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

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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

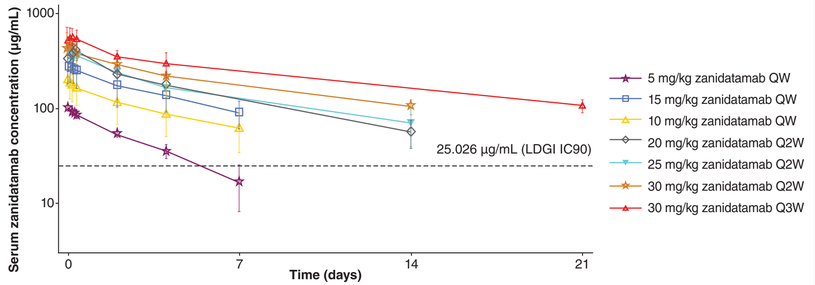
- To report optimal dose selection for zanidatamab in patients with HER2-positive BTC through pharmacometric modeling

Methods

- Source data included the 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 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

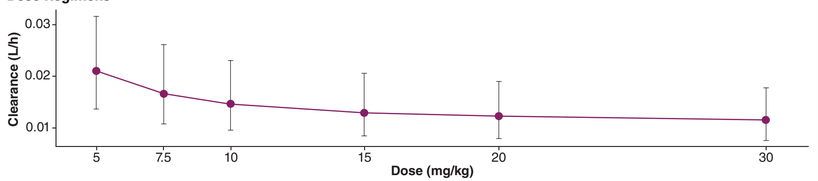


Dashed line represents the mean IC90 (25.0 µg/mL) for the LDGI assay derived from a gastrointestinal carcinoma/malignancy cell line (NCI-N87). This value was considered as the concentration threshold for zanidatamab treatment in patients with HER2-expressing locally advanced (unresectable) and/or metastatic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

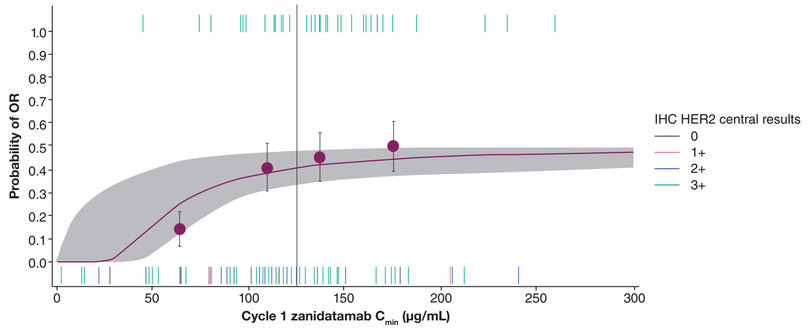
Table 1. Summary Statistics of Predicted Steady-State Zanidatamab Clearance Across Q2W Dose Regimens

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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Support and Acknowledgments: The authors thank all patients and their caregivers and the investigators, clinical trial researchers, personnel, and staff who contributed to the trials included in this study. This study was supported by Jazz Pharmaceuticals. Medical writing support, under the direction of the authors, was provided by Ellen Woon, PhD, of CMC Affinity, a division of IPG Health Medical Communications, with funding from Jazz Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines.

Disclosures: S Trueman, L Wu, S Girgis, K Vaidya, R Iannone, H Zhou, and **J Ma** are current employees of and may hold stock or stock ownership in Jazz Pharmaceuticals. **F Meric-Bernstam** has received consulting or personal fees from AbbVie, Aduro BioTech, Alkermes, AstraZeneca, DebioPharm, eFFECTOR Therapeutics, F. Hoffman-La Roche, Genentech, IBM Watson, Infinity Pharmaceuticals, Jackson Laboratory, Kolon Life Science, Lengo Therapeutics, OrigiMed, PACT Pharma, Parexel International, Pfizer, Samsung Bioepis, Seagen, Taiho Therapeutics, Tyra Biosciences, Xencor, Zymeworks, and Chugai; has served on an advisory board for Black Diamond, Biovica, Eisai, Eli Lilly, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Mersana Therapeutics, OnCusp Therapeutics, Puma Biotechnology, Seagen, Silverback Therapeutics, Spectrum Pharmaceuticals, and Zentalis; and research support, unrelated to this work and paid to her institution, from Aileron Therapeutics, AstraZeneca, Bayer Healthcare Pharmaceuticals, Calithera Biosciences, Curis, CytomX Therapeutics, Daiichi-Sankyo, Debiopharm International, eFFECTOR Therapeutics, Genentech, Guardant Health, Klus Pharma, Novartis, Puma Biotechnology, Taiho Pharmaceutical, and Takeda Pharmaceutical. **JJ Harding** has received research support from NCI P30-CA008748, NCI U01 CA238444 04, the Society of Memorial Sloan Kettering Cancer Center, Experimental Therapeutics Center, and Cycle for Survival; has received additional research support from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, CytomX, Debiopharm, Genoscience, Incyte, Kinnate Biopharma, Lilly, LoxoRLilly, Novartis, Pfizer, Polaris, Tvardi, Yuiva, and Zymeworks; and has received consulting fees from Adaptimmune, AstraZeneca, Bristol Myers Squibb, Eisai, Elevar, Exelixis, Genoscience (uncompensated), Hepion, Imvax, Merck data and safety monitoring board (DSMB), Medivir, QED, RayzeBio, Servier, Tempus, Tyra, and Zymeworks (uncompensated). **S Pant** has consulted for AskGene Pharma, Boehringer Ingelheim, Ipsen, Janssen, Novartis, and Zymeworks; and has received funding from 4D Pharma, Amal Therapeutics, Arcus Biosciences, Astellas Pharma, BioNtech, Boehringer Ingelheim, Bristol Myers Squibb, Elicio Therapeutics, Framewave, Immuneering, ImmunoMET, Ipsen, Janssen, Lilly, Mirati Therapeutics, NGM Biopharmaceuticals, Novartis, Pfizer, Rgenix, Xencor, and Zymeworks. **Y Zhao** is a current employee of BeiGene Ltd. and may hold stock or stock ownership in BeiGene Ltd. **P Garfin** is a former employee of and owned stock or stock options in Zymeworks; and is a current employee of and owns stock or stock options in Jazz Pharmaceuticals.

Poster presented at the ASCO GI Symposium 2025, January 23-25, 2025, San Francisco, CA, USA & Online #GI25