Background

Zanidatamab: A Bispecific HER2-Targeted Antibody
- A bispecific antibody that simultaneously binds two distinct sites on HER2: ECD4 (targeted by pertuzumab) and ECD2 (targeted by trastuzumab)
- Unique binding results in multiple mechanisms of action of zanidatamab that lead to improved binding, clustering, and receptor internalization and downstream inhibition of ligand-dependent and -independent proliferation, and potent activation of antibody-dependent cellular cytotoxicity

Data Supporting the Phase 2b Registration Trial

Results from the ongoing Phase 1 study (ZW25-101; NCT02922125) demonstrate that zanidatamab is well tolerated and has single-agent activity in patients with advanced HER2-expressing cancers, including BTC, that have progressed after standard of care therapies.1 Summary from 21 patients (data extract date Nov 16, 2020) are presented below (full details to be presented by Meric-Bernstam, F, et al. at ASCO-GI 2021 (abstract # 299)).

- All patients had tumors that were HER2-amplified (as detected by fluorescence in situ hybridization positivity (FISH) and had immunohistochemistry (IHC) fluorescence levels of IHC 3+ or 2+.
- Patients received 20 mg/kg zanidatamab intravenously (IV) every 2 weeks (Q2W).
- Key Safety Results: zanidatamab-related adverse events (AEs) occurred in 71% (15/21) of patients, grade 3 or 4, and consisted predominantly of diarrhea (43%) and infusion-related reactions (39%). A single treatment-related event was Grade 3 fatigue.
- Key Efficacy Results: The 20 mg/kg zanidatamab was well tolerated and had single-agent activity in patients with measurable disease who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to disease progression or an adverse event. The confirmed objective response rate was 40% (6/15) and the disease control rate was 65% (13/20).

The findings from the ZW25-101 study support further investigation of zanidatamab in patients with BTC.

ZW25-203 (NCT04466891): Global Phase 2b Study of Zanidatamab Monotherapy in HER2-amplified BTC

The current registrational Phase 2b trial (HERIZON-BTC-01; NCT04466891) is designed to further evaluate the anti-tumor activity of zanidatamab in patients with advanced or metastatic HER2-amplified BTC in the second-line and later setting.

Primary & Secondary Objectives:
- To evaluate the anti-tumor activity of zanidatamab in patients with advanced or metastatic HER2-amplified BTC
- To evaluate the safety and tolerability of zanidatamab
- To evaluate the pharmacokinetics of zanidatamab
- To evaluate the immunogenicity of zanidatamab

Exploratory Objectives:
- To evaluate the anti-tumor activity of zanidatamab by BTC anatomical subtypes
- To evaluate the utility of potential serum and tumor biomarkers
- To evaluate the effect of zanidatamab treatment on quality of life
- To evaluate the effect of zanidatamab treatment on disease-related pain and opioid use for pain control

Assessments
- CT or MRI scans will be performed at baseline and every 8 weeks during treatment, and treatment failure will be assessed according to RECIST 1.1 by independent central review (primary endpoint) and by the investigator (secondary endpoint).
- Responses are to be confirmed 4 weeks following initial documentation of objective response by the investigator.

Sample Size
- Total of 100 patients are planned to be enrolled, who will be grouped into 1 of 2 cohorts:
  - Cohort 1: approximately 75 patients with HER2 amplification detected by ISH and HER2 overexpression by IHC (i.e., IHC 2+ or 3+);
  - Cohort 2: approximately 25 patients with HER2 amplification detected by ISH and HER2 IHC 0 or 1+

ZW25-203 study sites have been planned in the following 9 countries: Canada, United States, Chile, United Kingdom, Spain, Italy, China and South Korea.

Key Eligibility Criteria
- Histology or cytologically confirmed BTC, including GBC, ICC or EGC
- Locally advanced or metastatic BTC and not eligible for curative resection, transplantation, or ablative therapies
- Patients must have progressed after treatment with a gemcitabine-based chemotherapy regimen
- Patients must have experienced disease progression after the most recent prior therapy
- Patients must test positive for HER2 amplification by DH assay at a central laboratory on a new biopsy or archival tissue; ICC assay will be used to detect HER2 protein expression level
- Patients must not have received any prior HER2-targeted therapy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Treatment
- Enrolled patients will receive zanidatamab 20 mg/kg intravenously (Q2W) until at least 1 treatment discontinuation criterion is met: investigator-determined radiographic disease progression per RECIST 1.1, uncontrolled clinical progression, unacceptable toxicity, consent withdrawal, physician decision, pregnancy, or patient or investigator decision not to continue treatment.

References

ZW25-203 Study Design & Key Endpoints

Primary Endpoint:
- Objective response rate

Secondary Endpoints:
- Duration of response
- Disease control rate
- Progression-free survival
- Overall survival
- Frequency & severity of AEs
- Frequency of SAEs and deaths

Acknowledgments

No external data donors and their family. Trains of the investigators, clinical trial associates, and staff who contributed to this trial and funding were reimbursed by Zymeworks Inc. and BeiGene, Ltd. ZW25-203 Study is sponsored by Zymeworks Inc. and BeiGene, Ltd., Beijing, China. This study is supported by Zymeworks Inc. and BeiGene, Ltd., Beijing, China.

ZW25-203 (NCT04466891): Global Phase 2b Study of Zanidatamab Monotherapy in HER2-amplified BTC

ClinicalTrials.gov Identifier: NCT04466891

The ZW25-203 study is currently open and recruiting patients.

ZW25-203 Participation

ZW25-203 Study & Key Endpoints

Patients with HER2-amplified BTC (N = 100: approx. 75 with IHC ≥ 2+ or ≥ 3+, 25 with IHC 0 or 1+)

- Day 1
- Day 15
- Zanidatamab 20 mg/kg IV (Q2W)

- Primary & Secondary Objectives:
  - To evaluate the anti-tumor activity of zanidatamab in patients with advanced or metastatic HER2-amplified BTC
  - To evaluate the safety and tolerability of zanidatamab
  - To evaluate the pharmacokinetics of zanidatamab
  - To evaluate the immunogenicity of zanidatamab

- Exploratory Objectives:
  - To evaluate the anti-tumor activity of zanidatamab by BTC anatomical subtypes
  - To evaluate the utility of potential serum and tumor biomarkers
  - To evaluate the effect of zanidatamab treatment on quality of life
  - To evaluate the effect of zanidatamab treatment on disease-related pain and opioid use for pain control

- 28 Day Cycles

- Every 8 weeks: CT/MRI

- Primary Endpoint:
  - Objective response rate

- Secondary Endpoints:
  - Duration of response
  - Disease control rate
  - Progression-free survival
  - Overall survival
  - Frequency & severity of AEs
  - Frequency of SAEs and deaths

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  - The author of this post is not affiliated with Zymeworks Inc. or BeiGene, Ltd.

- ZW25-101 Study is sponsored by Zymeworks Inc. and BeiGene, Ltd., Beijing, China. ClinicalTrials.gov Identifier: NCT02922125. This study is supported by Zymeworks Inc. and BeiGene, Ltd., Beijing, China. The author of this post is not affiliated with Zymeworks Inc. or BeiGene, Ltd.