A phase IIb, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers.

Shubham Pant, Michel Ducreux, James J. Harding, Milind M. Javle, Do-Youn Oh, Harpreet Singh Wasan, Allison Fortenberry, Neil C. Josephson, Anthony Mwatha, Kui Wang, Jia Fan; The University of Texas MD Anderson Cancer Center, Houston, TX; Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Seoul National University Hospital, Seoul, South Korea; Hammersmith Hospital, Division of Cancer, Imperial College London, London, United Kingdom; Zymeworks Inc., Vancouver, BC, Canada; Seattle Genetics, Bothell, WA; Zymeworks, Seattle, WA; BeiGene, Ltd., Shanghai, China; Department of Liver Surgery, Zhongshan Hospital and Liver Cancer Institute, Fudan University, Shanghai, China

Background: Advanced biliary tract cancers (BTCs), including gallbladder cancer (GBC) and cholangiocarcinoma (CC), have a poor prognosis. Zanidatamab (ZW25) is a novel bispecific antibody that targets HER2 domains ECD2 and ECD4, resulting in increased antibody binding density and improved receptor internalization and downregulation relative to trastuzumab. In an ongoing phase I trial (ZWI-ZW25-101; NCT02892123), single-agent zanidatamab was well tolerated and showed promising anti-tumor activity across HER2-expressing solid tumors, including BTCs. These results formed the basis for a phase IIb study of zanidatamab in patients with BTC. **Methods:** Study ZWI-ZW25-203 (NCT04466891) is a global, multicenter, open-label, single-arm, phase IIb trial designed to evaluate the anti-tumor activity of zanidatamab monotherapy in patients with HER2-amplified, inoperable and advanced or metastatic BTCs, including GBC and CC. Patients must have received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease and have experienced disease progression after (or developed intolerance to) their most recent prior therapy. New or archival tumor tissue is required from all patients for HER2 amplification and protein expression testing at a central lab using in situ hybridization (ISH) and immunohistochemistry (IHC) assays. Approximately 100 patients with HER2 amplification by ISH will be enrolled. Zanidatamab 20 mg/kg will be administered intravenously every 2 weeks until one of the treatment discontinuation criteria is met. The primary endpoint of the study is the confirmed objective response rate (ORR) by independent central review per the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Secondary endpoints include duration of response (DOR), proportion of patients with DOR $\geq$ 16 weeks, disease control rate, progression-free survival, overall survival, safety, quality of life, and disease-related pain. The safety and tolerability of zanidatamab will be assessed by recording the frequency and severity of adverse events, serious adverse events, and laboratory abnormalities, as well as the frequency of zanidatamab dose modifications. The study is currently open for enrollment. Clinical trial information: NCT04466891. Research Sponsor: Zymeworks, Inc. and BeiGene Ltd.