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Consensus Guidance for Management of Diarrhoea With Zanidatamab + Chemotherapy ± Tislelizumab in First-Line Advanced/Metastatic Gastroesophageal Adenocarcinoma: A Modified Delphi Panel Study

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Background

- GEAs account for ~1.5 million new diagnoses worldwide each year, with 60–70% of individuals diagnosed at regional or distant metastatic stage and a 5-year relative survival of only ~5–8% in metastatic disease.[1-3] Approximately 20% of GEA tumours overexpress HER2.[4]
- Zanidatamab, a dual HER2-targeted bispecific antibody, binds to two distinct sites on HER2, facilitating receptor clustering and exerting multiple antitumour mechanisms of action.[5]
- In the prespecified interim analysis of the phase 3 HERIZON-GEA-01 trial, zanidatamab, a dual HER2-targeted bispecific antibody, combined with FP with Pt-based CT with or without TIS significantly improved PFS in both zanidatamab arms, and the zanidatamab with CT with TIS regimen (triplet combination) yielded a statistically significant OS benefit versus trastuzumab with CT.[6]
- Diarrhoea was the most frequent TRAE (see inset below). Per protocol, mandatory loperamide prophylaxis aimed to reduce diarrhoea severity in the trial setting; however, no specific clinical guidance for the management of zanidatamab-with-CT–associated diarrhoea currently exists.[6-8]

HERIZON-GEA-01 (phase 3)[6] *1L HER2-positive advanced/metastatic GEA*

mPFS	mOS
12.4 mo (zanidatamab+CT+TIS) vs **8.1 mo** (trastuzumab+CT)	**26.4 mo** (zanidatamab+CT+TIS) vs **19.2 mo** (trastuzumab+CT)
HR 0.63 (0.51–0.78)	HR 0.72 (0.59–0.90)
P<0.001	*P*=0.004

Diarrhoea: Most frequent TRAE from zanidatamab arms
- Any grade: 76–82% (zanidatamab arms) vs 48% (trastuzumab arm)
- Grade ≥3: 20–25% (zanidatamab arms) vs 13% (trastuzumab arm)
- Median onset: ~1 week, predominantly in cycle 1
- Pt-FP backbone seen as main driver

Objective

- **To develop expert-driven, pragmatic recommendations** for the prevention and management of zanidatamab-associated diarrhoea in HER2-positive GEA, using a structured modified RAND/UCLA Delphi process informed by HERIZON-GEA-01 data.

Methods

- **A modified RAND/UCLA Delphi process** was led with 18 international, primarily GI oncologists from nine countries across three continents. A systematic PubMed/EMBASE literature review (including zanidatamab phase 1 and 2 trial data) and the phase 3 HERIZON-GEA-01 trial data informed a structured 26-item pre-meeting survey across four domains.
- Statements were iteratively refined across three virtual panel meetings and five anonymous offline voting rounds. Each statement was rated on a 9-point Likert scale. Consensus was defined as a median score ≥7 with no disagreement (RAND/UCLA appropriateness method); strong consensus required ≥80% of panellists scoring 7–9.

Modified RAND/UCLA Delphi process: Three phases

Phase 1: Evidence base
Literature review (PubMed/EMBASE; 2010–2025; 294 publications) + 26-item structured pre-meeting survey

Phase 2: Consensus building
3 virtual panel meetings (Jul 2025; Mar 2026 ×2)

Phase 3: Statement refinement
Iterative voting on 9-point Likert scale
5 anonymous offline voting rounds

Panel composition (N=18)
- **Region:** 44% Europe / 39% North America / 17% Asia-Pacific
- **Speciality:** 78% GI medical oncology / 22% other oncology
- **Trial involvement:** 83% zanidatamab experience, including 67% HERIZON-GEA-01 investigators
- **Institutions:** 100% academic / comprehensive cancer centres

Four thematic domains
1. Incidence, timing & risk attribution
2. Risk factors & baseline assessment
3. Prophylaxis & patient education
4. Grade-based management

Key results

18 International experts; 9 countries, 3 continents Response rate: 100%

109 Consensus statements across 4 thematic domains

100% Consensus rate (95% strong consensus; 57% with unanimous agreement)

Diarrhea profile and risk attribution

- When combined with CT in GI cancers, zanidatamab is perceived to have a distinct safety profile compared with other HER2-directed therapies, with higher incidence of GI events. Diarrhoea occurs earlier and more frequently with zanidatamab-based regimens, particularly with FP- and Pt-based backbones such as FOLFOX/CAPOX.
- The panel perceived the CT backbone as the predominant driver, although the bispecific HER2-binding mechanism of zanidatamab may contribute.
- Onset is predominantly in cycle 1 (median ~1 week); with proactive management, resolution generally occurs within the first few weeks of treatment.

Prevention pathway (see Figure 1)

- All patients should undergo a structured baseline risk assessment followed by mandatory cycle 1 prophylaxis with oral loperamide 4 mg BID from day 1 to at least day 7, independent of baseline risk.
- In FOLFOX regimens, omission of the 5-FU bolus is recommended to reduce GI toxicity. Proactive patient counselling at cycle 1, day 1, covering expected timing, dietary advice, hydration, reporting thresholds and rescue antidiarrhoeal use, together with healthcare team-led check-ins on days 2 and 7, is essential. From cycle 2, prophylaxis may be individualised based on tolerance, baseline constipation risk and clinical course.

Grade-based management (see Figure 2)

- A clinical decision algorithm provides grade-specific guidance integrating active therapy modifications (including CT dose reductions as an upfront measure), antidiarrhoeal escalation, supportive care and discontinuation criteria (Common Terminology Criteria for Adverse Events v5.0). Key principles:
  - **Grade 1**: Continue both zanidatamab and CT at full dose; intensify supportive care if persistent.
  - **Grade 2**: Continue zanidatamab with careful monitoring (100% agreement, clinical-judgment dependent); CT hold or dose reduction (FP first) if persistent for over 48 hours.
  - **Grade 3**: Interrupt CT immediately and hold zanidatamab until Grade 1 or less, with zanidatamab dose reduction options on resumption (1400 or 1800 mg once every 3 weeks per body weight); implement CT dose reductions, hospital-level supportive care, octreotide for refractory cases and full diagnostic workup. Recurrent Grade 3 or higher diarrhoea persisting for over 72 hours despite maximal antidiarrhoeal therapy and prior CT dose reduction warrants permanent zanidatamab discontinuation.
  - **Grade 4**: Interrupt CT immediately and hold zanidatamab; if lasting over 72 hours or for recurrence, permanently discontinue.
- Endoscopic evaluation should be considered for prolonged or refractory cases, with steroids reserved until infectious causes are reasonably excluded.

Figure 1. Clinical decision algorithm for the prevention of treatment-associated diarrhoea in patients with HER2-positive GEA receiving zanidatamab with CT with or without TIS

Patient initiating zanidatamab + chemotherapy +/- tislelizumab for HER2-positive GEA

BASELINE RISK ASSESSMENT

A structured baseline assessment is recommended to identify patients at higher risk of GI toxicity
This may include performance status, surgical history and medication review

Disease-related: GI anatomy and function	Patient-related: comorbidities and baseline patient status	Treatment-related: concomitant medications
• **Prior gastrectomy** (total or subtotal) or **oesophagectomy** • **Dumping syndrome or** related post-surgical **gastrointestinal dysfunction** (altered nutrient absorption, altered motility, short bowel)	• **Diabetes mellitus** (particularly in patients treated with metformin) • **Poor baseline nutritional status** (e.g., anorexia, hypoalbuminaemia) • **Supplementary drinks or complementary alternative medications[a]** • **Enteral feeding** • **Patient frailty** • **DPD deficiency**	• **Fluoropyrimidine- or oxaliplatin-based chemotherapy** backbones (potential additive gastrointestinal toxicity) • **Immunotherapy** (e.g., tislelizumab) • **Pro-motility, prokinetic agents** • **Metformin** • **Chronic antidiarrhoeal use** (masking symptoms or leading to rebound diarrhoea)

All patients should undergo formal nutritional screening using a validated tool (e.g., NRS-2002) prior to Cycle 1
Nutritional status should be reassessed periodically during treatment

MANDATORY CYCLE 1 PROPHYLAXIS IN ALL PATIENTS

All patients should receive mandatory prophylactic oral loperamide (4 mg BID) during Cycle 1 (Day 1 to at least Day 7), independent of baseline risk

- **Review and adjust concomitant medications that may exacerbate diarrhoea[b]**
- **Chemotherapy regimens:** omit 5-FU bolus to reduce GI toxicity risk
- **Interrupt loperamide if clinically significant constipation[c]**; implement supportive measures as clinically indicated
- **Early supportive hydration** (either increased oral and/or IV) may be considered during Cycle 1 in selected patients to support tolerability and reduce the risk of clinically significant diarrhoea
- **Supply oral antidiarrhoeal agents** to enable rapid initiation of rescue therapy at symptom onset

PATIENT EDUCATION & MONITORING[d]

HEALTHCARE TEAM
- **Proactive patient counselling at treatment initiation,** including education/checklists with expected timing of diarrhoea, diet and hydration, early reporting thresholds, and correct use of antidiarrhoeal medication
- **Healthcare team-led telephonic or virtual check-ins on Days 2 and 7 of Cycle 1:** to the patient or caregiver, to identify emerging diarrhoea and enable early intervention, particularly in patients receiving fluoropyrimidine- and platinum-based chemotherapy
  → It may be repeated in Cycle 2, based on the clinical course
  → This approach should be implemented routinely across treatment settings.

PATIENTS AND/OR CAREGIVERS
- **Patients should be encouraged to monitor body weight weekly** and report ongoing unintentional weight loss promptly to enable early intervention when clinically indicated
- **Symptom tracking during early cycles,** using paper or electronic tools, is an option that may facilitate timely reporting and early intervention for diarrhoea, and support patient engagement, depending on local workflows and nurse/caregiver/patient capability
- **In the event of diarrhoea, patients should be instructed to promptly contact the treating team or oncology nurse to enable timely assessment and intervention**

Diarrhoea during or after Cycle 1?

NO
- **Continue treatment per protocol**
- **In patients who tolerate loperamide without clinically significant complications, continuation of prophylactic loperamide into subsequent cycles**, including Cycles 2 and 3, may be considered; **prophylaxis may be individualised** based on patient tolerance, baseline constipation risk, and clinical course, with careful monitoring and patient education
- **Proactive follow-up phone calls on Days 2 and 7**

YES
- **Grade diarrhoea** per CTCAE v5.0
- **Continuation of loperamide prophylaxis** in subsequent cycles should be considered
- **Appropriate adjustment of the chemotherapy backbone** (particularly fluoropyrimidines), based on clinical judgment

→ SEE FIGURE 2: GRADE-BASED MANAGEMENT

[a]Complementary or alternative medicines used in addition to prescribed therapy may increase the risk or severity of diarrhoea and should be used with caution.
[b]Review of concomitant medications that may exacerbate diarrhoea (e.g. promotility agents, metformin) should be incorporated into routine care, with temporary dose adjustment, substitution, or discontinuation considered as appropriate, ideally with involvement of a pharmacist when available.
[c]No bowel movement for ≥72 hours OR clinically significant reduction in bowel frequency associated with symptoms (e.g., discomfort, bloating, straining).
[d]Monitoring workflows should be adapted to local resource availability and care models, ranging from intensive nurse-led or hospital-based monitoring in tertiary centres to simplified checklists or remote follow-up in community settings, while maintaining patient safety.

Figure 2. Grade-based management of treatment-associated diarrhoea in patients with HER2-positive GEA receiving zanidatamab with CT with or without TIS

Grade diarrhoea per CTCAE v5.0 → Select appropriate management pathway

GRADE 1 – CONTINUE <4 stools/day above baseline	GRADE 2 – CAUTION 4–6 stools/day above baseline	GRADE 3 – HOLD ≥7 stools/day above baseline; hospitalization indicated	GRADE 4 – HOLD OR DISCONTINUE Life-threatening; urgent intervention indicated
Active therapy • **Continue zanidatamab and chemotherapy**	**Active therapy** • **Zanidatamab can generally be continued in subsequent cycles** with careful clinical monitoring • **Chemo interruption or dose modification at physician's discretion** • **Fluoropyrimidine regimens:** 5-FU or capecitabine dose reduction is recommended as first-line strategy	**Active therapy** • **Immediate interruption of chemotherapy** • **Hold zanidatamab:** interruption may be individualised based on timing, severity and clinical context • **Resume zanidatamab** upon severity ≤ G1 / pretreatment level, at same dose or reduce to 1400 mg Q3W (<70 kg) or 1800 mg Q3W (≥70 kg) per clinician discretion, individualised based on recovery and prior tolerance • **Chemo dose reduction to be implemented** • **Chemo discontinuation if Ga3 recurs**	**Active therapy** • **Immediate interruption of chemotherapy** • **For Grade 4 diarrhoea, permanent discontinuation of zanidatamab is generally recommended** • **If G4 lasts >72 hours or G4 is recurrent:** ▲ **Permanently discontinue zanidatamab**
Antidiarrhoeal escalation • **Loperamide 4 mg** followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhoea, max 16 mg/d • May include **diphenoxylate/atropine** with close clinical monitoring	**Antidiarrhoeal escalation** • **Loperamide 4 mg** followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhoea, max 16 mg/d • Add **diphenoxylate/atropine** or **5-HT3 antagonists** per local guidelines • **Short-course SC octreotide** in selected prolonged or refractory Grade 2 cases	**Antidiarrhoeal escalation** • **Loperamide 4 mg** followed by 2 mg after each loose stool (or Q4H while awake) until no diarrhoea, max 16 mg/d • **Escalated loperamide** may be used in refractory cases • Add **diphenoxylate/atropine** per local guidelines • **Octreotide** 100–150 mcg SC Q8H in severe/refractory cases; in hospitalised pts, continuous IV infusion may be considered • **If refractory** to all agents above: GI consult	**Antidiarrhoeal escalation** • **Loperamide** 4 mg PO followed by 4 mg Q2H until resolution of diarrhoea, max 16 mg/d • **Diphenoxylate/atropine,** alternating with loperamide • **Octreotide** 100–150 mcg SC Q8H for persistent diarrhoea despite 48h of loperamide • **If refractory** to all agents above: GI consult
Supportive measures • **Supportive care** with particular attention to frail patients or those with baseline risk factors • **Increased oral hydration and/or IV hydration** • **Dietary adjustments** (avoid high-fat, high-osmolar, lactose-containing foods) • **Closer monitoring for frail patients** or those with multiple comorbidities	**Supportive measures** • **Hydration support** (oral/IV, with fluids containing water, salt and glucose) for reduced intake, dehydration, or anorexia, regardless of duration • **Electrolyte** monitoring and early replacement (frequently underestimated) • **Reassess within 24–48h:** no improvement → escalate	**Supportive measures & diagnostic workup** • **Hospital-level supportive care** especially in severe, uncontrolled diarrhoea, dehydration, electrolyte imbalance or significant comorbidities • **IV fluid replacement + electrolyte monitoring** and correction; continuous IV hydration in selected cases • **Nutritional support;** consider **parenteral nutrition** for significant deterioration (based on clinical trajectory) • **Diagnostic workup:** stool cultures (incl. *C. difficile*), laboratory assessment, CT + endoscopy if not resolving >7 days, multidisciplinary involvement (GI, nutrition)	**Supportive measures** • **Aggressive fluid hydration + clear liquid diet** • **Early parenteral nutrition** for severe dehydration, electrolyte imbalance, or inability to maintain adequate oral intake; decision individualised by overall clinical status and nutritional trajectory, not CTCAE grade alone
▶ **If Grade 1 persists** • **Closer monitoring; reassess supportive care strategy** • **Extension/intensification of prophylaxis** • **Both supportive care intensification and chemotherapy dose reductions** may be considered, based on patient preference, frailty, and overall clinical context • **Home-based/HCP-led monitoring** in selected pts with persistent low-grade symptoms	▶ **If Grade 2 persists** • **Evaluate for alternative aetiologies:** infection, immune-mediated colitis • **Infectious workup:** stool cultures / *C. difficile* testing	▶ **If Grade 3 persists** • **Octreotide 100–150 mcg SC Q8H**; in hospitalised pts, continuous IV infusion may be considered	

ENDOSCOPIC EVALUATION
- **Consider when:** prolonged symptoms, poor response to standard management, immune-mediated colitis or alternative aetiologies suspected
- **Not restricted to Ga3:** should be guided by clinical features, severity, duration and suspected etiology
- **Management/supportive measures should not be delayed;** steroids to be considered only after infectious causes reasonably excluded (overlapping infection remaining a clinical concern)

RECURRENT DIARRHOEA
- **Defined as Grade ≥2, or lasting >3 days after prior resolution**
- **Early multidisciplinary input recommended** (should not be delayed until symptoms become severe or refractory) ; **manage using same principles, escalation** based on severity/duration
- **Reassess risk factors, chemotherapy backbone and dosing, concomitant medications and nutritional status**
- **Both prophylaxis intensification and chemo modification should be considered**
- **Recurrent G3 >72h + maximal therapy: ▲ permanently discontinue zanidatamab**

WHEN TO ESCALATE CARE
- **Diarrhoea interfering with QoL or oral intake**
- **Associated symptoms:** anorexia, abdominal pain, nausea, vomiting, reduced oral hydration
- **Progression** despite supportive care/prophylaxis
- **Prolonged or severe diarrhoea**: early involvement of dietitians or nutrition specialists may be beneficial
- **GI consultation** for complex, persistent, or severe cases, to exclude alternative or immune-mediated causes

PERMANENT DISCONTINUATION CRITERIA
- ▲ **Recurrent Ga3 >72h** despite zanidatamab dose reduction + maximal antidiarrhoeal therapy (incl. loperamide, diphenoxylate/atropine and octreotide); assuming prior appropriate dose reduction of chemotherapy already implemented
- ▲ **Grade 4 lasting >72 hours** (permanent discontinuation of zanidatamab is generally recommended in G4)
- ▲ **Recurrent Grade 4**

Monitoring workflows should be adapted to local resource availability and care models, ranging from intensive nurse-led or hospital-based monitoring in tertiary centres to simplified checklists or remote follow-up in community settings, while maintaining patient safety.
FOLFOX was not used in HERIZON-GEA-01 (CAPOX backbone). The recommendation to omit the 5-FU bolus in FOLFOX regimens derives from the phase 2 study (Elimova et al. Lancet Oncol 2025) and broader clinical experience.
Diarrhoea graded per CTCAE v5.0. CTCAE version note. Grading thresholds in this algorithm follow CTCAE v5.0. CTCAE v6.0 (published 22 July 2025) preserves the quantitative thresholds for Grades 2–3 diarrhoea (4–6 stools/day, ≥7 stools/day, life-threatening, death); only the Grade 1 descriptor was refined from "<4 stools/day over baseline" to "change in consistency or frequency." These changes do not alter the grade-based management recommendations proposed here.

Conclusions

- This Delphi consensus provides the first evidence-informed, structured guidance for the prevention and management of zanidatamab-associated diarrhoea in 1L HER2-positive GEA.
- Mandatory cycle 1 loperamide prophylaxis, structured patient education, healthcare team-led monitoring (**Figure 1**) and a clear grade-based management algorithm (**Figure 2**) support clinicians in maintaining dose intensity and improving patient outcomes.
- The setting-adaptable framework facilitates real-world implementation across academic and community practices.

Key takeaways

Mandatory cycle 1 prophylaxis
- Loperamide 4 mg BID on day 1 → day ≥7 of cycle 1 for all patients

FOLFOX regimens
- Omit 5-FU bolus to reduce GI toxicity

Cycle 1 monitoring
- Proactive nurse-led calls day 2 & day 7

Treatment intensity preserved, CT dose reductions first
- Grade-based algorithm minimises dose disruption

Endoscopy for prolonged/refractory cases

Permanent zanidatamab discontinuation criteria
- Grade 4 >72 hours
- Recurrent Grade 4
- Recurrent Grade ≥3 >72 hours despite maximum therapy and prior CT dose reduction

Abbreviations: 1L, first line; 5-FU, 5-fluorouracil; 5-HT3, 5-hydroxytryptamine 3; BID, twice daily; CAPOX, oxaliplatin and capecitabine; CT, chemotherapy; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; DPD, dihydropyrimidine dehydrogenase; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, fluoropyrimidine; G, grade; GEA, gastroesophageal adenocarcinoma; GI, gastrointestinal; HCP, healthcare professional; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IV, intravenous; mOS, median overall survival; mPFS, median progression-free survival; NRS-2002, Nutritional Risk Screening 2002; OR, odds ratio; PFS, progression-free survival; PO, orally; Pt, platinum; Q3W, every 3 weeks; Q4H, every 4 hours; Q8H, every 8 hours; QoL, quality of life; QR, quick response; SC, subcutaneous; TIS, tislelizumab; TRAE, treatment-related adverse event.

References: **1**. Bray F et al. *CA Cancer J Clin.* 2024;74(3):229. **2**. National Cancer Institute. Stomach cancer. Available at: seer.cancer.gov [Accessed 29 May 2026]. **3**. National Cancer Institute. Esophageal cancer. Available at: seer.cancer.gov [Accessed 29 May 2026]. **4**. Bonomi M et al. *Int J Mol Sci.* 2024;25(7):3876. **5**. Weisser NE et al. *Nat Commun.* 2023;14(1):1394. **6**. Shitara K et al. *N Engl J Med.* 2026;394(20):2002–2014. **7**. Elimova E et al. *Lancet Oncol.* 2025;26(7):847–859. **8**. Meric-Bernstam F et al. *Nat Commun.* 2025;16(1):4293.

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