Phases (2) Phase 2 and (3) Phase 3 of Zanidatamab plus chemotherapy in first-line HER2-expressing Gastroesophageal Adenocarcinoma (GEA)

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Results

Table 1: Unique Binding Properties of Zanidatamab

![Table 1: Unique Binding Properties of Zanidatamab](image)

Table 2: Zanidatamab and/or Chemotherapy TRAEs

![Table 2: Zanidatamab and/or Chemotherapy TRAEs](image)

Conclusions

- In subjects with HER2+ positive GEA, zanidatamab combined with standard first-line chemotherapy demonstrated encouraging antitumor activity. The incidence of grade 3/4 TRAEs other than diarrhea was similar across regimens.
- Zanidatamab + CAPOX demonstrated grade 3/4 diarrhea, mainly in the first cycle. In addition, 31.3% of patients had grade 3 acute kidney injury, 20.5% of patients had grade 3 peripheral edema, and 11.6% of patients had grade 3 cardiac events. All patients with grade 3 acute kidney injury and 5 patients with grade 3 peripheral edema recovered.
- The overall incidence of grade 3/4 TRAEs other than diarrhea was lower in the zanidatamab and chemotherapy arms compared to the chemotherapy arms alone.

References


Acknowledgments

- The authors thank all the investigators, clinical trial researchers, clinical trial site personnel, and staff who contributed to the trial.

Figure 1: Unique Binding Properties of Zanidatamab

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Figure 2: ZWI-ZW52-201 Study Design for Subjects with HER2-expressing GEA

![Figure 2: ZWI-ZW52-201 Study Design for Subjects with HER2-expressing GEA](image)

Figure 3: Change in Target Lesion Size

![Figure 3: Change in Target Lesion Size](image)

Figure 4: Safety

![Figure 4: Safety](image)

Figure 5: Progression-Free Survival

![Figure 5: Progression-Free Survival](image)

Figures:

- Figure 1: Unique Binding Properties of Zanidatamab
- Figure 2: ZWI-ZW52-201 Study Design for Subjects with HER2-expressing GEA
- Figure 3: Change in Target Lesion Size
- Figure 4: Safety
- Figure 5: Progression-Free Survival

**Background**

- Zanidatamab (ZW25) is a humanized, trispecific, immunoglobulin G1 kappa IgG1κ trimer antibody directed against the extracellular domain (ECD4) and the dimerization domain (D6) of HER2 to demonstrate encouraging antitumor activity.
- Zanidatamab has a unique binding profile as it targets a portion of HER2 that is not accessible in other HER2-targeted agents.
- In Phase 1b/2 study (NCT04276493) evaluating zanidatamab + chemotherapy, the incidence of grade 3 diarrhea was 6%.
- In a randomized, global phase 3 study (HERIZON OA Study), zanidatamab demonstrated a confirmed objective response rate of 13% and a median duration of response of 6.0 months.

**Methods**

- Study design: ZWI-ZW52-201 (NCT03929666) was an open-label, multicenter, global, phase 2, open-label study to evaluate the safety, tolerability, and antitumor activity of zanidatamab with escalating-dose chemotherapy regimens. Subjects were randomly assigned to one of two dose-escalation arms: (1) Zanidatamab + mFOLFOX6 or (2) Zanidatamab + CAPOX. The primary endpoint was safety and tolerability. The secondary endpoints included antitumor activity, progression-free survival (PFS), and overall survival (OS).

**Key Eligibility Criteria**

- Patients with locally advanced, unresectable, or metastatic HER2+ positive GEA with measurable disease
- ECOG performance status 0-1
- At least 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Adequate bone marrow, renal, and hepatic function
- Life expectancy of at least 12 weeks

**Results**

- Of 94 subjects with HER2+ GEA, 93 (98.9%) continued on study treatment.
- 12 (13%) subjects had disease progression, 4 (4%) due to disease-related death, and 4 (4%) due to physician decision.
- The most frequent treatment-related adverse events (TRAEs) were grade 3 diarrhea (13 subjects), and grade 3 acute kidney injury (7 subjects). Other grade 3 TRAEs included grade 3 peripheral edema (3 subjects) and grade 3 cardiac events (3 subjects).
- Of 36 subjects with GEA enrolled, 19 (53%) achieved confirmed objective response (cORR) and a median duration of response (DOR) of 6.0 months.
- The most frequent grade 3 TRAEs included grade 3 diarrhea in 1 (3%) subject, grade 3 peripheral edema in 1 (3%) subject, grade 3 cardiac events in 1 (3%) subject, and grade 3 acute kidney injury in 1 (3%) subject.
- The most frequent grade 2 TRAEs were grade 2 peripheral edema (5 subjects) and grade 2 cardiac events (5 subjects).
- The incidence of grade 3 TRAEs was lower in subjects treated with zanidatamab and chemotherapy compared to those treated with chemotherapy alone.
- At the time of data extraction, 8 (13%) of 61 subjects were in response.

**Table 1: Characteristics and Baseline Comparisons**

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Age (years)</td>
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<td></td>
</tr>
<tr>
<td>Median</td>
<td>67 (27-125)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>32 (99)</td>
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<tr>
<td>White</td>
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<td>25 (86)</td>
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<td>23 (94)</td>
</tr>
<tr>
<td>Primary tumor location</td>
<td>Esophageal</td>
<td>14 (54)</td>
</tr>
<tr>
<td>Stage</td>
<td>I</td>
<td>20 (71)</td>
</tr>
<tr>
<td>Stage IV disease at diagnosis</td>
<td>c</td>
<td>29 (100)</td>
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**Table 2: Zanidatamab and/or Chemotherapy TRAEs**

<table>
<thead>
<tr>
<th>TRAE</th>
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<tr>
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<td>32 (99)</td>
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<tr>
<td>逶疹(grade 4)</td>
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<td>26 (93)</td>
</tr>
<tr>
<td>逶疹(grade 5)</td>
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<td>3 (10)</td>
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<tr>
<td>逶疹(grade 5+ AS)</td>
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<tr>
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<td>0 (0)</td>
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</tbody>
</table>

**Safety**

**Dose Confirmation and Dose Escaping Toxicities (DETs) – Part 1**

- Zanidatamab + CAPOX: No DLTs in 20 subjects. Dosing of zanidatamab + CAPOX was confirmed for Part 2.
- Zanidatamab + mFOLFOX6 in the first cohort, grade 3 or 4 in 20 subjects. PP continued to enrol until DLT.
- Zanidatamab + mFOLFOX6: 2 DLTs (diarrhea, grade 3) in 13 subjects, and 8/13 (62%) with grade 3 diarrhea; 2/13 (15%) with grade 3 acute kidney injury; 1/13 (8%) with grade 3 peripheral edema; and 1/13 (8%) with grade 3 cardiac event.

**Efficacy**

- Baseline characteristics: Efficacy was evaluable in 28 (100%) subjects with measurable disease.

**Table 3: Response Rates and DOR**

<table>
<thead>
<tr>
<th>Response Type</th>
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<td>PR</td>
<td>Zanidatamab + CAPOX</td>
<td>3 (14)</td>
</tr>
<tr>
<td>PR</td>
<td>Zanidatamab + mFOLFOX6</td>
<td>3 (14)</td>
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<tr>
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<td>Zanidatamab + CAPOX</td>
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<td>PR</td>
<td>Zanidatamab + mFOLFOX6</td>
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**Conclusions**

- In subjects with HER2+ positive GEA, zanidatamab combined with standard first-line chemotherapy demonstrated encouraging antitumor activity, without an increase in the incidence of grade 3 or 4 TRAEs compared to standard chemotherapy alone.
- Zanidatamab + CAPOX demonstrated grade 3 diarrhea more frequently compared to CAPOX alone; however, the incidence of grade 3 diarrhea was lower than in previous studies evaluating CAPOX alone.
- The incidence of grade 3 TRAEs was lower in subjects treated with zanidatamab and chemotherapy compared to those treated with chemotherapy alone.

**References**