Zanidatamab (ZW25), a HER2-targeted Bispecific Antibody, in Combination with Chemotherapy (chemo) for HER2-positive Breast Cancer (BC): Results from a Phase 1 Trial

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**METHODS**

**Trial Design**

- In Part 3 of this ongoing phase 1 trial (NCT04016780), we evaluated the safety and antitumor activity of zanidatamab in combination with chemotherapy in patients with HER2-positive metastatic BC (metastasis BC data from Parts 1 and 2 previously reported)6.
- Zanidatamab dosing was based on subject weight.
- To prevent or minimize infusion-related reactions, all subjects received prophylactic treatment with dexamethasone, diphenhydramine, and corticosteroids prior to administration of zanidatamab.

**Protocol Design**

- Zanidatamab, 20 mg/kg IV Q2W, was administered in combination withdocetaxel, capecitabine, or vinorelbine.
- Zanidatamab started the first day of chemotherapy.
- Zanidatamab was continued until disease progression.

**Primary Endpoint**

- Overall response rate (ORR) per RECIST v1.1.

**Secondary Endpoints**

- PFS probability.
- Safety.
- Clinical benefit rate (CBR).

**Study Population**

- Metastatic breast cancer patients with HER2-positive disease confirmed by centrally reviewed immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH).
- ECOG PS 0-1.
- No prior treatment with anti-HER2 monoclonal antibodies or HER2-directed bispecific antibodies.

**Treatment Regimens**

- ZW25-101: Zanidatamab 20 mg/kg IV Q2W, and docetaxel 75 mg/m² IV over 30 min on day 1 of every 21-day cycle.
- ZW25-102: Zanidatamab 20 mg/kg IV Q2W, and capecitabine 825 mg/m² twice daily on days 1-14 of every 21-day cycle.
- ZW25-103: Zanidatamab 20 mg/kg IV Q2W, and vinorelbine 25 mg/m² IV on days 1 and 15 of every 21-day cycle.

**Analysis Population**

- Safety analysis included all enrolled patients.
- Efficacy analysis included patients with evaluable target lesions.

**RESULTS**

**Safety**

- Adverse events of grade 3/4 were most frequently observed in the Zani + Vino arm.
- No infusion-related reactions or Grade 3/4 non-hematologic adverse events were observed.
- No treatment-related deaths occurred.

**Efficacy**

- Among the first 6 subjects dosed in the vinorelbine (25 mg/m²) cohort, 3 subjects had chemotherapy dose reductions due to grade 3-4 neutropenia count decreased in Cycle 1.
- Median follow-up time was 7.1 months.

**Table 1: Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Subjects</th>
<th>Median age, year (range)</th>
<th>Female sex, n (%)</th>
<th>Asian, n (%)</th>
<th>White, n (%)</th>
<th>ECOG PS 0-1, n (%)</th>
<th>White race, n (%)</th>
<th>Black race, n (%)</th>
<th>Hispanic race, n (%)</th>
<th>Other race, n (%)</th>
<th>Metastatic breast cancer, n (%)</th>
<th>Prior history of brain metastases, n (%)</th>
<th>Prior HER2-directed therapies, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zani + Vino</td>
<td>12</td>
<td>61 (39, 79)</td>
<td>8 (67)</td>
<td>7 (59)</td>
<td>5 (42)</td>
<td>10 (83)</td>
<td>7 (58)</td>
<td>2 (17)</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>5 (42)</td>
<td>3 (25)</td>
<td>5 (42)</td>
</tr>
</tbody>
</table>

**Table 3: Response Rates and DOR**

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>ORR (95% CI)</th>
<th>DOR (95% CI)</th>
<th>TTR (95% CI)</th>
<th>% PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zani + Vino</td>
<td>48.2, 97.7</td>
<td>NE</td>
<td>12.2, 24</td>
<td>48.2, 97.7</td>
</tr>
<tr>
<td>Zani + Doc</td>
<td>59.0, 100</td>
<td>59.0, 100</td>
<td>7.3, 30</td>
<td>59.0, 100</td>
</tr>
<tr>
<td>Zani + Cap</td>
<td>48.2, 97.7</td>
<td>NE</td>
<td>12.2, 24</td>
<td>48.2, 97.7</td>
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**CONCLUSIONS**

- Zanidatamab in combination with chemotherapy demonstrates encouraging antitumor activity in heavily pretreated subjects with HER2-positive BC.
- 34% confirmed objective response rate (ORR) and a median progression-free survival (PFS) of 5.9 months for the zanidatamab plus docetaxel cohort compared to historical data.
- Of responses are ongoing with response duration of 1.8 to 22.3+ months.
- Further clinical development with single-agent chemotherapy is well warranted.
- Ongoing evaluation of zanidatamab in a phase 3 trial of prior therapy.

**Acknowledgments**

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**Figure 5: Progression-Free Survival in All Subjects**

**Figure 3: Best Reduction in Target Lesions**

**Figure 2: ZW25-101 Trial Design for Patients with HER2-positive BC in Part 3**

**Figure 1: Unique Binding Properties of Zanidatamab**

- Receptor clustering, internalization, and degradation
- Inhibition of growth factor-dependent and independent tumor cell proliferation
- Antibody-dependent cellular cytotoxicity and phagocytosis, and complement dependent cytotoxicity
- In ongoing phase 1 and 2 trials, zanidatamab monotherapy has been well tolerated with durable responses in subjects with heavily pretreated metastatic HER2-positive BC and HER2-expressing cancers, including gastrointestinal adenocarcinomas and fallopian tract cancer.

**Table 2: Zanidatamab and/or Chemotherapy TREATMENT**

<table>
<thead>
<tr>
<th>Treatment Combination</th>
<th>Dose (mg/m²)</th>
<th>% Grade 1/2</th>
<th>% Grade 3/4</th>
<th>Cancer type</th>
<th>Metastasis status</th>
<th>Prior treatments (HER2-targeted)</th>
<th>Prior treatments (non-HER2)</th>
<th>Dose modifications</th>
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<tr>
<td>Zani + Vino</td>
<td>75</td>
<td>100</td>
<td>0</td>
<td>Breast</td>
<td>Yes</td>
<td>4 (21)</td>
<td>10 (45)</td>
<td>0</td>
</tr>
<tr>
<td>Zani + Doc</td>
<td>75-30</td>
<td>100</td>
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<td>10 (45)</td>
<td>0</td>
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**Figure 4: Safety**

- Safety was formally assessed by the Safety Monitoring Committee (SMC) after the first 6 subjects were enrolled to each cohort.
- Among the first 6 subjects showed in the zanidatamab (25 mg/m² weekly) cohort, 3 subjects had chemotherapy dose reductions due to grade 3-4 neutropenia count decreased in Cycle 1.
- 2 events of serious AEs, none related to treatment:
  - 1 subject experienced upper respiratory infection and pneumonia, and 1 subject experienced pleural effusion.

**Table 3: Response Rates and DOR**

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**ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; CBR = clinical benefit rate; CR = complete response; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; N = neratinib; L = lapatinib; DM1 = trastuzumab emtansine (T-DM1); C = tucatinib; T = trastuzumab; P = paclitaxel; M = monotherapy |