Asia Subgroup Overall Survival and Long-Term Follow-Up Results of the Phase 2b HERIZON-BTC-01 Study: Zanidatamab in Previously Treated Human Epidermal Growth Factor Receptor 2-Amplified Biliary Tract Cancer

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CONCLUSIONS

- **With longer follow-up, zanidatamab demonstrated a clinically meaningful, durable response and a manageable safety profile in patients from Asia with treatment-refractory human epidermal growth factor receptor 2 positive (HER2+) biliary tract cancer (BTC), consistent with the overall population**
- Zanidatamab demonstrated antitumor activity with an extended response
  - Confirmed objective response rate (ORR) was 42.0%; median duration of response (DoR) was 11.2 months; DoR ≥16 weeks was 81.0%
- Median progression-free survival (PFS) and overall survival (OS) were clinically meaningful and encouraging
  - Median PFS was 5.5 months; median OS was 13.4 months
- Zanidatamab treatment remained well tolerated, with manageable adverse events (AEs)

INTRODUCTION

- BTC has a poor prognosis and a higher incidence in Asia compared with other regions[1-3]
  - There remains a high unmet need for patients with advanced BTC due to the lack of effective therapies
- Despite reports of HER2 amplification and overexpression in BTC, to date there are no HER2-targeted therapies approved for BTC in most Asian countries[4,5]
- Zanidatamab is a bispecific monoclonal antibody that targets two non-overlapping domains of HER2[6]
- In patients with previously treated HER2+ BTC, zanidatamab demonstrated a meaningful clinical benefit with a manageable safety profile in the overall population and Asia subgroup (HERIZON-BTC-01 trial, NCT04466891)[7,8]
- Here, we report updated Asia subgroup analyses with long-term follow-up for Cohort 1 (HER2-amplified with either immunohistochemistry [IHC] 2+ or 3+), at the data cutoff of July 28, 2023

METHODS

Figure 1. Study Design

HERIZON-BTC-01 (NCT04466891): Phase 2b, open-label,multicenter study
Asia Subgroup (China + Republic of Korea)
Cohort 1: HER2 IHC 2+ or IHC 3+; Cohort 2: HER2 IHC 0 or IHC 1+

Inclusion criteria
- Adults diagnosed with HER2-amplified,[a] unresectable, locally advanced or metastatic BTC
- ≥1 prior systemic therapy for advanced disease, including gemcitabine
- 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
- Loss 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

Selected secondary endpoints
- ICR-assessed DCR,[d] DoR,[d] PFS[d]
- 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 Response Evaluation Criteria in Solid Tumours version 1.1. (RECIST v1.1) (efficacy analysis set).
Abbreviations: DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent central review; IV, intravenous; PD, progressive disease; Q2W, every 2 weeks.

- Eighty patients were enrolled in Global Cohort 1 and treated with zanidatamab: 50 from the Asia subgroup, and 30 from Rest of World
- In the Asia subgroup, 46 patients discontinued treatment and 4 remained on treatment at the data cutoff
  - Most discontinued due to radiographic progression (n=42)
  - Of all patients who discontinued treatment, 40 discontinued the study: 33 due to death and 7 due to withdrawal of consent. Six patients remained in survival follow-up at data cutoff
- In the Rest of World subgroup, 25 patients discontinued treatment and 5 remained on treatment at data cutoff
  - Twenty-three discontinued treatment due to radiographic progression
  - Twenty patients discontinued the study, 19 due to death and 1 due to withdrawal of consent. At data cutoff, 5 patients were in survival follow-up

RESULTS

Baseline Demographics and Characteristics

- Baseline characteristics were generally similar between the Asia subgroup and the Rest of World subgroup (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

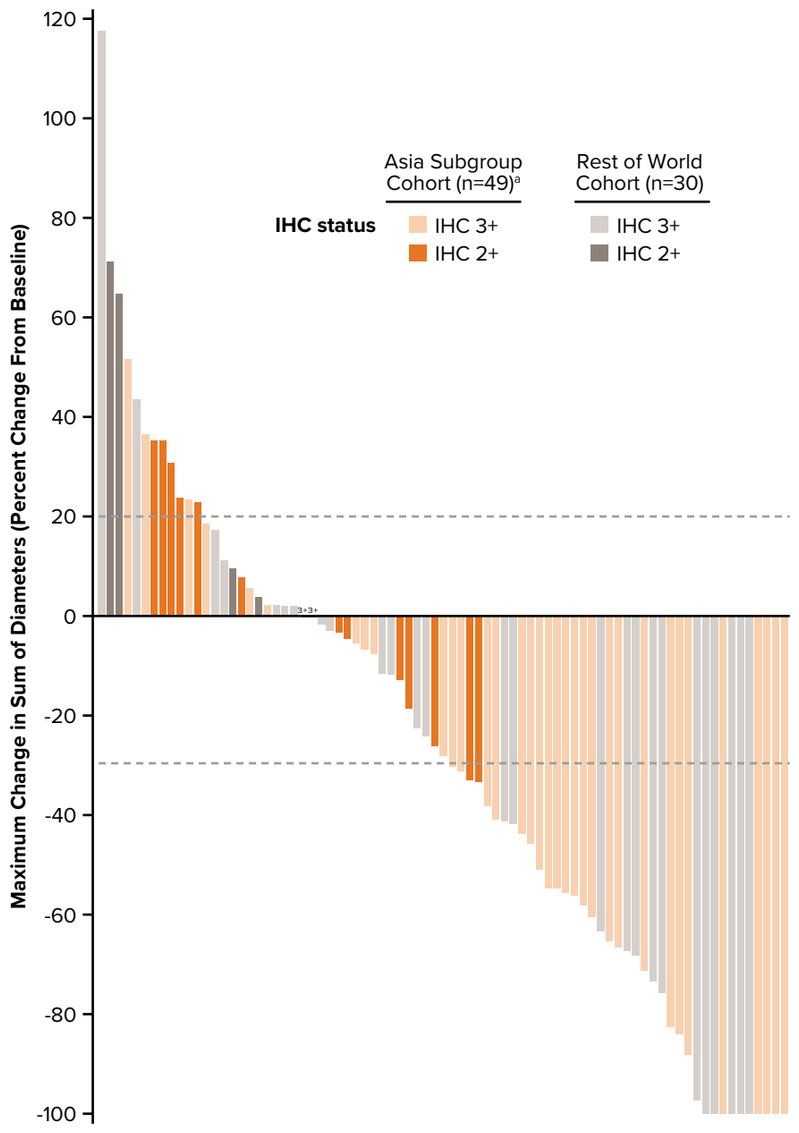
	Asia Subgroup Cohort 1 (n=50)	Rest of World Cohort 1 (n=30)
Median age, years (range)	63.5 (42-79)	66.0 (32-79)
Female, n (%)	30 (60.0)	15 (50.0)
ECOG performance status, n (%)		
0	11 (22.0)	11 (36.7)
1	39 (78.0)	19 (63.3)
Disease subtype, n (%)		
Gallbladder cancer	29 (58.0)	12 (40.0)
Intrahepatic cholangiocarcinoma	11 (22.0)	12 (40.0)
Extrahepatic cholangiocarcinoma	10 (20.0)	6 (20.0)
HER2 status,[a] n (%)		
IHC 3+	36 (72.0)	26 (86.7)
IHC 2+	14 (28.0)	4 (13.3)
Disease stage at study entry,[b] n (%)		
IIIA/IIIB	0 (0.0)/7 (14.0)	1 (3.3)/1 (3.3)
IV/IVB	12 (24.0)/31 (62.0)	15 (50.0)/13 (43.3)
Mean time (SD) from initial diagnosis to metastatic/locally advanced, months	6.3 (11.7)	2.0 (4.2)
Mean target lesion sum of diameters (SD) per ICR,[c] mm	69.2 (37.4)	94.0 (56.4)

Data cutoff: July 28, 2023. Median (range) study follow-up time for Cohort 1 was 21.95 (16.1-33.9) months. [a]All patients were in situ hybridization+ at screening. [b]Disease staging categories varied by disease type; categories IV and IVB are mutually exclusive. [c]Sum of diameters of target lesions selected for disease response assessment by ICR per RECIST v1.1. Percentages may not add up to 100 due to rounding.
Abbreviations: ICR, independent central review; SD, standard deviation.

Disease Response

- Clinically meaningful antitumor activity and extended response was seen in patients from the Asia and Rest of World subgroups (**Figure 2**)

Figure 2. Confirmed Response Rates, Duration of Response, and Best Change in Target Lesion Size



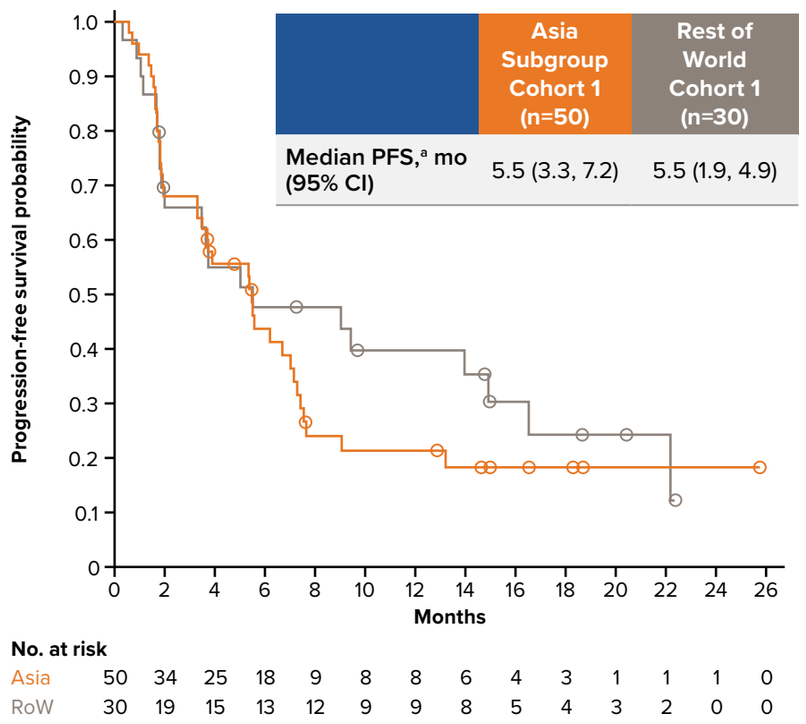
	Asia Subgroup Cohort 1 (n=50)	Rest of World Cohort 1 (n=30)
Confirmed best overall response, n (%)		
CR	0 (0.0)	2 (6.7)
PR	21 (42.0)	10 (33.3)
Stable disease	13 (26.0)	9 (30.0)
Progressive disease	15 (30.0)	9 (30.0)
Not evaluable[a]	1 (2.0)	0 (0.0)
Confirmed objective overall response rate, % 95% CI	42.0 28.2, 56.8	40.0 22.7, 59.4
Disease control rate,[b] % 95% CI	68.0 53.3, 80.5	70.0 50.6, 85.3
Clinical benefit rate,[c] % 95% CI	48.0 33.7, 62.6	46.7 28.3, 65.7
Median duration of response, months 95% CI	11.2 3.9, NE	20.6 7.4, NE
Duration of response ≥16 weeks, n (%)	17 (81.0)	11 (91.7)

Data cutoff: July 28, 2023. The 95% CI was estimated using the Clopper-Pearson method.
[a]No evaluable postbaseline response assessment in 1 patient.. [b]Best overall response of stable disease or confirmed CR or PR. [c]Stable disease ≥24 weeks or confirmed best overall response of CR or PR. Target lesion size figure: Target lesion reduction in Cohort 1 by ICR (ICR response evaluable analysis set). Only patients with measurable disease at baseline and at least one post-baseline assessment are included.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.

Survival

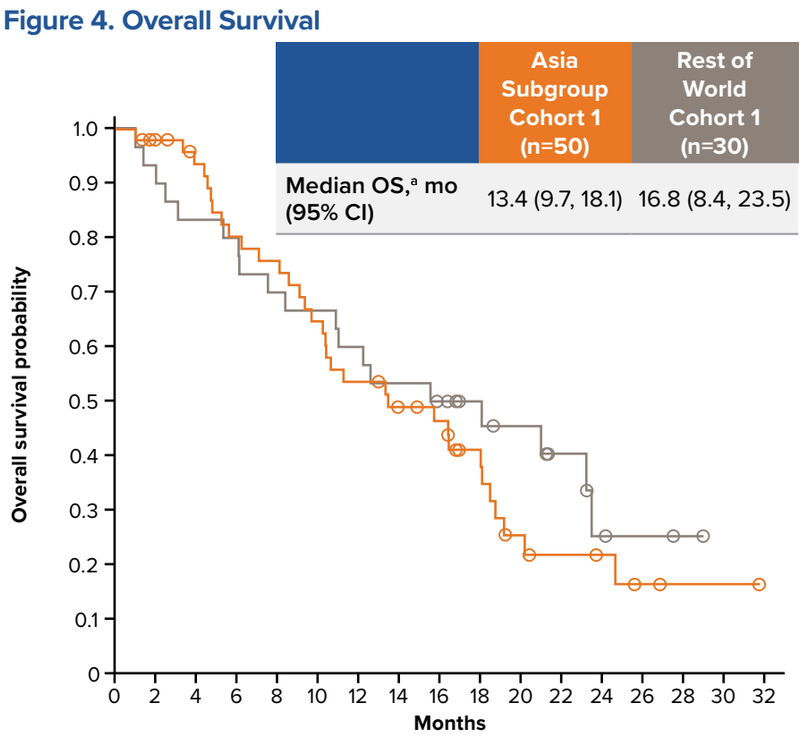
- PFS (**Figure 3**) and OS (**Figure 4**) in the Asia subgroup were consistent with the Rest of World subgroup

Figure 3. Progression-Free Survival



Data cutoff: July 28, 2023.
[a]Median PFS was estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
Abbreviation: RoW, Rest of World.

Figure 4. Overall Survival



Data cutoff: July 28, 2023.
[a]Median OS was estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.

Safety and Tolerability

- Zanidatamab was well tolerated, with manageable AEs (**Table 2**)

Table 2. TRAEs and AEs of Special Interest

TRAEs	Asia Subgroup Cohort 1 (n=50)	Rest of World Cohort 1 (n=30)
Patients with at least one TRAE, n (%)	35 (70.0)	26 (86.7)
Grade ≥3 TRAEs	7 (14.0)	10 (33.3)
Serious TRAEs	3 (6.0)	5 (16.7)
TRAEs leading to death	0 (0.0)	0 (0.0)
TRAEs leading to treatment discontinuation	1 (2.0)	1 (3.3)

AEs of Special Interest, n (%)	Asia Any Grade	Asia Grade ≥3	Rest of World Any Grade	Rest of World Grade ≥3
Infusion-related reactions	21 (42.0)	0 (0.0)	7 (23.3)	1 (3.3)
Confirmed cardiac events[a]	4 (8.0)	2 (4.0)	1 (3.3)	1 (3.3)
Non-infectious pulmonary toxicity	0 (0.0)	0 (0.0)	1 (3.3)	1 (3.3)

Data cutoff: July 28, 2023. Adverse events (safety analysis set) were classified based on the Medical Dictionary for Regulatory Activities v25.0 and were graded for severity using CTCAE v5.0.
Please note numerical differences in the rates of AEs between Asia and Rest of World subgroups are attributed to the small number of patients and cannot be meaningfully concluded.
[a]Confirmed cardiac events were the subset of potential cardiac events that were clinically reviewed by the sponsor 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 v5.0, Common Terminology Criteria for Adverse Events version 5.0; LVEF, left ventricular ejection fraction; TRAE, treatment-related adverse event.

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DISCLOSURES

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