Zanidatamab for HER2-amplified, advanced, biliary tract cancer: Results of a global, single-arm, phase 2b study (HERIZON-BTC-01)

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SUMMARY

Background: Human epidermal growth factor receptor 2 (HER2) is overexpressed/amplified in a biliary tract cancer (BTC) subset. Zanidatamab, a bispecific antibody targeting two distinct HER2 epitopes, exhibited tolerability and preliminary antitumor activity in HER2-expressing or *HER2*-amplified treatment refractory BTC.

Methods: HERIZON-BTC-01 (NCT04466891) is a global, multicentre, single-arm, phase 2b trial of zanidatamab in patients with *HER2* (*ERBB2*)-amplified, unresectable, locally advanced, or metastatic BTC with disease progression on prior gemcitabine-based therapy. All eligible patients were required to have *HER2*-amplified BTC by in situ hybridisation (i.e., ISH+) per central testing. Patients were assigned into cohorts based on HER2 immunohistochemistry (IHC) score: cohort 1 (IHC 2+ / 3+; HER2-positive) and cohort 2 (IHC 0 / 1+). Patients received zanidatamab 20 mg/kg intravenously every 2 weeks (2QW). The primary endpoint was confirmed objective response rate (cORR) in cohort 1 as assessed by independent central review (ICR).

Findings: Eighty-seven patients were enrolled between September 2020 and March 2022: 80 in cohort 1 (56·3% [45 patients] female, median age 64 [range 32 – 79 years]), seven in cohort 2 (71·4% [5 patients] male, median age 62 [range 56 – 77 years]). At the time of the data cutoff, 18 subjects (20·7%; 17 in Cohort 1, 1 in Cohort 2) were continuing to receive zanidatamab; 69 (79·3%) discontinued treatment (radiographic progression in 64 subjects, 73·6%). The median duration of study follow-up was 12·4 months (IQR: 9.4, 17.2). The cORR in cohort 1 was 41·3% (95% confidence interval [CI]: 30·4, 52·8). The most common treatment-related adverse events

(TRAE) were diarrhoea (32 patients, 36·8%) and infusion-related reaction (29 patients, 33·3%). Sixteen patients (18·4%) had grade 3 TRAEs; most common were diarrhoea (4 patients, 4·6%) and ejection fraction decreased (3 patients, 3·4%). No grade 4 or 5 TRAEs were reported.

Interpretation: Zanidatamab demonstrated meaningful clinical benefit with a manageable safety profile in patients with treatment refractory HER2-positive BTC. These results support the potential of zanidatamab as a future treatment option in HER2-positive BTC.

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RESEARCH IN CONTEXT

Evidence before the study

We searched PubMed for publications assessing human epidermal growth factor receptor 2 (HER2)-targeted treatments in patients with HER2-expressing/amplified biliary tract cancer (including gallbladder cancer [GBC], intrahepatic cholangiocarcinoma [ICC], and extrahepatic cholangiocarcinoma [ECC]; BTC) published up to 01 March 2023 (i.e., the completion of the first draft of this manuscript), with no start date noted. We searched publications for "biliary tract cancer," "gallbladder cancer," and/or "cholangiocarcinoma" with "HER2" or "ERBB2", filtering for therapeutic uses of HER2-targeted agents in clinical settings without language restrictions.

Twelve separate entries described clinical studies or experiences treating advanced BTC with HER2 inhibitors. Antitumor responses were observed in patients with *HER2*-amplified advanced BTC and treated with various anti-HER2 agents as monotherapy, with combinations of more than one HER2-targeting agent, or with anti-HER2 agent(s) combined with chemotherapy. The results from most of these studies support HER2 as a potential actionable target in HER2-expressing/amplified BTC.

Added value of this study

This is a phase 2 single-arm study (NCT04466891) evaluating the antitumor activity and safety of zanidatamab (ZW25) in the treatment of patients with *HER2*-amplified BTC. Advanced BTC represents a patient population with a historically poor prognosis. There are no approved HER2-targeted therapies for this molecular subset of BTC, and thus there is a significant unmet medical

need. The results of this trial show that zanidatamab is well tolerated and has very encouraging single-agent activity, both in terms of response rate and duration of response, in pre-treated patients with advanced *HER2*-amplified BTC. To our knowledge, this is the largest phase 2 trial to date of a HER2-targeted agent in patients with BTC.

Implications of all the available evidence

The results of the current study support zanidatamab as a potential therapy for patients with HER2-positive (in situ hybridisation [ISH]+ and immunohistochemistry [IHC] 2+ / 3+) advanced BTC. Based on these results, efforts are underway to continue to develop zanidatamab as a treatment for HER2-positive BTC, including in clinical studies in combination with first-line chemotherapy and as a monotherapy treatment option for advanced BTC.

INTRODUCTION

Biliary tract cancer (BTC), including gallbladder cancer (GBC), and intra- and extrahepatic cholangiocarcinoma (ICC and ECC, respectively), accounts for < 1% of adult cancers.[1,2] Most patients present with incurable, locally advanced or metastatic disease with five-year overall survival 19·1% for regional disease and 3·0% for distant disease.[3,4] In the first-line setting, patients may be treated with palliative cisplatin and gemcitabine (CISGEM)[5] or CISGEM plus durvalumab, improving overall survival compared with CISGEM alone.[6] Additional lines of cytotoxic therapy yield median overall survival of only 6·2 – 8·6 months with treatment responses < 15%.[7,8] Therefore, there is a significant unmet need in BTC.

Precision medicines targeting specific molecular subtypes of BTC are beneficial for select patients (e.g., therapies targeting FGFR2 or IDH1 alterations).[9–12] Molecular profiling has identified that human epidermal growth factor receptor 2 (HER2, ERBB2) is mutated, amplified, and/or overexpressed in 19·1% – 31·3% of GBC, 17·4% – 18·5% of ECC, and 3·7%– 4·8% of ICC.[13,14] Small studies suggest that targeting HER2 alterations in BTC has clinical benefit.[15–18]

Zanidatamab targets HER2 via two different antigen binding domains: the HER2 dimerisation domain and the extracellular juxtamembrane domain. This biparatopic format geometry results in HER2 binding in *trans* which leads to the formation of receptor/antibody clusters, receptor internalisation, and HER2 downregulation.[19] In preclinical studies, zanidatamab exhibited antitumor activity in HER2-driven neoplasia that is superior to both trastuzumab monotherapy and trastuzumab combined with pertuzumab.[19] A phase 1 zanidatamab trial demonstrated manageable safety with antitumor activity in multiple HER2-expressing/amplified tumour

types.[20] This study included a cohort of patients with BTC where 20 mg/kg zanidatamab 2QW elicited cORR of 38%.[20] The current trial, HERIZON-BTC-01, tests the hypothesis that zanidatamab is an active therapy for a *HER2*-amplified BTC patient population.

METHODS

Study design and participants

HERIZON-BTC-01 (Clinicaltrials.gov identifier: NCT04466891; ZWI-ZW25-203) is a global, multicentre, open-label, single-arm, phase 2b trial of zanidatamab in patients with *HER2*-amplified, unresectable, locally advanced, or metastatic BTC who progressed on prior gemcitabine-based therapy (Supplemental Figure S1). Patients with *HER2*-amplified tumours (*HER2*/Chr17 ratio ≥ 2·0;) by central laboratory ISH were enrolled into prospectively defined cohorts based on HER2 immunohistochemistry IHC) score: cohort 1 (IHC 2+ / 3+; defined as "HER2-positive" herein) and cohort 2 (IHC 0 / 1+). The study was conducted in accordance with the Declaration of Helsinki and International Good Clinical Practice guidelines and overseen by an independent data monitoring committee. The study protocol and amendments were approved by independent ethics committees or institutional review boards at each study site. All patients provided written informed consent. Eligible patients were age 18 or older with pathologically confirmed, unresectable, locally advanced or metastatic, *HER2*-amplified GBC, ECC or ICC and had received at least one prior gemcitabine-containing systemic chemotherapy regimen for unresectable locally advanced or metastatic disease, or in the neoadjuvant/adjuvant setting with progression or recurrence within 6 months of completion. Additional inclusion criteria included: at least one measurable target lesion per Response Evaluation Criteria in Solid Tumours version

1·1 (RECIST);[21]; left ventricular ejection fraction (LVEF) ≥ 50%; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria included prior treatment with HER2-targeting agents, and untreated or symptomatic central nervous system metastases or leptomeningeal disease. Complete eligibility criteria are included in the study protocol (Supplemental). Patients self-reported sex and/or gender and race and/or ethnicity.

Procedures

Patients received zanidatamab 20 mg/kg by intravenous infusion with premedication for infusion-related reactions (IRRs) including corticosteroids, antihistamines, and acetaminophen on Days 1 and 15 of each 28-day cycle, as previously described.[20] Dose modifications were specified in the protocol (Supplemental) and included: infusion rate reduction by 50% for IRRs, dose holds for at least 4 weeks and until recovery for decrease in LVEF, and discontinuation for interstitial lung disease grade ≥2. Patients received zanidatamab until disease progression, death, withdrawal of consent, physician decision, or loss to follow-up. Treatment decisions were based on investigator assessments of response.

Fresh or archival tumour biopsies were collected from all patients for central laboratory assessment of HER2 status by ISH and IHC. *HER2* (*ERBB2*) gene amplification status was determined by the VENTANA HER2 Dual ISH DNA Probe Cocktail assay (Test: Ventana Medical Systems, Inc., Tuscon, AZ, USA). *HER2* gene status was classified as non-amplified (*HER2*/Chr17 ratio < 2·0) or amplified (*HER2*/Chr17 ratio ≥ 2·0). The investigational VENTANA HER2/*neu* (4B5) IHC assay (Test: Ventana Medical Systems, Inc., Tuscon, AZ,

USA) was used to assess the HER2 protein expression of the same BTC tumour specimens tested with the HER2 Dual ISH assay.

Tumours were assessed by computed tomography or magnetic resonance imaging at baseline and approximately every eight weeks during the trial. Response assessments were performed by ICR and by the investigator per RECIST. Partial and complete responses (PR and CR) were confirmed with a subsequent scan performed at least four weeks after the first response. Suspected clinical progression was confirmed radiographically whenever possible. Disease assessments continue until disease progression or start of new anticancer therapy. Survival follow-up continues until death, withdrawal of consent, loss to follow-up, or trial completion.

Adverse events (AEs) were assessed at each visit and monitored throughout the trial with severity graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5·0. AEs of special interest were predefined as IRRs, cardiac events of absolute decrease in LVEF of $\geq$ 10 percentage points from pre-treatment baseline and absolute value < 50% and/or grade $\geq$ 2 heart failure, and non-infectious pulmonary toxicity. LVEF was assessed by multiple gated acquisition scan or echocardiogram performed at baseline, prior to Cycle 3 Day 1, and every 12 weeks thereafter. Laboratory evaluations (haematology, chemistry, and liver function tests) were performed on day 1 and 15 of each cycle and again at end of treatment and 30 day safety follow-up visits.

Outcomes

The primary endpoint was cORR by ICR for cohort 1, where cORR was defined as the proportion of patients who received zanidatamab and had a confirmed best overall response of

CR or PR. Secondary efficacy endpoints included: cORR by investigator; duration of response (DOR: time from first objective response [CR or PR] that is subsequently confirmed to disease progression or death from any cause) by ICR and investigator; disease control rate (DCR: percentage of patients with confirmed CR, confirmed PR, or stable disease [SD]) by ICR and investigator; progression-free survival (PFS: time from the first dose of zanidatamab to disease progression or death from any cause) by ICR and investigator; and overall survival (OS: time from first dose to death due to any cause). Cohort 1 subgroup cORRs based on geography, HER2 IHC status (2+ / 3+), anatomic site (GBC, ICC, ECC), number of prior therapies for advanced diseases, or disease stage at baseline were also examined. Patients who received prior PD–1 or PD–L1 inhibitors were analysed post-hoc. Time to first confirmed objective response was defined as the time from the first dose of zanidatamab to the earliest date a patient had an objective response that was subsequently confirmed. Only patients who had a confirmed objective response were included in the analysis of DOR. Duration of study follow-up was defined as the time from first dose to the date of data cutoff. These endpoints were also evaluated for cohort 2. Safety analyses included frequency and severity of treatment-emergent AEs, serious AEs, laboratory abnormalities, and frequency of zanidatamab dose modification or discontinuation. Pharmacokinetic and immunogenicity sampling was limited and will be analysed and reported elsewhere.

Statistical analysis

This study is registered as a single-arm trial with ClinicalTrials.gov, number NCT04466891. The sample size of approximately 75 patients was informed by Clopper-Pearson exact binomial 95%

confidence intervals (CIs). With 75 patients in cohort 1, there was a 92% chance of observing cORR with lower limit of the 95% CI excluding a historical response rate of 10%, if the true cORR was 25%.

A preclinical study with zanidatamab demonstrated that it binds to HER2-low-expressing tumour cells (MCF7) in vitro at a greater saturation than either trastuzumab or pertuzumab.[19] As it was predicted approximately 25% of screened patients with *HER2*-amplified BTC would have IHC 0 / 1+ tumours (data not shown), a cohort of 25 patients was planned to explore clinical benefit from zanidatamab treatment in this population. There was no statistical assumption tested for the exploratory cohort 2.

The primary efficacy analysis set included all patients in cohort 1 who received any zanidatamab. No interim analyses were planned. Safety was analysed in all patients in both cohorts who received any zanidatamab. Patients who had not progressed/died at the time of the analysis were censored for DOR and PFS at the time of their last tumour assessment. For OS analysis, patients who were still in survival follow-up at the data cutoff date were censored at the date they were last known alive.

Binomial Clopper-Pearson 95% CIs were calculated for categorical response outcomes. Medians for time-to-event endpoints such as DOR, PFS, and OS were estimated using the Kaplan-Meier method and corresponding 95% CIs were computed using the Brookmeyer and Crowley method[22] with log-log transformation.[23] The proportion of patients without an event at specific timepoints was also estimated using the Kaplan-Meier method along with two-sided 95% CIs based on the Greenwood estimator.[24] For PFS and DOR analysis, subjects who progressed after two or more consecutive missed response assessments were censored at the date of the last CR,

PR, SD or non-CR/non-PD. All statistical analyses and graphing were performed using SAS version 9·4.

Role of the funding source

Zymeworks BC Inc. and BeiGene Ltd. were involved in study design and data collection. Zymeworks BC Inc., Jazz Pharmaceuticals plc, and BeiGene Ltd. were involved with data analysis, data interpretation, and writing of this report.

RESULTS

HERIZON-BTC-01 enrolled 87 patients at 32 sites in 9 countries between September 2020 and March 2022. Of 847 patients prescreened for *HER2* amplification, 171 patients (20%) had *HER2*-amplified tumours. A total of 131 patients entered study screening, and 87 patients with *HER2*-amplified tumours were enrolled; 80 had HER2 IHC 2+ / 3+ tumours (cohort 1; HER2-positive) and seven had HER2 IHC 0 / 1+ (cohort 2) (Figure 1). The number of patients with HER2 IHC 0 / 1+ tumours was lower than expected, and cohort 2 enrolment was stopped when cohort 1 was completely enrolled. HER2 testing was performed on archival tumour samples for 72 of 87 and on fresh tumour tissue for 15 of 87 enrolled patients.

All enrolled patients received at least one dose of zanidatamab. Median duration of treatment was 5·06 months (interquartile range [IQR] 1·87 – 8·84; range, 0·5 – 19·8 months); patients received a median of 6·0 cycles (IQR 2·0 – 9·0; range, 1 – 21 cycles). As of the data cutoff date (10 October 2022), 18 patients (20·7%) remained on zanidatamab and 23 patients (26·4%) had

discontinued zanidatamab and continued survival follow-up (Figure 1). Radiographic progression was the most common reason for zanidatamab discontinuation (64 patients, 73·6%). Two patients discontinued treatment due to clinical progression, two to adverse event, and one to consent withdrawal. The remainder continued on treatment at the time of the data cutoff. Median duration of study follow-up was 12·4 months (IQR 9.4 – 17.2). Thirty-seven patients discontinued the study due to death, and 9 due to withdrawal of consent. The rest remained on study or in survival follow-up. Baseline characteristics are presented in Table 1.

The primary endpoint was cORR by ICR in cohort 1 (HER2-positive). All 80 patients were included in the analysis. The cORR in cohort 1 was 41·3% (95% CI: 30·4, 52·8), including one confirmed CR (1·3%) and 32 confirmed PRs (40·0%) based on ICR and investigator assessment (Table 2). Results discussed in text are based on confirmed responses per ICR unless otherwise specified. Median time to first confirmed response was 1·8 months (IQR 1·7 – 2·0; range, 1·6 – 5·5 months) with 75·8% of responses observed at the first tumour assessment after treatment initiation. The DCR was 68·8% (95% CI: 57·4, 78·7) with 22 patients (27·5%) having SD. The majority (54 patients, 67·5%) of cohort 1 had a decrease in measured tumour burden (Figure 2a). Responses assessed by the investigators were consistent with those by ICR, with a cORR of 41·3% (95% CI: 30·4, 52·8) (Table 2). No responses to zanidatamab were observed in cohort 2.

The median DOR for the 33 cohort 1 patients with confirmed objective response was 12·9 months (95% CI: 5·95, not estimable; range, 1·5 – 16·9+ months) with 16 (48·5%) patients having ongoing responses at the time of the data cutoff (Figure 2b and Supplemental Figure S2). Among the 33 patients with a response, 27 (81·8%; 95% CI: 64·5, 93·0) had response duration

of at least 16 weeks (Table 2). Treatment durations for patients with best overall response of confirmed CR or PR or stable disease are shown in Figure 2b.

Responses were observed in preplanned subgroups and the descriptive cORRs for subgroups in cohort 1 based on geography, anatomic site (GBC, ICC, ECC), number of prior therapies for advanced diseases, or disease stage at baseline were consistent with the primary analysis (Figure 3). While responses were observed in patients with *HER2*-amplified IHC 2+ / 3+ tumours, in the 62 patients with IHC 3+ BTC, cORR was higher (51·6%; 95% CI: 38·6, 64·5) than in the 18 patients with IHC 2+ BTC (5·6%; 95% CI: 0·1, 27·3). A post-hoc analysis demonstrated that responses were also observed in patients who had prior treatment with PD-1 or PD-L1 inhibitors. Of the 21 patients who received prior PD-1 or PD-L1 inhibitors, nine had confirmed responses (42·9%; 95% CI: 21·8, 66·0).

The median PFS in cohort 1 was 5·49 months (95% CI: 3·65, 7·16; range, 0·3 – 18·5+ months) (Supplemental Figure S3). The estimated Kaplan-Meier overall survival rate at 9 months was 69·9% (95% CI: 57·8, 79·1) for cohort 1; median OS data were immature at the time of data cutoff.

Most of the 87 patients treated with zanidatamab (96·6%) experienced at least one treatment-emergent AE (TEAE) (Supplemental Table S1), and 63 patients (72·4%) experienced at least one TEAE that was considered by the investigator to be related to zanidatamab treatment (TRAE). The most common (> 10%) TRAEs were diarrhoea (32 patients, 36·8%) and IRR (29 patients, 33·3%) (Table 3). Most patients (32 of 38) who experienced diarrhoea had grade 1 or 2 events, and all but two events (both grade 3) were managed in the outpatient setting, typically with loperamide. Most diarrhoea events (87 of 99) resolved by the time of data cutoff, with median

time to resolution of 2·0 days (range, 1 – 267). Sixteen patients (18·4%) experienced grade 3 TRAEs; of these, diarrhoea (4·6%), ejection fraction decreased (3·4%), and anaemia (2·3%) occurred in more than 1 patient. No grade 4 or higher TRAEs were reported.

Serious TRAEs occurred in seven patients (8·0%) and no event occurred in more than one patient. Overall, five patients died within 30 days of last treatment dose: three due to disease progression and two due to TEAEs (hepatic failure and underlying cancer) not considered related to zanidatamab treatment by the investigator. One patient experienced a multiple organ dysfunction TEAE unrelated to zanidatamab treatment that led to death 32 days after last treatment dose.

TRAEs led to dose delays in five patients (5·7%): three due to ejection fraction decreased and one each to due to diarrhoea and platelet count decreased. Three patients (3·4%) had dose reduction for TRAEs; diarrhoea and nausea led to dose reduction in one patient, and both diarrhoea and weight decreased led to dose reduction in the other two. Overall, the mean relative dose intensity, calculated as the percentage of actual dose per week over the intended dose per week, was 97·7% (standard deviation 6.1%). Two patients experienced TRAEs that led to zanidatamab discontinuation: ejection fraction decreased (grade 2) in one patient, and pneumonitis (grade 3) in the other.

Regarding TEAEs of special interest, 29 patients (33·3%) experienced an IRR, nearly all of whom (28 of 29 patients) had low-grade (grade 1 or 2) events, and all events resolved; the most common IRR symptoms were chills, pyrexia, and hypertension. The single grade 3 IRR resolved with supportive measures and did not preclude zanidatamab retreatment. Most patients who experienced IRRs (26 of 29 patients) had them during the first cycle, and most patients who had

IRRs (23 of 29 patients) did not have recurrent IRRs. A total of 22 patients (25·3%) had infusion interruption due to IRR. Confirmed cardiac events occurred in five patients (5·7%), all reported as ejection fraction decreased, with three patients having grade 3 events with absolute decreases from baseline of 17 to 36 percentage points. Of the three patients with grade 3 confirmed cardiac events, two patients received medical treatment and had zanidatamab doses delayed; one of these two patients subsequently recovered and the other had improvement. The third patient did not have any dose adjustment and recovered from the event. Three of the five confirmed cardiac events occurred during Cycle 2 and the other two occurred at Cycle 6 or later. For the two cardiac events that had resolved by data cutoff, the times to resolution were 27 days and 85 days, respectively. All cardiac events were clinically asymptomatic and confounded by pre-existing or concurrent conditions. One patient (1·1%) experienced grade 3 pneumonitis in Cycle 8 that was considered to be related to zanidatamab; the patient had no known risk factors at baseline. Zanidatamab treatment was withdrawn, and the pneumonitis was ongoing at grade 1 when the patient discontinued from the study.

The most common anti-cancer therapies received after discontinuation of study therapy included: folinic acid, fluorouracil and oxaliplatin (FOLFOX) or other 5-FU based therapies; levantinib, pyrotinib, nivolumab, and platinum (either cisplatin or oxaliplatin).

DISCUSSION

To our knowledge, the HERIZON-BTC-01 study is the largest clinical trial reported to date for the BTC *HER2*-amplified subset. The results herein are also consistent with a previously reported phase 1 trial of zanidatamab in which a cORR of 38% was observed for 21 response-

evaluable patients with *HER2*-amplified or HER2-expressing BTC,[20] demonstrating reproducible efficacy of zanidatamab in the BTC HER2 amplified subset. Most patients treated with zanidatamab in HERIZON-BTC-01 had some degree of tumour shrinkage observed early in treatment, providing further support for the utility of zanidatamab in a patient population that requires tumour control.

Acknowledging the hazards of cross-trial, indirect comparison, the antitumour activity observed for zanidatamab in HER2-positive BTC patients compares favourably to historic controls. The current treatment paradigm after a gemcitabine-containing first-line regimen is either additional cytotoxic chemotherapy or precision medicine if an actionable driver is identified and a corresponding precision medicine is available. FOLFOX and nano-liposomal irinotecan with fluorouracil and leucovorin result in ORRs of approximately 5% and 15% with median PFS values of 4·0 and 7·1 months, respectively.[7,8] It is notable that in this current trial zanidatamab demonstrated a cORR where the lower bound of the 95% CI is several-fold higher than these historic data, with a median duration of response longer than those previously reported. While the PFS reported in this study is shorter than that reported in the NIFTY study, it is challenging to interpret PFS in single-arm studies, where both biologic and clinical factors specific to the genomic population under study might influence outcomes and predictive/prognostic implications of HER2 amplification or expression in BTC have not been fully established for patients with advanced disease; some reports suggest patients with BTC with HER2 aberrations have similar or less favourable outcomes when receiving combination chemotherapy compared to the outcomes seen in the general BTC patient population.[25–33]

Patients with BTC harbouring actionable mutations targeted by approved precision medicines generally do not have overlapping HER2-positive disease.[10,12,25,26] Approved precision medicines

for each actionable genomic BTC subset also have unique operating characteristics; IDH1 inhibition, which is largely cytostatic, offers a low ORR of 2·4% and a short median PFS of 2·7 months, albeit with a meaningful proportion of patients with *IDH1*-mutant BTC exhibiting extended disease control (PFS at 12-months 22%).[34] In contrast, multiple FGFR2 inhibitors have shown clinical benefit with response rates ranging from 23% to 42%, median DOR 5 – 9·7 months, and median PFS 6·9 – 9·0 months in FGFR2 fused/rearranged tumours.[10,12] Several studies suggest that targeting HER2 may reduce tumour burden in patients with *HER2*-amplified and/or HER2-expressing BTC (ORR 23 – 36%, median DOR 4·9 – 10·8 months),[16,18,35] though these studies are limited by small sample size (25 – 39 patients), restricted geographic region, and/or non-uniform local HER2 testing. Taken together with the 38% ORR observed in the 21 patients with BTC in the zanidatamab phase 1 trial, the current findings from the HERIZON-BTC-01 trial strongly support HER2 as a therapeutic target for BTC and indicate zanidatamab may provide meaningful clinical benefit and represent a potential new targeted therapy for the treatment of HER2-positive BTC.

Based on the pre-specified subgroup analyses, zanidatamab provided treatment benefit regardless of anatomic subtype, geography, and lines of prior treatment. Sixty-three percent of patients were enrolled in Asia, possibly reflecting regional differences in disease and/or HER overexpression prevalence.[36,37] The ORRs were similar in patients enrolled in Asia compared with those enrolled in the rest of the world, indicating that geographic variation is unlikely to impact the therapeutic utility of zanidatamab (Figure 3).

Preplanned analysis based on HER2 expression level showed response in HER2 IHC 2+ / 3+ BTC. While the trial was not designed to distinguish treatment effect by HER2 status, higher response rates were observed in patients with HER2 IHC 3+ than those with HER2 IHC 2+ BTC.

It is not clear whether this trend is due to sample size, intrinsic differences between IHC 2+ / 3+ tumours, or heterogeneity of HER2 expression in the tumours.[20] The numbers of patients with HER2 IHC 2+ BTC tumours enrolled in other studies were too small to draw any conclusions.[16,20] Further studies should explore this possible differential benefit and its potential implications for patient management.

A post-hoc analysis of response in patients who had received prior PD-(L)1 therapy showed a response rate consistent with the overall results in cohort 1. As immunotherapy enters the first-line treatment space, these observations suggest that zanidatamab treatment has the potential to provide benefit to patients whose disease has progressed after receiving PD-(L)1 inhibitors in first-line therapy.

Zanidatamab showed a tolerable safety profile consistent with the data observed in patients who received zanidatamab monotherapy in the phase 1 trial.[20] The incidence of diarrhoea and cardiac events was consistent with on-target HER2 inhibition, and IRRs were predominately low grade and all resolved. There were few events leading to zanidatamab treatment discontinuation and no treatment-related deaths. This safety profile suggests that zanidatamab treatment is likely acceptable for patients who have already received cytotoxic therapy or who would be intolerant to cytotoxic therapy.

Study limitations include: single arm design; small sample size of subgroups for comparative analysis; exclusion of patients with non-measurable disease; exclusion of HER2 overexpressed tumors without HER2 amplification (currently being evaluated in NCT03929666); and short duration of follow for time to event endpoints. Correlative analysis is ongoing to nominate biomarkers for response and resistance.

In summary, zanidatamab demonstrated meaningful efficacy, including rapid and durable responses, with a favourable safety profile in the treatment of patients with HER2-positive BTC. These data support zanidatamab's potential as a new targeted therapy after failure of a first-line gemcitabine-based regimen, expanding the precision medicine options. Continued development of zanidatamab is currently ongoing for the treatment of HER2-positive BTC in combination with standard first-line CISGEM (NCT03929666). Additionally, zanidatamab is being evaluated for other HER2-expressing solid tumours, including in a phase 3 trial for first-line treatment of gastroesophageal adenocarcinoma (NCT05152147).

CONTRIBUTORS

JJH, JF, D-YO, HW, MD and SP were part of the Study Steering Committee (SSC). The SSC, Zymeworks BC Inc., and BeiGene Ltd. contributed to the design of the study. JJH, JF, D-YO, HJC, JWK, H-MC, LeB, H-CS, TM, FX, J-PM, JY, JB, M-AL, MAT, EYC, DUK, HW, MD, SP collected the data. YB and LB analysed the data. All authors accessed and interpreted the data. JJH, JF, YB, LB, JM, and PG drafted the manuscript. All authors participated in critically reviewing, revising, and approving the final version of this manuscript. The corresponding author had full access to all data in this study and holds final responsibility for the decision to submit the manuscript for publication.

DECLARATION OF INTERESTS

1. JJH reports support from Zymeworks to self (uncompensated, steering committee), and research support to institution for this work; grants or contracts from Bristol Myers Squibb,

Boehringer Ingelheim, CytomX, Debiopharm, Eli Lilly, Genoscience, Incyte, Loxo @ Lilly, Novartis, Polaris, Pfizer, Zymeworks, and Yiviva outside of this work; consulting fees from Adaptimmune, AstraZeneca, Bristol Myers Squibb, Exelexis, Elevar, Eisai, Genoscience (uncompensated), Hepion, Imvax, Merck (data and safety monitoring board [DSMB]) Medivir, QED, Tyra, and Zymeworks (uncompensated) outside of this work; and participation on a DSMB or advisory board for Adaptimmune, AstraZeneca, Bristol Myers Squibb, Exelexis, Elevar, Eisai, Genoscience (uncompensated), Hepion, Imvax, Merck (DSMB), Medivir, QED, Tyra, and Zymeworks (uncompensated) outside of this work.

2. JF declares no competing interests.
3. D-YO reports grants or contracts from AstraZeneca, Novartis, Array, Eli Lilly, Servier, BeiGene, MSD, and Handok to institution outside of this work; and participation on advisory boards for AstraZeneca, Novartis, Genentech/Roche, Merck Serono, Bayer, Taiho, ASLAN, Halozyme, Zymeworks, BMS/Celgene, BeiGene, Basilea, Turning Point, Yuhan, Arcus Biosciences, and IQVIA outside of this work.
4. HJC reports consulting fees to self from Roche and AstraZeneca outside of this work.
5. JWK reports grants or contracts from Inno.N and Jeil Pharm outside of this work; and consulting fees from AstraZeneca, Beyond Bio, Eisai, MSD, BeiGene, Bristol Myers Squibb/Celgene, GC Cell, ONO, Sanofi-Aventis, Servier, and TCUBEit outside of this work.
6. H-MC reports funding for clinical trial from Zymeworks Inc. to institution for this work.
7. LeB declares no competing interests.
8. HC-S reports consulting fees from TopAlliance outside of this work; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from TopAlliance and AstraZeneca outside of this work.

9. TM declares no competing interests.
10. FX declares no competing interests.
11. J-PM reports payment or honoraria for lectures from MSD, BMS, Bayer, Astellas, and Merck outside of this work .
12. JY declares no competing interests.
13. JB reports consultancy fees from Taiho, Incyte, Servier, BMS outside of this work; grants or contracts for research from Incyte outside of this work; and payment or honoraria as a speaker from Incyte and Servier outside of this work.
14. M-AL declares no competing interests.
15. MAT reports payment or honoraria as a speaker from Natera and Caris outside of this work.
16. EYC declares no competing interests.
17. DUK declares no competing interests.
18. HW reports support from Zymeworks for this work; consulting fees from Oncosil outside of this work; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Servier, Pierre Fabre, Incyte, Bayer, Merck KGaA, Amgen, Roche/Genentech/FM, SIRTEX Medical, BMS (Celgene), BTG, and Seagen outside of this work; payment for expert testimony from Oncosil outside of this work; support for attending meetings and/or travel from Pierre Fabre, Servier, and Merck KGaA outside of this work; participation on a DSMB or advisory board from Incyte, Bayer, Merck KGaA, Amgen, Roche/Genentech/FM, SIRTEX Medical, Erytech Pharma, BMS (Celgene), BTG, and Seagen outside of this work; and leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid from Pfizer and Zymeworks (trial steering committee for both) outside of this work.

19. MD reports participation on advisory boards from Roche, Merck Serono, Amgen, Bayer, Servier, Pierre Fabre, BeiGene, Astra Zeneca, Daiichi Sankyo, Merck-Sharp-Dohme, and Boehringer Ingelheim outside of this work; speaker in symposia from Roche, Merck Serono, Bayer, Merck-Sharp-Dohme, Servier, Pierre Fabre, and Daiichi Sankyo outside of this work; institutional research funding from Roche, Merck Serono, and Keocyt outside of this work; and participation in independent data monitoring committees for Roche and Pancan outside of this work. Spouse is head of the oncology business unit at Sandoz France.
20. YB reports employment by BeiGene Ltd at the time of the study and ownership of BeiGene stock or stock options outside of this work.
21. LB reports employment by Zymeworks at the time of the study and ownership of Zymeworks stock or stock options outside of this work.
22. JM reports ownership of stock or stock options of BeiGene Ltd. as an employee.
23. PG reports employment by Zymeworks at the time of the study; support for attending meetings and/or travel from Zymeworks Inc. outside of this work; and ownership of Zymeworks Inc and Seagen stock or stock options outside of this work.
24. SP reports advisory/consultancy fees to self from Zymeworks, Ipsen, Novartis, Janssen, Boehringer Ingelheim, and AskGene Pharma outside of this work; and research grant/funding to their institution from Mirati Therapeutics, Lilly, Xencor, Novartis, Rgenix, Bristol-Myers Squibb, Astellas Pharma, Framewave, 4D Pharma, Boehringer Ingelheim, NGM Biopharmaceuticals, Janssen, Arcus Biosciences, Elicio Therapeutics, BioNtech, Ipsen, Zymeworks, Pfizer, ImmunoMET, Immuneering, Amal Therapeutics outside of this work.

DATA SHARING

Deidentified patient-level data and supporting clinical trial documents may be available upon request by qualified researchers through the Zymeworks website. Data transfer agreements and approval by the trial management team may be required. Please see the website www.zymeworks.com/datarequest for details.

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FIGURE CAPTIONS

Figure 1: Trial profile

[a] Other reasons included one each of: BTC not confirmed, inadequate cardiac function, consent withdrawal, concurrent hepatobiliary disorders, prior or concurrent malignancy, significant infection, and QTcF > 470 ms.

Figure 2a: Target lesion reduction per independent central review (ICR) – (cohort 1 – HER2-positive)

BTC = biliary tract cancer; ECC = extrahepatic cholangiocarcinoma; GBC = gallbladder cancer; ICC = intrahepatic cholangiocarcinoma; IHC = immunohistochemistry

* indicates patients with IHC 2+ status, all other patients had IHC status of 3+.

One patient without post-baseline response assessment was excluded from this analysis.

Figure 2b: Treatment duration per RECIST 1·1 by independent central review (ICR) – (cohort 1 – HER2-positive)

Note: Treatment decisions were based on investigator assessments of response.

BTC = biliary tract cancer; E = extrahepatic cholangiocarcinoma; G = gallbladder cancer; I = intrahepatic cholangiocarcinoma; IHC = immunohistochemistry

Figure 3: Objective response rate per independent central review (ICR) by subgroups (cohort 1 – HER2-positive)

CI = confidence interval; ECC = extrahepatic cholangiocarcinoma; GBC = gallbladder cancer; ICC = intrahepatic cholangiocarcinoma; IHC = immunohistochemistry

Reference lines show bounds of 95% confidence interval for the overall group.