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Zanidatamab Dose Optimization in Patients With HER2-Positive Biliary Tract Cancer

Sheryl Trueman,[1]* Liviawati Wu,[1] Suzette Girgis,[1] Kedar Vaidya,[1] Funda Meric-Bernstam,[2] James J. Harding,[3] Shubham Pant,[2] Yi Zhao,[4] Phillip Garfin,[1] Robert Iannone,[1] Honghui Zhou,[1] Joanne Ma[1]

[1]Jazz Pharmaceuticals, Palo Alto, CA, USA; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]BeiGene Ltd., Beijing, China

*Presenting author.

Background

- Biliary tract cancer (BTC) encompasses a group of rare and aggressive gastrointestinal tract cancers, including gallbladder cancer (GBC) and intrahepatic and extrahepatic cholangiocarcinoma (iCCA and eCCA)[1]
- For patients with unresectable, locally advanced/metastatic disease that has progressed after first-line therapy, subsequent chemotherapy is associated with a low response rate[2,3]
- Human epidermal growth factor receptor 2 (HER2) is a rational target for precision therapy in BTC as its amplification/overexpression has been reported across subtypes (GBC: 19-31%, iCCA: 4-5%, eCCA: 17-19%)[4-6]
- Until recently, there have been no Food and Drug Administration-approved HER2-directed therapies specifically for patients with HER2-positive BTC[7,8]
- Zanidatamab is a dual HER2-targeted bispecific antibody that targets 2 distinct sites on HER2, promoting receptor clustering and driving multiple mechanisms of action, including[9]:
  - Facilitation of HER2 internalization and subsequent degradation
  - Reduction of HER2 homo- and hetero-dimerization
  - Immune-mediated effects (complement-dependent cytotoxicity as well as antibody-dependent cellular cytotoxicity and phagocytosis)
- In November 2024, zanidatamab received accelerated approval for the treatment of patients with previously treated unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) BTC based the results of the phase 2 HERIZON-BTC-01 trial[6,7,10]
- In HERIZON-BTC-01, zanidatamab (20 mg/kg intravenously [IV] every 2 weeks [Q2W]) demonstrated a 41% confirmed objective response rate (cORR) among 80 patients with previously treated HER2-positive BTC (IHC 3+/2+ ISH+)[6,10]
  - The cORR was 52% among the subgroup of patients (n=62) with HER2-positive IHC 3+ BTC[6,10]
- The safety profile of zanidatamab was manageable with good tolerability among all 87 patients treated in HERIZON-BTC-01[10]
  - The most common treatment-related adverse events of any grade were diarrhea (37%) and infusion-related reactions (IRR; 33%)[10]
    - Grades 3-4 diarrhea and IRRs were infrequent (5% and 1%, respectively)[10]

Objective

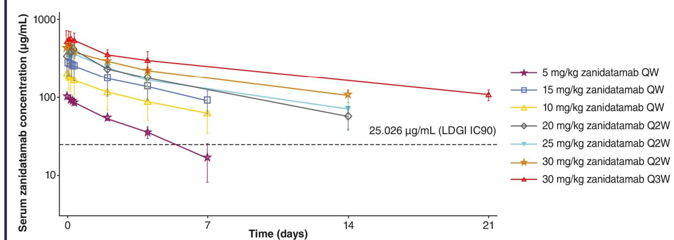
- To report optimal dose selection for zanidatamab in patients with HER2-positive BTC through pharmacometric modeling

Methods

- Source data included the ZWI-ZW25-101 study (Study 101; NCT02892123), HERIZON-BTC-01 (NCT04466891), and in vitro study for ligand-dependent cellular growth inhibition (LDGI) in HER2-expressing human cancer cell lines[6,10,11]
- The ZWI-ZW25-101 study was a phase 1 dose-escalation and expansion study that investigated the safety, tolerability, pharmacokinetics, and antitumor activity of zanidatamab in previously treated patients with locally advanced/metastatic HER2-expressing solid tumors[11]
  - Doses ranged from 5-30 mg/kg including every week (QW), Q2W, and Q3W[11]
- HERIZON-BTC-01 was a global, single-arm, phase 2 study that investigated the antitumor activity and safety of zanidatamab in previously treated patients with unresectable, locally advanced/metastatic *HER2*-amplified BTC[6,10]
  - Patients received zanidatamab 20 mg/kg IV Q2W[6,10]
- In the LDGI study, cancer cells were cultured in media containing 50 ng/mL epidermal growth factor and were treated with zanidatamab concentrations ranging from 0.002-37.454 µg/mL
  - The 90% inhibitory concentration (IC90) value for LDGI was obtained using the logistic dose-response model
- To assess target saturation, the population pharmacokinetic model was used to predict clearance at steady state following 5-30 mg/kg Q2W
- The clinical utility of zanidatamab was evaluated based on the correlation of zanidatamab concentrations with both efficacy and safety data

Results

Figure 1. Study 101 (Part 1): Zanidatamab Mean (± SD) Concentration-Time Profiles Following First IV Dose at Cycle 1 at Different Dose Levels

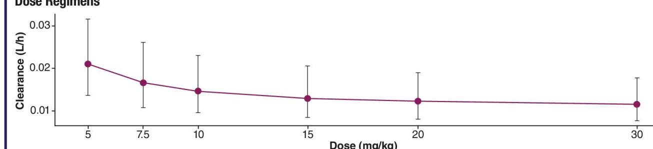


Dashed line represents the mean IC90 (25.0 µg/mL) for the LDGI assay derived from a gastrointestinal carcinoma/malignancy cell line (NCI-N87). This value was considered as the concentration threshold for zanidatamab treatment in patients with HER2-expressing locally advanced (unresectable) and/or metastatic cancers.

HER2, human epidermal growth factor receptor 2; IC90, 90% inhibitory concentration; IV, intravenous; LDGI, ligand-dependent cellular growth inhibition; Q2W, every 2 weeks; Q3W, every 3 weeks; QW, every week; SD, standard deviation.

- Study 101 included 192 patients with HER2-expressing solid tumors
- The trough concentration (C_{trough}) values following the first zanidatamab 5 mg/kg QW dose were below the IC90 (25.0 µg/mL) for LDGI
  - No confirmed responses were observed at this dose
- The C_{trough} values following the first zanidatamab dose of 10 mg/kg QW or 20 mg/kg Q2W were above IC90 for LDGI
  - The 2 dose levels demonstrated a cORR of 25% and 29%, respectively

Figure 2. Predicted Median Steady-State Zanidatamab Clearance vs Dose Following Different Zanidatamab Q2W Dose Regimens



Circles and error bars represent the median and 10th-90th percentiles, respectively, CLss of 1000 simulated patients with BTC who received 25 zanidatamab doses of 5, 7.5, 10, 15, 20, and 30 mg/kg Q2W. CLss was calculated as dose (mg) divided by the AUC 0-14 days, ss (µg·h/mL) at steady-state.

AUC, area under the curve; BTC, biliary tract cancer; CLss, steady-state clearance; Q2W, every 2 weeks.

- The predicted clearance suggests that the target-mediated elimination pathway was saturated at the dose level of 20 mg/kg Q2W since clearance was comparable to that of the higher dose of 30 mg/kg Q2W

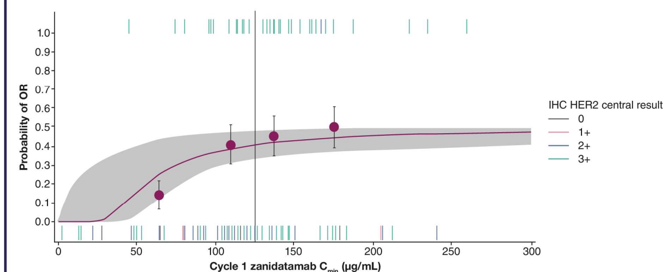
Table 1. Summary Statistics of Predicted Steady-State Zanidatamab Clearance Across Q2W Dose Regimens

Pharmacokinetic Parameter	5 mg/kg	7.5 mg/kg	10 mg/kg	15 mg/kg	20 mg/kg	30 mg/kg
CLss (L/h)[a]	0.0210	0.0166	0.0146	0.0130	0.0123	0.0115
Median (10th-90th percentiles)	0.0137-0.0316	0.0108-0.0261	0.0095-0.0231	0.0084-0.0206	0.0079-0.0190	0.0076-0.0178

[a]Calculated as dose (mg) divided by the AUC 0-14 days, ss (µg·h/mL) at steady-state.

AUC, area under the curve; CLss, steady-state clearance; Q2W, every 2 weeks.

Figure 3. Zanidatamab Exposure-Efficacy Relationship in Patients With BTC



The line represents the model-based predicted probability of OR. The shaded region represents the 90% prediction interval around the model predictions. The circles represent observed OR ± 1 SD and are plotted at the median cycle 1 C_{min} for each quartile. The hash marks at the top and bottom of the figure represent the individual cycle 1 C_{min} for OR (yes and no, respectively). The vertical line represents the median C_{min}.

BTC, biliary tract cancer; CI, confidence interval; C_{min}, minimum concentration; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OR, objective response; SD, standard deviation.

- The exposure-response analysis (based on the data from HERIZON-BTC-01) demonstrated that the majority of patients had an exposure range on the plateau of the efficacy curve following the zanidatamab 20 mg/kg Q2W dose regimen
- In this cohort of patients, diarrhea was manageable. No patients discontinued treatment due to diarrhea in Study 101 (parts 1 and 2) or HERIZON-BTC-01[6,10,11]
  - While there was an overall trend of diarrhea with higher exposure, there was no statistically significant exposure-response relationship for clinically meaningful grade ⩾3 diarrhea

Conclusions

- This analysis supports the approved dose of zanidatamab (20 mg/kg Q2W) for patients with HER2-positive BTC based on:
  - Reaching the desired target exposure (IC90 for LDGI)
  - Saturating target-mediated elimination pathway
  - The exposure-response analysis showing that exposures following this dose support the efficacy (exposures for the majority of patients on the plateau) and safety (no correlation with grade ⩾3 diarrhea) balance in the BTC population

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