A Phase 2b, Open-label, Single-arm Study of Zanidatamab (ZW25) Monotherapy in Patients with Advanced or Metastatic HER2-amplified Biliary Tract Cancer (BTC): HERIZON-BTC-01 Study

Shubham Pant[1]; Michel Ducreux[2]; James J. Harding[3]; Milind M. Javle[1]; Do-Youn Oh[4]; Harpreet Singh Wasan[5]; Allison Fortenberry[6]; Neil Josephson[6]; Anthony Mwatha[6]; Kui Wang[7]; Jia Fan[8]. (Corresponding author: SPant@mdanderson.org)

1. The University of Texas MD Anderson Cancer Center, Houston, TX, US; 2. Institut Gustave Roussy, Villejuif, France; 3. Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4. Seoul National University Hospital, Seoul, South Korea; 5. Imperial Hammersmith Academic Health Trust, London, UK; 6. Zymeworks Inc., Vancouver, BC, Canada; 7. BeiGene, Ltd., Beijing, China; 8. Fudan University, Shanghai, China

Background

- Biliary tract cancer (BTC), including gallbladder cancer (GBC), extrahepatic cholangiocarcinoma (ECC) and intrahepatic cholangiocarcinoma (ICC), are aggressive, rare tumors
- Patients with unresectable, locally advanced or metastatic BTC have a poor prognosis and treatment options are limited after first line treatment[1]
- Approximately 19% of GBC, 17% of ECC and 5% of ICC overexpress human epidermal growth factor receptor 2 (HER2),[2] a validated therapeutic target for HER2+ breast cancer and HER2-overexpressing gastroesophageal adenocarcinoma (GEA)[3]
- Based on data from on ongoing Phase 1 study (see below), the FDA has recently granted Breakthrough Therapy designation for zanidatamab in patients with previously-treated HER2 gene-amplified BTC

Zanidatamab: A Bispecific HER2-targeted Antibody

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

ECD=extracellular domain

Data Supporting the Phase 2b Registrational Trial

Results from the ongoing Phase 1 study (ZW25-101; NCT02892123) 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.[4] Summary data 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, were Grade 1 or 2 in severity, and consisted predominantly of diarrhea (43%) and infusion-related reactions (33%). A single treatment-related serious AE (Grade 2 fatigue) was reported
- **Key Efficacy Results:** in the 20 response-evaluable patients (all treated patients with measurable disease who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to death or clinical progression), the confirmed objective response rate was 40% (8/20) 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.

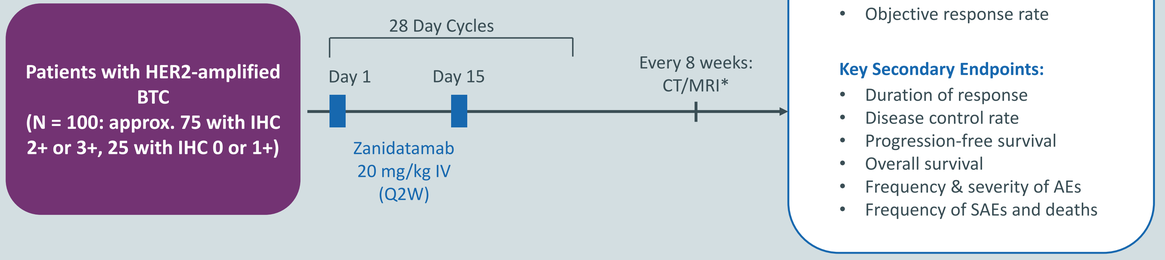
Primary & Secondary Objectives:

- 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 subtype
- 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

ZW25-203 Study Design & Key Endpoints



AE = adverse event; CT = computed tomography scan; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IV = intravenous; MRI = magnetic resonance imaging; SAE = serious adverse event.
* for tumor assessment per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1.[5]

Key Eligibility Criteria

- Histologically- or cytologically-confirmed BTC, including GBC, ICC, or ECC
- Locally advanced or metastatic BTC and not eligible for curative resection, transplantation, or ablative therapies
- Patients must have progressed after treatment with a gemcitabine-containing regimen
- Patients must have experienced disease progression after (or developed intolerance to) the most recent prior therapy
- Patients must test positive for HER2 amplification by ISH assay at a central laboratory on a new biopsy or archival tissue; IHC 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, unequivocal clinical progression, unacceptable toxicity, consent withdrawal, physician decision, pregnancy, start of a subsequent anticancer therapy, or study termination by the sponsor.

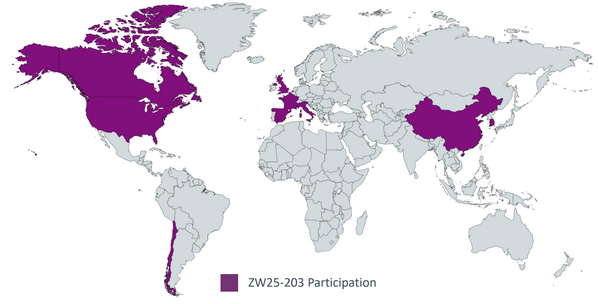
Assessments

- CT and/or MRI scans will be performed at baseline and every 8 weeks during treatment. Disease response 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

- A 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, France, Italy, China and South Korea



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

References

1.Valle JW, et al. Cancer Discov. 2017;7(9):943-962; 2. Galdy S, et al. Cancer Metastasis Rev. 2017 Mar;36(1):141-157; 3. Oh DY and Bang YJ. Nat Rev Clin Oncol. 2020 Jan;17(1):33-48; 4. Oh DY, et al. Ann Oncol. 2019;30(Supplement_9):ix22; 5. Eisenhauer EA, et al. Eur J Cancer. 2009;45(2):228-247.

Acknowledgments

We sincerely thank all patients and their families. Thanks to all the investigators, clinical trial researchers, personnel and staff who contributed to the trial in any way. Thanks also to Dr. Michael Press and Ms. Ivonne Villalobos at USC Medical Center Pathology Lab for support of HER2 testing.

ZW25-101 study is sponsored by Zymeworks Inc.
ZW25-203 study is sponsored by Zymeworks Inc. and BeiGene, Ltd.

Gastrointestinal Cancers Symposium
Jan 15-17, 2021
(Abstract #:TPS352)