China Subgroup Results of the Phase (Ph) 2b HERIZON-BTC-01 Study: Zanidatamab in Previously-Treated HER2-Amplified Biliary Tract Cancer (BTC)

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Disclosures

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Background

- There remains a high unmet need for patients with advanced BTC in China due to higher incidence[1,2] and the lack of effective chemotherapies in later-line settings[3-5]
- Zanidatamab is a novel human epidermal growth factor receptor 2 (HER2)–targeted bispecific antibody that binds in a trans fashion to two non-overlapping extracellular domains of HER2[6-8]
- In the primary and updated analyses of the HERIZON-BTC-01 study,[9] zanidatamab demonstrated a meaningful clinical benefit with a manageable safety profile in patients with treatment-refractory HER2+ BTC

Objective: To present efficacy and safety results for participants enrolled in Cohort 1 (HER2 immunohistochemistry 2+ or 3+) of HERIZON-BTC-01 from China at the data cutoff of July 28, 2023.

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5. Yoo et al. *Lancet Oncol.* 2021;22(11):1560-1572. 6. Weisser et al. *Nat Commun.* 2023;14:1394. 7. Kahraman S, Yalcin S. *Onco Targets Ther.* 2021;14:4149-4162. 8. Bedard et al. Poster presented at: SABCS 2021; December 7-10, 2021; San Antonio, TX. Poster P2-13-07. 9. Harding et al. *Lancet Oncol.* 2023;24(7):772-782.

Study Design

HERIZON-BTC-01: Phase 2b, open-label, multicenter study (NCT04466891)

Inclusion criteria

- Adults diagnosed with HER2-amplified,[a] unresectable, locally advanced or metastatic BTC
- ≥1 prior systemic therapy for advanced disease, including gemcitabine
- Experiencing progressive disease/intolerance following the most recent prior therapy
- ECOG PS 0-1

→ **Zanidatamab**
20 mg/kg IV Q2W[b] →

Continue until treatment discontinuation due to

- Adverse event
- Death
- Lost to follow-up
- Withdrawal by patient
- Physician decision (non-AE, non-PD)
- Pregnancy
- Progressive disease[c]
- Study termination

Primary endpoint[d]

- ICR-assessed confirmed ORR

Select secondary endpoints

- ICR-assessed DCR,[e] DoR,[e] PFS[e]
- Overall survival
- Adverse events

[a]Assessed by in situ hybridization. [b]On Days 1 and 15 of each 28-day cycle. [c]Either radiographic progression or unequivocal clinical progression, defined as worsening or reemergence of preexisting symptoms relating to underlying cancers (eg, increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes, or a marked deterioration in ECOG PS. [d]As assessed by ICR per RECIST v1.1. [e]As assessed by ICR.

Abbreviations: AE, adverse event; BTC, biliary tract cancer; 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; IV, intravenous; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q2W, every 2 weeks; RECIST v 1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

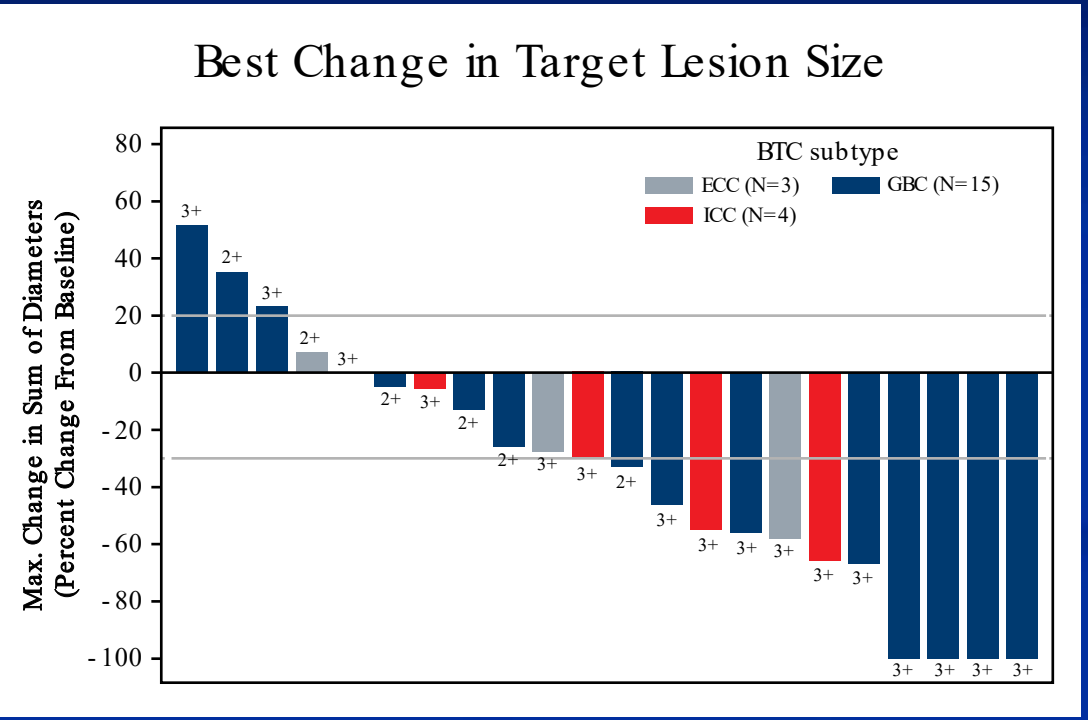
Baseline Demographics and Disease Characteristics

	China Cohort 1 (N=22)	Global Cohort 1 (N=80)
Median age (range), years	60 (42.0- 79.0)	64 (32.0- 79.0)
Female, n (%)	12 (54.5)	45 (56.3)
ECOG Performance Status, n (%)		
0	6 (27.3)	22 (27.5)
1	16 (72.7)	58 (72.5)
Disease subtype, n (%)		
Gallbladder cancer	15 (68.2)	41 (51.3)
Intrahepatic cholangiocarcinoma	4 (18.2)	23 (28.8)
Extrahepatic cholangiocarcinoma	3 (13.6)	16 (20.0)
HER2 status,[a] n (%)		
IHC3+	16 (72.7)	62 (77.5)
IHC2+	6 (27.3)	18 (22.5)
Disease stage at study entry, n (%)		
IIIA/IIIB	0 (0.0)/4 (18.2)	1 (1.3)/8 (10.0)
IVA/IVB	4 (18.2)/14 (63.6)	27 (33.8)/44 (55.0)
Prior systemic therapy for metastatic or locally advanced disease		
Median (range)	1 (1.0- 5.0)	1 (1.0- 7.0)

Data cutoff: July 28, 2023. Median duration of study follow-up was 19.8 months (range, 16.5-26.3), with 2 patients (9.1%) remaining on study treatment. [a]All patients were ISH (in situ hybridization)+ at screening.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

Disease Response

	China Cohort 1 (N=22)	Global Cohort 1 (N=80)
Confirmed best overall response, n (%)		
Complete response	0 (0.0)	2 (2.5)
Partial response	9 (40.9)	31 (38.8)
Stable disease	9 (40.9)	22 (27.5)
Progressive disease	4 (18.2)	24 (30.0)
Not evaluable	0 (0.0)	1 (1.3)
Confirmed objective response rate,[a] %	40.9	41.3
95%CI	20.7-63.6	30.4-52.8
Disease control rate,[b] %	81.8	68.8
95%CI	59.7-94.8	57.4-78.7



Clinically meaningful antitumor activity was seen in patients from China, comparable with that in the overall population

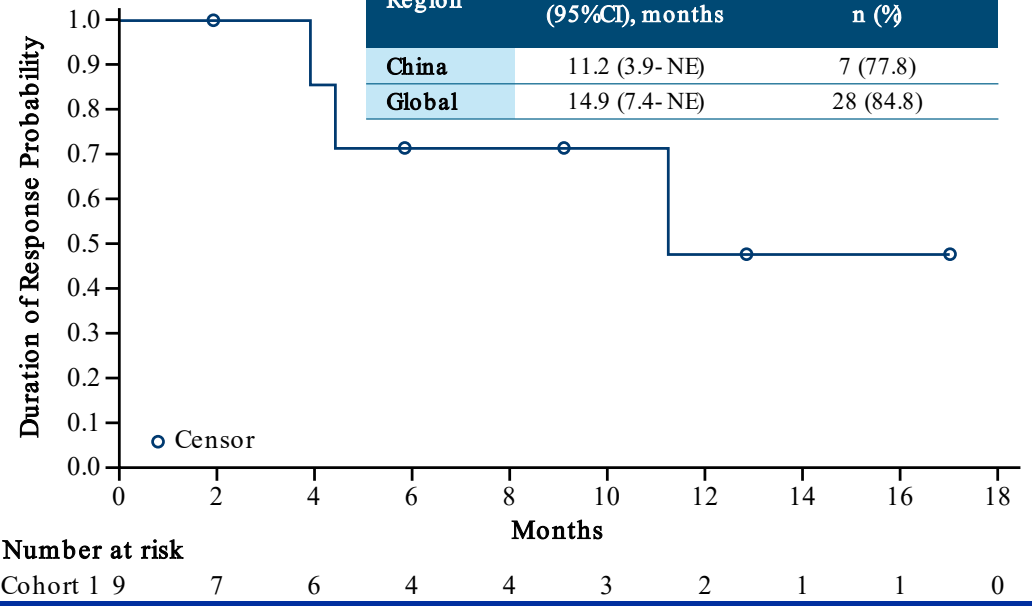
Disease response table: ICR-assessed per RECIST v1.1 (Efficacy Analysis Set, subgroup from China). The 95%CI was estimated using the Clopper-Pearson method unless otherwise indicated. [a]Includes only confirmed CRs and PRs. [b]Best overall response of stable disease or non-CR/non-PD or confirmed CR or PR. Target lesion size figure: Target lesion reduction in Cohort 1 by ICR (Response Evaluable Analysis Set, subgroup from China). IHC status for each patient is displayed above the individual bars. Only patients with measurable disease at baseline and at least one post-baseline assessment are included in the figure.

Abbreviations: BTC, biliary tract cancer; CI, confidence interval; CR, complete response; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; ICR, independent central review; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

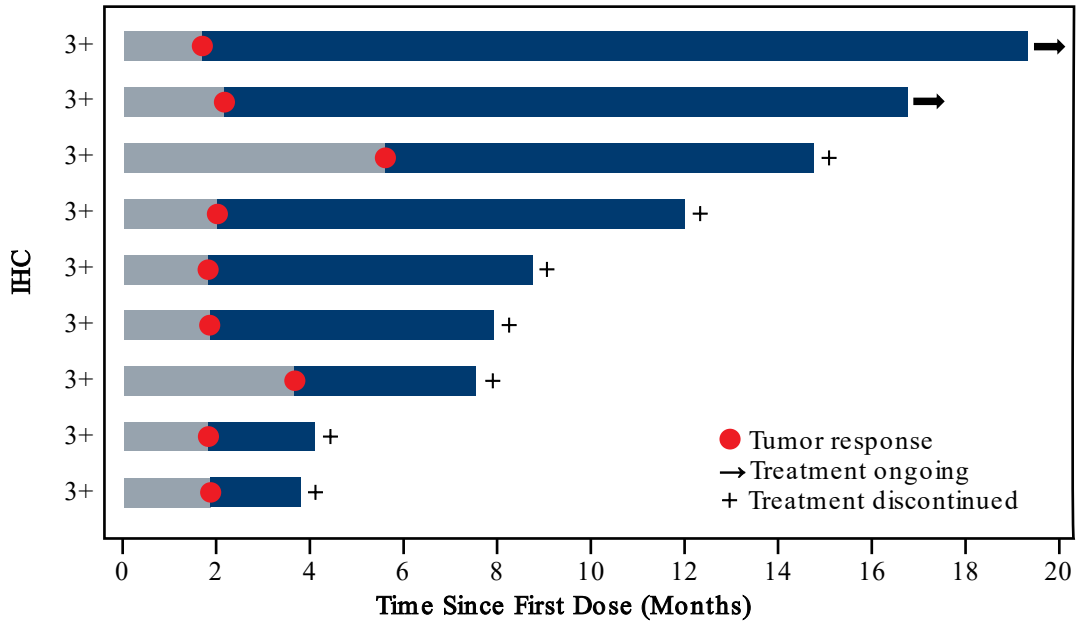
Duration of Response in Confirmed Responders

Duration of Response

Region	Median DoR[b] (95%CI), months	DoR ≥16 weeks n (%)
China	11.2 (3.9- NE)	7 (77.8)
Global	14.9 (7.4- NE)	28 (84.8)



Treatment Duration



Among confirmed responders, response was durable with a median DoR of 11.2 months, and 7 patients (77.8%) had a response duration of ≥16 weeks

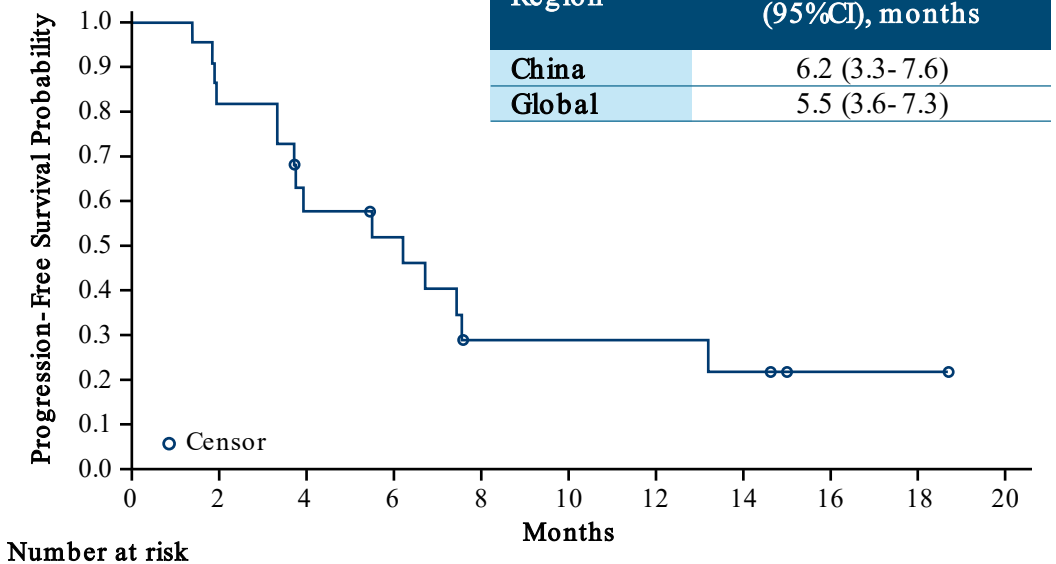
Duration of response graph: Duration of response in Cohort 1 by ICR per RECIST v1.1 (ICR response Evaluable Analysis Set, subgroup from China). Duration of response was defined as the first confirmed objective response (complete response or partial response) to documented progressive disease per RECIST v1.1 or death from any cause. Only patients who had a confirmed objective response were included in the analysis. Median duration of response was estimated by Kaplan-Meier method with 95%CI estimated using the Brookmeyer and Crowley method with log-log transformation. Treatment duration graph: Treatment duration for Cohort 1 confirmed responders by ICR per RECIST v1.1 (Efficacy Analysis Set, subgroup from China).

Abbreviations: CI, confidence interval; DoR, duration of response; ICR, independent central review; IHC, immunohistochemistry; NE, not estimable; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Progression-Free Survival and Overall Survival

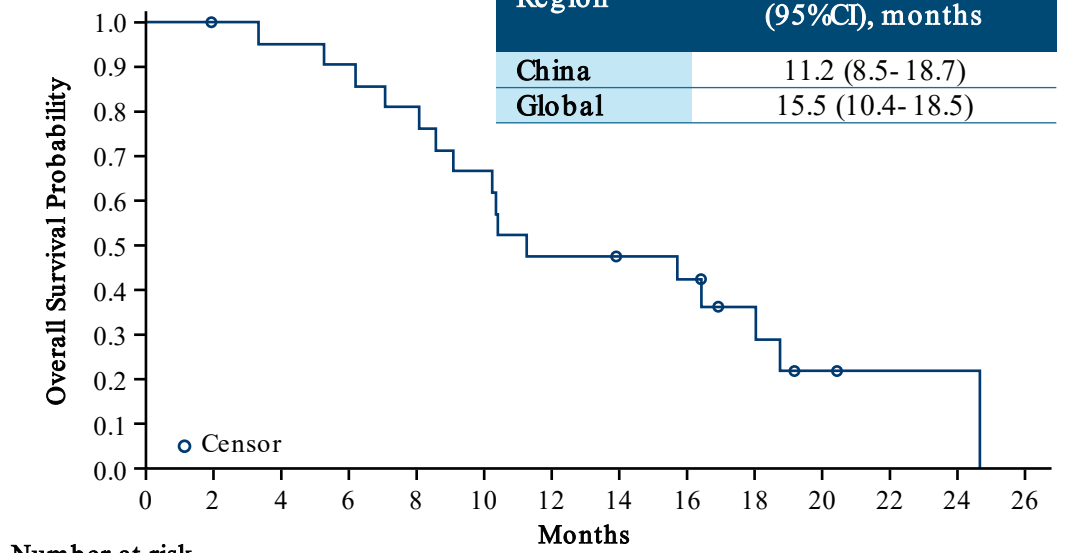
Progression-Free Survival

Region	Median PFS (95%CI), months
China	6.2 (3.3-7.6)
Global	5.5 (3.6-7.3)



Overall Survival

Region	Median OS (95%CI), months
China	11.2 (8.5-18.7)
Global	15.5 (10.4-18.5)



Progression-free survival in Cohort 1 by ICR per RECIST v1.1 (Efficacy Analysis Set, subgroup from China). Data from 7 patients were censored due to ongoing radiographic follow-up without events (2 patients) and initiation of subsequent anticancer therapy (5 patients). Overall survival in Cohort 1 (Efficacy Analysis Set, subgroup from China). The analysis of OS included 16 events of death (72.7% all-cause mortality). Median overall survival was estimated by Kaplan-Meier method with 95%CI estimated using Brookmeyer and Crowley method with log-log transformation. Data from 6 patients were censored because they were still alive (5 patients) or they withdrew consent (1 patient), as of the data cutoff date.

Abbreviations: CI, confidence interval; ICR, independent central review; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

Safety

Treatment-related adverse events (TRAEs)	China Cohort I (N=22)		Global Cohort I (N=80)	
Patients with at least one TRAE,[a] n (%)	16 (72.7)		61 (76.3)	
Grade ≥ 3 TRAEs	6 (27.3)		17 (21.3)	
Serious TRAEs	3 (13.6)		8 (10.0)	
TRAEs leading to death	0 (0.0)		0 (0.0)	
TRAEs leading to treatment discontinuation[a]	0 (0.0)		2 (2.5)	
Common TRAEs,[a] n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infusion-related reactions	8 (36.4)	0 (0.0)	28 (35.0)	1 (1.3)
Diarrhea	7 (31.8)	1 (4.5)	32 (40.0)	4 (5.0)
Alanine aminotransferase increased	4 (18.2)	1 (4.5)	6 (7.5)	1 (1.3)
Aspartate aminotransferase increased	4 (18.2)	1 (4.5)	6 (7.5)	2 (2.5)
Ejection fraction decreased	3 (13.6)	1 (4.5)	9 (11.3)	3 (3.8)
Adverse event of special interest, n (%)				
Infusion-related reactions	8 (36.4)		28 (35.0)	
Confirmed cardiac events[b]	1 (4.5)		5 (6.3)	
Non-infectious pulmonary toxicity	0 (0.0)		1 (1.3)	

Adverse events (Safety Analysis Set, subgroup from China) were classified based on the Medical Dictionary for Regulatory Activities (MedDRA) v25.0 and were graded for severity using CTCAE v5.0. [a]Patients with multiple events for a given preferred term were counted only once for each preferred term. [b]Confirmed cardiac events were the subset of potential cardiac events that were clinically reviewed by Zymeworks and were determined to be consistent with cardiac events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value <50% and/or grade ≥ 2 heart failure.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; LVEF, left ventricular ejection fraction.

Conclusions

- In patients from China with treatment-refractory HER2+ BTC and a history of poor outcomes and high unmet needs:
  - Zanidatamab monotherapy demonstrated a clinically meaningful benefit consistent with findings in the primary analyses
  - Zanidatamab treatment was well tolerated with manageable adverse events

Abbreviations: BCT, biliary tract cancer; HER2, human epidermal growth factor receptor 2.

Acknowledgments

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