Zanidatamab in Previously Treated HER2-Positive (HER2+) Biliary Tract Cancer (BTC): Overall survival (OS) and Longer Follow-Up From the Phase 2b HERIZON-BTC-01 Study

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Background

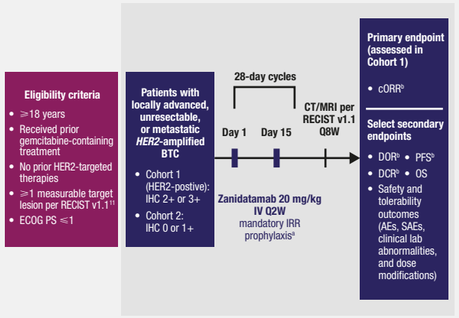
- Biliary tract cancer (BTC) encompasses a group of rare and aggressive gastrointestinal tract cancers, including gallbladder cancer (GBC) and intrahepatic and extrahepatic cholangiocarcinoma (iCCA and eCCA, respectively)[1]
- BTC accounts for less than 1% of adult cancers and is associated with a poor prognosis (5-year survival of 15% overall and 3% for metastatic disease)[2,3]
- After failure of first-line treatment, subsequent chemotherapy is associated with a median overall survival (OS) of approximately 6-9 months and poor tolerability[4,5]
- Human epidermal growth factor receptor 2 (HER2) protein overexpression or gene amplification is observed in a subset of patients with BTC (approximately 19-31% of GBC, 4-5% of iCCAs, and 17-19% of eCCAs)[6,7]; therefore, HER2 is a rational therapeutic target in BTC
- Zanidatamab is a dual HER2-targeted bispecific antibody that targets 2 distinct sites on HER2, promoting HER2 receptor crosslinking and driving multiple mechanisms of action, including[8]:
  - 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 on the results of the phase 2b HERIZON-BTC-01 trial (NCT04466891)[9]
- In the HERIZON-BTC-01 trial, after a median follow-up of 12.4 months (data cutoff: October 10, 2022), zanidatamab showed encouraging antitumor activity (41.3% confirmed objective response rate [cORR]) with rapid and durable responses and a manageable safety profile in patients with previously treated HER2-positive BTC[10]
  - OS data were not yet mature at the time of the primary analysis[10]

Objective

- To assess the efficacy, including OS, and safety of zanidatamab in patients with HER2-positive BTC enrolled in HERIZON-BTC-01

Methods

Figure 1. Study Design



[a]Prophylactic treatment included corticosteroids (hydrocortisone 100 mg IV or dexamethasone 10 mg IV), antihistamines (diphenhydramine 50 mg oral or IV), and acetaminophen (650-1000 mg oral); [b]Per ICR.
AE, adverse event; BTC, biliary tract cancer; cORR, confirmed objective response rate; CT, computerized tomography; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; IRR, infusion-related reaction; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival, PFS, progression-free survival; Q2W, once every 2 weeks; Q8W, once every 8 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SAE, serious adverse event.

- HERIZON-BTC-01 is an open-label, global, phase 2b study of zanidatamab in previously treated patients with advanced or metastatic *HER2*-amplified BTC (**Figure 1**)
  - Patients with centrally confirmed *HER2*-amplified tumors (assessed by in situ hybridization) were prospectively assigned into 1 of 2 cohorts:
    - HER2-positive: Cohort 1 (centrally confirmed IHC 2+ or 3+)
    - Others: Cohort 2 (centrally confirmed IHC 0 or 1+)
- Updated efficacy analyses reported here include only Cohort 1 (final Cohort 2 data were previously reported).[10] Safety analyses include all patients

Results

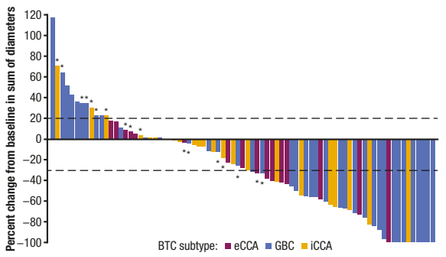
Table 1. Baseline Demographics and Patient Disease Characteristics[9]

Characteristic	HER2-Positive (Cohort 1; n=80)	All Patients (N=87)
Age, median (IQR)	64.0 (57.5, 70.0)	64.0 (58.0, 70.0)
Female, n (%)	45 (56.3)	47 (54.0)
Race, n (%)[a]		
Asian	52 (65.0)	57 (65.5)
White	23 (28.8)	25 (28.7)
Other	5 (6.2)	5 (5.7)
ECOG PS, n (%)		
0	22 (27.5)	23 (26.4)
1	58 (72.5)	64 (73.6)
BTC subtype, n (%)		
GBC	41 (51.3)	45 (51.7)
iCCA	23 (28.8)	26 (29.9)
eCCA	16 (20.0)	16 (18.4)
HER2 status by central assessment, n (%)		
IHC 3+	62 (77.5)	62 (71.3)
IHC 2+	18 (22.5)	18 (20.7)
IHC 1+	0 (0)	3 (3.4)
IHC 0	0 (0)	4 (4.6)
Lines of prior therapy for metastatic or locally advanced disease, median (IQR)[b,c]	1.0 (1, 2)	1.0 (1, 2)
Previous systemic therapy, n (%)		
Gemcitabine-based[b]	80 (100)	87 (100)
Gemcitabine + cisplatin[d]	61 (76.2)	65 (74.7)
Fluoropyrimidine-based[d,e]	27 (33.8)	31 (35.6)
PD-1/PD-L1 inhibitor[d]	21 (26.2)	22 (25.3)
Gemcitabine + fluoropyrimidine[d]	5 (6.2)	5 (5.7)

[a]Numbers may not sum to 100% due to rounding to the nearest integer; [b]Includes gemcitabine-based therapies received in the adjuvant/neoadjuvant setting if progression occurred within 6 months of completion of therapy or surgery; [c]Total regimens as designated by the investigator; [d]Patients were counted at most once under each regimen type received and may be counted in multiple categories; [e]Excludes regimens in combination with gemcitabine.
BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry; IQR, interquartile range; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

- From September 15, 2020, to March 16, 2022, 80 patients were enrolled in Cohort 1 and 7 patients were enrolled in Cohort 2. Data cutoff for this analysis was July 28, 2023
- The baseline demographics and disease characteristics have been previously reported[10] and are summarized in **Table 1**
- The median (range) duration of follow-up was 21.9 (16-34) months
- Zanidatamab treatment was ongoing for 9 (11%) patients, and 11 (14%) patients were in survival follow-up

Figure 2. Target Lesion Reduction in Patients With HER2-Positive BTC (Cohort 1)[a]



[a]Indicates patients with tumors of IHC 2+ status; all other patients had tumors with IHC status of 3+.
[b]Only patients with measurable disease at baseline and at least 1 post-baseline assessment were included (n=79).
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.
BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry.

Table 2. Disease Response in Patients With HER2-Positive BTC (Cohort 1)

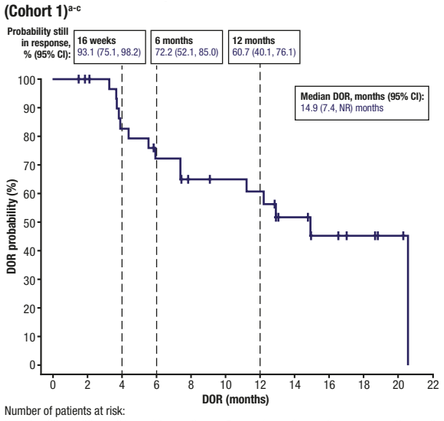
Antitumor Activity (Cohort 1)[a]	n=80
cORR,[b] n (%) [95% CI]	33 (41.3) [30.4, 52.8]
Complete response, n (%)	2 (2.5)
Partial response, n (%)	31 (38.8)
Stable disease, n (%)	22 (27.5)
Progressive disease, n (%)	24 (30.0)
DCR,[c] n (%) [95% CI]	55 (68.8) [57.4, 78.7]
CBR,[d] n (%) [95% CI]	38 (47.5) [36.2, 59.0]

Antitumor Activity in IHC Subgroups	IHC 3+ (n=62)	IHC 2+ (n=18)
cORR, n (%) [95% CI]	32 (51.6) [38.6, 64.5]	1 (5.6) [0.1, 27.3]

[a]Efficacy analysis (ie, all patients in Cohort 1 who received any dose of zanidatamab) per ICR; [b]One patient was not evaluable; [c]Best overall response of stable disease or confirmed complete response or partial response; [d]Stable disease ≥24 weeks or confirmed best overall response of complete response or partial response.
BTC, biliary tract cancer; CBR, clinical benefit rate; CI, confidence interval; cORR, confirmed objective response rate; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry.

- With additional follow-up, the cORR remained consistent with the primary analysis (41.3%; IHC 3+ subset: 51.6%)
  - One additional patient achieved a complete response (n=2; 2.5%)

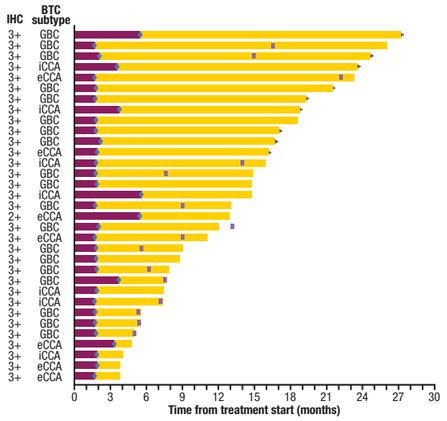
Figure 3. Duration of Response in Patients With HER2-Positive BTC (Cohort 1)[a-c]



[a]Per ICR in patients with confirmed responses (n=33); [b]Estimates per Kaplan-Meier method; median DOR CIs based on the Brookmeyer and Crowley method with log-log transformations; [c]CIs at 16 weeks, 6 months, and 12 months based on the Greenwood method.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; NR, not reached.

- With additional follow-up, the median duration of response (DOR; 95% confidence interval [CI]) increased by approximately 2 months to 14.9 (7.4, not reached [NR]) months compared with the primary analysis[10]
  - **The median DOR (95% CI) in patients with IHC 3+ tumors was 14.9 (7.4, NR) months**
  - The DOR in the 1 responder with IHC 2+ tumors was 7.5 months
- Among all patients in Cohort 1, the median OS (95% CI) was 15.5 (10.4, 18.5) months
  - **In patients with IHC 3+ tumors, the median OS (95% CI) was 18.1 (12.2, 23.2) months**

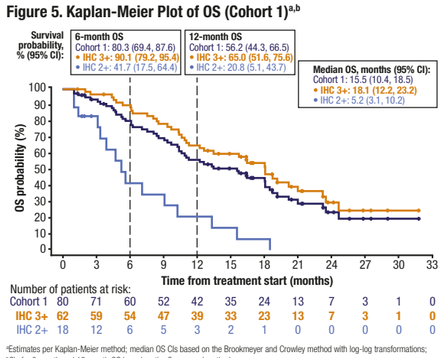
Figure 4. Treatment Duration and Response by Time Point in Confirmed Responders per ICR (Cohort 1)[a]



[a]Patients with confirmed responses only (n=33).
BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; ICR, independent central review; IHC, immunohistochemistry.

- At the time of data cutoff, 8 patients had an ongoing response and were continuing to have radiographic follow-up, where the longest response was 20.3 months
- Median progression-free survival (PFS; 95% CI) was maintained (5.5 [3.6, 7.3] months) compared with the primary analysis[10]; the longest PFS time was 25.7 months, which was ongoing at the time of data cutoff
  - **In patients with IHC 3+ tumors, the median PFS (95% CI) was 7.2 (5.4, 9.4) months**
  - In patients with IHC 2+ tumors, the median PFS (95% CI) was 1.7 (1.0, 3.3) months

Figure 5. Kaplan-Meier Plot of OS (Cohort 1)[a,b]



[a]Estimates per Kaplan-Meier method; median OS CIs based on the Brookmeyer and Crowley method with log-log transformations; [b]CIs for 6-month and 12-month OS based on the Greenwood method.
CI, confidence interval; IHC, immunohistochemistry; OS, overall survival.

- Median OS (95% CI) was 15.5 (10.4, 18.5) months; the longest survival time was 31.8 months, which was censored without death at the time of data cutoff

Table 3. Overall Safety of Zanidatamab (Cohorts 1 and 2)

	N=87
Any TEAE, n (%)	84 (96.6)
Any TRAE, n (%)	63 (72.4)
Grade 1-2	45 (51.7)
Grade 3-4[a]	18 (20.7)
Grade 5	0 (0)
Serious TRAEs, n (%)[b]	8 (9.2)
TRAEs leading to treatment discontinuation, n (%)	2 (2.3)[c]

	All grades	Grades 3-4
Most common TRAEs,[d] n (%)		
Diarrhea	32 (36.8)	4 (4.6)
Infusion-related reaction	29 (33.3)	1 (1.1)
Ejection fraction decreased	9 (10.3)	3 (3.4)
Nausea	8 (9.2)	1 (1.1)
Alanine aminotransferase increased	6 (6.9)	1 (1.1)
Aspartate aminotransferase increased	6 (6.9)	2 (2.3)
Vomiting	6 (6.9)	0 (0)
Fatigue	5 (5.7)	0 (0)
Anemia	4 (4.6)	3 (3.4)
AESI, n (%)		
Infusion-related reaction	29 (33.3)	1 (1.1)
Confirmed cardiac events	5 (5.7)	3 (3.4)
Non-infectious pulmonary toxicities	1 (1.1)	1 (1.1)

[a]One patient experienced a grade 4 TRAE (aspartate aminotransferase increased); [b]Included alanine aminotransferase increased and aspartate aminotransferase increased (both occurred in 1 patient), anemia, diarrhea, ejection fraction decreased, enteritis, infusion-related reaction, oral candidiasis, and pneumonitis (each occurred in 1 patient); [c]One was due to pneumonitis and the other was due to ejection fraction decreased; [d]Any-grade TRAE reported in ≥5% of patients or grade ≥3 TRAE in ≥2 patients.
AESI, adverse event of special interest; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

- With additional follow-up, zanidatamab continued to have a manageable safety profile with no new safety signals identified
- There were no deaths related to zanidatamab treatment
- Treatment-related adverse events (TRAEs) leading to dose reductions remained infrequent
  - Grade 3 diarrhea (n=1), grade 1 diarrhea and grade 1 nausea (n=1), and grade 2 weight decreased (n=1)
- One patient experienced serious TRAEs since the primary analysis[10] (alanine aminotransferase increased and aspartate aminotransferase increased)
- No additional patients discontinued treatment due to TRAEs since the primary analysis[10]

Conclusions

- With additional follow-up from the primary analysis, zanidatamab continues to demonstrate durable and sustained responses (cORR of 41.3%; 51.6% in IHC 3+ subset), with a median DOR of 14.9 months
- The median OS of 18.1 months in the HER2 IHC 3+ subset (15.5 months in Cohort 1) is notable in this patient population who historically have poor outcomes after gemcitabine-based treatment
- The safety profile of zanidatamab monotherapy remained manageable with favorable tolerability
  - Serious or high-grade TRAEs were infrequent, as were treatment discontinuations due to TRAEs
  - There were no treatment-related deaths
- The clinical development of zanidatamab in the treatment of HER2-positive BTC continues with the ongoing, global, randomized phase 3 study (HERIZON-BTC-02; NCT06282575) of zanidatamab in combination with standard-of-care therapy in the first-line setting for patients with HER2-positive BTC

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