# Phase Ib/II Study of Zanidatamab in Combination with Tislelizumab and Chemotherapy in First-Line HER2-Positive Gastric/Gastroesophageal Junction Adenocarcinoma

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## ABSTRACT

**Purpose:** This phase Ib/II trial (NCT04276493) assessed the antitumor activity, safety, and pharmacokinetics (PK) of zanidatamab in combination with tislelizumab and chemotherapy in patients with advanced HER2-positive (HER2+) gastric cancer/gastroesophageal junction cancer (GEJC).

**Patients and Methods:** Adult patients with previously untreated, unresectable, locally advanced/metastatic HER2+ gastric cancer/GEJC received zanidatamab 30 mg/kg i.v. (cohort A) or zanidatamab 1800 mg i.v. (weight <70 kg)/2,400 mg i.v. (weight ≥70 kg; cohort B) once every 3 weeks (Q3W). Both cohorts received tislelizumab 200 mg i.v. once every 3 weeks and standard chemotherapy [capecitabine and oxaliplatin (CAPOX)] once every 3 weeks. Primary endpoints were investigator-assessed confirmed objective response rate (cORR) per RECIST v1.1, in addition to the frequency and severity of adverse events (AE) and serious AEs. Secondary endpoints included investigator-assessed progression-free survival (PFS), duration of response (DoR), overall survival (OS), PK, and immunogenicity of zanidatamab.

**Results:** As of December 7, 2023, 33 patients (cohort A, $n = 19$; cohort B, $n = 14$) received treatment. The confirmed objective response rate was 75.8%; the median duration of response, progression-free survival, and overall survival were 23.3, 16.7, and 32.4 months, respectively. The most common treatment-related AEs (TRAEs) were diarrhea (100%), nausea (63.6%), and decreased appetite (48.5%). Treatment-related AEs of grade ≥3 were reported in 22 (66.7%) patients; diarrhea was the most common (27.3%).

**Conclusions:** Zanidatamab, in combination with tislelizumab and CAPOX, demonstrated clinically meaningful antitumor activity with a manageable safety profile as first-line therapy for patients with HER2+ gastric cancer/GEJC. These results support a further development of zanidatamab and tislelizumab with chemotherapy in this patient population in the ongoing phase III HERIZON-GEA-01 trial (NCT05152147).

## Introduction

Gastric cancer and gastroesophageal junction cancer (GEJC) are both the fifth most frequently diagnosed cancer and the fifth leading cause of cancer-related deaths globally according to GLOBOCAN 2022 data (1). Incidence rates are higher in Eastern Asia and Eastern Europe compared with North America and Northern Europe (1). Most cases of gastric cancer/GEJC occurring in Western countries are diagnosed at an advanced state, thereby reducing the opportunity for a surgical cure (2–4). Chemotherapy regimens containing platinum and fluoropyrimidine have become the mainstay for the first-line treatment of patients with newly diagnosed, unresectable, or metastatic gastric cancer/GEJC, but only approximately 30% to 60% of patients respond (5–11).

Approximately 20% of patients with gastric cancer and 30% of patients with GEJC present with tumors that are HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+ with in-situ hybridization [ISH] positivity); refs. 12–15). Based on the ToGA trial, trastuzumab in combination with platinum and fluoropyrimidine became a standard treatment for patients with previously untreated HER2+ gastric cancer/GEJC (15). Other trials have assessed the addition of novel HER2-targeted therapies, including pertuzumab,

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## Translational Relevance

Historically, trastuzumab has been the only HER2-targeted option for first-line treatment of patients with advanced gastric cancer/gastroesophageal junction cancer (GEJC). Data from recent clinical trials have shown that anti–PD-1 monoclonal antibodies, such as tislelizumab, provide clinical benefit to patients with gastric cancer/GEJC. Zanidatamab is a novel, humanized, bispecific monoclonal antibody directed against HER2, with diverse mechanisms of action due to its unique binding properties. Here, we present results from a phase Ib/II study (NCT04276493) that shows that zanidatamab, in combination with tislelizumab and chemotherapy, has a manageable safety profile while demonstrating clinically meaningful antitumor activity as first-line treatment for patients with HER2+ gastric cancer/GEJC. A phase III trial (HERIZON-GEA-01; NCT05152147) evaluating the addition of tislelizumab to zanidatamab and chemotherapy in this setting is ongoing.

to standard chemotherapy with or without trastuzumab but did not show improved overall survival (OS; refs. 16, 17), underscoring the continued unmet need for more effective HER2-targeted therapies for HER2+ gastric cancer/GEJC.

The clinical benefit of immune checkpoint inhibitors has been demonstrated in gastric cancer/GEJC, including in patients with HER2+ disease. Data from a phase Ib/II and phase II study evaluating the anti–PD-1 antibody pembrolizumab in combination with trastuzumab and chemotherapy in previously untreated patients with HER2+ gastric cancer/GEJC showed promising antitumor activity (18, 19). In the phase III KEYNOTE-811 trial, the addition of pembrolizumab to first-line trastuzumab and chemotherapy significantly improved progression-free survival (PFS) and OS in patients with HER2+ gastric cancer/GEJC, especially in those with a PD-L1 combined positive score ≥1 (20). Based on these data, the US FDA, the European Medicines Agency, and the China National Medical Products Administration approved the use of pembrolizumab with trastuzumab and chemotherapy as first-line treatment for patients with HER2+ gastric cancer/GEJC whose tumors express PD-L1 combined positive score ≥1.

Tislelizumab is a high-affinity humanized immunoglobulin G4 monoclonal antibody targeted against PD-1 that was engineered to minimize Fcγ receptor binding on macrophages (21, 22). In the phase III RATIONALE-305 trial, tislelizumab plus chemotherapy provided a significant OS benefit versus placebo plus chemotherapy in patients with previously untreated, HER2-negative, advanced gastric cancer/GEJC (23). Data from RATIONALE-305 provided the basis for the approval of tislelizumab by the US FDA, European Medicines Agency, and China National Medical Products Administration in combination with fluoropyrimidine and platinum for the first-line treatment of patients with advanced gastric cancer/GEJC (24–26).

Zanidatamab (also known as ZW25 and JZP598) is a novel, humanized, bispecific, immunoglobulin G isotype 1–like antibody directed against the juxtamembrane extracellular domain and the dimerization domain of HER2. The unique properties of zanidatamab drive binding to HER2 across a range of expression levels, formation of receptor clusters, and receptor internalization, resulting in HER2 downregulation. Zanidatamab inhibits growth factor–dependent and growth factor–independent tumor cell proliferation and activates immune-mediated responses, including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity (27). In xenografts of a high HER2-expressing (IHC 3+) gastric tumor cell line (NCI-N87), zanidatamab had significantly greater antitumor activity than trastuzumab or trastuzumab plus pertuzumab (27). Data from a phase I dose-escalation and -expansion trial (NCT02892123) demonstrated that single-agent zanidatamab was safe and provided preliminary evidence of antitumor activity across a range of solid tumors with HER2 overexpression or amplification (28).

Collectively, the bispecific structure of zanidatamab, preclinical data, and clinical data suggest that zanidatamab, in combination with tislelizumab and chemotherapy, has the potential to provide clinical benefit to patients with HER2+ gastric cancer/GEJC. A phase Ib/II trial was designed to evaluate the preliminary antitumor activity, safety, and pharmacokinetics (PK) of zanidatamab in combination with tislelizumab and chemotherapy for patients with gastric cancer/GEJC and with chemotherapy as the first-line treatment for patients with HER2+ breast cancer. This study included two cohorts receiving flat dosing and weight-based dosing regimens to determine the appropriate dosing for future studies. We presented interim trial results from the gastric cancer/GEJC cohort previously (29, 30). Here, we present updated results specifically from patients with gastric cancer/GEJC, with a data cutoff date of December 7, 2023, especially from an efficacy and safety perspective.

## Patients and Methods

### Study design

BGB-A317-ZW25-101 (NCT04276493) was a phase Ib/II, open-label, multicenter trial enrolling patients in China and Republic of Korea, with a 28-day screening period prior to the first treatment dose (Supplementary Fig. S1). The trial evaluated the clinical activity, safety, and PK of zanidatamab with chemotherapy in patients with unresectable, locally advanced, or metastatic HER2+ breast cancer (cohort 1) or with tislelizumab and chemotherapy in patients with HER2+ gastric cancer/GEJC (cohort 2).

In the gastric cancer/GEJC cohort, patients received zanidatamab 30 mg/kg i.v. every 3 weeks (cohort A) or a flat dosage of zanidatamab [1,800 mg (patients with body weight <70 kg) or 2,400 mg (patients with body weight ≥70 kg); cohort B] plus tislelizumab 200 mg every 3 weeks i.v. plus CAPOX {capecitabine orally [1,000 mg/m$^2$ twice daily, days 2 (evening)–16 (morning) for cycles 1 and 2 and days 1 (evening)–15 (morning) for cycles 3 to 6] and oxaliplatin intravenously (130 mg/m$^2$, day 2 for cycles 1 and 2 and day 1 for cycles 3–6)} every 3 weeks for up to six cycles (Supplementary Fig. S1). After cycle 6, oxaliplatin was discontinued and continuation of capecitabine as maintenance treatment was at the investigator's discretion. Zanidatamab and tislelizumab were administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation was met. All patients received acetaminophen, diphenhydramine, and a corticosteroid 30 to 60 minutes prior to zanidatamab infusion as infusion-related reaction (IRR) prophylaxis. After October 2020, all patients received anti-diarrhea prophylaxis with cycle 1 (loperamide 4 mg twice daily for the first 7 days of cycle 1). After cycle 1, loperamide prophylaxis was at the investigator's discretion; however, if patients developed grade ≥2 diarrhea during cycle 1, prophylaxis was recommended with subsequent cycles.

Tumor imaging by CT scans or MRI was performed as baseline within 28 days prior to administration of the first treatment dose

and every 6 weeks (±7 days) from the first day of cycle 1 during the first 36 weeks and then every 12 weeks (±7 days) until disease progression, withdrawal of consent, death, or starting a subsequent anticancer therapy, whichever occurred first. Responses were assessed by the investigator using RECIST v1.1 (31). Patients with disease suspected of pseudoprogression were allowed to continue study treatment beyond initial disease progression per RECIST v1.1 following discussion with sponsor and re-consent.

Safety was assessed by monitoring adverse events (AE), serious AEs (SAE), laboratory results, vital signs, physical examinations, Eastern Cooperative Oncology Group performance status change, electrocardiogram results, echocardiogram (ECHO)/multigated acquisition (MUGA) scan, and other examinations. AEs were recorded during the study (AE from the time of the first dose of study drug and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study drug(s) or until the initiation of a subsequent anticancer therapy, whichever occurred first. After this period, all drug-related SAEs were recorded. Immune-mediated AEs (imAE) were recorded up to 90 days after the last dose of tislelizumab, regardless of whether or not the patient started a subsequent anticancer therapy.

Blood sampling for PK assessment for both zanidatamab and tislelizumab was collected at cycles 1, 2, 5, 9, 17, 26, and 35 and every 17 cycles thereafter and at the end of treatment (if the patient had completed less than 6 months of treatment), for either sparse or serial PK collection. For zanidatamab PK characterization, serial PK samples from up to 13 patients (seven patients from cohort A and six patients from cohort B) were planned to characterize the PK profiles of zanidatamab in the targeted patient population. PK parameters (defined in "Endpoints and assessments") were determined using a standard noncompartmental method. Only sparse PK sampling was conducted for tislelizumab, considering that numerous data have been generated and well characterized in previous studies (32, 33). Samples to assess anti-zanidatamab and anti-tislelizumab antibodies were collected only in patients who received study drug(s) and at sites able to adequately perform sampling, handling, and processing.

The study protocol and all amendments were approved by each site's institutional review board or ethics committee. The study was performed in accordance with the protocol and its amendments and Good Clinical Practice Guidelines. All patients provided written informed consent before enrollment.

### Study population

In the gastric cancer/GEJC cohort, eligible patients were aged ≥18 years with histologically or cytologically confirmed, unresectable, locally advanced, or metastatic gastric cancer/GEJ adenocarcinoma and HER2+ disease, as defined by HER2 IHC 3+ or HER2 IHC 2+ together with ISH positivity. HER2 status determined by the central laboratory or investigational site/local laboratory was acceptable for study entry. Patients were required to have ≥1 measurable lesion according to RECIST v1.1 and Eastern Cooperative Oncology Group performance status of 0 or 1. Patients had not received previous systemic anticancer therapy for unresectable, locally advanced, or metastatic disease, including any approved or investigational anti-EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, or checkpoint inhibitors. Prior use of trastuzumab and/or pertuzumab in the neoadjuvant or adjuvant setting was not allowed. Patients were not eligible if they had received prior therapies targeting PD-1, PD-L1, PD-L2, or any other T-cell costimulation or checkpoint pathways or if they had active autoimmune disease or a history of autoimmune disease that might relapse.

### Endpoints and assessments

In the gastric cancer/GEJC cohort, the primary objectives were evaluation of preliminary antitumor activity and assessment of safety and tolerability of zanidatamab with tislelizumab and chemotherapy. Antitumor activity was measured by confirmed objective response rate (cORR), defined as the proportion of patients who had a best overall response of confirmed complete response (CR) or partial response (PR) as assessed by investigator per RECIST v1.1. Safety was assessed by the incidence and severity of AEs and SAEs, graded according to the NCI Common Terminology Criteria for Adverse Events version 5.0 guidelines (34).

Secondary endpoints included duration of response (DoR), time to response (TTR), PFS, disease control rate (DCR), and OS. DoR was defined as the time from the first determination of an objective response until the first documentation of progression or death, whichever occurred first, in patients with confirmed objective tumor responses. TTR was defined as the time from the start date of study drug to the first determination of an objective response in patients with confirmed objective tumor responses. PFS was defined as the time from the start date of study drug to the date of the first objectively documented tumor progression or death, whichever occurred first. DCR was defined as the proportion of patients with best overall response of confirmed CR, PR, and stable disease. OS was defined as the time from the start date of study drug to the date of death due to any cause.

The planned sample size included approximately 30 enrolled patients based on the following: per binomial distribution, for an event of 1% incidence rate, the chance of detecting any safety signal is about 26% in 30 patients. The probability of observing a safety event of interest increases to 79% in 30 patients when the underlying rate is 5%. Assuming 80% of patients are evaluable for efficacy analyses, approximately 24 patients are expected. If the true ORR is 80%, the sample size can estimate the expected proportion with 16% precision with a 95% confidence interval (CI).

PK parameters and immunogenicity were also analyzed as a secondary endpoint. PK parameters were determined using a standard noncompartmental method (Pheonix WinNonlin, USA). The parameters were summarized with descriptive statistics, including the following parameters if data were available:

- $C_{max}$ (mg/mL): observed maximum plasma concentration during a sample interval.
- $C_{trough}$ (μg/mL): observed concentration at the end of dosing interval.
- $T_{max}$ (hours): observed time to maximum plasma concentration during a sampling interval.
- $t_{½}$ (hours): terminal elimination half-life.
- $AUC_{0\text{-}t}$ (hours*mg/mL): area under the plasma concentration–time curve (AUC) from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation.
- $AUC_{0\text{-}tau}$: AUC during the dosing interval.
- $AUC_{0\text{-}inf}$: AUC from time zero to infinity.
- CL (mL/hour): apparent clearance.
- Vz (mL): apparent volume of distribution.

The zanidatamab and tislelizumab PK concentration data collected sparsely before dose and after dose (end of infusion) were tabulated and summarized by visit/cycle with descriptive statistics.

An exploratory endpoint evaluated PD-L1 expression as a predictive biomarker of antitumor activity. PD-L1 expression was retrospectively evaluated by a central laboratory using the VENTANA PD-L1 (SP263) assay (35) and determined by PD-L1 score assessed by tumor area positivity score, which was defined as the total percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated.

### Statistical analysis

The efficacy-evaluable analysis set, which was the primary analysis set for tumor response, included all patients who received ≥1 dose of study drug and had ≥1 postbaseline tumor response assessment unless any clinical progressive disease or death occurred within 10 weeks after the first dose. The cORR and DCR were calculated with 95% CI estimated using the Clopper–Pearson method. Time-to-event variables (DoR, PFS, and OS) were estimated using the Kaplan–Meier method, and median values were presented with two-sided 95% CI calculated by the Brookmeyer–Crowley method. The safety analysis set, which was the primary analysis set for safety, consisted of all patients who received ≥1 dose of any component of study treatment. Descriptive statistics were used to summarize safety data.

Zanidatamab-related AEs of special interest (AESI) included zanidatamab-related IRRs, cardiac events, and non-infectious pulmonary toxicities, which were considered treatment emergent if the AE start date was within 30 days of the last dose of zanidatamab. Zanidatamab-related IRRs were defined using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of "infusion related reaction" or event identified by the investigator as IRRs and related to zanidatamab. Potential cardiac events were defined as grade ≥2 AEs in the Broad Cardiac Failure–Standardized MedDRA Queries or ECHO/MUGA scan results that indicated a postbaseline decrease in left ventricular ejection fraction (LVEF) of ≥10% from baseline and a value of <50%. Confirmed cardiac events were defined as the subset of potential cardiac events that were clinically reviewed by the sponsor and determined to be consistent with cardiac events of absolute decrease in LVEF of ≥10% from baseline and absolute value <50%, and/or grade ≥2 heart failure. Noninfectious pulmonary toxicities were defined by the broad interstitial lung disease–Standardized MedDRA Queries.

Tislelizumab-related AESI included imAEs, which were defined as AEs that could result in autoimmune disorders, and tislelizumab-related IRRs, defined using MedDRA preferred term of "infusion related reaction" or event identified by the investigator as IRRs and related to tislelizumab.

## Results

### Patient disposition and baseline characteristics

A total of 33 patients (cohort A, $n = 19$; cohort B, $n = 14$) were enrolled from March 26, 2020, to June 28, 2021, and received treatment in the gastric cancer/GEJC cohort. As of December 7, 2023, after a median (range) study follow-up of 30.1 (2.1–42.0) months, 14 patients (42.4%) remained in the study (Supplementary Table S1). Eight patients (24.2%) remained on treatment and 25 patients (75.8%) discontinued from study treatment. The most common reason for treatment discontinuation was progressive disease ($n = 16$; 48.5%).

Demographics and baseline characteristics were generally similar between cohorts (**Table 1**). Overall, the median (range) age was 64 years (29–80). Most patients were male ($n = 29$; 87.9%), had gastric cancer ($n = 28$; 84.8%), and were Korean ($n = 25$; 75.8%; Supplementary Table S2). Most patients had a HER2 status of IHC 3+ by local laboratory ($n = 25$; 75.8%) or central laboratory ($n = 24$; 72.7%) assessment. Four patients (12.1%, all from cohort A) received prior systemic therapies in the adjuvant setting (disease-free interval from the completion of adjuvant therapy >6 months). Thirty-two patients had available tissue for retrospective PD-L1 testing; 18 (54.5%) had a PD-L1 score of ≥5% and 24 (72.7%) patients had a PD-L1 score of ≥1%.

### Treatment exposure

In cohort A, the median (range) duration of exposure was 8.5 (0.7–40.3) months for zanidatamab and 8.9 (0.7–42.0) months for tislelizumab. The median (range) relative dose intensity (RDI) was 96.2% (68.2%–101.4%) for zanidatamab and 96.9% (40.4%–101.9%) for tislelizumab. The median (range) RDI of capecitabine was 75.1% (21.8%–111.8%) and of oxaliplatin, which was discontinued after cycle 6, was 83.6% (60.1%–104.5%).

In cohort B, the median (range) duration of exposure was 19.3 (2.8–32.1) months for zanidatamab and 19.3 (1.4–32.0) months for tislelizumab. The median (range) RDI was 96.5% (68.2%–100.7%) for zanidatamab and 96.7% (86.6%–101.2%) for tislelizumab. The median (range) RDI of capecitabine was 74.9% (24.5%–109.7%) and of oxaliplatin was 91.6% (56.2%–103.4%).

### Antitumor activity

All patients treated were evaluable for efficacy. The cORR by investigator was 75.8% [95% CI, 57.7%–88.9%; cohort A, 78.9% (54.4%–93.9%); cohort B, 71.4% (41.9%–91.6%); **Table 2**]. One patient achieved a confirmed CR in cohort A. The DCR was 100% [95% CI, 89.4%–100%; cohort A, 100% (82.4%–100%); cohort B, 100% (76.8%–100.0%)]. Most patients ($n = 31$; 93.9%) had a decrease in target lesion size (**Fig. 1A**) and nine patients (27.3%) exhibited responses lasting more than 2 years (**Fig. 1B**). The response rates were similar when excluding four patients (12.1%; all from cohort A) who received prior adjuvant anticancer therapy (Supplementary Table S3).

The median (95% CI) PFS was 16.7 (8.2–27.8) months, with a 24-month progression-free rate of 45.5% [**Fig. 2A**; cohort A, median PFS of 8.3 (5.6–32.4) months, with a 24-month progression-free rate of 36.7%; cohort B, median PFS of 24.6 (8.8–not estimable) months, with a 24-month progression-free rate of 56.3%]. Three patients received treatment beyond progression. Among the 25 patients who discontinued study treatment, 19 patients (76.0%) received subsequent second-line systemic therapy. The median (95% CI) OS was 32.4 (15.7–not estimable) months, with a 24-month survival rate of 60.5% [**Fig. 2B**; cohort A, median OS of 31.4 (9.4–not estimable) months, with a 24-month survival rate of 52.6%; cohort B, median OS was not estimable (11.8–not estimable) months, with a 24-month survival rate of 71.4%]. The median PFS and OS remained comparable when six patients with discordant HER2 positivity were excluded (Supplementary Fig. S2A and S2B).

Among responders ($n = 25$), the median (range) TTR was 5.9 (4.1–37.3) weeks overall. The median (95% CI) DoR was 23.3 (7.4–31.1) months, with a 24-month event-free rate of 41.1% [**Fig. 2C**; cohort A, median DoR of 15.4 (4.9–not estimable) months, with a 24-month event-free rate of 37%; cohort B, median DoR of 23.7 (7.4–not estimable) months, with a 24-month event-free rate of

**Table 1.** Demographics and baseline characteristics.

| Characteristic | Cohort A (*n* = 19) | Cohort B (*n* = 14) | All patients (*N* = 33)[a] |
|---|---|---|---|
| Median (range) age, years | 66.0 (29–80) | 61.5 (42–72) | 64.0 (29–80) |
| <65 | 8 (42.1) | 9 (64.3) | 17 (51.5) |
| ≥65 | 11 (57.9) | 5 (35.7) | 16 (48.5) |
| Sex | | | |
| Male | 17 (89.5) | 12 (85.7) | 29 (87.9) |
| Female | 2 (10.5) | 2 (14.3) | 4 (12.1) |
| Race | | | |
| Chinese | 4 (21.1) | 4 (28.6) | 8 (24.2) |
| Korean | 15 (78.9) | 10 (71.4) | 25 (75.8) |
| Median (range) weight, kg | 67.4 (42.5–86.4) | 59.0 (42.4–79.9) | 64.2 (42.4–86.4) |
| ECOG PS | | | |
| 0 | 5 (26.3) | 6 (42.9) | 11 (33.3) |
| 1 | 14 (73.7) | 8 (57.1) | 22 (66.7) |
| Disease stage at study entry | | | |
| Stage IV | 19 (100) | 14 (100) | 33 (100) |
| Median (range) time from initial diagnosis to study entry, months | 1.2 (0.2–25.3) | 0.9 (0.2–35.6) | 1.0 (0.2–35.6) |
| Location of primary tumor | | | |
| Stomach | 15 (78.9) | 13 (92.9) | 28 (84.8) |
| Gastroesophageal junction | 4 (21.1) | 1 (7.1) | 5 (15.2) |
| Metastatic sites[b] | | | |
| Lymph nodes | 12 (63.2) | 12 (85.7) | 24 (72.7) |
| Liver | 11 (57.9) | 7 (50.0) | 18 (54.5) |
| Peritoneum | 7 (36.8) | 5 (35.7) | 12 (36.4) |
| Lung | 4 (21.1) | 4 (28.6) | 8 (24.2) |
| Bone | 2 (10.5) | 1 (7.1) | 3 (9.1) |
| Other | 6 (31.6) | 1 (7.1) | 7 (21.2) |
| Number of metastatic sites | | | |
| 1 | 4 (21.1) | 3 (21.4) | 7 (21.2) |
| 2 | 9 (47.4) | 7 (50.0) | 16 (48.5) |
| ≥3 | 6 (31.6) | 4 (28.6) | 10 (30.3) |
| HER2 status (by local laboratory) | | | |
| IHC 3+ | 16 (84.2) | 9 (64.3) | 25 (75.8) |
| IHC 2+/ISH+[c] | 3 (15.8) | 5 (35.7) | 8 (24.2) |
| HER2 status (by central laboratory) | | | |
| IHC 3+ | 15 (78.9) | 9 (64.3) | 24 (72.7) |
| IHC 2+/ISH+[c] | 1 (5.3) | 2 (14.3) | 3 (9.1) |
| Negative | 3 (15.8) | 3 (21.4) | 6 (18.2) |
| Lauren classification | | | |
| Diffuse type | 4 (21.1) | 4 (28.6) | 8 (24.2) |
| Intestinal type | 4 (21.1) | 1 (7.1) | 5 (15.2) |
| Mixed type | 1 (5.3) | 1 (7.1) | 2 (6.1) |
| Unknown | 10 (52.6) | 8 (57.1) | 18 (54.5) |
| PD-L1 score[d] | | | |
| ≥5% | 12 (63.2) | 6 (42.9) | 18 (54.5) |
| <5% | 7 (36.8) | 7 (50.0) | 14 (42.4) |
| ≥1% | 14 (73.7) | 10 (71.4) | 24 (72.7) |
| <1% | 5 (26.3) | 3 (21.4) | 8 (24.2) |
| Not available | 0 | 1 (7.1) | 1 (3.0) |
| Treatment setting of prior systemic therapies | | | |
| Neoadjuvant | 0 | 0 | 0 |
| Adjuvant | 4 (21.1) | 0 | 4 (12.1) |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Data cutoff: December 7, 2023. Data are presented as *n* (%) unless otherwise indicated.

[a]One patient received the mRNA COVID-19 vaccine during treatment, which would have had minimal or no impact on the results.

[b]A patient could have multiple metastatic sites.

[c]IHC 2+/ISH+ referred to patients with IHC 2+ and ISH+.

[d]PD-L1 score was defined as VENTANA PD-L1 (SP263) tumor area positivity score. The tumor area positivity score was defined as the percentage of the tumor area (tumor and any desmoplastic stroma) covered by tumor cells with PD-L1 membrane staining at any intensity and tumor-associated immune cells with PD-L1 staining at any intensity, as visually estimated.

**Table 2.** Antitumor activity.

| | Cohort A (*n* = 19) | Cohort B (*n* = 14) | All patients (*N* = 33) |
|---|---|---|---|
| cORR (95% CI) | 15 (78.9) [54.4–93.9] | 10 (71.4) [41.9–91.6] | 25 (75.8) [57.7–88.9] |
| Best overall response[a] | | | |
| CR | 1 (5.3) | 0 | 1 (3.0) |
| PR | 14 (73.7) | 10 (71.4) | 24 (72.7) |
| Stable disease | 4 (21.1) | 4 (28.6) | 8 (24.2) |
| Progressive disease | 0 | 0 | 0 |
| DCR[b] (95% CI) | 19 (100) [82.4–100] | 14 (100) [76.8–100] | 33 (100) [89.4–100] |

Data cutoff: December 7, 2023. Efficacy-evaluable analysis set. Data are presented as *n* (%) unless otherwise indicated. Using the Clopper–Pearson method, 95% CI was estimated.
[a]CR and PR were confirmed per RECIST v1.1.
[b]DCR was defined as the proportion of patients with best overall response of CR, PR, and stable disease by investigator per RECIST v1.1.

46.7%]. The median DoR was also similar after excluding six patients with discordant HER2 positivity (Supplementary Fig. S2C). Tumor responses were observed regardless of PD-L1 expression (PD-L1 score cutoff of 1% or 5%; Supplementary Table S4).

### Safety and tolerability

All treated patients were included in the safety analysis. All patients experienced ≥1 treatment-emergent AE (TEAE); most patients ($n = 26$; 78.8%) experienced grade ≥3 TEAEs. The most common TEAEs were diarrhea and nausea, which occurred in 100% and 66.7% of patients, respectively. All patients experienced ≥1 treatment-related AE (TRAE; **Table 3**). Overall, 32 patients (97%) and 28 patients (84.8%) had TRAEs considered related to zanidatamab and tislelizumab, respectively. The most common TRAEs, reported in ≥10% of all patients, are presented in **Table 3**. TRAEs of grade ≥3 were reported in 22 (66.7%) patients; grade ≥3 TRAEs considered related to zanidatamab and tislelizumab occurred in 17 patients (51.5%) and 19 patients (57.6%), respectively. Diarrhea was the most common grade ≥3 TRAE, occurring in 27.3% of patients (**Table 3**); no grade 4 or 5 treatment-related diarrhea was reported. Treatment-related grade 3 diarrhea occurred in six of 24 patients who received antidiarrheal prophylaxis, compared with three of nine patients without prophylaxis. Treatment-related diarrhea led to treatment modification for 14 patients (42.4%); however, no patients discontinued zanidatamab because of diarrhea.

SAEs were reported in 17 patients (51.5%); treatment-related SAEs were reported in 11 patients (33.3%), including zanidatamab-related SAEs in eight patients (24.2%) and tislelizumab-related SAEs in seven patients (21.2%). TEAEs leading to death were reported in four patients [12.1%; peritonitis ($n = 1$), pneumonia and pneumonitis ($n = 1$), sudden death ($n = 1$), and COVID-19 ($n = 1$)]; among these, fatal TRAEs were reported in two patients (6.1%). One patient had both pneumonitis and pneumonia (pneumonitis was considered related to zanidatamab, tislelizumab, and oxaliplatin; pneumonia was considered related to zanidatamab, tislelizumab, oxaliplatin, and capecitabine). The other patient had sudden death related to capecitabine.

TRAEs leading to treatment discontinuation were reported in eight patients (24.2%), including three patients (9.1%) each considered related to zanidatamab or tislelizumab. Zanidatamab-related and tislelizumab-related AEs leading to treatment modification were reported in 26 patients (78.8%) and 16 patients (48.5%), respectively.

AESIs of zanidatamab are presented in Supplementary Table S5. Three (9.1%) patients had confirmed grade ≥3 cardiac events, of whom two patients (6.1%) had reported AEs (ejection fraction decreased). One patient had LVEF decrease based on ECHO/MUGA without a reported AE as the investigator determined that it was nonclinically significant. No confirmed grade 4 to 5 cardiac events were reported. No grade ≥3 IRRs were reported. Noninfectious pulmonary toxicities were reported for two patients (6.1%), one of whom experienced a fatal event.

AESIs of tislelizumab are presented in Supplementary Tables S6 and S7. ImAEs related to tislelizumab were reported in 11 patients (33.3%). Tislelizumab-related imAEs of grade ≥3 were reported in four patients (12.1%). Tislelizumab-related IRRs were reported in two patients (6.1%). No grade ≥3 tislelizumab-related IRRs were reported.

### PK parameters and immunogenicity

After first dose (cycle 1), the geometric mean of $AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$, and $C_{max}$ was comparable between cohorts A and B (106.9 vs. 105.7, 94.3 vs. 88.7 hours*mg/mL, and 0.586 mg/mL vs. 0.589 mg/mL, respectively). $T_{max}$ and $t_{1/2}$ were also in the same magnitude between two cohorts (**Table 4**). This comparability was also observed after the second dose of zanidatamab (cycle 2), for which $AUC_{0\text{-t}}$ and $C_{max}$ were 97.7 hours*mg/mL and 0.574 mg/mL in cohort A and 102.1 hours*mg/mL and 0.590 mg/mL in cohort B, respectively (**Table 4**). The results demonstrated that the drug exposure had no difference in patients with gastric cancer/GEJC in both cycle 1 and cycle 2 with either body weight–based dosing or flat dosing regimens. The geometric mean for $C_{trough}$ accumulation ratio (C9/C1) was approximately from 1.9 to 2.1 among cohorts (Supplementary Table S8), suggesting that the current drug dose interval (21 days) is within the range of the effective $t_{1/2}$ of zanidatamab (19.5–22.5 days). Only sparse PK were collected for tislelizumab, and drug exposure was in the same range of previous tislelizumab-related studies.

The overall incidence of antidrug antibodies (ADA; treatment-emergent ADA) in zanidatamab was 6.3% (two of 32 patients, one for each cohort). In addition, although 12.5% (four of 32 patients) tested positive for neutralizing antibodies in total, this relatively high positive rate of neutralizing antibodies may be induced by the interference of soluble HER2 due to the low tolerance of the assay as most of the samples were cycle 1 day 1 predose samples (Supplementary Table S9). In the interim, the overall incidence of ADAs in tislelizumab (treatment-emergent ADA) was 43.8% (14 of 32 patients); of these, 3.1% (one of 32 patients) had treatment-boosted ADA response and 40.6% (13 of 32 patients) had treatment-induced

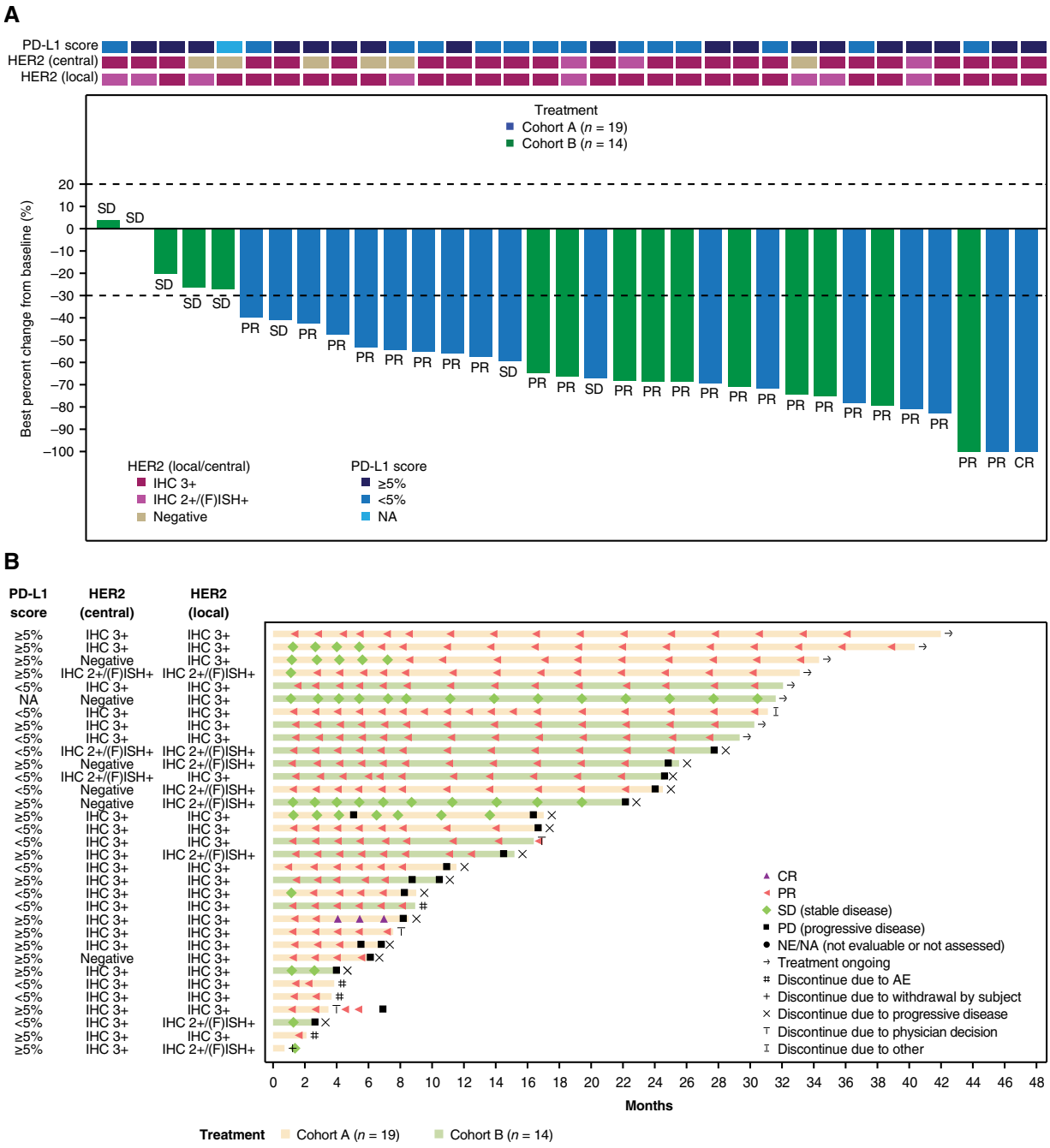


**Figure 1.**
Data cutoff: December 7, 2023. Efficacy-evaluable analysis set. **A,** Best percent change from baseline in target lesion sum of diameter. Best overall response per investigator assessment. **B,** Duration of treatment and best overall response. (F)ISH, (fluorescence) *in situ* hybridization; NA, not applicable; NE, not estimable.

ADA response. In addition, no patients were positive for neutralizing antibodies.

## Discussion

In this phase Ib/II, open-label trial, zanidatamab in combination with tislelizumab and CAPOX demonstrated a clinically meaningful antitumor activity in patients with HER2+ gastric cancer/GEJC. At a median study follow-up of 30.1 months, the cORR was 75.8%, with a median DoR of 23.3 months, demonstrating durable disease response to study treatment. No clinically meaningful difference in efficacy was observed in PD-L1 subgroups with cutoffs of 1% or 5%. Patients obtained long-term survival benefit from study treatment, with a median OS of 32.4 months and a 24-month survival rate of

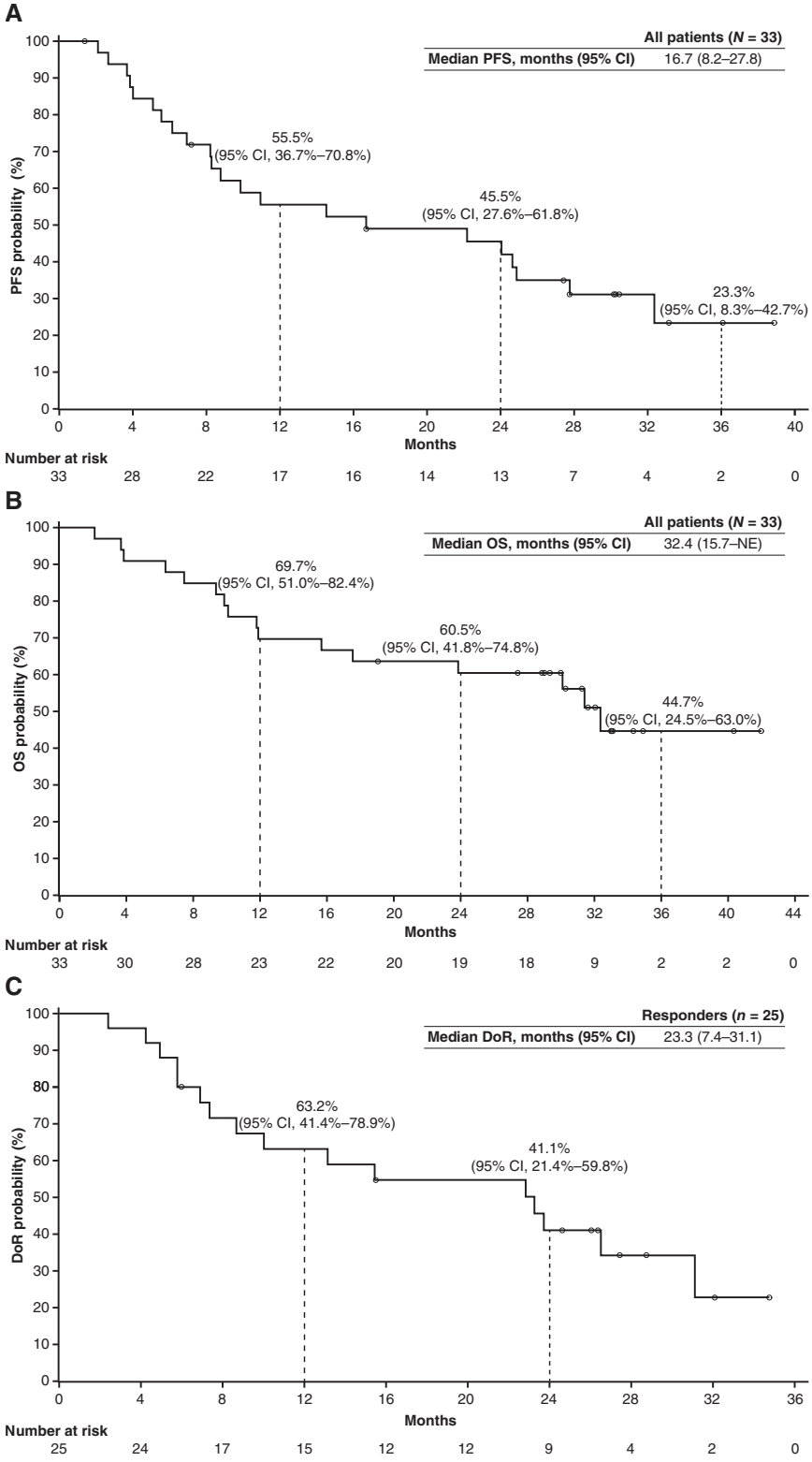


**Figure 2.**

PFS (**A**), OS (**B**), and DoR (**C**). Data cutoff: December 7, 2023. Efficacy-evaluable analysis set (**A**) and (**C**) and safety analysis set (**B**). PFS, OS, and DoR per investigator assessment. The median values were estimated by the Kaplan–Meier method with 95% CI estimated using the Brookmeyer–Crowley method with log–log transformation. Landmark rates were estimated using the Kaplan–Meier method with 95% CI estimated using the Greenwood formula. NE, not estimable.

60.5%. This study included a small number of patients and is not designed for a statistical comparison of antitumor activity compared with standard of care; however, we observed a promising antitumor activity for zanidatamab in combination with tislelizumab and chemotherapy, appearing to be similar or numerically better than pembrolizumab plus trastuzumab in combination with

**Table 3.** TRAEs[a].

| | Cohort A (*n* = 19) | | Cohort B (*n* = 14) | | All patients (*N* = 33) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Patients with ≥1 TRAE | 19 (100) | 13 (68.4) | 14 (100) | 9 (64.3) | 33 (100) | 22 (66.7) |
| TRAE related to zanidatamab | 18 (94.7) | 11 (57.9) | 14 (100) | 6 (42.9) | 32 (97.0) | 17 (51.5) |
| TRAE related to tislelizumab | 15 (78.9) | 10 (52.6) | 13 (92.9) | 9 (64.3) | 28 (84.8) | 19 (57.6) |
| TRAEs occurring in ≥10% of all treated patients | | | | | | |
| Diarrhea[b] | 19 (100) | 7 (36.8) | 14 (100) | 2 (14.3) | 33 (100) | 9 (27.3) |
| Nausea | 11 (57.9) | 1 (5.3) | 10 (71.4) | 0 | 21 (63.6) | 1 (3.0) |
| Decreased appetite | 10 (52.6) | 2 (10.5) | 6 (42.9) | 0 | 16 (48.5) | 2 (6.1) |
| Vomiting | 7 (36.8) | 0 | 6 (42.9) | 0 | 13 (39.4) | 0 |
| Peripheral sensory neuropathy | 8 (42.1) | 0 | 4 (28.6) | 0 | 12 (36.4) | 0 |
| Pyrexia | 8 (42.1) | 0 | 4 (28.6) | 0 | 12 (36.4) | 0 |
| Palmar-plantar erythrodysesthesia | 8 (42.1) | 1 (5.3) | 3 (21.4) | 0 | 11 (33.3) | 1 (3.0) |
| Hypokalemia | 6 (31.6) | 2 (10.5) | 3 (21.4) | 0 | 9 (27.3) | 2 (6.1) |
| Stomatitis | 6 (31.6) | 1 (5.3) | 2 (14.3) | 0 | 8 (24.2) | 1 (3.0) |
| Weight decreased | 4 (21.1) | 0 | 4 (28.6) | 0 | 8 (24.2) | 0 |
| Lipase increased | 4 (21.1) | 2 (10.5) | 3 (21.4) | 1 (7.1) | 7 (21.2) | 3 (9.1) |
| Fatigue | 4 (21.1) | 1 (5.3) | 3 (21.4) | 1 (7.1) | 7 (21.2) | 2 (6.1) |
| Pruritus | 4 (21.1) | 0 | 3 (21.4) | 0 | 7 (21.2) | 0 |
| Dry skin | 3 (15.8) | 0 | 3 (21.4) | 1 (7.1) | 6 (18.2) | 1 (3.0) |
| Rash | 0 | 0 | 6 (42.9) | 1 (7.1) | 6 (18.2) | 1 (3.0) |
| Chills | 4 (21.1) | 0 | 2 (14.3) | 0 | 6 (18.2) | 0 |
| Ejection fraction decreased | 2 (10.5) | 2 (10.5) | 3 (21.4) | 1 (7.1) | 5 (15.2) | 3 (9.1) |
| AST increase | 3 (15.8) | 1 (5.3) | 2 (14.3) | 0 | 5 (15.2) | 1 (3.0) |
| Amylase increased | 2 (10.5) | 0 | 3 (21.4) | 0 | 5 (15.2) | 0 |
| Peripheral edema | 2 (10.5) | 0 | 3 (21.4) | 0 | 5 (15.2) | 0 |
| Anemia | 2 (10.5) | 2 (10.5) | 2 (14.3) | 0 | 4 (12.1) | 2 (6.1) |
| Platelet count decreased | 1 (5.3) | 1 (5.3) | 3 (21.4) | 1 (7.1) | 4 (12.1) | 2 (6.1) |
| Abdominal pain | 2 (10.5) | 1 (5.3) | 2 (14.3) | 0 | 4 (12.1) | 1 (3.0) |
| ALT increase | 1 (5.3) | 0 | 3 (21.4) | 0 | 4 (12.1) | 0 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Data cutoff: December 7, 2023. Safety analysis set. Data are presented as *n* (%). AEs were graded for severity using NCI Common Terminology Criteria for Adverse Events v5.0 and coded to MedDRA v26.0 lowest level term, preferred term, and primary system organ class. Patients with more than one event for a given preferred term were counted only once at the maximum severity for the preferred term.

[a]Treatment-related is defined as related to any component of study treatment. TRAEs include events considered by the investigator to be related or with missing assessment of the causal relationship.

[b]Treatment-related grade ≥3 diarrhea occurred in six of 24 patients who received antidiarrheal prophylaxis compared with three of nine patients without antidiarrheal prophylaxis.

fluoropyrimidine and platinum-based chemotherapy, in patients with locally advanced or metastatic HER2+ gastric cancer/GEJC, in both the intent-to-treat population and PD-L1–positive subgroup of the KEYNOTE-811 study (20).

Zanidatamab in combination with tislelizumab and CAPOX exhibited a manageable and tolerable safety profile. The median RDIs were ≥95% for both body weight–based dosing and flat dosing of zanidatamab, indicating tolerability of the combination. The incidence of TRAEs in both body weight–based dosing and flat dosing cohorts of zanidatamab in this study was generally comparable. The safety profile was consistent with the known risks of each study treatment component (21, 28). No new safety signals were observed with the combination, and most AEs reported were of mild-to-moderate severity.

In this study, diarrhea tended to be more frequent and more severe than that reported in KEYNOTE-811 (20). Here, diarrhea was reported in all patients and was the most common all grade and grade ≥3 TRAE. However, most cases of diarrhea were grade 1 or 2 and were managed with dose modification without discontinuation of zanidatamab. Notably, the incidence of treatment-related grade 3 diarrhea was numerically lower in patients who received mandated antidiarrheal prophylaxis.

Among zanidatamab-related AESI, four patients had confirmed cardiac events, including three cases of grade 3 severity; these events were managed with dose delay. Among tislelizumab-related AESI, imAEs of grade ≥3 were reported in four patients and were managed using systemic corticosteroids or hormone replacement therapy. Two patients experienced TRAEs leading to death as assessed by the investigator, including one patient with pneumonitis and pneumonia and a second patient with sudden death.

The zanidatamab PK characterization was comparable without drug exposure difference between body weight–based dosing (cohort A) and flat dosing regimens (cohort B). Because of the assay capacity limitation, a relatively high positive rate of neutralizing antibodies (most of the samples were cycle 1 day 1 predose samples) was observed, which may be induced by the interference of soluble HER2 due to the low tolerance of the assay. The second generation of ADA assay has been developed and

**Table 4.** Zanidatamab PK parameters.

| Parameter (units) | Cohort A | Cohort B |
|---|---|---|
| Cycle 1 | | |
| *n* | 6 | 6 |
| $AUC_{0\text{-}t}$ (hours*mg/mL) | 94.3 | 88.7 |
| *n* | 7 | 6 |
| $AUC_{0\text{-}tau}$ (hours*mg/mL) | 89.1 | 88.1 |
| *n* | 7 | 5 |
| $AUC_{0\text{-}inf}$ (hours*mg/mL) | 106.9 | 105.7 |
| *n* | 7 | 6 |
| $C_{max}$ (mg/mL) | 0.586 | 0.589 |
| *n* | 7 | 6 |
| $T_{max}$ (hours) | 4.46 | 4.30 |
| *n* | 7 | 6 |
| $t_{1/2}$ (hours) | 194.12 | 240.15 |
| *n* | 7 | 6 |
| $V_z$ (mL) | 4,711.22 | 5,768.39 |
| | 7 | 6 |
| CL (mL/hour) | 16.82 | 16.65 |
| Cycle 2 | | |
| *n* | 5 | 5 |
| $AUC_{0\text{-}t}$ (hours*mg/mL) | 97.7 | 102.1 |
| *n* | 6 | 6 |
| $C_{max}$ (mg/mL) | 0.574 | 0.590 |
| *n* | 6 | 6 |
| $T_{max}$ (hours) | 2.42 | 2.76 |

Data cutoff: October 31, 2023. Efficacy-evaluable analysis set. Data are presented as the geometric mean, which was calculated as the exponential of the arithmetic mean for concentrations of study drug in the logarithmic scale. $AUC_{0\text{-}t}$ (hours*mg/mL), AUC from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation; $AUC_{0\text{-}tau}$, AUC during the dosing interval; $AUC_{0\text{-}inf}$, AUC from time zero to infinity; CL (mL/hour), apparent clearance; $C_{max}$ (mg/mL), observed maximum plasma concentration during a sample interval; $T_{max}$ (hours), observed time to maximum plasma concentration during a sampling interval; $t_{½}$ (hours), terminal elimination half-life, determined from the quotient 0.693/λz; $V_z$ (mL), apparent volume of distribution.

applied in ongoing zanidatamab clinical studies. The ADA effects in zanidatamab PK will be further evaluated by combining multiple clinical trial studies in the future. There was no significant difference in tislelizumab PK and ADA results compared with previous related tislelizumab studies.

This study has several limitations. This single-arm, nonrandomized trial was not designed to analyze the contribution of each treatment component and was conducted without prospective PD-L1 testing; therefore, the magnitude of contribution of tislelizumab and zanidatamab and correlation between PD-L1 expression and clinical outcomes of patients with HER2+ gastric cancer/GEJC cannot be quantified directly. Furthermore, studies have shown that HER2-targeted treatment, such as trastuzumab, can downregulate HER2 expression and upregulate PD-L1 (36). We did not evaluate whether there were changes in HER2 and PD-L1 expression in each individual patient during the study treatment. The contribution of treatment components and HER2/PD-L1 expression in patients can be further evaluated in future randomized controlled studies. Efficacy endpoints were assessed by investigators without central review of imaging, which may have introduced bias in efficacy assessments. Additionally, as this trial only enrolled patients from China and Korea, potential geographic differences compared with patients from other global regions in clinical presentation of disease should be considered (16). Finally, although not a limitation, most patients in the current study were male and had gastric cancer. Given that gastric cancer prognosis by sex remains controversial, with some reporting worse prognosis in males but others reporting no significant sex differences, this requires further investigation in future studies (37, 38).

Notably, HER2 status by central laboratory testing was not required for study entry. In this study, HER2 status of six patients was negative by central lab testing but positive in local lab tests (**Table 1**). Nevertheless, all six patients had best overall response of PR or SD with shrinkage of target lesions (**Fig. 1A**). Discordance in HER2 positivity between central and local laboratories, especially in patients with HER2 IHC 2+ tumors, is an issue in solid tumors (11, 39, 40). This discordance could have a variety of causes, including heterogeneity between tissue specimens from the same patient, evolution of the tumor over time in the case of specimens taken at multiple timepoints, differences between primary and metastatic tumors, or interlaboratory variation (11, 39, 40).

In summary, the combination of zanidatamab with tislelizumab and chemotherapy had a manageable safety profile with clinically meaningful and durable responses as the first-line treatment for patients with HER2+ gastric cancer/GEJC. PK profiles of zanidatamab were also similar between the flat dosing and the weight-based dosing regimens. These support the ongoing phase III HERIZON-GEA-01 trial (NCT05152147), evaluating the combination of zanidatamab (using the flat dosing tested in cohort B of this study) and chemotherapy, with or without tislelizumab, as first-line treatment for patients with advanced HER2+ gastroesophageal adenocarcinoma.

## Data Availability

On request, and subject to certain criteria, conditions, and exceptions, BeOne Medicines, Ltd. will provide access to individual deidentified participant data from BeOne Medicines–sponsored studies that meet the applicable criteria. The study presented in this article meets the criteria for an applicable BeOne Medicines–sponsored study. BeOne Medicines shares data only when permitted by applicable data privacy and security laws and regulations, and when it is feasible to do so without compromising the privacy of the study participants, and other considerations. Data requests may be submitted to ClinicalTrials@beonemed.com.

## Authors' Disclosures

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## Authors' Contributions

**K.-W. Lee:** Study conceptualization; acquisition and interpretation of data, writing–review and editing. **L.-Y. Bai:** Acquisition and interpretation of data. **M. Jung:** Conceptualization, study conceptualization; acquisition and interpretation of data. **J. Ying:** Acquisition and interpretation of data. **Y.-H. Im:** Acquisition and interpretation of data. **D.-Y. Oh:** Conceptualization, writing–review and editing, study conceptualization; acquisition and interpretation of data. **J.Y. Cho:** Acquisition and interpretation of data. **S.C. Oh:** Acquisition and interpretation of data. **Y. Chao:** Acquisition and interpretation of data. **J.W. Kim:** Acquisition and interpretation of data. **Y. Chen:** Conceptualization, writing–review and editing, study conceptualization; analysis; and interpretation of data. **V. Li:** Conceptualization, writing–review and editing, study conceptualization; analysis; and interpretation of data. **S. Chen:** Conceptualization, writing–review and editing, study conceptualization; analysis; and interpretation of data. **Y.-K. Kang:** Acquisition and interpretation of data.

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## Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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