SINGAPORE 2023 ESMO ASIA

Zanidatamab in Patients With Previously Treated Advanced Human Epidermal Growth Factor Receptor 2-Positive Biliary Tract Cancer: Asia Subgroup Analysis of the Phase 2b HERIZON-BTC-01 Study

Huichuan Sun,[1] Jin Won Kim,[2] Hye Jin Choi,[3] Heung-Moon Chang,[4] Lequn Bao,[5] Jie'er Ying,[6] Feng Xie,[7] Lee Myung-Ah,[8] Dong Uk Kim,[9] Tianqiang Song,[10] Hongming Pan,[11] Guohua Yu,[12] Kainan Li,[13] Qiang Yan,[14] Xiaotian Wu,[15] Yuanyuan Bao,[16] Phillip Garfin,[17] Jiafang Ma,[18] Jia Fan,[1] Do-Youn Oh[19]

[1]Department of Liver Surgery and Transplantation, Zhongshan Hospital of Fudan University, Shanghai, China; [2]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul, Republic of Korea; [3]Department of Internal Medicine, Severance Hospital Yonsei University Health System, Seoul, Republic of Korea; [4]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [5]Department of Hepatobiliary and Pancreatic Surgery, Hubei Cancer Hospital, Wuhan City, China; [6]Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [7]Department of Biliary Tract Surgery III, Eastern Hepatobiliary Surgery Hospital, Affiliated to Naval Medical University, Shanghai, China; [8]Division of Medical Oncology, Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Republic of Korea; [9]Department of Gastroenterology, Pusan National University Hospital, Busan, Republic of Korea; [10]Department of Hepatobiliary Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [11]Department of Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China; [12]Department of Oncology, Weifang People's Hospital, Weifang, China; [13]Department of Oncology, Shandong Provincial Third Hospital, Cheeloo College of Medicine, Shandong University, Shandong, China; [14]Department of Hepatobiliary Surgery, Huzhou Central Hospital, Huzhou, China; [15]Department of Data Science, Jazz Pharmaceuticals, Palo Alto, CA, USA; [16]Department of Clinical Development, BeiGene (Shanghai) Co., Ltd., Shanghai, China; [17]Department of Clinical Research, Hematology/Oncology, Jazz Pharmaceuticals, Palo Alto, CA, USA; [18]Department of Clinical Development, BeiGene (Beijing) Co., Ltd., Beijing, China; [19]Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea.

Declaration of Interests

Huichuan Sun declares an institutional membership with the China Anti-Cancer Association with no financial interest.

Acknowledgements: This study was sponsored by BeiGene, Ltd, Jazz Pharmaceuticals, and Zymeworks Inc. Medical writing support, under the direction of the authors, was provided by Saxony Olivier, MMed For Path, of Ashfield MedComms, an Inizio company, and was funded by BeiGene, Ltd. Editorial support was provided by Elizabeth Hermans, PhD, of BeiGene, Ltd.

Background

Biliary tract cancer (BTC) is more prevalent in patients from Asia compared with the rest of the world[1-3]

HERIZON-BTC-01 study: Zanidatamab demonstrated meaningful clinical benefit with a manageable safety profile in the overall population of patients with treatment-refractory HER2+ BTC[4]

Here we report the analysis of efficacy and safety in the Asia subgroup of Cohort 1 (patients with HER2 IHC 2+ or 3+ BTC of HERIZON-BTC-01)

1. World Health Organization IARC. Gallbladder Fact Sheet, Globocan 2020. Accessed September 11, 2023. https://gco.iarc.fr/today/data/factsheets/cancers/12-Gallbladder-fact-sheet.pdf;
2. Randi G, et al. *Int J Cancer*. 2006;118(7):1591-1602; 3. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17(9):557-588; 4. Harding JJ, et al. *Lancet Oncol*. 2023;24(7):772-782.
Abbreviations: BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

Study Design

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

- Asia subgroup analysis in Cohort 1 (HER2 IHC 2+ or 3+)[a] comprising patients from China and the Republic of Korea

Inclusion criteria
- ≥18 years with HER2+,[b] inoperable, locally advanced/metastatic BTC
- ≥1 prior systemic therapy for advanced disease, including gemcitabine
- PD after, or developed intolerance to, most recent prior therapy
- ECOG performance status 0-1

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

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[d]
- Study termination

Primary endpoint[e]
- ICR-assessed confirmed ORR

Key secondary endpoints[e]
- ICR-assessed DCR, DoR, PFS
- Adverse events

[a]Cohort assigned prior to analysis. [b]To be eligible for enrollment in HERIZON-BTC-01, all patients were required to have HER2 ISH-positive tumors. Patients in Cohort 1 were also HER2 IHC2+ or IHC3+ by IHC. [c]On Days 1 and 15 of each 28-day cycle.
[d]Either radiographic progression or unequivocal clinical progression, defined as worsening or re-emergence of pre-existing 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. [e]Per RECIST version 1.1.

Abbreviations: AE, adverse event; BTC, biliary tract cancer; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; Q2W, once every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Harding JJ, et al. Lancet Oncol. 2023;24(7):772-782.

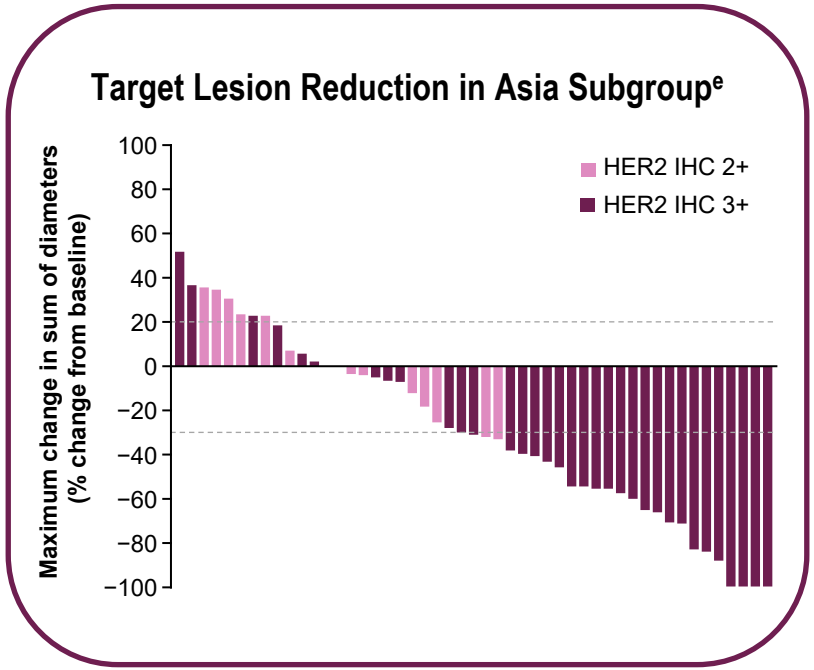
Baseline Characteristics[a]

	Asia Subgroup Cohort 1 (n=50)	Overall Population (Asian + Non-Asian) Cohort 1 (n=80)[1]
Median age, years (range)	63.5 (42-79)	64.0 (32-79)
Female sex, n (%)	30 (60.0)	45 (56.3)
ECOG performance status, n (%)		
0	11 (22.0)	22 (27.5)
1	39 (78.0)	58 (72.5)
HER2 IHC status,[b] n (%)		
IHC2+	14 (28.0)	18 (22.5)
IHC3+	36 (72.0)	62 (77.5)
Disease subtype, n (%)		
Gallbladder cancer	29 (58.0)	41 (51.3)
Intrahepatic cholangiocarcinoma	11 (22.0)	23 (28.8)
Extrahepatic cholangiocarcinoma	10 (20.0)	16 (20.0)
Prior systemic therapy for advanced disease,[c] median number of regimens (range)	1 (1-5)	1 (1-7)
Tumor stage at study entry,[d] n (%)		
IIIA/IIIB	0 (0.0)/7 (14.0)	1 (1.3)/8 (10.0)
IV/IVB	12 (24.0)/31 (62.0)	27 (33.8)/44 (55.0)

[a]In the safety analysis set, defined as all patients who received any amount of zanidatamab. [b]All patients enrolled in the study were ISH+ at screening, based on central laboratory evaluation.
[c]Includes gemcitabine-based therapies received in the adjuvant/neoadjuvant setting if progression occurred within 6 months of completion of surgery. [d]Disease staging categories varied by disease type; categories IV and IVB are mutually exclusive.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
[1]Harding JJ, et al. Lancet Oncol. 2023;24(7):772-782.

Disease Response[a]

	Asia Subgroup Cohort 1 (n=50)	Overall Population (Asian + Non-Asian) Cohort 1 (n=80)[1]
Confirmed ORR, % (95% CI)	**42.0** (28.2, 56.8)	**41.3** (30.4, 52.8)
Confirmed BOR, n (%)		
Complete response	0 (0)	1 (1.3)
Partial response	21 (42.0)	32 (40.0)
Stable disease	13 (26.0)	22 (27.5)
Progressive disease	15 (30.0)	24 (30.0)
Not evaluable[b]	1 (2.0)	1 (1.3)
Confirmed DCR, % (95% CI)	68.0 (53.3, 80.5)	68.8 (57.4, 78.7)
Median DoR,[c] months (95% CI)	7.4 (3.9, NE)	12.9 (5.9, NE)
DoR ≥16 weeks, % (95% CI[d])	76.2 (52.8, 91.8)	81.8 (64.5, 93.0)



Median study follow-up time 11.3 months (range: 6.9-22.3). Data cutoff date October 10, 2022.

[a]Per RECIST v1.1 by ICR in the efficacy-analysis set, defined as all patients in Asia subgroup who received any amount of zanidatamab. [b]One patient died before first postbaseline tumor assessment.

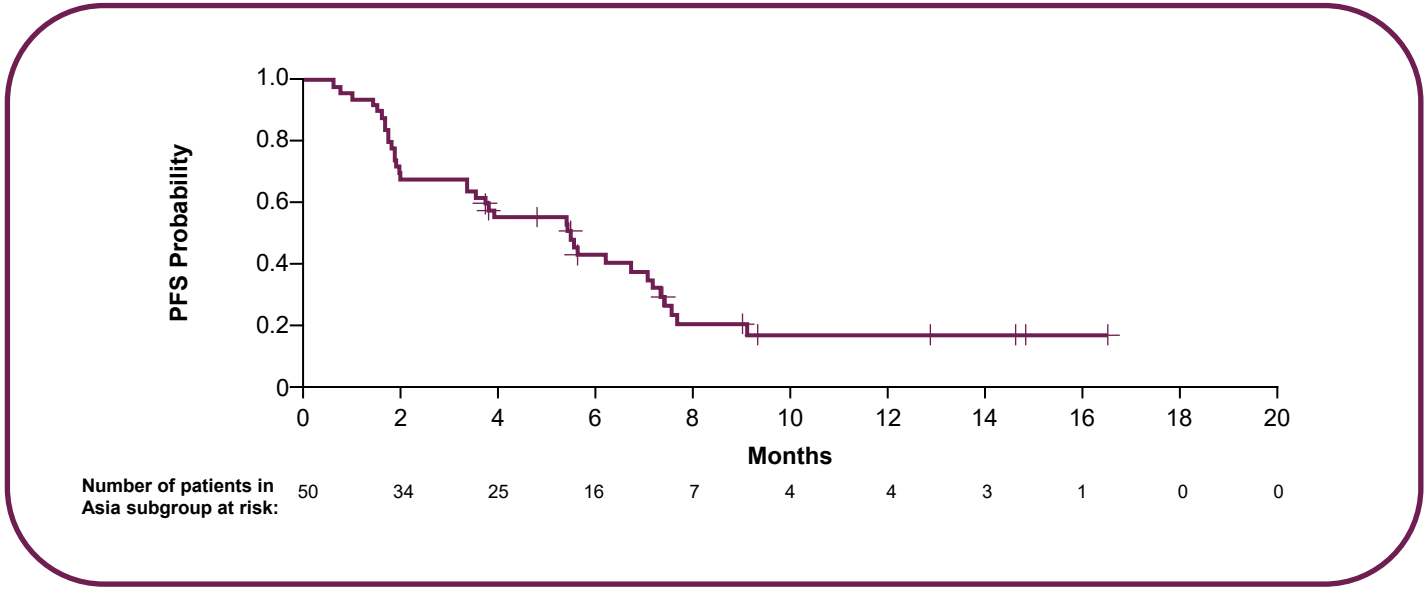
[c]Estimated by the Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method with log-log transformation. [d]Estimated using the Clopper-Pearson exact binomial method.

[e]Per RECIST v1.1 by ICR in the ICR response-evaluable analysis set. Of the 50 patients in the Asia subgroup, one did not have a postbaseline response assessment and was excluded from the ICR response-evaluable analysis set.

Abbreviations: BOR, best overall response; CI, confidence interval; DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; NE, not estimable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

[1]Harding JJ et al. Lancet Oncol. 2023;24(7):772-782.

Progression-Free Survival in Asia Subgroup[a]



- PFS in the Asia subgroup (median PFS 5.5 months; 95% CI: 3.3, 7.0) was consistent with the overall study population (median PFS 5.5 months; 95% CI: 3.6, 7.2)[1]

Median study follow-up time 11.3 months (range: 6.9-22.3).
[a]Per RECIST version 1.1 by ICR in the efficacy analysis set, defined as all patients in Asia subgroup who received any amount of zanidatamab.
Abbreviations: CI, confidence interval; ICR, independent central review; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[1]Harding JJ, et al. Lancet Oncol. 2023;24(7):772-782.

Safety Summary

	Asia Subgroup Cohort 1 (n=50)		Overall Population (Asian + Non-Asian) Cohort 1 (n=80)	
Patients with ≥1 TRAE[a]	35 (70.0)		61 (76.3)	
Grade ≥3	5 (10.0)		15 (18.8)	
Serious TRAE	2 (4.0)		7 (8.8)	
Leading to treatment discontinuation[b]	1 (2.0)		2 (2.5)	
Leading to death	0 (0.0)		0 (0.0)	
Adverse events of special interest, n (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infusion-related reactions	21 (42.0)	0 (0.0)	28 (35.0)	1 (1.3)
Confirmed cardiac events	4 (8.0)	2 (4.0)	5 (6.3)	3 (3.8)
Non-infectious pulmonary toxicity	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)
Most common TRAEs[c]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Diarrhea	17 (34.0)	1 (2.0)	38 (47.5)	4 (5.0)
Infusion-related reactions	21 (42.0)	0 (0.0)	28 (35.0)	1 (1.3)
Ejection fraction decreased	6 (12.0)	2 (4.0)	8 (10.0)	3 (3.8)

- None of the patients in the Asia subgroup experienced grade 4 or 5 TRAEs

Data are n (%). Adverse events were recorded using the Medical Dictionary for Regulatory Activities version 25.0, with severity graded by the investigator using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
[a]Treatment-related is defined as related to zanidatamab. [b]Treatment discontinuation is defined as discontinuation of zanidatamab. One patient in the Asia subgroup discontinued zanidatamab due to a TRAE of ejection fraction decreased.
[c]Any-grade TRAEs in ≥10% of patients in the safety analysis set.
Abbreviation: TRAE, treatment-related adverse event.

Conclusions

Zanidatamab demonstrated antitumor activity with durable responses in patients with treatment-refractory HER2+ BTC in the Asia subgroup

- Confirmed ORR was 42.0%; median DoR was 7.4 months

Zanidatamab demonstrated clinically meaningful PFS in the Asia subgroup

- Median PFS of 5.5 months

The safety profile of zanidatamab was tolerable and manageable in the Asia subgroup

Overall, these data were consistent with those from the overall study population, demonstrating that zanidatamab provides clinically meaningful benefit with a manageable safety profile in patients from Asia with HER2+ BTC

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