Letters

RESEARCH LETTER

Zanidatamab in HER2-Positive Metastatic Biliary Tract Cancer: Final Results From HERIZON-BTC-01

Metastatic biliary tract cancer (BTC) has a poor prognosis (median overall survival [OS] <13 months with first-line therapies and 6-9 months for subsequent chemotherapy).[1,2] Human epidermal growth factor receptor 2 (HER2; encoded by *ERBB2*) overexpression occurs in a subset of BTC and is a precision therapy target.[3]

Zanidatamab, a dual HER2-targeted bispecific antibody, received accelerated US approval for adults with previously treated, unresectable, or metastatic HER2-positive (immunohistochemistry [IHC] score of 3+) BTC and conditional authorization in the European Union and China based on the phase 2 HERIZON-BTC-01 trial.[4,5] Here, we report the final analysis of HERIZON-BTC-01, which includes OS and patient-reported outcome of worst pain in patients with *ERBB2*-amplified BTC with an IHC score of 3+ or 2+ after 33 months of follow-up.

Supplemental content

Methods | In HERIZON-BTC-01 (NCT04466891),[4] patients with *ERBB2*-amplified, locally advanced, or metastatic BTC with disease progression with or following prior gemcitabine-based therapy received zanidatamab, 20 mg/kg, intravenously every 2 weeks in 28-day cycles. Trial sites received local independent ethics committee approval. Participants provided written informed consent. The trial protocol is in Supplement 1 and the statistical analysis plan in Supplement 2.

The primary end point was confirmed objective response rate (cORR) by independent central review. Secondary end points included duration of response, disease control rate, progression-free survival, OS, and safety outcomes. Patient-reported worst pain in the last 24 hours was evaluated using the Brief Pain Inventory-Short Form (rated 0 [no pain] to 10 [worst pain imaginable]). Analyses were conducted using SAS version 9.4.

Results | Between September 15, 2020, and March 16, 2022, 80 patients (45 [56%] female; 35 [44%] male; median [range] age, 64 [32-79] years) with IHC 2+ or 3+ tumors were enrolled. The median (range) follow-up was 33.4 (28.0-45.0) months, an additional 21 months from the initial report.[4] Thirty-five patients (44%) received anticancer therapy after discontinuing zanidatamab.

The cORR was 41.3% (95% CI, 30.4-52.8), the median duration of response was 14.9 months (95% CI, 7.4-24.0), and the median OS was 15.5 months (95% CI, 10.4-18.7) (**Table**; **Figure**, A). At the time of best overall response, zanidatamab responders demonstrated reduced mean (SD) worst pain scores compared with baseline (complete response, −4.0 [not evaluable]; partial response, −1.0 [2.5]), and those with progressive disease reported an increase (2.4 [2.9]); 59 patients (74%) completed the question at both assessments.

In 62 patients with IHC 3+ tumors, cORR was 51.6% (95% CI, 38.6-64.5), and median OS was 18.1 months (95% CI, 12.2-22.9) (Table; Figure, A). Among 18 patients with IHC 2+ tumors, there was 1 partial response (cORR, 5.6%; 95% CI, 0.1-27.3), and median OS was 5.2 months (95% CI, 3.1-10.2).

Overall, 61 patients (76%) experienced 1 or more treatment-related adverse event (TRAE). Grade 3 TRAEs occurring in more than 2 patients were diarrhea (4 [5.0%]), decreased ejection fraction (3 [3.8%]), and anemia (3 [3.8%]) (Figure, B). There were no treatment-related deaths. Two patients (3%) discontinued zanidatamab due to TRAEs.

Discussion | To our knowledge, HERIZON-BTC-01 remains the largest trial with the longest reported median follow-up (33.4 months) of a HER2-targeted treatment in HER2-positive BTC.[4,6]

Table. Disease Response by Independent Central Review in Patients With HER2-Overexpressing Advanced Biliary Tract Cancer

Measure	Patients, No. (%)		
	All patients (n = 80)	IHC 3+ tumors (n = 62)	IHC 2+ tumors (n = 18)
cORR, No. (%; 95% CI)	33 (41; 30-53)	32 (52; 39-65)	1 (6; 1-27)
Confirmed BOR			
Complete response	3 (4)	3 (5)	0
Partial response	30 (38)	29 (47)	1 (6)
Stable disease	22 (28)	17 (27)	5 (28)
Progressive disease	24 (30)	13 (21)	11 (61)
Not evaluable[a]	1 (1)	0	1 (6)
DCR, No. (%; 95% CI)[b]	55 (69; 57-79)	49 (79; 67-88)	6 (33; 13-59)
DOR			
Total, No.	33	32	1
Median (95% CI), mo	14.9 (7.4-24.0)	14.9 (7.4-24.0)	NE[c]
PFS, median (95% CI), mo	5.5 (3.7-7.3)	7.2 (5.4-9.4)	1.7 (1.1-3.3)

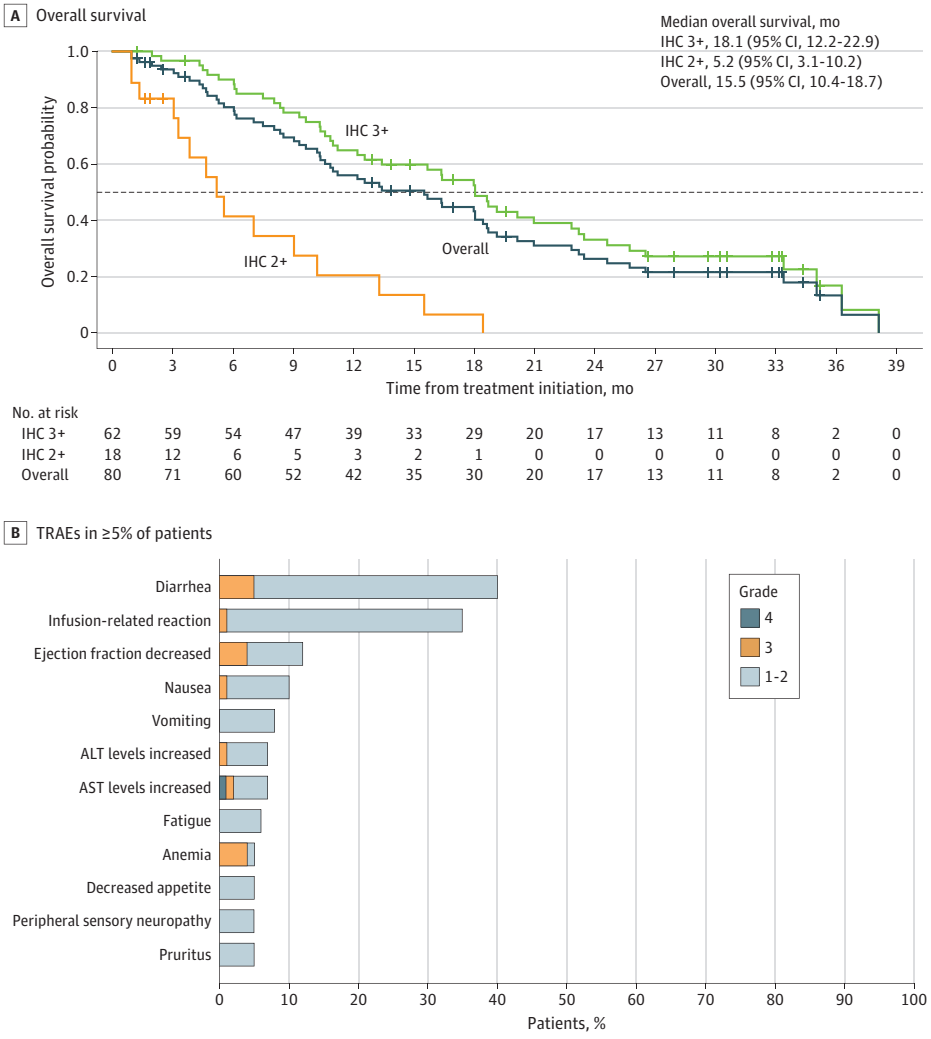
Abbreviations: BOR, best overall response; cORR, confirmed object response rate; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; PFS, progression-free survival.

[a] No evaluable postbaseline response assessment.

[b] Disease control was defined as a BOR of stable disease or confirmed complete response or partial response.

[c] The responder in the IHC 2+ tumor subset was censored at 7.5 months.

Figure. Long-Term Outcomes in Patients With HER2-Overexpressing Advanced Biliary Tract Cancer



A, Overall survival defined as the time from first dose to the date of death. B, Percentage of patients who experienced common (5% or more of patients) treatment-related adverse events (TRAEs). No grade 5 TRAEs were reported. ALT indicates alanine transaminase; AST, aspartate transaminase; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

The median OS of 15.5 months (18.1 months in the IHC 3+ subset) is notable for this treatment-refractory population.[1,2] Relative to IHC 3+ tumors, the more modest activity in IHC 2+/amplified tumors observed here supports reflex IHC testing and identifies a cohort for deeper investigation.

Durable responses were maintained; 2 patients with partial response from the primary analysis converted to complete response, supporting continued benefit with zanidatamab.[4] Furthermore, pain reduction among zanidatamab responders suggests potential positive impact on quality of life. No new safety concerns or treatment-related deaths were observed, and treatment-related discontinuations remained low with extended use.[4] Limitations include the post hoc nature of the subset analyses and the potential of nonrandom missing data for pain scores.

These findings support the clinically meaningful benefit of zanidatamab for patients with treatment-refractory HER2-positive BTC. The ongoing phase 3 HERIZON-BTC-302 trial (NCT06282575) is evaluating zanidatamab with standard-of-care first-line treatment in patients with HER2-positive (IHC 3+ or IHC 2+/amplified) BTC.

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Data Sharing Statement: See Supplement 4.

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