Zanidatamab (ZW25) in HER2-positive Biliary Tract Cancer (BTC): Results From a Phase 1 Study

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Background
- Bilary tract cancers (BTC), including cholangiocarcinoma (CC) and gallbladder cancer, are aggressive, rare tumors.
- Patients with unexcetable, locally advanced or metastatic BTCs have a poor prognosis and treatment options are limited after first line treatment.
- Second line chemotherapy yields objective response rates (ORR) of < 10% and the median survival of these patients is 6 months.
- Approximately 19% of gallbladder cancers, 17% of extrahepatic CC and 5% of intrahepatic CC express human epidermal growth factor receptor 2 (HER2).
- Zanidatamab (ZW25) is a novel HER2-targeted, bispecific antibody that simultaneously binds two distinct sites on HER2: the ECD4 (same target as that of trastuzumab) and the ECD2 (same target as that of pertuzumab).
- Unique binding of zanidatamab to HER2 results in multiple mechanism of action, including: improved binding, clustering, and receptor internalization and downregulation, inhibition of fädependent and independent proliferation, and potent activation of antibody-dependent cellular cytotoxicity.

Methods
- ZW25-102 (NCT03891223) is a first-in-human, 3-part, Phase 1 study (Figure 1) that evaluates zanidatamab in HER2 expressing cancers, including BTCs.
- Determine maximum tolerated dose (MTD) and recommended dose (RD) of zanidatamab.
- Characterize safety and tolerability of zanidatamab.
- Evaluate potential anti-tumor effects of zanidatamab.

Key Eligibility Criteria
- Advanced HER2 expressing cancer progressing after standard of care therapy
- BTC patients were required to be HER2 immunohistochemistry (IHC) 3+ or IHC2+/fluorescence in situ hybridization (FISH)+ per central assessment.
- Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in Part 1 and 1.1 or 1.1a in Part 2.

Results

Part 1: RD for zanidatamab monotherapy was determined to be 10 mg/kg QW and 20 mg/kg QDW.
- 15 patients with BTC were treated in Part 2 of the study at the RD of 20 mg/kg Q2W. 1 patient due to progressive disease and 1 due to per protocol.
- BCT patient characteristics are presented in Table 1.

Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>median (IQR) or %</th>
<th>Median age (range), years</th>
<th>Sex, Female, %</th>
<th>Race, %</th>
<th>Diagnosis, %</th>
<th>Gallbladder</th>
<th>Intrahepatic cholangiocarcinoma</th>
<th>Extrahepatic cholangiocarcinoma</th>
<th>Median prior systems (range)</th>
<th>Patient characteristic (HER2 targeted group), %</th>
<th>ECOG PS, %</th>
<th>Grade 3 or higher zanidatamab related AEs, %</th>
<th>DSAE, %</th>
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<tbody>
<tr>
<td>63 (42-78)</td>
<td>14 (67)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>12 (57)</td>
<td>1 (5)</td>
<td>5 (24)</td>
<td>3 (15)</td>
<td>2 (1-8)</td>
<td>5 (24)</td>
<td>0</td>
<td>10 (50)</td>
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Safety
- Zanidatamab was well-tolerated in patients with BTCs with no patient experiencing a Grade 3 or higher zanidatamab-related AE (Table 2).
- A single zanidatamab-related serious AE (Grade 2 fatigue) was reported in one patient. The patient was hospitalized, treated with IV fluids, and recovered within a day.
- Two deaths were reported during the study — one due to progressive disease and one due to an unrelated AE (cardiac arrest in the setting of low perfusion).

Table 2: Zanidatamab-related AEs

<table>
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<tr>
<th>median (IQR) or %</th>
<th>Patients with treatment-emergent AEs, %</th>
<th>Patients with zanidatamab-related AEs (occurring in ≥ 25% of BTC patients)</th>
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<tr>
<td></td>
<td>21 (100)</td>
<td>7 (33)</td>
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Efficacy
- Twenty (95%) patients were response evaluable.
- Tumor shrinkage observed in majority of patients with response-evaluable measurable disease.

Conclusions
- Zanidatamab was well tolerated and demonstrated promising anti-tumor activity in patients with HER2+ BTC that has progressed after prior therapies, including HER2-targeted agents.
- All zanidatamab-related AEs were mild or moderate in severity (Grade 1 or 2).
- The confirmed objective response was 40% (9/20), disease control rate was 65% (13/20), and median duration of response was 7.4 months.
- Based on these results, zanidatamab has the potential to address unmet need in patients with HER2+ BTC.
- A registration-enabling global Phase 2 study (ZW25-203; HER201N-BTC-03) in HER2-amplified BTC is now open for enrollment.

Acknowledgments
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References

NCT03891223 is a first-in-human, 3-part, Phase 1 study that evaluates zanidatamab in HER2 expressing cancers, including BTCs. The study is sponsored by Zymeworks Inc and BeiGene, Ltd. Zanidatamab is an investigational agent; the safety and efficacy have not been established.