Consensus guidance for management of nausea/vomiting in patients treated with zolbetuximab + chemotherapy: A RAND/UCLA modified Delphi panel study

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BACKGROUND

- The phase 3 SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) studies reported statistically significant improvement in PFS and OS with first-line zolbetuximab + chemotherapy (SPOTLIGHT: mFOLFOX6; GLOW: CAPOX) in patients with HER2-negative, LA unresectable or mG/GEJ adenocarcinoma whose tumors were CLDN18.2-positive[1,2]
- In phase 1–3 clinical studies, the most common TEAEs with zolbetuximab treatment were nausea and vomiting[1-8]
- In SPOTLIGHT and GLOW, approximately three-quarters of patients experienced nausea, and two-thirds of patients experienced vomiting[1,2,9]
  - The occurrences of nausea or vomiting were most common during the first zolbetuximab infusion and decreased thereafter
  - The median time to the first occurrence of nausea and/or vomiting was less than 1 hour after starting the first zolbetuximab infusion (48 minutes in SPOTLIGHT and 57 minutes in GLOW)
  - In SPOTLIGHT, the median time to the first occurrence of vomiting was shorter than that of nausea
- Nausea and vomiting led to higher rates of discontinuations in the zolbetuximab arms versus the placebo arms in both SPOTLIGHT and GLOW[1,2,9]
- Guidance for the prevention and management of nausea and vomiting based on clinical studies of zolbetuximab is limited

OBJECTIVE

- This study aims to develop consensus-based guidelines for the prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy

METHODS

- The international RAND/UCLA modified Delphi panel included 15 expert panelists (**Table 1**) who were key opinion leaders in G/GEJ cancers and were involved in phase 2 or 3 clinical studies of zolbetuximab + chemotherapy
- The study schematic for the modified Delphi panel on the prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy is as follows:

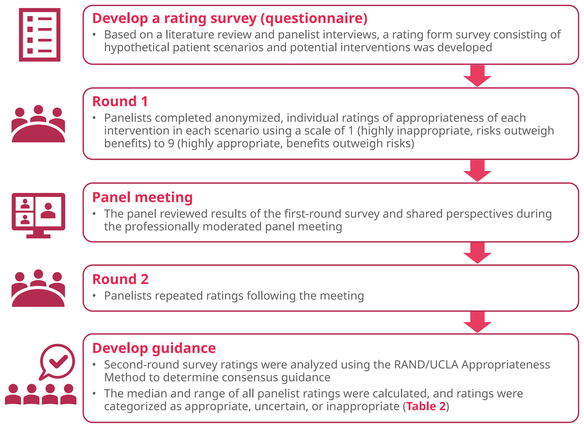


Table 1. Expert Panelists Who Participated in the Modified Delphi Panel

Name	Affiliation	City	Country
Samuel Klempner, MD	Massachusetts General Hospital	Boston	USA
Robert Pazo-Cid, MD	Miguel Servet University Hospital	Zaragoza	Spain
Sara Lonardi, MD	Veneto Institute of Oncology	Padua	Italy
Leslie Swanson, ARNP	Fred Hutch Cancer Center	Seattle	USA
Matthew Arango, PharmD	The Ohio State University James Comprehensive Cancer Center	Columbus	USA
Peter Enzinger, MD	Dana-Farber Cancer Institute	Boston	USA
Andrew Ko, MD	UCSF Helen Diller Family Comprehensive Cancer Center	San Francisco	USA
Gina Vaccaro, MD	Tennessee Oncology	Lebanon	USA
Kensei Yamaguchi, MD	Cancer Institute Hospital of Japanese Foundation for Cancer Research	Tokyo	Japan
Anwaar Saeed, MD	University of Pittsburgh Medical Center	Pittsburgh	USA
Keun-Wook Lee, MD	Seoul National University Bundang Hospital	Seongnam	South Korea
Kohei Shitara, MD	National Cancer Center Hospital East	Kashiwa	Japan
David Ilson, MD, PhD	Memorial Sloan Kettering Cancer Center	New York	USA
Jaffer Ajani, MD	MD Anderson Cancer Center	Houston	USA
Manish Shah, MD	Weill Cornell Medicine	New York	USA

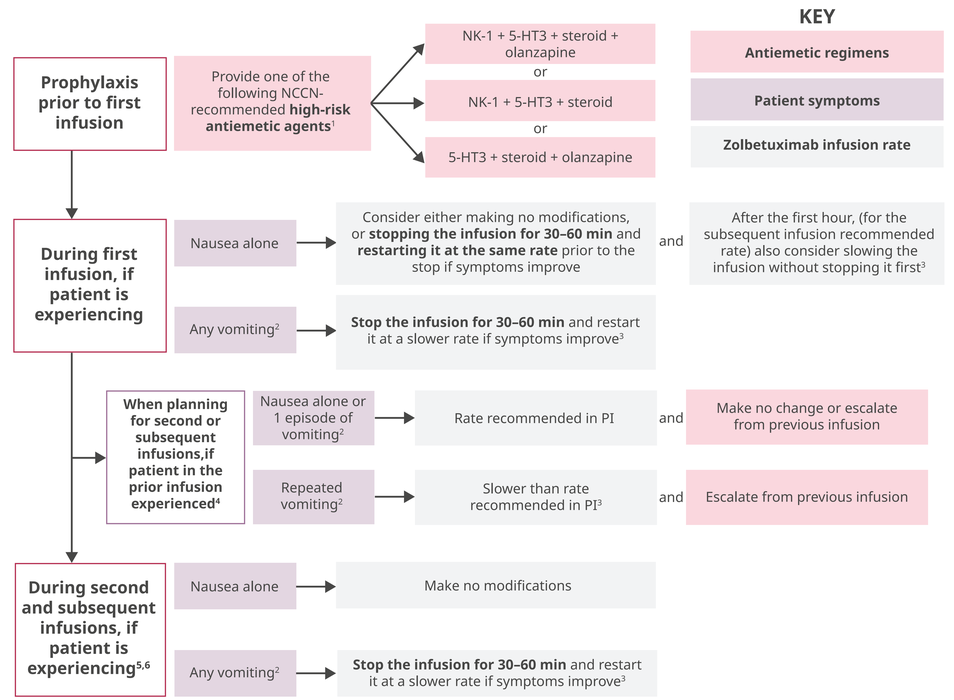
Table 2. Analysis of Rating Scores for the RAND/UCLA Modified Delphi Panel

Agreement	Median score of 7–9	Experts agree that the approach is **appropriate**
	Median score of 4–6	Experts agree that the approach **may or may not be appropriate**
	Median score of 1–3	Experts agree that the approach is **inappropriate**
Disagreement	≥ 3 ratings of 1–3 and ≥ 3 ratings of 7–9	**No conclusions** can be made

RESULTS

- Experts reviewed 382 scenarios, reaching agreement in 85% (n = 324) of the scenarios for Round 2
- The flow chart for prevention and management of nausea and vomiting is shown in **Figure 1**

Figure 1. Consensus Guidance on the Prevention and Management of Nausea and Vomiting in Patients Treated With Zolbetuximab + Chemotherapy



[1]NCCN-recommended high emetic risk regimens: NK-1 + 5-HT3 + steroid + olanzapine, or NK-1 + 5-HT3 + steroid, or 5-HT3 + steroid + olanzapine. Either oral or IV antiemetics may be appropriate based on individual patient circumstances.

[2]IV hydration may be appropriate depending on individual patient circumstances.

[3]If infusion was running at PI rate, slow rate by 50%; if infusion rate had already been slowed to 50%, slow by an additional 50% (ie, 25% of the initial rate).

[4]Adjust your plan for subsequent infusions based on the patient's symptoms during prior infusions.

[5]Begin second and subsequent infusions at the rate that was best tolerated during previous infusion (eg, if the prior infusion was tolerated at the PI rate, subsequent infusions should be given at the same rate; if infusion rate was slowed to 50% of PI rate and symptoms improved, start subsequent infusions at this rate).

[6]With second and/or subsequent infusions, the degree of nausea and vomiting is expected to diminish. In these cases, patients may tolerate titration of the infusion rate by increments of 25% (eg, if infusion rate was slowed to 50% and the patient remained asymptomatic for 30–60 min, consider increasing the rate to 75%) back to 100% or maximum tolerated infusion rate. Continue to closely monitor the patient for any recurrence of symptoms and administer additional antiemetic medications as needed to manage symptoms effectively.

CONCLUSIONS

- Consensus statements were developed using the modified Delphi method and can be utilized by clinicians to help guide the prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy
  - The panel recommends using any of the NCCN's high-emetic risk regimens prophylactically, prior to the first zolbetuximab infusion
  - Based on patient symptoms of nausea and/or vomiting, recommendations include modifying the zolbetuximab infusion rate, interrupting zolbetuximab infusions for 30–60 min, administering antiemetic medications not used for prophylaxis, and/or providing IV hydrations
  - Zolbetuximab should not be discontinued without first attempting to modify or temporarily interrupt the infusion and/or without providing additional treatment for nausea and vomiting in the absence of hypersensitivity reactions or IRRs
  - If zolbetuximab and chemotherapy are given on the same day, zolbetuximab must be given first; if zolbetuximab infusion has been modified to the point where chemotherapy cannot be completed on the same day, chemotherapy can be administered on the following day

Abbreviations

5-HT3, 5-hydroxytryptamine 3 receptor antagonists; ARNP, Advanced Registered Nurse Practitioner; CLDN18.2, claudin 18 isoform 2; G/GEJ, gastric/gastroesophageal junction; HER2, human epidermal growth factor receptor-2; IRR, infusion-related reaction; IV, intravenous; LA, locally advanced; mG/GEJ, metastatic gastric/gastroesophageal junction; NCCN, National Comprehensive Cancer Network; NK-1, neurokinin-1; MD, Doctor of Medicine; OS, overall survival; PFS, progression-free survival; PharmD, Doctor of Pharmacy; PhD, Doctor of Philosophy; PI, prescribing information; TEAEs, treatment-emergent adverse events; UCSF, the University of California, San Francisco.

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Conflicts of Interest

SJK reports receiving consulting fees from Astellas Pharma and Novartis; receiving honoraria from Merck Sharp & Dohme; serving a consulting or advisory role for Amgen, Astellas Pharma, Novartis, Pfizer, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, IMAB, Mersana Therapeutics, Natera, AstraZeneca, Daiichi Sankyo, Laboratoires Servier, Coherus BioSciences; serving as a committee member for National Comprehensive Cancer Network; and had received stocks from Turning Point Therapeutics (by June 2022) and Nuvalent (by November 2022). **SNG** is a full-time employee of Partnership for Health Analytic Research. **SB** and **RF** are full-time employees of Astellas Pharma Inc.

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