergent diarrhea generally occurred early in treatment and resolved within 3 weeks, and few patients discontinued zanidatamab due to diarrhea

	Zanidatamab + tislelizumab + CT (n = 294) ^a	Zanidatamab + CT (n = 305) ^a	Trastuzumab + CT (n = 302)
Treatment-related diarrhea, n (%)			
Any grade	240 (81.6)	233 (76.4)	146 (48.3)
Grade ≥3	72 (24.5)	61 (20.0)	39 (12.9)
Treatment-related diarrhea leading to discontinuation, n (%)			
Any component	22 (7.5)	15 (4.9)	5 (1.7)
Zanidatamab or trastuzumab	12 (4.1)	4 (1.3)	0
Tislelizumab	6 (2.0)	—	—
Time to first onset of diarrhea, median (IQR), days			
Any grade	7.0 (14.5)	6.0 (12.0)	10.0 (30.0)
Grade ≥3	16.0 (43.0)	11.0 (23.0)	37.0 (56.0)
Duration of first diarrhea event, median (95% CI), days			
Any grade	14.0 (11.0–18.0)	17.0 (13.0–20.0)	10.0 (7.0–15.0)
Grade ≥3	8.0 (7.0–9.0)	9.0 (6.0–11.0)	9.0 (6.0–12.0)

Mandatory diarrhea prophylaxis for patients in the zanidatamab-containing arms

Loperamide (4 mg BID) for the first 7 days of cycle 1 only

^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. BID, twice daily; CT, chemotherapy; IQR, interquartile range.

Discussion

- HERIZON-GEA-01 is the first phase 3 study in mGEA to demonstrate a median PFS >1 year and a median OS >2 years

- These findings support zanidatamab as a promising new standard in HER2-targeting agents, with potential to replace trastuzumab in first-line treatments for HER2+ mGEA

- The clinically meaningful survival benefit further supports zanidatamab plus tislelizumab and CT as an important new treatment option for this patient population

- **Treatment with zanidatamab-containing regimens** led to a **clinically meaningful prolongation of PFS** that was **statistically superior** to trastuzumab + CT (**>4-month prolongation of median PFS**)
- **Zanidatamab + tislelizumab + CT** demonstrated a **clinically meaningful and statistically superior prolongation of OS** vs trastuzumab + CT (**>7-month prolongation of median OS**)
- At this interim analysis, there was a **strong trend** toward statistical significance for OS **favoring zanidatamab + CT** vs trastuzumab + CT (**5-month improvement in median OS**)
 - The trial is ongoing with additional OS analyses planned for zanidatamab + CT
- The PFS and OS benefits were generally observed across key prespecified subgroups, **including in patients with PD-L1 TAP scores <1% and ≥1%**
- The safety profile was **consistent with the known profiles of each individual treatment**
 - For patients who experienced diarrhea, events generally occurred **early in treatment and resolved within 3 weeks**



A copy of the presentation slides and an infographic summary of the results can be accessed via the QR code

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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.

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Lay Summary

Why did we perform this research?

- Current treatments for people with locally advanced or metastatic gastroesophageal adenocarcinoma (or mGEA) only provide modest benefit
- Some of these tumors have too much of a protein called human epidermal growth factor receptor 2 (or HER2) on the cell surface (also known as HER2-positive)

How did we perform this research?

- This study looked at whether a medicine called zanidatamab, which targets HER2, could help people with previously untreated HER2-positive mGEA
- People in this study could receive one of three possible treatments:
 - 1) Zanidatamab combined with a medicine called tislelizumab, which targets a protein called PD-1, plus standard chemotherapy
 - 2) Zanidatamab plus standard chemotherapy
 - 3) Trastuzumab, which is the current standard medicine for targeting HER2 in mGEA, plus standard chemotherapy

What were the results of this research?

- People who received zanidatamab plus chemotherapy with and without tislelizumab survived longer without their cancer getting worse than people treated with trastuzumab plus chemotherapy
- People who received zanidatamab with tislelizumab and chemotherapy survived longer in general than people treated with trastuzumab plus chemotherapy
 - More time is needed to tell if those who received zanidatamab plus chemotherapy also experienced this benefit
- There were no new concerning side effects with either zanidatamab or tislelizumab

HER2, human epidermal growth factor receptor 2; mGEA, advanced or metastatic gastroesophageal adenocarcinoma; PD-1, programmed cell death protein 1.