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Characterization and Management of Gastrointestinal Adverse Events With Zanidatamab + Chemotherapy ± Tislelizumab in First-Line HER2-Positive Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma: Analysis From HERIZON-GEA-01

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Objective

- To further characterize gastrointestinal (GI) adverse events (AEs) and management of diarrhea in the phase 3 HERIZON-GEA-01 trial of first-line (1L) zanidatamab + chemotherapy (CT) ± tislelizumab vs trastuzumab + CT in patients with human epidermal growth factor receptor 2 (HER2)-positive advanced or metastatic gastroesophageal adenocarcinoma (mGEA)

Conclusions

- The safety profile of 1L zanidatamab-containing regimens for HER2-positive mGEA supports a favorable benefit-risk profile given the clinically significant survival benefits; diarrhea was more frequent in the zanidatamab-containing arms vs the trastuzumab + CT arm
- In zanidatamab-treated patients, most diarrhea events were grade 1 or 2, consistent with findings from previous phase 2 trials,[7,8] and first onset typically occurred within 2 weeks of starting treatment
- Grade ≥3 diarrhea was rare after cycle 6 when patients could discontinue CT; recurrent grade ≥3 diarrhea was infrequent
- Across treatment arms, diarrhea led to zanidatamab dose reductions in approximately 10% of patients and chemotherapy dose reductions in approximately 20%
- The rate of constipation was similarly low across treatment arms, and antidiarrheal prophylaxis did not result in more constipation in the zanidatamab-containing arms
- Diarrhea should be managed with prophylactic loperamide, close monitoring and treatment of symptoms when they occur, and CT dose modifications as needed

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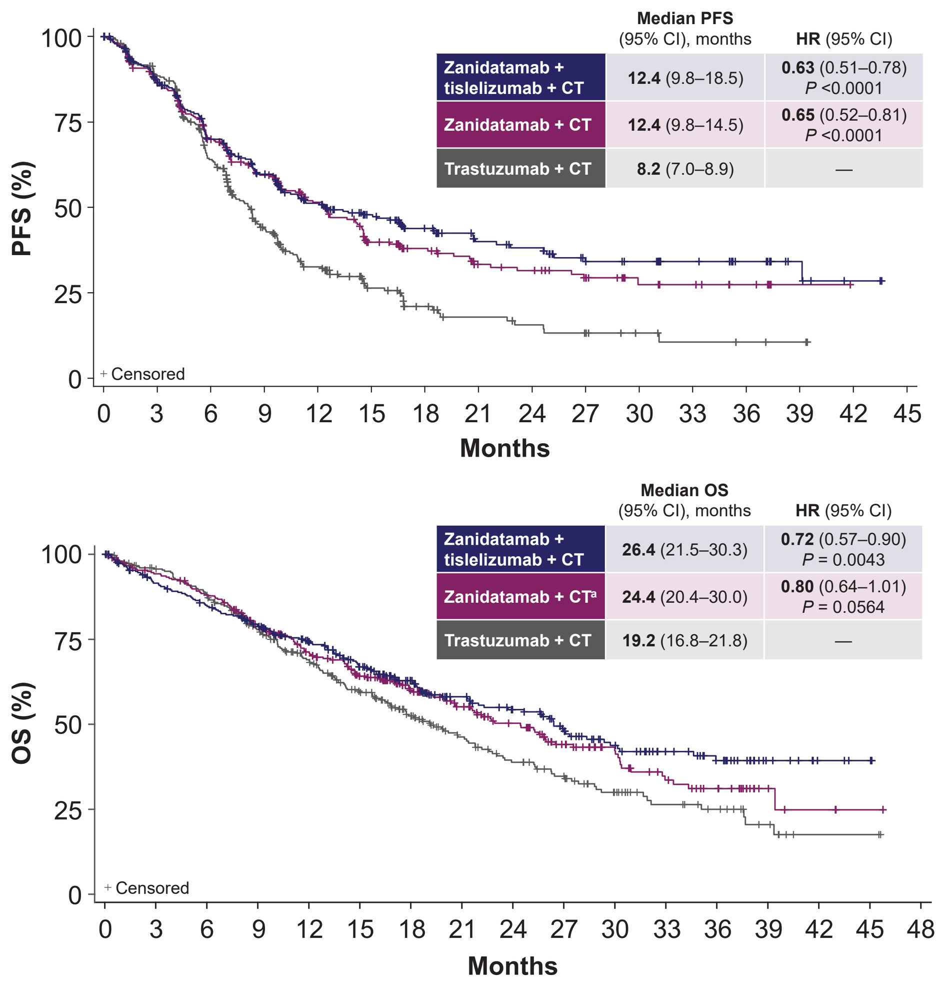
Introduction

- Survival outcomes with current 1L standard of care for HER2-positive mGEA remain modest, with a median overall survival (OS) of 14–20 months; there is an unmet need for effective HER2-targeted treatment options with manageable safety profiles[1–3]
- Zanidatamab is a HER2-directed bispecific antibody that binds to the HER2 extracellular domains 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:[4]
  - Increasing HER2 internalization
  - Reducing phosphorylation of EGFR, HER2, and HER3 and blocking downstream signaling
  - Inducing immune-mediated effects (complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity and phagocytosis)
- Tislelizumab is a high-affinity immune checkpoint inhibitor targeting programmed cell death protein 1 and is specifically engineered to minimize Fcγ receptor binding on macrophages[5,6]
- A phase 2 trial of 1L zanidatamab + physician's choice CT and a phase 1b/2 trial of 1L zanidatamab + tislelizumab + capecitabine and oxaliplatin (CAPOX) both demonstrated promising activity with manageable safety profiles in patients with HER2-positive mGEA[7,8]
  - Diarrhea, a common toxicity with HER2-targeted agents and CT,[9,10] was the most common AE in both studies and was mitigated by prophylactic loperamide[7,8]
- In the global phase 3 HERIZON-GEA-01 trial (NCT05152147), replacing trastuzumab + CT with zanidatamab + CT ± tislelizumab significantly improved progression-free survival and, with tislelizumab, yielded a statistically significant OS benefit, with a median OS >2 years, in patients with untreated HER2-positive mGEA (Figure 1)[11]
- AEs were manageable and consistent with the known safety profiles of the individual agents; diarrhea was the most common AE across treatment arms

Figure 1. Primary PFS and first interim analysis of OS from HERIZON-GEA-01



[a]OS was not significant in the zanidatamab + CT arm vs the trastuzumab + CT arm at the first interim analysis, and additional OS analyses are planned.
CT, chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Methods

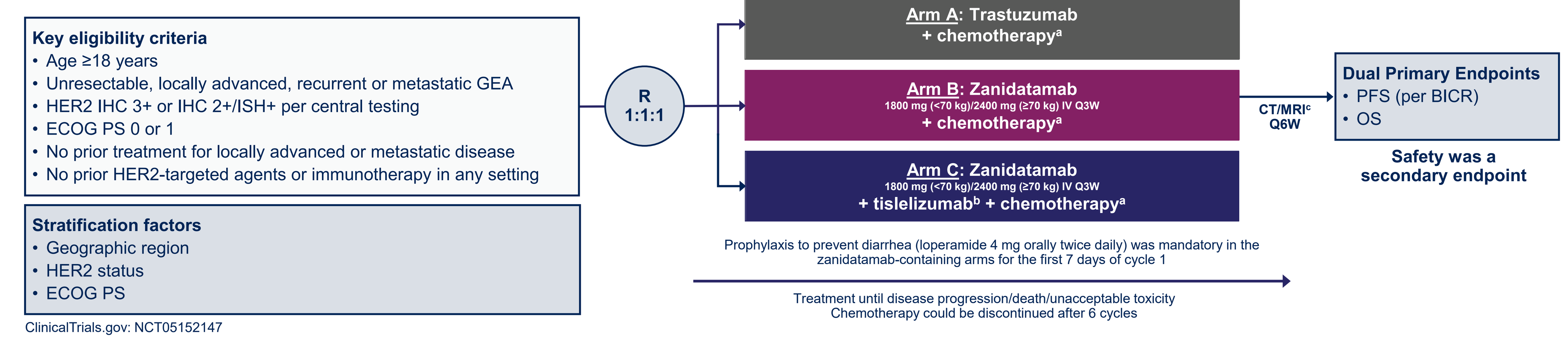
- HERIZON-GEA-01 is a global, randomized, open-label, phase 3 trial of zanidatamab + CT ± tislelizumab vs trastuzumab + CT in previously untreated patients with HER2-positive mGEA (Figure 2)
- Physician's choice of CT included CAPOX or 5-FU + cisplatin (FP) and could be discontinued after 6 cycles at the discretion of the treating physician; zanidatamab and tislelizumab could be continued until disease progression or unacceptable toxicity
- All patients in the zanidatamab-containing arms received mandatory prophylaxis for diarrhea (loperamide 4 mg orally twice daily for the first 7 days of cycle 1; each cycle was 21 days), which could be continued beyond the first week at the discretion of the treating physician
  - Grade ≥3 diarrhea was managed with fluid hydration, antidiarrheal medication, and zanidatamab dosing delays or CT dose modifications; zanidatamab dose reductions were required for recurrent grade ≥3 events (Supplemental Information)
- Frequency and severity of AEs were secondary endpoints; AEs were monitored throughout the study and reported from the start of dosing to 30 days after the last dose of study drug in all patients who received any amount of any study drug

Table 1. Diarrhea grading per CTCAE v5.0[12]

Grade 1	Increase of <4 stools per day over baseline or mild increase in ostomy output compared to baseline
Grade 2	Increase of 4–6 stools per day over baseline, moderate increase in ostomy output compared to baseline, or diarrhea limiting instrumental ADL
Grade 3	Increase of ≥7 stools per day over baseline, hospitalization indicated, severe increase in ostomy output compared to baseline, or diarrhea limiting self-care ADL
Grade 4	Life-threatening consequences or urgent intervention indicated
Grade 5	Death

ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events.

Figure 2. HERIZON-GEA-01 study design



ClinicalTrials.gov: NCT05152147

[a]Physician's choice of capecitabine + oxaliplatin or 5-FU + 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.
AE, adverse event; 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; ISH, in situ hybridization; IV, intravenously; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

Results

- Median duration of follow-up at data cutoff (October 1, 2025) was 25.9 months (range, 7.5–46.0)

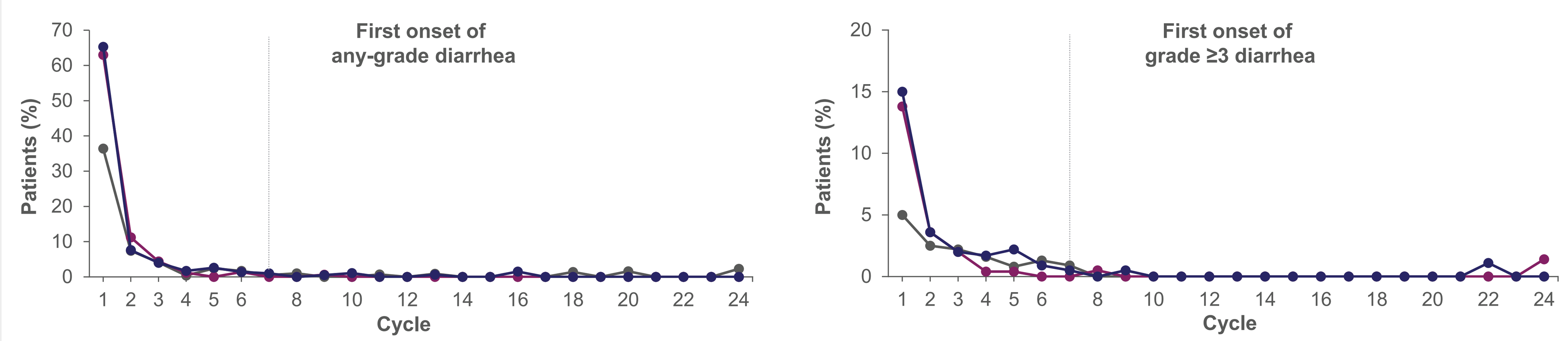
Table 2. Overall GI AE and diarrhea safety summary (safety analysis set)

	Zanidatamab + tislelizumab + CT (n = 294)	Zanidatamab + CT (n = 305)	Trastuzumab + CT (n = 302)
Treatment duration, median (IQR), wk	43.1 (17.6–74.3)	31.0 (14.3–68.1)	30.0 (18.1–50.3)
Number of CT cycles, median (IQR)	6.0 (4.0–13.0)	6.0 (4.0–11.0)	7.0 (5.0–10.0)
CT >6 cycles	139 (47.3)	126 (41.3)	161 (53.3)
Any-grade GI AEs[a]	276 (93.9)	285 (93.4)	254 (84.1)
Any-grade GI TRAEs[a]	268 (91.2)	273 (89.5)	277 (75.2)
Occurring in >10% of patients in any arm			
Diarrhea	240 (81.6)	233 (76.4)	146 (48.3)
Nausea	151 (51.4)	153 (50.2)	128 (42.4)
Vomiting	112 (38.1)	120 (39.3)	84 (27.8)
Stomatitis	49 (16.7)	41 (13.4)	38 (12.6)
Any-grade AEs of constipation	48 (16.3)	50 (16.4)	49 (16.2)
Any-grade TRAEs of constipation	11 (3.7)	12 (3.9)	19 (6.3)
Grade ≥3 AEs of diarrhea	73 (24.8)	61 (20.0)	39 (12.9)
Grade ≥3 TRAEs of diarrhea	72 (24.5)	61 (20.0)	39 (12.9)
Zanidatamab- or trastuzumab-related diarrhea	192 (65.3)	204 (66.9)	40 (13.2)
Tislelizumab-related diarrhea	118 (40.1)	—	—
Serious diarrhea[b]	45 (15.3)	31 (10.2)	12 (4.0)
Diarrhea leading to hospitalization	44 (15.0)	31 (10.2)	12 (4.0)
Immune-mediated AEs of colitis[c]	8 (2.7)	4 (1.3)	4 (1.3)

All data are shown as n (%) unless otherwise indicated.
[a]Categorized as GI AEs per MedDRA system organ class. Patients with multiple GI AEs or multiple GI TRAEs were only counted once. A full table of GI AEs can be found in the Supplemental Information. [b]One patient had grade 5 diarrhea in the zanidatamab + tislelizumab + CT arm. [c]Certain AEs were prospectively categorized as immune-mediated and were classified as immune-mediated in all treatment arms even if the AE was not related to immunotherapy treatment. Immune-mediated AEs were identified using a custom MedDRA query.
AE, adverse event; CT, chemotherapy; GI, gastrointestinal; IQR, interquartile range; MedDRA, Medical Dictionary for Regulatory Activities; TRAE, treatment-related AE.

- GI AEs occurred in >80% of patients in all treatment arms
- Diarrhea was the most common GI treatment-related AE, and most diarrhea events were grade 1/2
- Rates of any-grade constipation were similar across treatment arms
  - Most treatment-related constipation was grade 1/2; 1 patient in the trastuzumab + CT arm had grade ≥3 treatment-related constipation

Figure 3. First onset of diarrhea by cycle

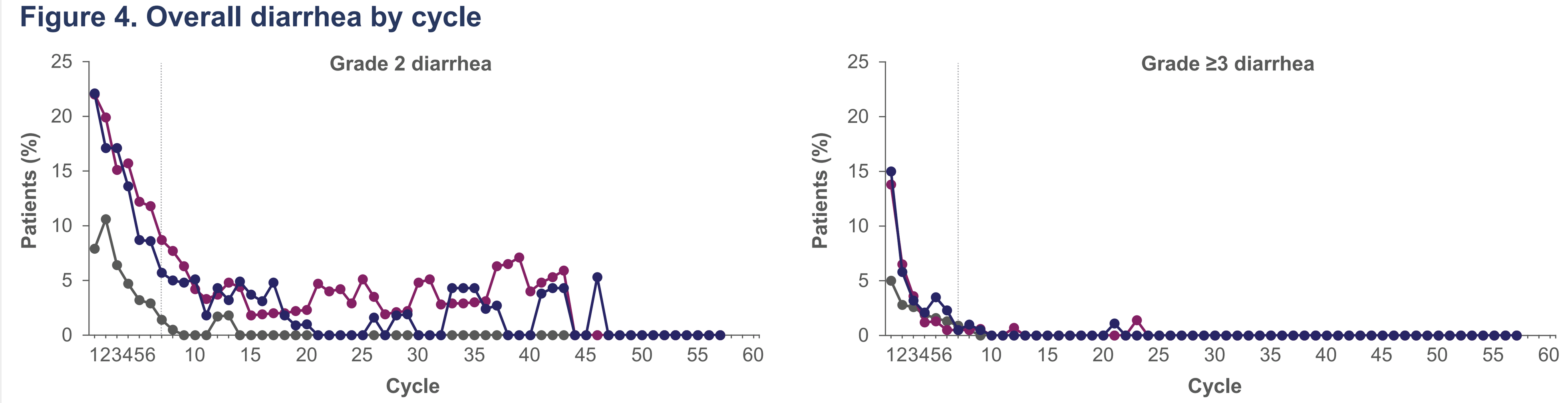


Number of patients at risk by cycle	1	2	3	4	5	6	8	10	12	14	16	18	20	22	24
Zanidatamab + tislelizumab + CT	294	275	252	242	229	220	201	178	163	143	131	114	100	88	75
Zanidatamab + CT	305	276	276	242	230	221	183	165	136	114	106	99	87	75	68
Trastuzumab + CT	302	284	284	257	247	239	192	157	121	100	80	69	61	52	44

Percentages calculated as a proportion of the patients at risk per cycle. The dashed line indicates the time at which patients could discontinue CT at the discretion of the treating physician (after completion of cycle 6).
CT, chemotherapy.

- Most patients experienced first-onset diarrhea during cycle 1, with a median time to first onset <2 weeks and median duration <2.5 weeks across treatment arms
- Among patients with any-grade diarrhea, first-onset was infrequent after cycle 6 (when patients could discontinue CT) and occurred in 12/244 (4.9%) patients with zanidatamab + tislelizumab + CT, 1/241 (0.4%) with zanidatamab + CT, and 11/161 (6.8%) with trastuzumab + CT

Figure 4. Overall diarrhea by cycle



Number of patients at risk by cycle	1	2	3	4	5	6	10	15	20	25	30	35	40	45	50	55
Zanidatamab + tislelizumab + CT	294	275	252	242	229	220	178	135	100	70	53	46	29	23	14	6
Zanidatamab + CT	305	276	276	242	230	221	165	110	87	59	42	33	25	15	11	2
Trastuzumab + CT	302	284	284	257	247	239	157	87	61	37	23	17	11	5	4	2

Percentages calculated as a proportion of the patients at risk per cycle. The dashed line indicates the time at which patients could discontinue CT at the discretion of the treating physician (after completion of cycle 6).
CT, chemotherapy.

- Higher overall rates of grade 2 and grade ≥3 diarrhea were observed in the zanidatamab-containing arms vs the trastuzumab + CT arm early in treatment; grade ≥3 diarrhea was rare after cycle 6 across treatment arms
- Among patients with any-grade diarrhea, recurrent events that were grade 3 or higher in severity occurred in 11.1% (27/244) with zanidatamab + tislelizumab + CT, 7.5% (18/241) with zanidatamab + CT, and 8.1% (13/161) with trastuzumab + CT; the median (range) time from onset of initial diarrhea to a recurrent event that was grade 3 or higher in severity was 26 (2–420), 17 (2–206), and 40 (8–96) days, respectively

Table 3. Management of diarrhea

	Zanidatamab + tislelizumab + CT (n = 294)	Zanidatamab + CT (n = 305)	Trastuzumab + CT (n = 302)
Dose delays due to diarrhea	47 (16.0)	42 (13.8)	25 (8.3)
Zanidatamab or trastuzumab	40 (13.6)	41 (13.4)	23 (7.6)
Tislelizumab	37 (12.6)	—	—
CT	39 (13.3)	37 (12.1)	24 (7.9)
Dose reductions due to diarrhea[a]	74 (25.2)	80 (26.2)	43 (14.2)
Zanidatamab	29 (9.9)	33 (10.8)	—
CT	64 (21.8)	72 (23.6)	43 (14.2)
Treatment discontinuations due to diarrhea	22 (7.5)	15 (4.9)	5 (1.7)
Zanidatamab or trastuzumab	12 (4.1)	4 (1.3)	1 (0.3)
Tislelizumab	8 (2.7)	—	—
CT	17 (5.8)	15 (4.9)	5 (1.7)
Any protocol-mandated loperamide prophylaxis[b]	280 (95.2)	292 (95.7)	—
Concomitant medications for diarrhea	200 (68.0)	197 (64.6)	108 (35.8)
Received by >5% of patients in any arm			
Loperamide (excluding protocol-mandated prophylaxis)[c]	188 (63.9)	180 (59.0)	89 (29.5)
Montmorillonite	24 (8.2)	18 (5.9)	11 (3.6)
Diosmectite	17 (5.8)	24 (7.9)	10 (3.3)
Sodium chloride	18 (6.1)	7 (2.3)	6 (2.0)

All data are shown as n (%).
[a]Dose reductions of trastuzumab or tislelizumab were not permitted. [b]Loperamide prophylaxis was mandated for the first 7 days of cycle 1 in the zanidatamab-containing arms; prophylaxis was not given to all patients due to protocol-permitted withholding for constipation, early treatment discontinuations after infusion-related reactions, or isolated protocol deviations where patients were not administered loperamide. [c]Includes loperamide and loperamide hydrochloride given for treatment purposes.
CT, chemotherapy.

- Dose delays, dose reductions, and discontinuations of zanidatamab and tislelizumab due to diarrhea were infrequent
- Diarrhea could typically be managed with loperamide and CT dose reductions
  - Octreotide and lomotil were prescribed for diarrhea in <4% and <3% of patients across treatment arms, respectively