Zanidatamab (ZW25), a novel anti-HER2 bispecific antibody, monotherapy as second-line treatment for patients (pts) with advanced or metastatic HER2-amplified biliary tract cancer (BTC): A Phase 2b trial-in-progress

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Objective:

HER2 amplification/overexpression in BTC may be associated with clinical benefit to HER2-targeted agents. HER2 is expressed in ≈26% of BTC cases. After first-line treatment, there is a lack of effective systemic therapies for advanced/metastatic BTC.

Zanidatamab binds two distinct extracellular domains of HER2 across a range of expression levels (low to high) and induces formation of large receptor clusters and antibody-mediated internalization resulting in HER2 downregulation. Zanidatamab inhibits growth factor-dependent and -independent tumor cell proliferation and potently activates antibody-dependent cellular cytotoxicity and phagocytosis and complement-dependent cytotoxicity.

Zanidatamab monotherapy was well tolerated and demonstrated antitumor activity in HER2-expressing BTC (confirmed objective response rate [cORR] 40%) in a Phase 1 trial (NCT02892123).

This abstract provides the study design and methods for the ZW25-203 study (NCT04466891).

Methods:

This global, multicenter, open-label Phase 2b trial aims to evaluate the antitumor activity and safety of zanidatamab monotherapy in pts with HER2-amplified, advanced/metastatic BTC, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.

Eligible pts must have ≥ 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease and experienced disease progression after (or developed intolerance to) their most recent prior therapy, be ≥ 18 years of age and have an ECOG performance status ≤ 1. Pts previously treated with HER2-targeted agents are ineligible.

HER2 amplification and protein expression is tested centrally using *in situ* hybridization (ISH) and immunohistochemistry (IHC) assays. Approximately 100 pts with HER2 amplification by ISH will be enrolled. Pts will be divided into two cohorts: IHC 2+/3+ (cohort 1; n≈75) and IHC 0/1+ (cohort 2; n≈25).

Zanidatamab IV 20 mg/kg every 2 weeks is administered until disease progression, toxicity, consent withdrawal, subsequent therapy, or study termination.

The primary endpoint is cORR. Secondary endpoints include duration of response (DoR), proportion of pts with DoR ≥ 16 weeks, disease control rate, progression-free survival (all by RECIST 1.1 independent central and investigator review), overall survival and safety.