Exposure-Adjusted Analyses of Safety Patterns in HERIZON-GEA-01: Zanidatamab With and Without Tislelizumab and Chemotherapy in 1L HER2-Positive Metastatic Gastroesophageal Adenocarcinoma

Sun Young Rha,[1] Elena Elimova,[2] Sun Jin Sym,[3] Kohei Shitara,[4] Josep Tabernero,[5] Changzheng Li,[6] Jaffer A. Ajani,[7] Filippo Pietrantonio,[8] Yuan Yuan,[9] Katherine Wex,[10] Na Zhao,[9] Jonathan Grim,[10] Zinan Bao,[11] Vincent Li,[11] Lin Shen[12]

[1]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [3]Gachon University Gil Medical Center, Incheon, Republic of Korea; [4]Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [5]Department of Oncology, Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]Shandong Cancer Hospital and Institute, Shandong, China; [7]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [9]BeOne Medicines, Ltd, Shanghai, China; [10]Jazz Pharmaceuticals, Palo Alto, CA, USA; [11]BeOne Medicines, Ltd, Beijing, China; [12]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China

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Supplemental figures can be found here

CONCLUSIONS

- In HERIZON-GEA-01, treatment exposure was longest with zanidatamab + tislelizumab + chemotherapy (CT), which also had the highest incidence of grade ≥3 treatment-emergent adverse events (TEAEs)
- In this post hoc exposure-adjusted event rate (EAER) analysis, after accounting for differences in treatment exposure, any-grade and grade ≥3 TEAE rates were generally comparable across the zanidatamab + tislelizumab + CT, zanidatamab + CT, and trastuzumab + CT arms
- In the EAER analysis, after accounting for differences in treatment exposure, all-grade and grade ≥3 diarrhea TEAE rates were generally comparable between the zanidatamab + tislelizumab + CT and zanidatamab + CT arms
  - Limitations of the EAER analysis include that it does not account for event duration or cumulative adverse event (AE) burden and may be less informative for AEs with non-constant risk over time
- In the per-cycle analysis, diarrhea TEAE incidence generally decreased over successive treatment cycles, during which CT could be reduced or discontinued per protocol or standard of care
  - TEAEs leading to zanidatamab or trastuzumab discontinuation also generally decreased over successive cycles in each treatment arm
- Longer-duration use of zanidatamab + tislelizumab + CT was not associated with incremental safety concerns beyond those observed with zanidatamab + CT alone
- Overall, the EAER and per-cycle analyses provide complementary context for interpreting observed AE incidence, which was generally comparable across treatment arms when interpreted in the context of the known zanidatamab safety profile and differences in treatment exposure

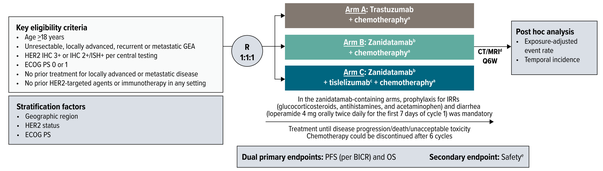
INTRODUCTION

- Despite recent advances in first-line treatment, including FDA approval of zanidatamab-containing regimens, opportunities remain to further improve outcomes for patients with HER2-positive mGEA while maintaining manageable safety profiles[1-4]
- Zanidatamab is a HER2-targeted bispecific antibody that binds two nonoverlapping HER2 extracellular domains, promoting receptor clustering and internalization, inhibiting HER2 signaling, and inducing immune-mediated antitumor activity[5]
- Tislelizumab is a high-affinity anti–programmed cell death 1 protein immune checkpoint inhibitor engineered to minimize Fcγ receptor binding on macrophages[6,7]
- In the global phase 3 HERIZON-GEA-01 trial (NCT05152147), at the first interim analysis data cutoff, zanidatamab + CT ± tislelizumab significantly improved progression-free survival vs trastuzumab + CT in patients with previously untreated HER2-positive mGEA[8]
  - At the second interim analysis (IA2) data cutoff, both zanidatamab + tislelizumab + CT (27.0 vs 19.6 months; HR 0.65 [95% CI, 0.52-0.80]) and zanidatamab + CT (22.9 vs 19.6 months; HR, 0.76 [95% CI, 0.62-0.93]) improved median OS vs trastuzumab + CT
  - Grade ≥3 TEAEs occurred in 84.0%, 76.1%, and 75.2% of patients receiving zanidatamab + tislelizumab + CT, zanidatamab + CT, and trastuzumab + CT, respectively at the IA2 data cutoff; however, interpretation of these observed AE incidences should consider differences in treatment exposure across arms
  - At the IA2 data cutoff, median treatment duration was longer in the zanidatamab arms (zanidatamab + tislelizumab + CT, 10.7 months; zanidatamab + CT, 7.2 months) than in the trastuzumab + CT arm (6.9 months), potentially confounding comparisons of absolute AE incidence
- Here, we present an exploratory post hoc analysis of HERIZON-GEA-01 using data from the IA2 data cutoff to evaluate exposure-adjusted TEAE rates and the relationship between treatment duration and AE incidence

METHODS

- HERIZON-GEA-01 is a global, randomized, open-label, phase 3 trial comparing zanidatamab + CT ± tislelizumab with trastuzumab + CT in previously untreated patients with HER2-positive mGEA (**Figure 1**)
- For the post hoc EAER analysis, EAERs were calculated among patients who received ≥1 dose of study treatment to account for differences in treatment exposure that may confound comparisons of AE incidence across treatment arms
  - All EAERs are expressed as EAER per 100 patient-months = (Total events / Total patient-months) × 100. Patients with multiple occurrences of the event were counted multiple times in the numerator. The exposure time is the treatment duration in all patients with or without the event; the 95% CI was calculated by exact Poisson method
- A post hoc temporal incidence analysis was performed to characterize AE patterns over time by treatment cycle[9]
  - For each cycle, the denominator (N) included patients on treatment at that cycle, based on exact treatment end dates (with 21-day extrapolation for missing visits), and the numerator (n) included patients with ≥1 merged AE record with onset during that cycle; incidence was calculated as n/N × 100

Figure 1. Study Design



[a]Physician's choice of capecitabine + oxaliplatin or 5-fluorouracil + cisplatin. Chemotherapy was administered for at least six cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met. [b]Dose of 1800 mg IV Q3W for patients weighing <70 kg and 2400 mg IV Q3W for those ≥70 kg. [c]Tislelizumab 200 mg was administered IV Q3W. [d]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks. [e]For this post hoc analysis, overlapping adverse events with the same preferred term and continuous start/end dates in an individual patient were merged and counted as a single event, with the highest observed grade per Common Terminology Criteria for Adverse Events version 5.0 assigned.

Abbreviations: BICR, blinded independent central review; 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, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

RESULTS

- At the data cutoff of 25 July 2026, 901 patients had received ≥1 dose of study treatment and were included in the safety analysis (**Table 1**)
- Median treatment duration and cumulative patient-months of exposure was longer with zanidatamab + tislelizumab + CT than with the other two treatments (**Table 1**)
- The incidence of grade ≥3 TEAEs was higher with zanidatamab + tislelizumab + CT than with the other two treatment arms (**Table 1**)

Table 1. Treatment Exposure and TEAEs by Study Arm

	Zani + Tis + CT n = 294	Zani + CT n = 305	Tras + CT n = 302
Median treatment duration, mo	10.7	7.2	6.9
Median Cycles, min-max	14.0 (1-77)	10.0 (1-69)	10.0 (1-71)
Patient-months of exposure	4331.2	3687.0	2940.4
TEAEs			
Any grade, n (%)	293 (99.7)	301 (98.7)	297 (98.3)
Grade ≥3, n (%)	245 (84.0)	232 (76.1)	227 (75.2)
Serious, n (%)	176 (59.9)	155 (50.8)	131 (43.4)
Diarrhea, any grade, n (%)	244 (83.0)	241 (79.0)	161 (53.3)
Diarrhea, grade ≥3, n (%)	74 (25.2)	61 (20.0)	39 (12.9)
Leading to zani/tras discontinuation, n (%)	39 (13.3)	35 (11.5)	17 (5.6)
Leading to tisle discontinuation, n (%)	57 (19.4)	1 (0.3)[b]	0

DCO: 25 July 2026

[a]Five patients who had been assigned to the zani + tis + CT group did not receive tis. Data from these patients are summarized in the zanidatamab–CT group. [b]Overlapping TEAEs with the same preferred term in an individual patient were clustered and reported as a single TEAE, with the worst grade assigned.[c]This patient was randomized to the zani + tis + CT group but experienced a grade 3 infusion-related reaction on Cycle 1 Day 1 before receiving tis. The event was recorded as leading to tis discontinuation, and the patient was included in the zani + CT group for the safety analysis.

Abbreviations: CT, chemotherapy; TEAEs, treatment-emergent adverse events; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

EAER Analysis of TEAEs

- After adjustment for treatment exposure using EAERs, any-grade and grade ≥3 TEAEs were generally comparable across treatment arms (**Table 2**)
- EAERs for all-grade and grade ≥3 diarrhea TEAEs leading to treatment discontinuation remained higher in the zanidatamab arms than in the trastuzumab arm (**Table 2**)

Table 2. EAER Analysis of TEAEs

	Zani+ Tis + CT n = 294	Zani + CT n = 305	Tras + CT n = 302
Any grade			
Events, n	6429	5640	4778
EAER (95% CI)	149.9 (146.3, 153.6)	153.0 (149.0, 157.0)	165.5 (158.0-167.2)
Grade ≥3			
Events, n	865	650	633
EAER (95% CI)	20.0 (18.7-21.4)	17.6 (16.3-19.0)	21.5 (19.9-23.3)
Serious			
Events, n	370	247	203
EAER (95% CI)	8.5 (7.7-9.5)	6.7 (5.9-7.6)	6.9 (6.0-7.9)
Diarrhea, all grades			
Events, n	702	638	333
EAER (95% CI)	16.2 (15.0-17.5)	17.3 (16.0-18.7)	11.3 (10.1-12.6)
Diarrhea, grade ≥3			
Events, n	87	74	43
EAER (95% CI)	2.0 (1.6-2.5)	2.0 (1.6-2.5)	1.5 (1.1-2.0)
Leading to zani/tras discontinuation			
Events, n	39	35	17
EAER (95% CI)	0.9 (0.6-1.2)	1.0 (0.7-1.3)	0.6 (0.3-0.9)

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All EAERs are expressed as EAER per 100 patient-months = (Total events / Total patient-months) × 100. Patients with multiple occurrences of the event were counted multiple times in the numerator. The exposure time is the treatment duration in all patients with or without the event. The 95% CI was calculated by exact Poisson method.

Abbreviations: CT, chemotherapy; EAER, exposure-adjusted event rate; TEAE, treatment-emergent adverse event; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

EAER Analysis of Common TEAEs by Preferred Term

- After adjustment for treatment exposure, EAERs were generally comparable across treatment arms for the most common any-grade TEAE preferred terms (EAER ≥5 events per 100 patient-months in any treatment arm; **Table 3**) and grade ≥3 TEAE preferred terms (EAER ≥0.5 events per 100 patient-months in any treatment arm; **Table 4**)
  - Diarrhea remained the most frequently reported AE, with comparable EAERs between the two zanidatamab-containing arms (**Table 3**)

Table 3. EAER Analysis of All-Grade TEAEs by Preferred Term

	Zani+ Tis + CT n = 294		Zani + CT n = 305		Tras + CT n = 302	
Preferred Term	**Events**	**EAER (95% CI)**	**Events**	**EAER (95% CI)**	**Events**	**EAER (95% CI)**
Diarrhea	702	16.2 (15.0-17.5)	638	17.3 (16.0-18.7)	333	11.3 (10.1-12.6)
Neutrophil count decreased	233	5.4 (4.7-6.1)	211	5.7 (5.0-6.6)	266	9.1 (8.0-10.2)
Nausea	278	6.4 (5.7-7.2)	242	6.6 (5.8-7.4)	233	7.9 (6.9-9.0)
Anemia	259	6.0 (5.3-6.8)	228	6.2 (5.4-7.0)	218	7.4 (6.5-8.5)
White blood cell count decreased	193	4.5 (3.9-5.1)	189	5.1 (4.4-5.9)	205	7.0 (6.1-8.0)
Vomiting	281	6.5 (5.8-7.3)	223	6.1 (5.3-6.9)	175	6.0 (5.1-6.9)
Platelet count decreased	134	3.1 (2.6-3.7)	121	3.3 (2.7-3.9)	187	6.4 (5.5-7.3)
Hypokalemia	242	5.6 (4.9-6.3)	208	5.6 (4.9-6.5)	100	3.4 (2.8-4.1)

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All EAERs are expressed as EAER per 100 patient-months = (Total events / Total patient-months) × 100. Patients with multiple occurrences of the event were counted multiple times in the numerator. The exposure time is the treatment duration in all patients with or without the event. The 95% CI was calculated by exact Poisson method.

Abbreviations: CT, chemotherapy; EAER, exposure-adjusted event rate; TEAE, treatment-emergent adverse event; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

Table 4. EAER Analysis of Grade ≥3 TEAEs by Preferred Term

	Zani+ Tis + CT n = 294		Zani + CT n = 305		Tras + CT n = 302	
Preferred Term	**Events**	**EAER (95% CI)**	**Events**	**EAER (95% CI)**	**Events**	**EAER (95% CI)**
Hypokalemia	107	2.5 (2.0-3.0)	84	2.4 (1.8-2.8)	44	1.5 (1.1-2.0)
Neutrophil count decreased	47	1.1 (0.8-1.4)	33	0.9 (0.6-1.3)	75	2.6 (2.0-3.2)
Anemia	54	1.3 (0.9-1.6)	51	1.4 (1.0-1.8)	64	2.2 (1.7-2.8)
Diarrhea	87	2.0 (1.6-2.5)	74	2.0 (1.6-2.5)	43	1.5 (1.1-2.0)
Platelet count decreased	17	0.4 (0.2-0.6)	16	0.4 (0.3-0.7)	33	1.1 (0.8-1.6)
Neutropenia	26	0.6 (0.4-0.9)	19	0.5 (0.3-0.8)	21	0.7 (0.4-1.1)
Decreased appetite	26	0.6 (0.4-0.9)	20	0.5 (0.3-0.8)	17	0.6 (0.3-0.9)
Nausea	24	0.6 (0.4-0.8)	14	0.4 (0.2-0.6)	10	0.3 (0.2-0.6)
Weight decreased	22	0.5 (0.3-0.8)	19	0.5 (0.3-0.8)	9	0.3 (0.1-0.6)

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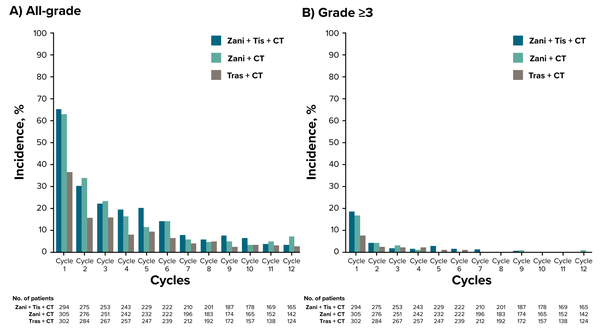
All EAERs are expressed as EAER per 100 patient-months = (Total events / Total patient-months) × 100. Patients with multiple occurrences of the event were counted multiple times in the numerator. The exposure time is the treatment duration in all patients with or without the event. The 95% CI was calculated by exact Poisson method.

Abbreviations: CT, chemotherapy; EAER, exposure-adjusted event rate; TEAE, treatment-emergent adverse event; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

TEAE Incidence by Cycle

- The incidence of all-grade and grade ≥3 diarrhea TEAEs decreased in general with successive treatment cycles in each treatment arm, with a progressive decline from Cycle 7 onward (**Figure 2**) that continued beyond Cycle 12 (**Supplemental Figure 1**); a similar temporal pattern was observed for TEAEs overall (**Supplemental Figure 2**)

Figure 2. Incidence of Diarrhea TEAEs by Cycle



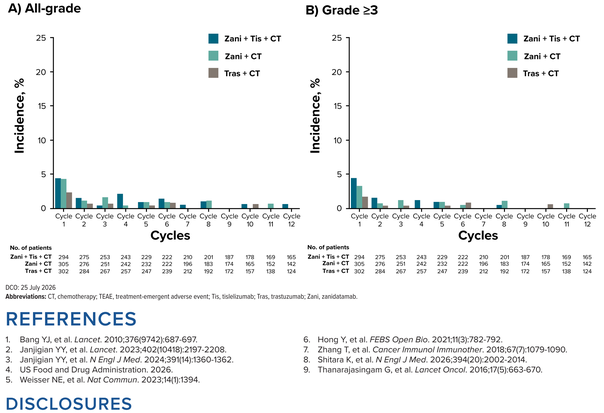
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Abbreviations: CT, chemotherapy; TEAE, treatment-emergent adverse event; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

TEAEs leading to Zanidatamab or Trastuzumab Discontinuation by Cycle

- The incidence of all-grade and grade ≥3 TEAEs leading to zanidatamab or trastuzumab discontinuation generally decreased with successive treatment cycles in each treatment arm (**Figure 3**)
  - Discontinuation rates were comparable between the zanidatamab + tislelizumab + CT and zanidatamab + CT arms during cycle 1; most of the discontinuations in cycles 1-3 were due to Grade ≥3 TEAEs

Figure 3. Incidence of TEAEs leading to Zanidatamab or Trastuzumab Discontinuation by Cycle



DCO: 25 July 2026

Abbreviations: CT, chemotherapy; TEAE, treatment-emergent adverse event; Tis, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

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DISCLOSURES

SYR: Advisory board: Amgen, LG Biochemical, Astellas, Boehringer Ingelheim, Ono Pharmaceuticals, Qureator, Inc., Daiichi Sankyo, AstraZeneca, BeOne Medicines, Ltd, Indivumed, MSD; Honoraria: MSD, Daiichi Sankyo, AstraZeneca, BeOne Medicines, Ltd, Astellas, Amgen, Indivumed, Jazz Pharmaceuticals, Roche, Ono Pharmaceuticals; Research funding (payable to institution): MSD, BMS, Lilly, Daiichi Sankyo; Other: Merck, MSD, BeOne Medicines, Ltd, Jazz Pharmaceuticals.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. The authors also thank Ye Chen for her contributions to the development of this work. This study was sponsored by BeOne Medicines, Ltd. Medical writing support was provided by Colton Smith, PhD, of Nucleus Global, an Inizio company, and was supported by BeOne Medicines.

CORRESPONDENCE: Sun Young Rha; rha7655@yuhs.ac

Presented at the ESMO Congress 2026; October 23-27, 2026; Madrid, Spain