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

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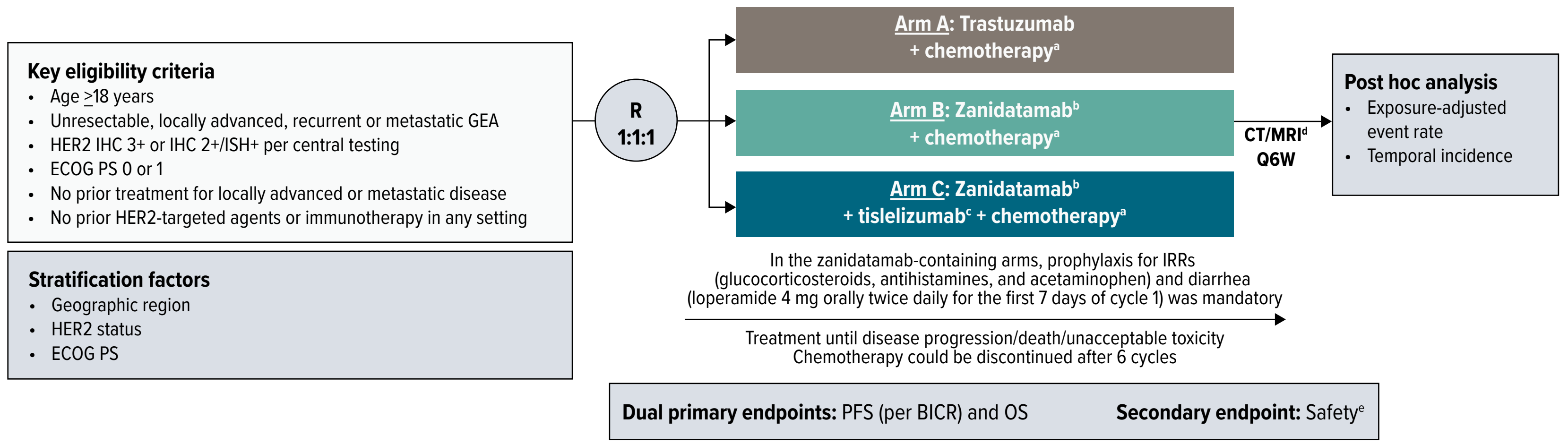
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CONCLUSIONS

- 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

- 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 cycle⁷
 - 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



⁷Physician'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. ⁸Dose of 1800 mg IV Q3W for patients weighing <70 kg and 2400 mg IV Q3W for those ≥70 kg. ⁹Tislelizumab 200 mg was administered IV Q3W. ¹⁰CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks. 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 ^a	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^b			
Any grade, n (%)	293 (99.7)	301 (98.7)	297 (98.3)
Grade ≥3, n (%)	247 (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) ^c	0

DCO: 25 July 2026
^aFive 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. ^bOverlapping TEAEs with the same preferred term in an individual patient were clustered and reported as a single TEAE, with the worst grade assigned. ^cThis 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)	162.5 (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)

DCO: 25 July 2026
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	Events	Events
Diarrhea	702	638	333
Neutrophil count decreased	233	211	266
Nausea	278	242	233
Anemia	259	228	218
White blood cell count decreased	193	189	205
Vomiting	281	223	175
Platelet count decreased	134	121	187
Hypokalemia	242	208	100

DCO: 25 July 2026
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

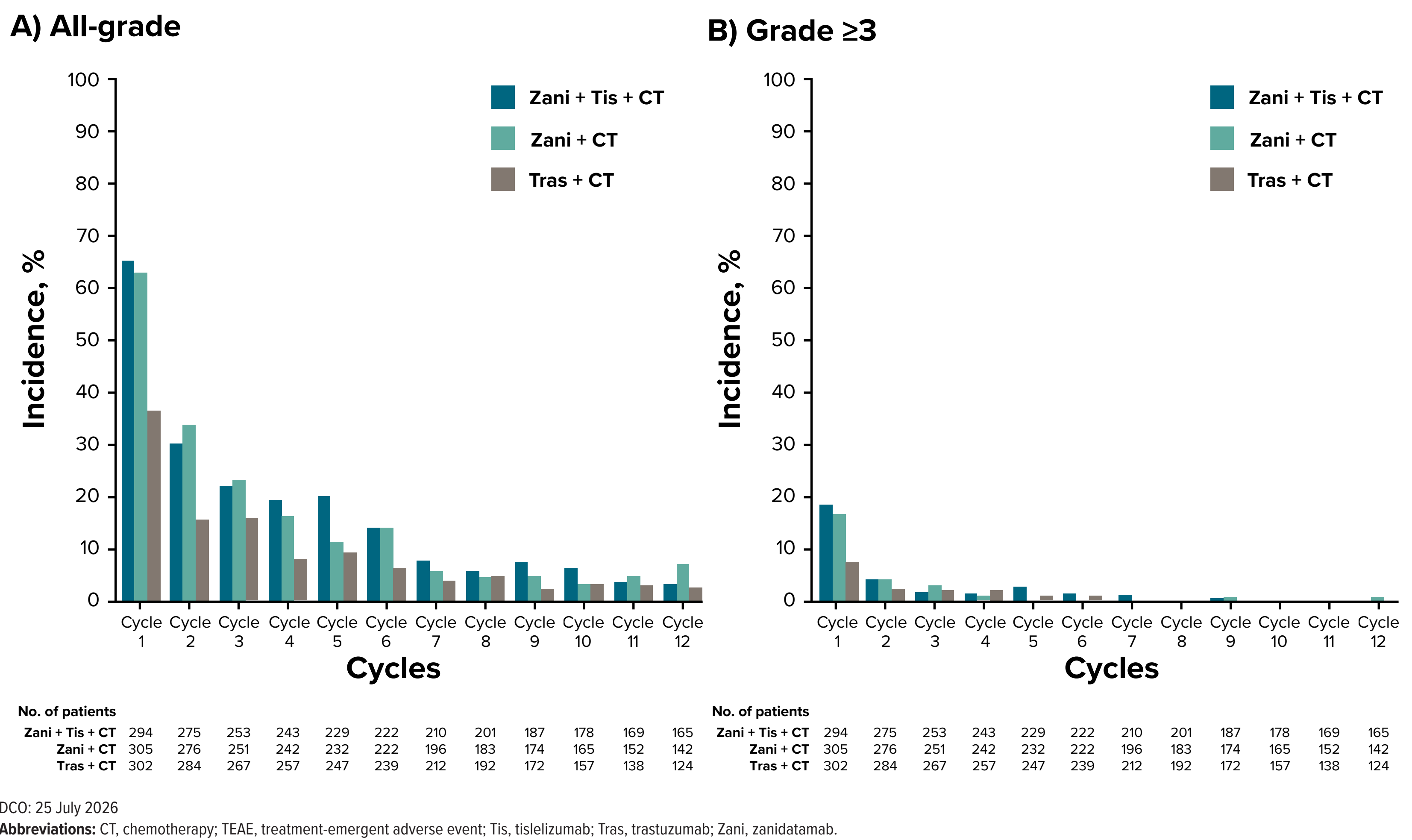
	Zani+ Tis + CT n = 294	Zani + CT n = 305	Tras + CT n = 302
Preferred Term	Events	Events	Events
Hypokalemia	107	84	44
Neutrophil count decreased	47	33	75
Anemia	54	51	64
Diarrhea	87	74	43
Platelet count decreased	17	16	33
Neutropenia	26	19	21
Decreased appetite	26	20	17
Nausea	24	14	10
Weight decreased	22	19	9

DCO: 25 July 2026
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**)

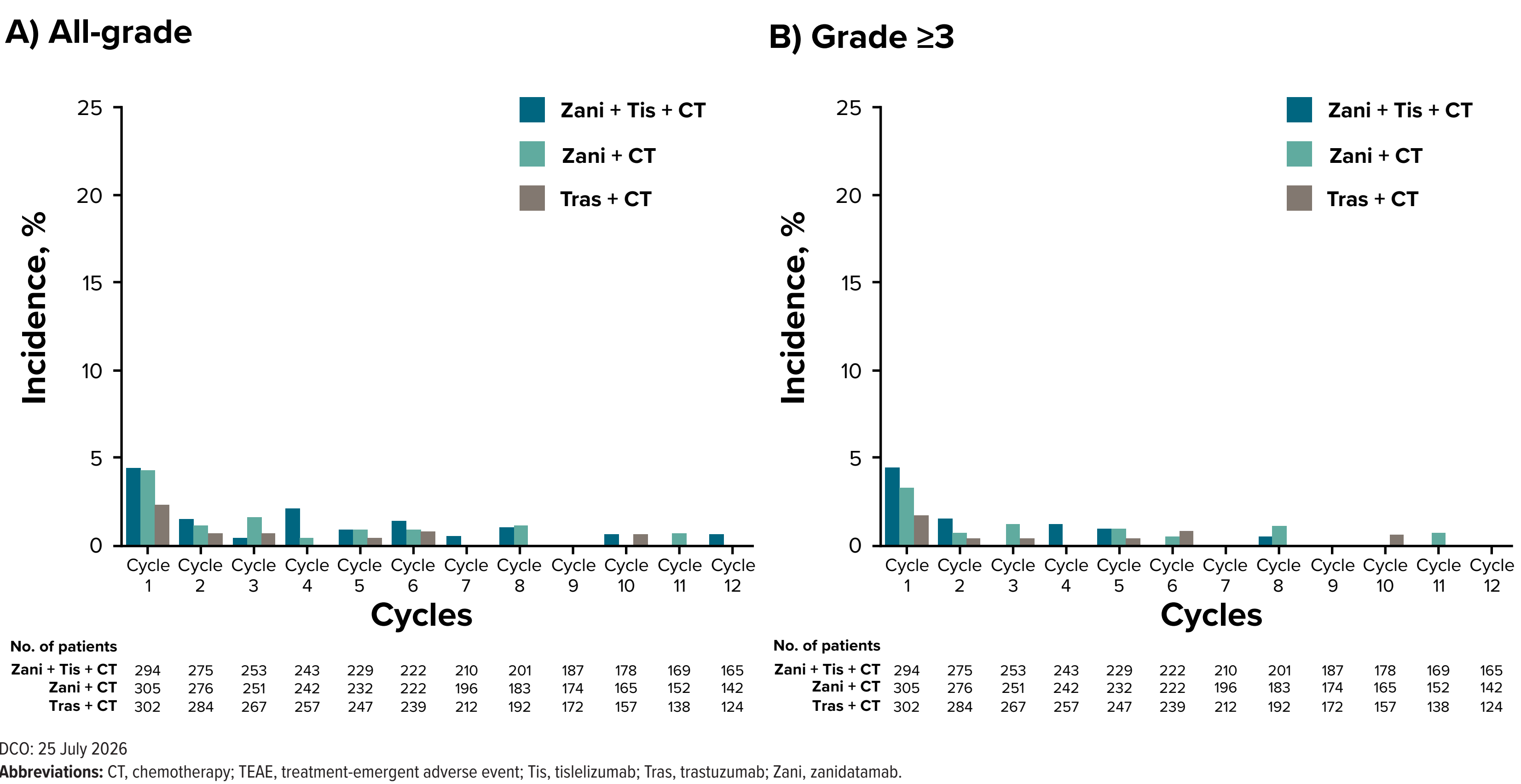
Figure 2. Incidence of Diarrhea TEAEs by Cycle



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



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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.

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