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

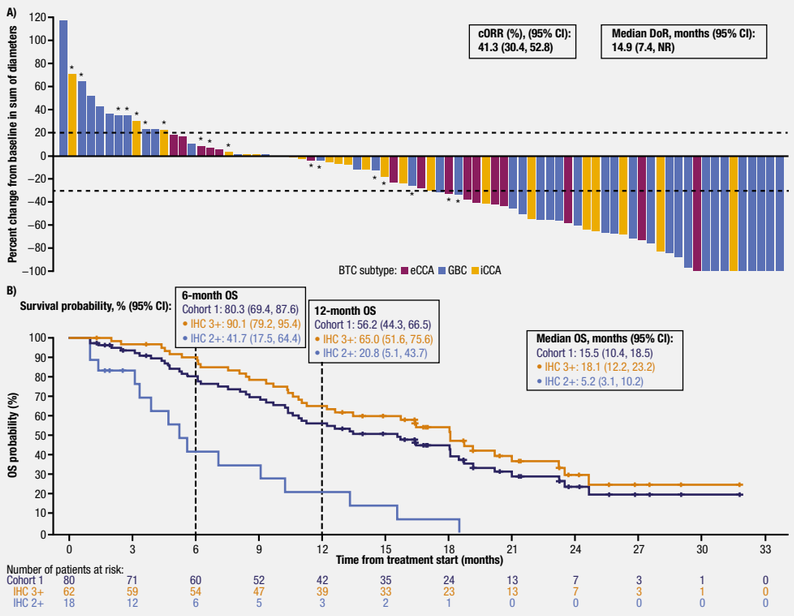
Teresa Macarulla,[1] James J. Harding,[2] Shubham Pant,[3] Charles Mei,[4] Phillip Garfin,[4] Takuji Okusaka[5]

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

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-dimerisation
  - Facilitation of HER2 internalisation and subsequent degradation
- Combining zanidatamab with an immune checkpoint inhibitor may have synergistic antitumour 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 antitumour 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+ tumours)[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 tumours of IHC 2+ status; all other patients had tumours 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 tumours; [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.

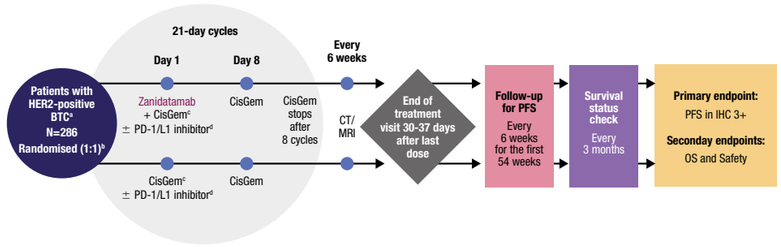
BTC, biliary tract cancer; CI, confidence interval; cORR, confirmed objective response rate; DoR, duration of response; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; NR,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

Objective

- HERIZON-BTC-302 is an ongoing, global, phase 3, randomised, 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 randomisation will continue to receive the same PD-1/L1 inhibitor after randomisation; [c]Up to 2 cycles of systemic therapy with CisGem ± a PD-1/L1 inhibitor are allowed per protocol prior to randomisation; 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 randomisation 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 Tumours version 1.1.

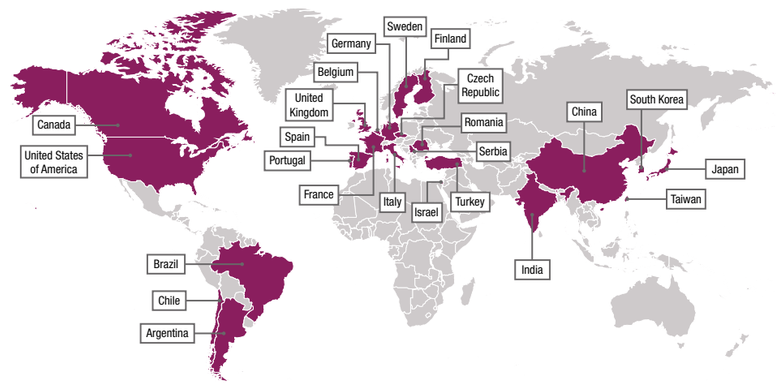
Table 2. Select Patient Eligibility Criteria

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+ • ECOG PS ⩽1 • Have assessable disease per RECIST v1.1[15] • 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 treatments (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 • Adequate haematologic, renal and hepatic function • LVEF ⩾50% as determined by either echocardiogram or MUGA	• 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 • Prior treatment with checkpoint inhibitors, other than durvalumab or pembrolizumab, outside of the ⩽2 cycles of prior therapy allowed per protocol • History of interstitial lung disease or non-infectious pneumonitis • History of life-threatening hypersensitivity to monoclonal antibodies or known hypersensitivity to any components of the combination therapy • 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

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 hybridisation; 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 Tumours version 1.1.

Study Status

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



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