CT253

HERIZON-BTC-302: A Phase 3 Trial of Zanidatamab With Standard-of-Care Therapy vs SOC Alone For First-Line Treatment of Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Advanced/Metastatic Biliary Tract Cancer

James J. Harding,[1,*] Teresa Macarulla,[2] Xiaotian Wu,[3] Phillip M. Garfin,[3] Takuji Okusaka,[4] Shubham Pant[5]

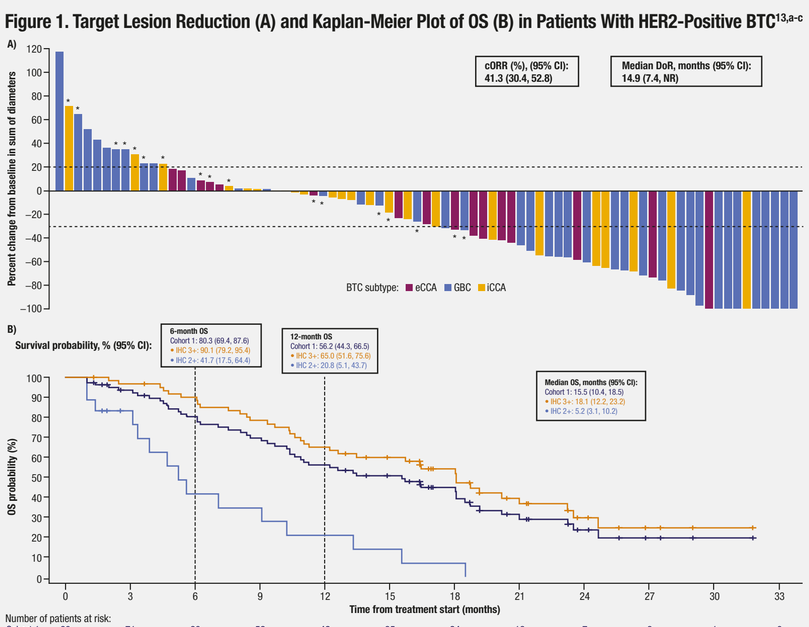
[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Vall d'Hebrón University Hospital, Vall d´Hebrón Institute of Oncology, Barcelona, Spain; [3]Jazz Pharmaceuticals, Philadelphia, PA, USA; [4]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo, Japan; [5]MD Anderson Cancer Center, Houston, TX, USA

*Presenting author

Background

- Standard-of-care first-line treatment for metastatic biliary tract cancer (BTC) is cisplatin plus gemcitabine (CisGem) ± pembrolizumab or durvalumab, which is associated with a median overall survival of approximately 13 months[1-3]
- Human epidermal growth factor receptor 2 (HER2) is amplified or overexpressed in a subset of patients with BTC (19-31% of gallbladder cancer, 4-5% of intrahepatic cholangiocarcinomas, and 17-19% of extrahepatic cholangiocarcinomas); therapies targeting HER2 have demonstrated clinical benefit in this subset of patients[4-6]
- Zanidatamab is a dual HER2-targeted bispecific antibody that binds to 2 distinct domains on HER2 in a *trans* configuration, promoting HER2 receptor crosslinking and driving multiple mechanisms of action, including[7]:
  - Immune-mediated effects: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis
  - Reduction of HER2 homo- and hetero-dimerization
  - Facilitation of HER2 internalization and subsequent degradation
- Combining zanidatamab with an immune checkpoint inhibitor may have synergistic antitumor effects in patients with HER2-positive cancers[8-10]
- 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 on the results of the global, single-arm, phase 2b HERIZON-BTC-01 trial[11,12]
- In the HERIZON-BTC-01 trial, zanidatamab monotherapy showed durable and sustained antitumor activity in patients with previously treated HER2-positive metastatic BTC[12,13] (**Figure 1**)
  - Zanidatamab led to a median overall survival of 15.5 months (18.1 months in patients with IHC 3+ tumors)[13]
- Zanidatamab monotherapy also had a manageable safety profile in a phase 1 trial and in the phase 2 HERIZON-BTC-01 trial[12-14]
  - Serious or grade 3/4 treatment-related adverse events (TRAEs) were infrequent, as were discontinuations due to TRAEs[13]
  - No treatment-related deaths were reported[13]

Figure 1. Target Lesion Reduction (A) and Kaplan-Meier Plot of OS (B) in Patients With HER2-Positive BTC[13,a-c]



*Indicates patients with tumors of IHC 2+ status; all other patients had tumors with IHC status of 3+.

[a]Only patients with measurable disease at baseline and ⩾1 post-baseline assessment were included (n=79). Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors; [b]Estimates per Kaplan-Meier method; median OS CIs based on the Brookmeyer and Crowley method with log-log transformations; [c]CIs for 6-month and 12-month OS based on the Greenwood method.

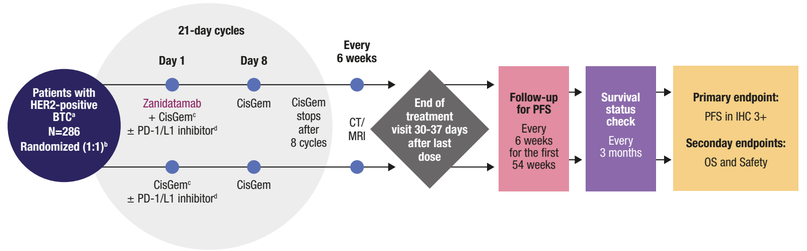
BTC, biliary tract cancer; CI, confidence interval; cORR, confirmed objective response rate; DoR, duration of response; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; NR, not reached; OS, overall survival.

Objective

- HERIZON-BTC-302 is an ongoing, global, phase 3, randomized, open-label trial (NCT06282575) investigating the efficacy and safety of zanidatamab with CisGem ± a PD-1/L1 inhibitor vs CisGem alone ± a PD-1/L1 inhibitor (physician's choice of pembrolizumab or durvalumab if locally approved) as first-line treatment for patients with advanced HER2-positive BTC (**Figure 2**)

Study Design

Figure 2. HERIZON-BTC-302



[a]Patients will be enrolled based on central assessment of HER2 status; [b]Patients who receive 1 of the allowed PD-1/L1 inhibitors prior to randomization will continue to receive the same PD-1/L1 inhibitor after randomization; [c]Up to 2 cycles of systemic therapy with CisGem ± a PD-1/L1 inhibitor are allowed per protocol prior to randomization; these cycles, if received, are counted towards the 8 cycles of CisGem; [d]PD-1/L1 inhibitor is physician's choice of durvalumab (20 mg/kg IV [weight <30 kg] or 1500 mg IV [weight ⩾30 kg]) or pembrolizumab (200 mg IV), where approved under local regulations.

BTC, biliary tract cancer; CisGem, cisplatin plus gemcitabine; CT, computed tomography; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenously; MRI, magnetic resonance imaging; OS, overall survival; PD-1/L1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival.

Table 1. Study Endpoints

Primary Endpoint	Secondary Endpoints	Exploratory Endpoints
• PFS (IHC 3+ subgroup)	• Select secondary endpoints: – OS in the IHC 3+ subgroup and in the overall population – PFS in the overall population • Additional secondary endpoints: – cORR and DoR per RECIST v1.1[15] – Frequency, severity, seriousness, and relatedness of treatment-emergent adverse events – Patient-reported physical functioning and symptom scores (IHC 3+ subgroup and overall population)	• PFS-2[a] • Potential biomarkers predictive of response and/or resistance • Change from baseline in patient-reported HRQoL outcomes

[a]Defined as the time from randomization to disease progression (either clinical progression or per RECIST v1.1[15]), as reported by the investigator, or death from any cause, following the start of subsequent anticancer therapy.

cORR, confirmed objective response rate; DoR, duration of response; HRQoL, health-related quality of life; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; PFS-2, second progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

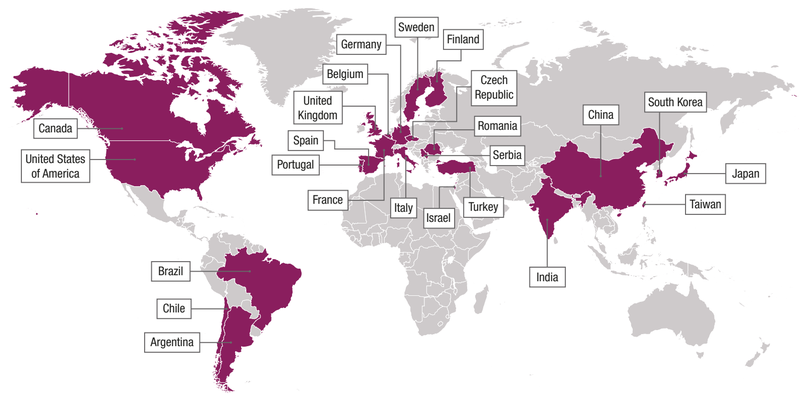
Table 2. Select Patient Eligibility Criteria

Select Inclusion Criteria	Select Exclusion Criteria
• Aged ⩾18 years who have locally advanced, unresectable or metastatic HER2-positive BTC defined as IHC 3+ or IHC 2+/ISH+	• Prior treatment with a HER2-targeted agent, except for patients who completed HER2-targeted treatment for breast cancer >5 years prior to their diagnosis of BTC
• ECOG PS ⩽1	• Prior treatment with checkpoint inhibitors, other than durvalumab or pembrolizumab, outside of the ⩽2 cycles of prior therapy allowed per protocol
• Have assessable disease per RECIST v1.1[15]	• History of interstitial lung disease or non-infectious pneumonitis
• Received ⩽2 cycles of a gemcitabine-based regimen ± a PD-1/L1 inhibitor (physician's choice of pembrolizumab or durvalumab where approved under local regulations) for advanced, unresectable, or metastatic disease – Prior adjuvant or neoadjuvant treatment (including investigational products) for earlier stage disease are permitted if therapy was completed >6 months prior to expected date of first dose of study therapy	• History of life-threatening hypersensitivity to monoclonal antibodies or known hypersensitivity to any components of the combination therapy
• Adequate hematologic, renal, and hepatic function	• Untreated CNS metastases, symptomatic CNS metastases, or those who have received radiation treatment for CNS metastases within 4 weeks of expected date of first dose of study therapy
• LVEF ⩾50% as determined by either echocardiogram or MUGA	

BTC, biliary tract cancer; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LVEF, left ventricular ejection fraction; MUGA, multiple gated acquisition scan; PD-1/L1, programmed cell death protein 1/programmed death-ligand 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Study Status

- This global phase 3 study is currently recruiting patients with planned recruitment in up to 30 countries (**Figure 3**)



References: 1. Kelley RK, et al. *Lancet.* 2023;401:1853-1865. **2.** Oh DY, et al. *Lancet Gastroenterol Hepatol.* 2024;9(8):694-704. **3.** Vitale E, et al. *Front Oncol.* 2024;14:1409132. **4.** Galdy S, et al. *Cancer Metastasis Rev.* 2017;36(1):141-157. **5.** Hiraoka N, et al. *Hum Pathol.* 2020;105:9-19. **6.** Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. **7.** Weisser NE, et al. *Nat Commun.* 2023;14(1):1394. **8.** Janjigian YY, et al. *Lancet.* 2023,402(10418):2197-2208. **9.** Tabernero J, et al. Presented at ESMO 2022; Poster presentation P-26. **10.** Tabernero J, et al. *Future Oncol.* 2022;18(29):3255-3266. **11.** FDA grants accelerated approval to zanidatamab-hrii for previously treated unresectable or metastatic HER2-positive biliary tract cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanidatamab-hrii-previously-treated-unresectable-or-metastatic-HER2. Accessed March 13, 2025. **12.** Harding JJ, et al. *Lancet Oncol.* 2023;24(7):772-782. **13.** Pant S, et al. Presented at ASCO 2024; Poster presentation 4091. **14.** Meric-Bernstam F, et al. *Lancet Oncol.* 2022;23(12):1558-1570. **15.** Eisenhauer EA, et al. *Eur J Cancer.* 2009;45(2):228-247.

Support and Acknowledgments: This study is sponsored by Jazz Pharmaceuticals. Medical writing support, under the direction of the authors, was provided by Mai Moawed, B. Pharm, 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: 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, Loxo@Lilly, Novartis, Pfizer, Polaris, Tvardi, Yiviva, 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). **T Macarulla** has an advisory role at Ability Pharmaceuticals SL, AstraZeneca, Basilea Pharma, Baxter, BioLineRX, Celgene, Eisai, Incyte, and Ipsen; has received speaker's fees from Janssen and Lilly; and has received direct research funding from Merck Sharp & Dohme, Novocure, QED Therapeutics, Roche Farma, Sanofi-Aventis, Servier, and Zymeworks. **X Wu** is a current employee of and owns stock or stock options in Jazz Pharmaceuticals. **PM 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. **T Okusaka** has an advisory role at AstraZeneca, Eisai, FUJIFILM Toyama Chemical, and Nihon Servier; has received speaker's fees from AstraZeneca, Chugai Pharma, Daiichi-Sankyo, Eisai, Incyte, Kyowa Kirin, Myriad Genetics, Nihon Servier, Novartis, Ono, Taiho, and Yakult; and has received research support from AstraZeneca, Bristol Myers Squibb, Chiome Bioscience, Eisai, Incyte, Syneos Health, and Sysmex. **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.

Poster presented at the American Association for Cancer Research (AACR) Annual Meeting, April 25-30, 2025, Chicago, IL, USA