Results from the pivotal phase (Ph) 2b HERIZON-BTC-01 study: Zanidatamab in previously- treated HER2-amplified biliary tract cancer (BTC)

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Background: For patients (pts) with locally advanced/metastatic BTC who progress after first-line treatment (tx), standard tx offers limited clinical benefit with modest improvement in survival. HER2- targeted therapies have improved survival in breast and gastric cancer, but there is no approved HER2- targeted therapy for BTC. Zanidatamab (zani), a HER2-targeted bispecific antibody, has shown durable responses in a subset of pts with BTC in a Ph 1 trial.

Methods: HERIZON-BTC-01, an open-label, global Ph 2b study (NCT04466891), evaluated zani (20 mg/kg IV every 2 wks) in pts with HER2-amplified, locally advanced unresectable or metastatic BTC (gallbladder cancer [GBC], intra-/extra-hepatic cholangiocarcinoma [ICC/ECC]) who had received prior gemcitabine-containing therapy; pts with prior HER2-targeted therapies were excluded. Pt cohort assignment was based on tumor immunohisto- chemistry (IHC) status: Cohort 1 for IHC 2+/3+ (HER2 positive), or Cohort 2 for IHC 0/1+. Tumors were assessed every 8 wks per RECIST 1.1. The primary endpoint was confirmed objective response rate (cORR) by independent central review (ICR) in Cohort 1. Secondary endpoints included other efficacy and safety outcomes.

Results: Enrollment is complete with 87 pts (Cohort 1, n=80; Cohort 2, n=7) treated. Median age was 64 yrs (range, 32-79); 54% were female; 66% were Asian; 52% had GBC, 30% ICC, and 18% ECC. Pts had a median of 1 line (range, 1-7) of prior therapy in the locally advanced/ metastatic setting. In Cohort 1, cORR was 41% with median duration of response (DOR) of 12.9 months (m; 95% CI: 5.95, not estimable); median study follow-up time was 12.4 m. Among the 33 responders at the data cut (10OCT2022), 49% had ongoing responses and 82% had a DOR of $16 wks. Median time to first response was 1.8 m (range, 1.6-5.5). Progression-free survival and overall survival are being evaluated. No responses were observed in Cohort 2. In both cohorts (N=87), tx-related adverse events (TRAEs) occurred in 72% of pts; TRAEs in $10% of pts were diarrhea (37%) and infusion-related reaction (33%). Gr 3 TRAEs occurred in 18% of pts, with diarrhea (4.6%) and ejection fraction (EF) decreased (3.4%) in ₋3% of pts. Two pts (2.3%) discontinued zani due to an AE (EF decreased and non-infectious pneumonitis). Seven pts had serious TRAEs; no AE preferred term occurred in ₋1 pt. No zani-related Gr 4 AEs or deaths were reported.

Conclusions: Results of the pivotal HERIZON- BTC-01 study indicate that the HER2 bispecific antibody zani demonstrates rapid, durable responses with a manageable safety profile in pts with tx-refractory HER2-positive BTC. Given these data, zani continues to be developed as a tx option in HER2-positive BTC. Clinical trial information: NCT04466891. Research Sponsor: Zymeworks BC Inc.

	Cohort 1 (n=80)	Cohort 2 (n=7)
cORR, % (95% CI)	41 (30, 53)	0 (0, 41)
Confirmed Best Objective Response, n (%)		
CR	1 (1)	0
PR	32 (40)	0
SD	22 (28)	1 (14)
PD	24 (30)	3 (43)
Disease Control Rate, % (95% CI)	69 (57, 79)	43 (10, 82)