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# 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 (HER2)-Amplified Biliary Tract Cancer (BTC)

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# DECLARATION OF INTERESTS

Prof. Jin Won Kim reports consulting fees from AstraZeneca, BeiGene, Ltd., BeyondBio, Bristol Myers Squibb/Celgene, Eisai, GC Cell, MSD, ONO Pharmaceutical, Sanofi-Aventis, Servier, and TCUBEit, Inc.; and study grants/contracts from Samyang Biopharmaceuticals Corp., and Boryung.

# Background

- Biliary tract cancer (BTC) has a poor prognosis with 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 IHC 2+ or 3+), at the data cutoff of July 28, 2023

**Abbreviations:** HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

1. World Health Organization IARC. Gallbladder Fact Sheet, Globocan 2022. Accessed October 3, 2024. https://gco.iarc.who.int/media/globocan/factsheets/cancers/12-gallbladder-fact-sheet.pdf 2. Banales et al. *Nat Rev Gastroenterol Hepatol.* 2020;17(9):557-588. 3. Mirallas et al. *ESMO Open.* 2022;7(3):100503. 4. Valle et al. *Cancer Discov.* 2017;7(9):943-962. 5. Ayasun et al. *Cancers (Basel).* 2023;15(9):2628. 6. Meric-Bernstam et al. *Lancet Oncol.* 2022;23(12):1558-1570. 7. Harding et al. *Lancet Oncol.* 2023;24(7):772-782. 8. Sun et al. *Ann Oncol.* 2023;34:S1522-S1523.

# 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]**

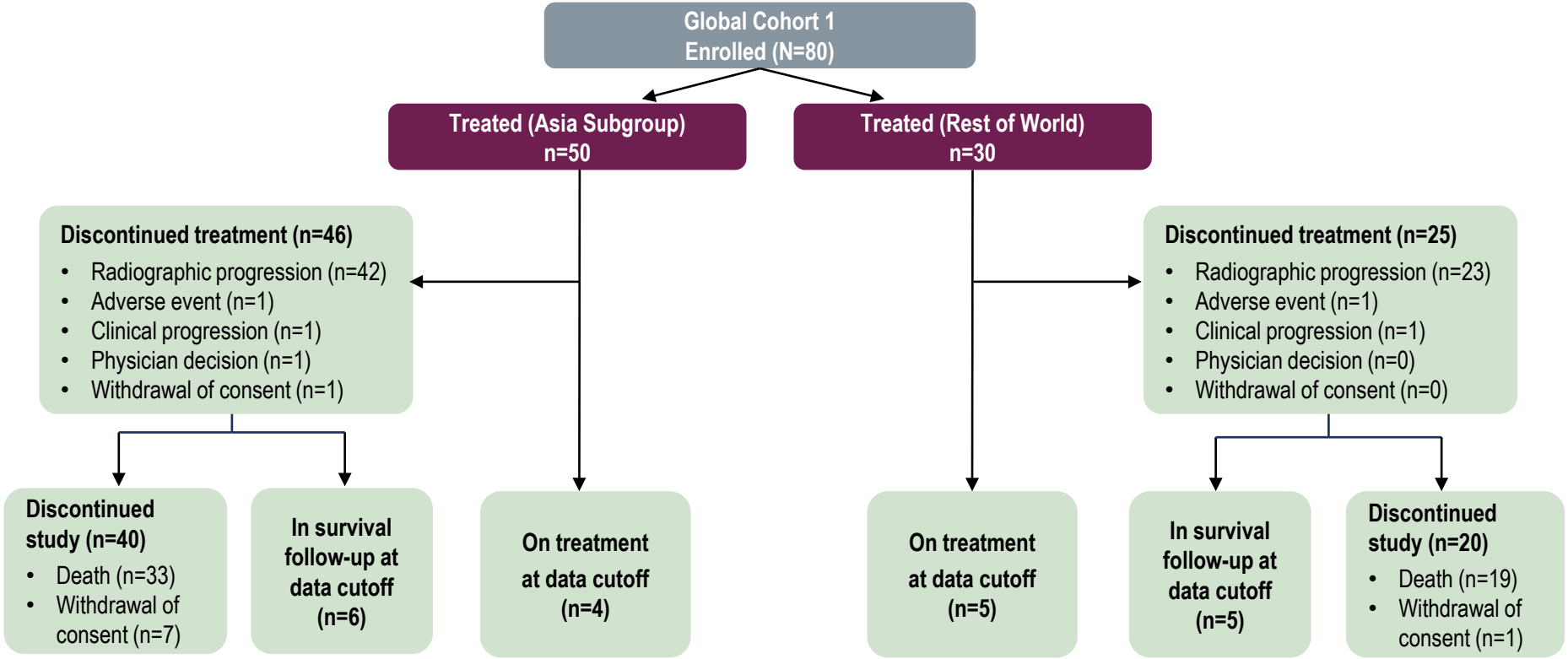
- ICR-assessed confirmed ORR

**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 RECIST v1.1 (Efficacy Analysis Set).
**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.

# Patient Disposition




Data cutoff: July 28, 2023.

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# Baseline Demographics and Disease Characteristics

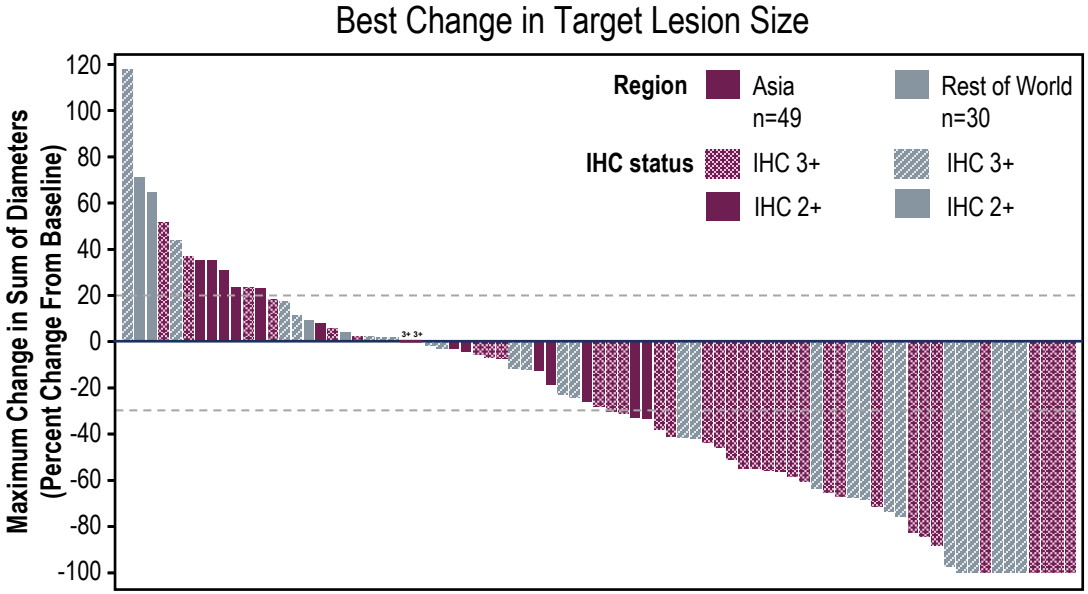
| | Asia Subgroup Cohort 1 (n=50) | Rest of World Cohort 1 (n=30) |
|---|---|---|
| **Median age (range), years** | 63.5 (42-79) | 66.0 (32-79) |
| **Female, n (%)** | 30 (60.0) | 15 (50.0) |
| **ECOG Performance Status, n (%)** | | |
| 0 | 11 (22.0) | 11 (36.7) |
| 1 | 39 (78.0) | 19 (63.3) |
| **Disease 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 ISH (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:** ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, standard deviation.

# Disease Response

| | Asia Cohort 1 (n=50) | Rest of World Cohort 1 (n=30) |
|---|---|---|
| **Confirmed best overall response, n (%)** | | |
| Complete response | 0 (0.0) | 2 (6.7) |
| Partial response | 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 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 |




- Clinically meaningful antitumor activity was seen in patients from the Asia and Rest of World subgroups

Data cutoff: July 28, 2023. The 95% CI was estimated using the Clopper-Pearson method.

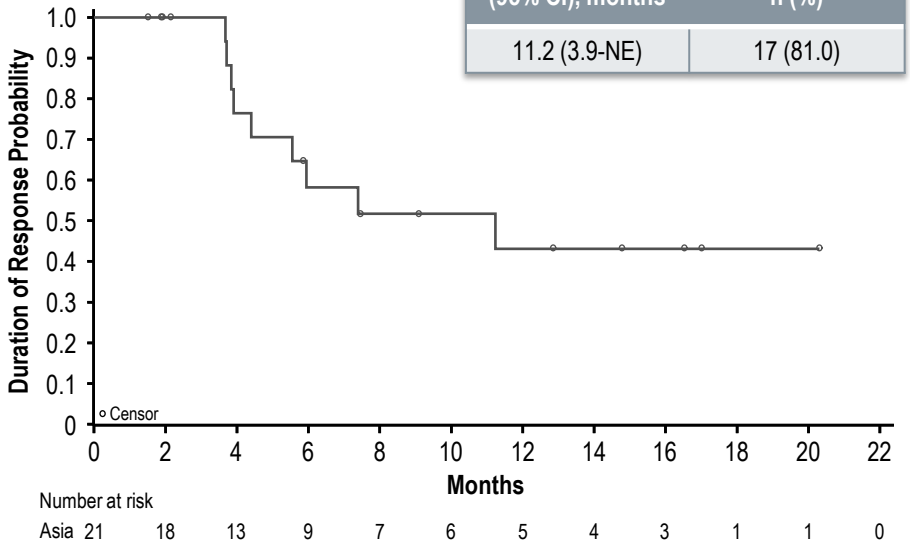
[a]No evaluable post-baseline response assessments. [b]Best overall response of stable disease or confirmed CR or PR. [c]Stable disease ≥24 weeks or confirmed best overall response of CR or PR. Target lesion size figure: Target lesion reduction in Cohort 1 by ICR (ICR Response Evaluable Analysis Set). Only patients with measurable disease at baseline and at least one post-baseline assessment are included.

**Abbreviations:** CI, confidence interval; CR, complete response; ICR, independent central review; IHC, immunohistochemistry; PR, partial response.

# Duration of Response in Asia Subgroup

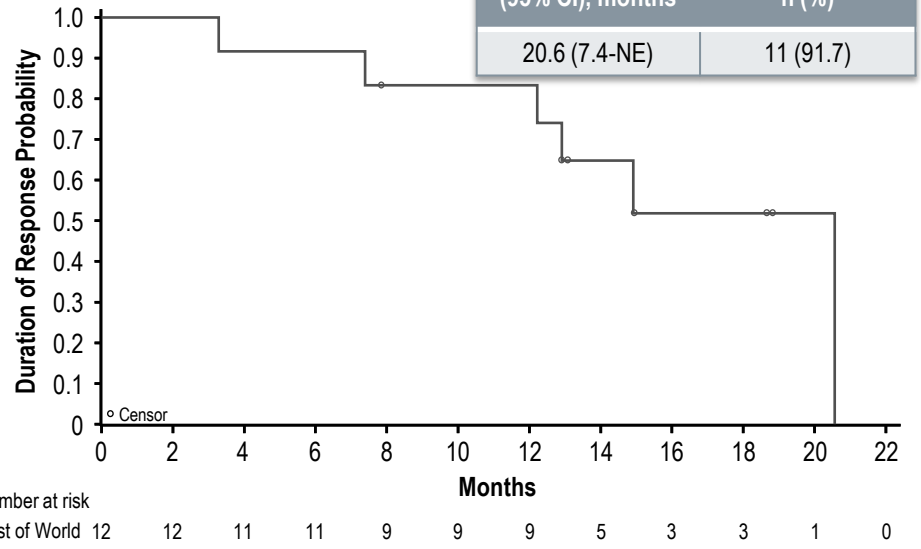
## Asia

| Median DoR[a] (95% CI), months | DoR ≥16 weeks n (%) |
|---|---|
| 11.2 (3.9-NE) | 17 (81.0) |



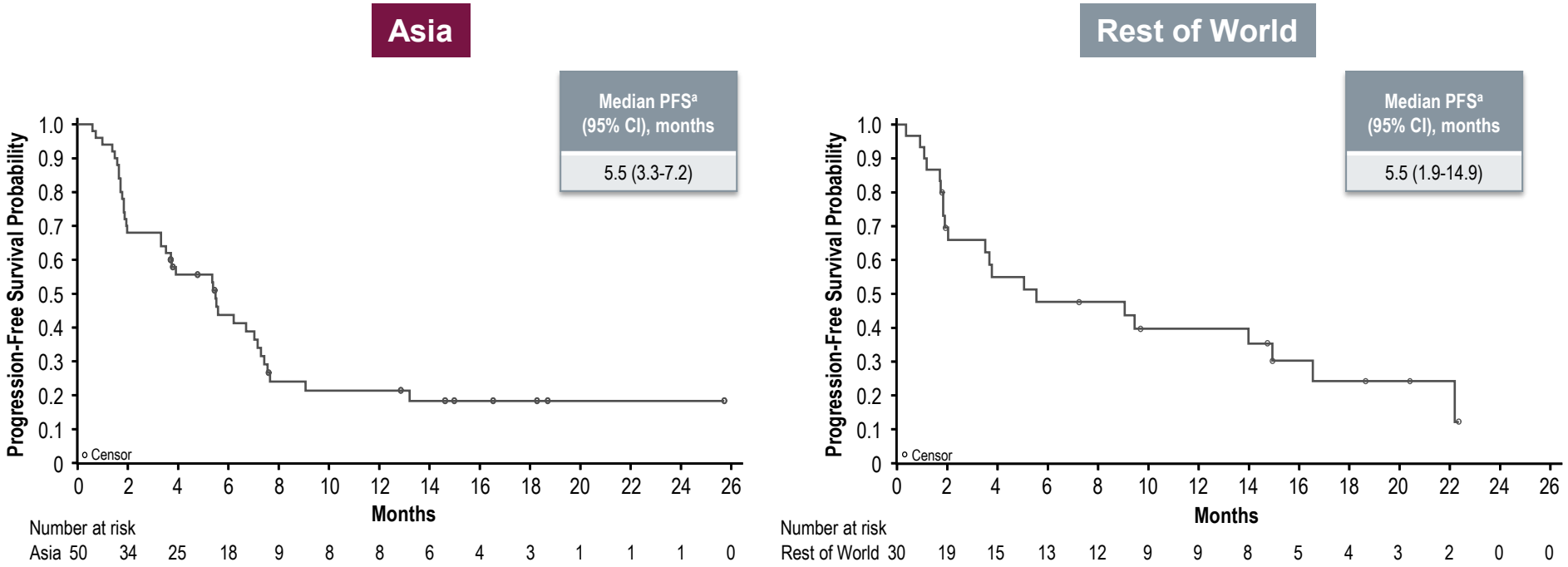

## Rest of World

| Median DoR[a] (95% CI), months | DoR ≥16 weeks n (%) |
|---|---|
| 20.6 (7.4-NE) | 11 (91.7) |




Data cutoff: July 28, 2023. DoR analysis included patients with confirmed objective response, with percentages based on the number of confirmed responders.
[a]Median DoR was estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.
**Abbreviations:** CI, confidence interval; DoR, duration of response; NE, not evaluable.

# Progression-Free Survival in Asia Subgroup



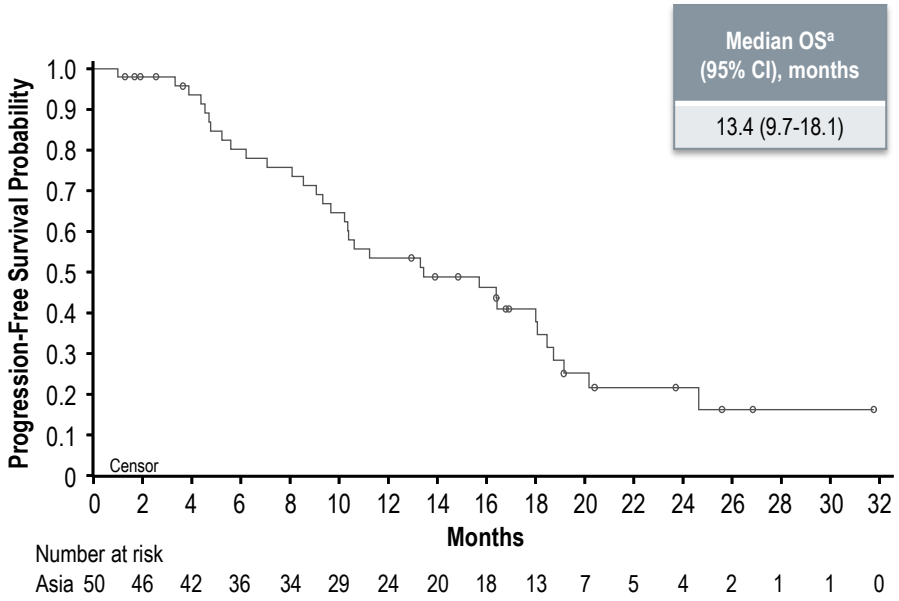

Data cutoff: July 28, 2023.

[a]Median PFS was estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation.

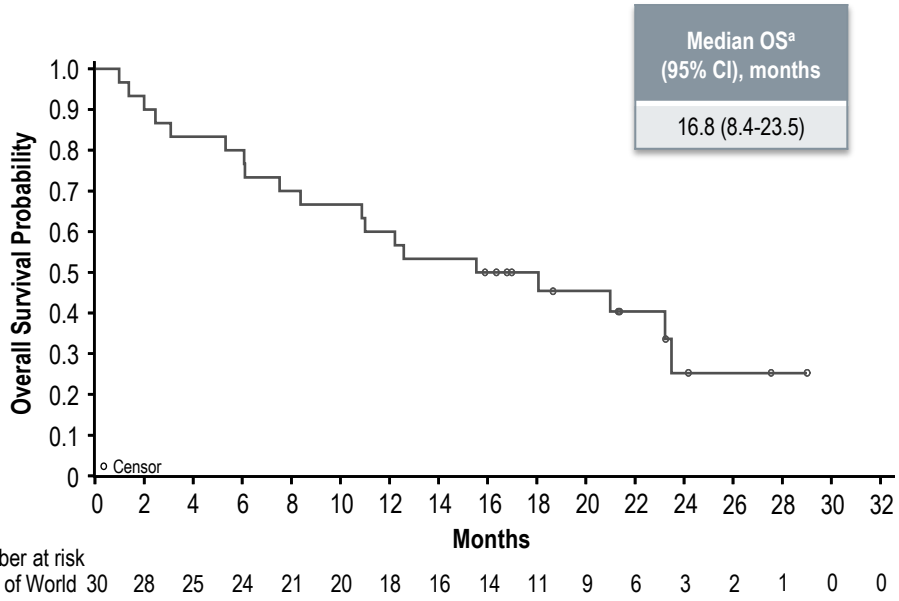
**Abbreviations:** CI, confidence interval; PFS, progression-free survival.

# Overall Survival in Asia Subgroup

## Asia




## Rest of World




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.

**Abbreviations:** CI, confidence interval; OS, overall survival.

# Safety in Asia Subgroup

| Treatment-related adverse events (TRAEs) | Asia 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) | |
| **Adverse event of special interest, n (%)** | **Any Grade** | **Grade ≥3** | **Any Grade** | **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 (MedDRA) v25.0 and were graded for severity using CTCAE v5.0. Please note numerical differences in the rates of adverse events 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.

# Conclusions

With longer follow-up, zanidatamab demonstrated a clinically meaningful, durable response and a manageable safety profile in patients from Asia with treatment-refractory HER2+ BTC, consistent with the overall population

- Zanidatamab demonstrated antitumor activity with an extended response
  - Confirmed ORR was 42.0%; median DoR was 11.2 months; DoR ≥16 weeks was 81.0%
- Median PFS and 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

**Abbreviations:** BTC, biliary tract cancer; DoR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

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