2023 ASCO® ANNUAL MEETING

Results from the Pivotal Phase 2b HERIZON-BTC-01 Study: Zanidatamab in Previously-treated HER2-amplified Biliary Tract Cancer (BTC)

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Unmet Need in Patients with Biliary Tract Cancer (BTC)

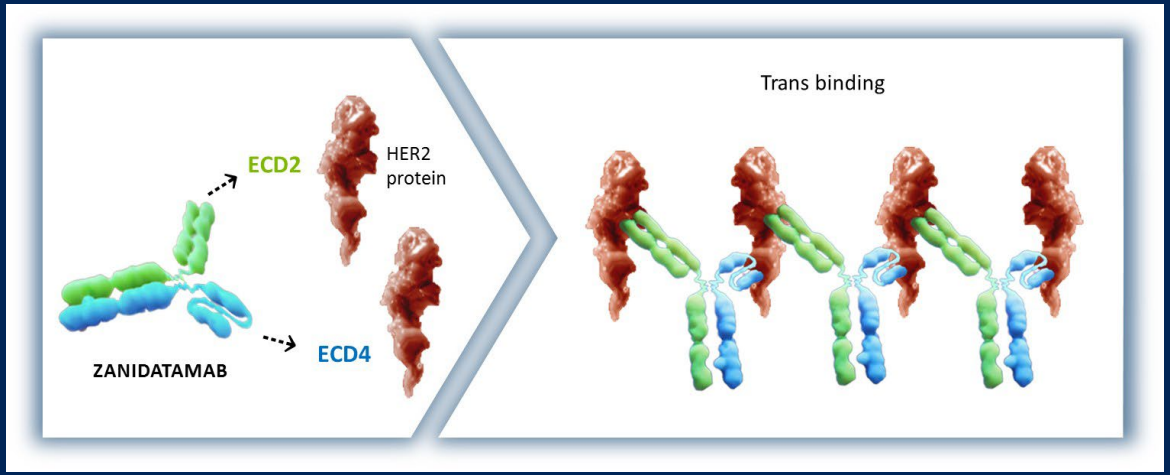
- BTC is uncommon (< 1% of all adult cancers)[1,2]
- For patients with locally advanced/metastatic BTC, standard 2L+ offers limited clinical benefit
  - ORR 5 – 15%[3,4]
  - mPFS 4.0 mo[3]
- HER2 amplification/overexpression is observed in a subset of BTC
  - 19 – 31% of GBC, 17 – 19% of ECC, 4 – 5% of ICC[5,6]
- HER2-targeted therapies have clinical benefit in breast, gastric cancer and lung cancer. There are no approved HER2-targeted therapies for BTC.

2L+ = second line or later (treatment); ECC = extrahepatic cholangiocarcinoma; GBC = gallbladder cancer; HER2 = human epidermal growth factor receptor 2; ICC = intrahepatic cholangiocarcinoma; mPFS = median progression-free survival; ORR = overall response rate.

[1] Valle JW, et al. Lancet 2021;397:428–44. [2] Siegel RL, et al. CA Cancer J Clin 2022;72:7–33. [3] Lamarca A, et al. Lancet Oncol 2021;22:690–701. [4] Yoo C, et al. Lancet Oncol 2021;22:1560–72. [5] Galdy S, et al. Cancer Metastasis Rev 2017;36:141–57. [6] Hiraoka N, et al. Hum Path 2020;105:9–19.

Zanidatamab is a HER2-targeted Bispecific Antibody with a Unique Mechanism of Action (MOA)

- Zanidatamab simultaneously binds 2 separate HER2 molecules in *trans*[1]
- Unique binding properties of zanidatamab to HER2 result in multiple MOAs[1]
- Preclinical studies demonstrate greater activity than trastuzumab ± pertuzumab[1]
- Zanidatamab has shown a manageable safety profile and encouraging antitumor activity in patients with HER2-expressing BTC in a Phase 1 trial[2]



ECD = extracellular domain

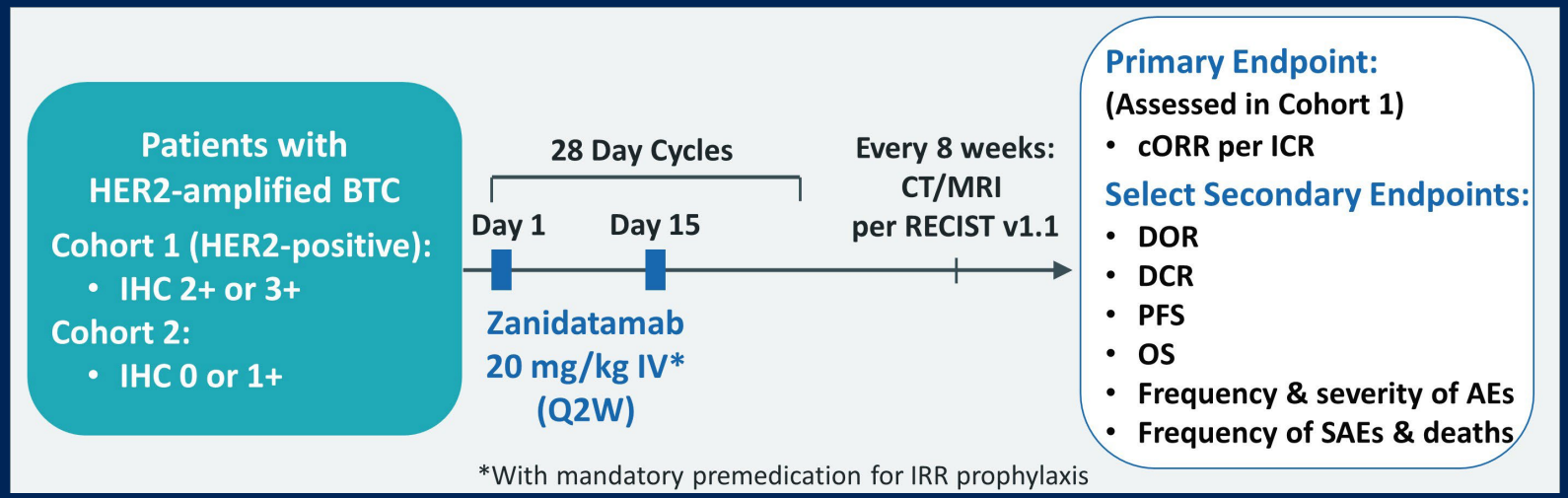
[1] Weisser NE, et al. Nature Commun 2023;14:1394. [2] Meric-Bernstam F, et al. Lancet Oncol 2022;23:1558–1570.

HERIZON-BTC-01 Study Design

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1

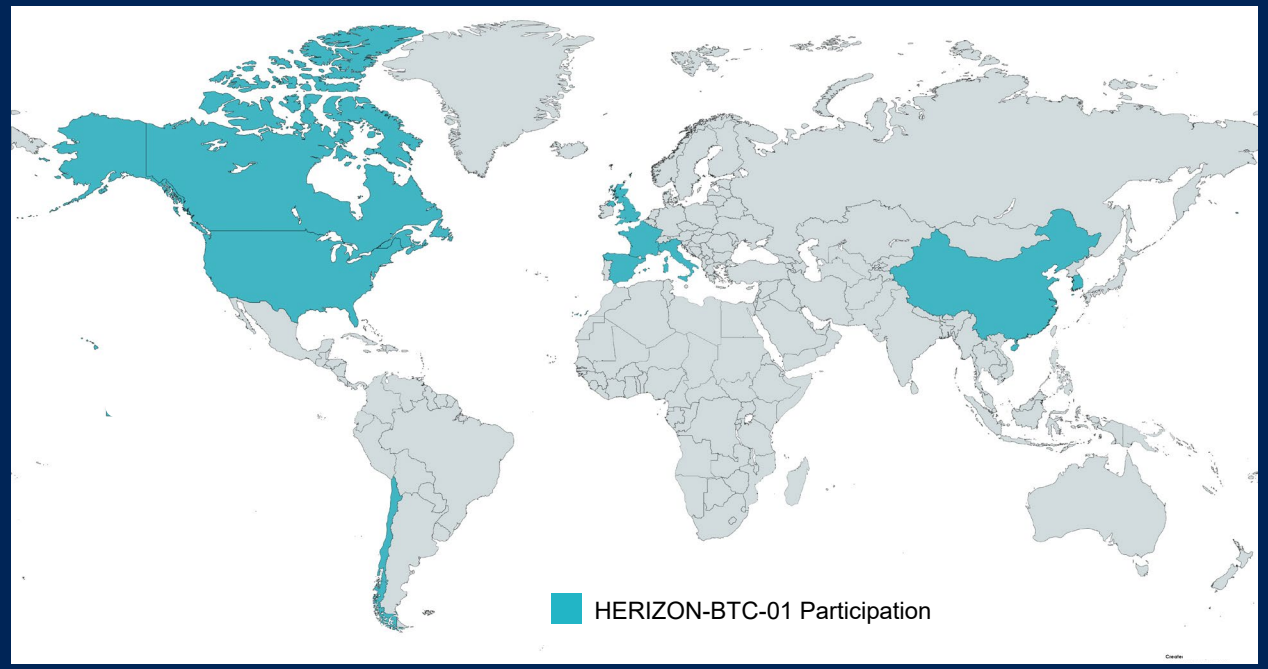


[1] Excludes ampullary

AE = adverse event; cORR = confirmed objective response rate; CT = computed tomography scan; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ICR = independent central review; IHC = immunohistochemistry; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; Q2W = every two weeks; RECIST= Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

Enrollment

- Enrollment: September 2020 – March 2022
- Sites: 32 in Asia, Europe, North America, & South America
- Data cutoff date for the primary analysis: 10 October 2022
- Study is ongoing but recruitment is complete: 87 patients treated
  - Cohort 1: 80 patients
  - Cohort 2: 7 patients



* The focus of this presentation will be on HER2-positive BTC (Cohort 1), as Cohort 2 contained a small sample size and did not reveal any responses nor unique safety signals.

Demographics and Baseline Disease Characteristics (Cohort 1)

		(N = 80)
Age, years, median (range)		64 (32, 79)
Sex: Female, n (%)		45 (56.3)
Race, n (%)	Asian	52 (65.0)
	White	23 (28.8)
	Other / Not Reported	5 (6.3)
ECOG PS, n (%)	0	22 (27.5)
	1	58 (72.5)
BTC Subtype, n (%)	GBC	41 (51.3)
	ICC	23 (28.8)
	ECC	16 (20.0)
HER2 Status, n (%)	IHC 2+	18 (22.5)
	IHC 3+	62 (77.5)

		(N = 80)
Disease stage at baseline, n (%)	Stage III	9 (11.3)
	Stage IV	71 (88.8)
Prior therapies in the locally advanced/metastatic setting, median (range)		1 (1, 7)
Regimen received, n (%)*	CISGEM	61 (76.3)
	Fluoropyrimidine-based	27 (33.8)
	PD-1 / PD-L1 inhibitor	21 (26.3)
	Other	5 (6.3)

CISGEM = cisplatin and gemcitabine; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1.

* Patients are counted at most once under each regimen type received and may be counted in multiple categories

Disease Response in Patients with HER2-positive BTC (Cohort 1)

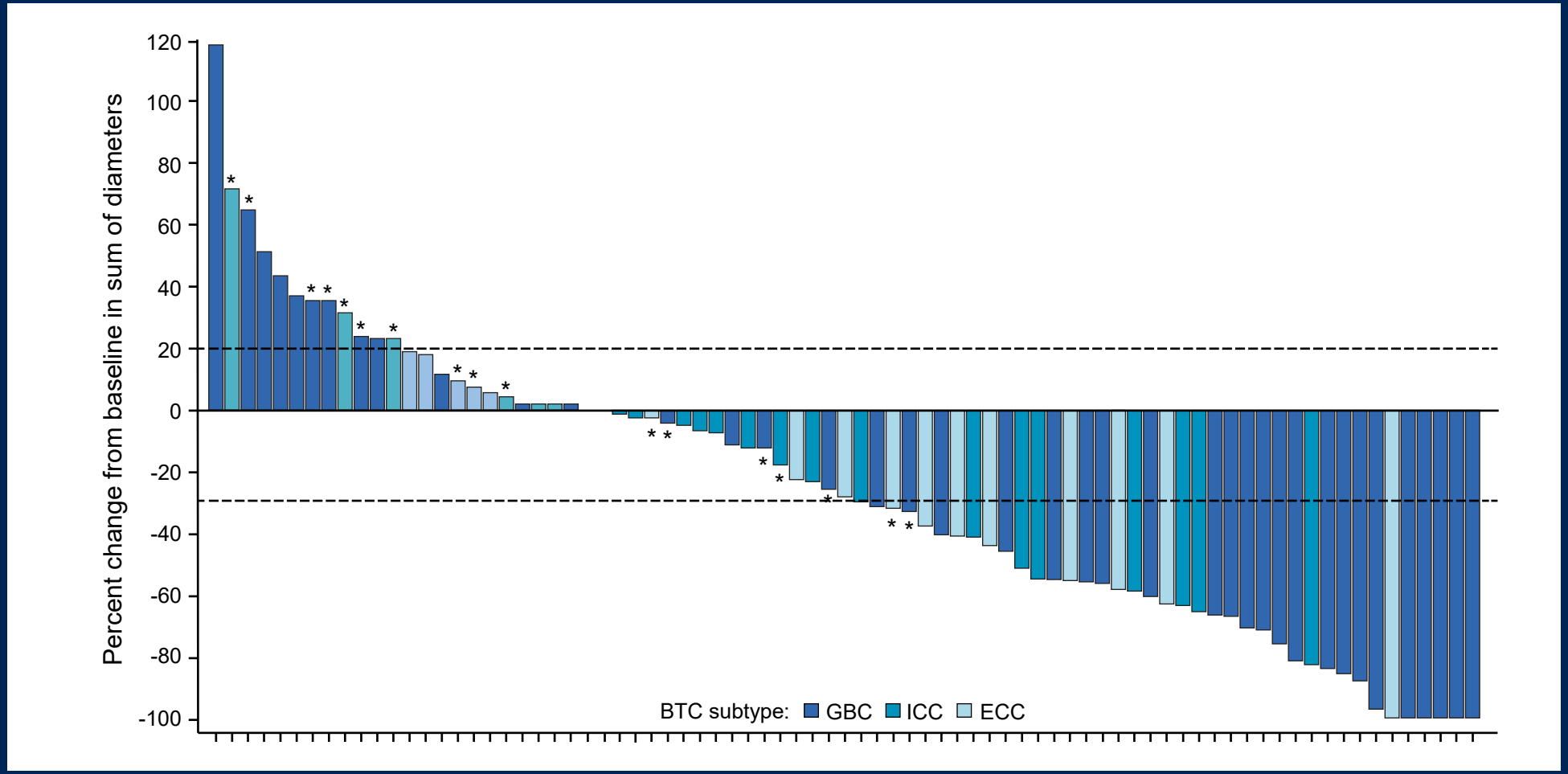
- 16 patients had ongoing responses at the time of data cutoff

		By ICR Assessment (N = 80)	By Investigator Assessment (N = 80)
cORR, % (95% CI)		41.3 (30.4, 52.8)	41.3 (30.4, 52.8)
Confirmed BOR, n (%)	CR	1 (1.3)	4 (5.0)
	PR	32 (40.0)	29 (36.3)
	SD	22 (27.5)	21 (26.3)
	PD	24 (30.0)	25 (31.3)
	NE[1]	1 (1.3)	1 (1.3)
DCR [CR + PR + SD], % (95% CI)		68.8 (57.4, 78.7)	67.5 (56.1, 77.6)
CBR [CR + PR + (SD ≥ 6 months)], % (95% CI)		47.5 (36.2, 59.0)	47.5 (36.2, 59.0)

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

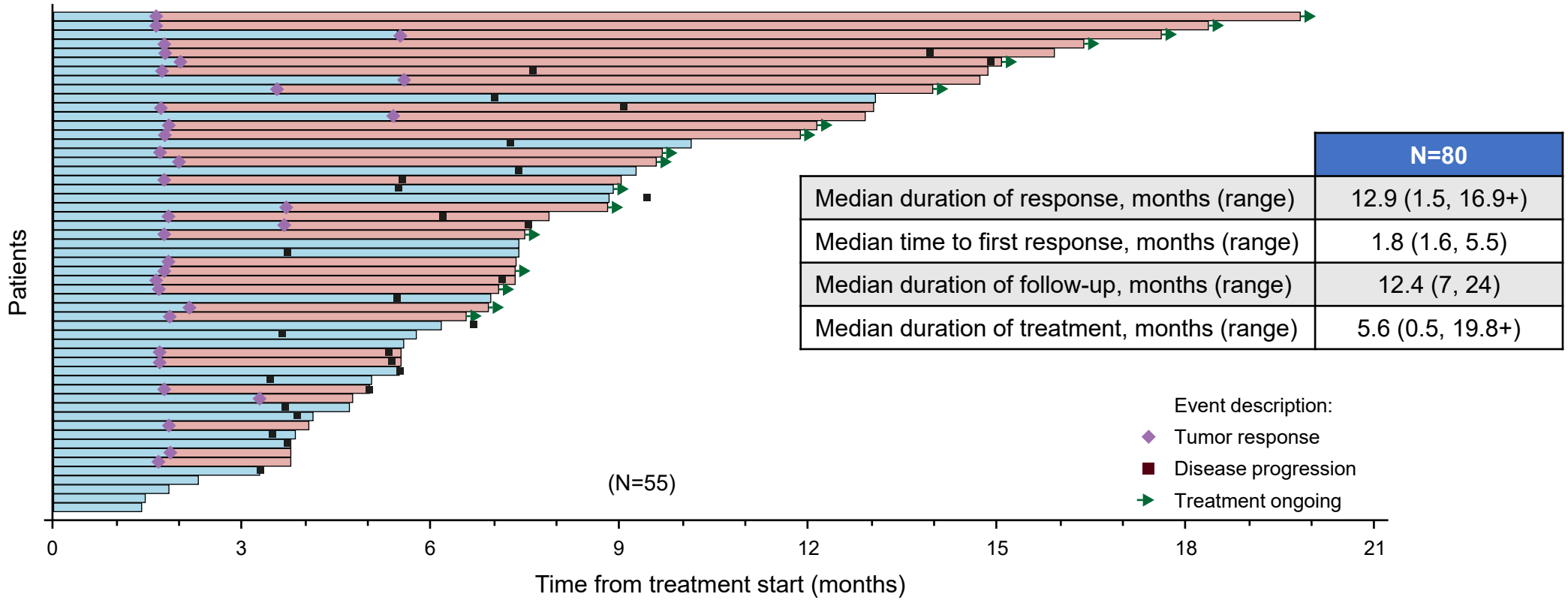
[1] NE = one patient died prior to first post-baseline tumor assessment.

Majority of evaluable patients (68.4%) had a decrease in target lesions (Cohort 1)



*Indicates patients with IHC 2+ status; all other patients had IHC status of 3+.
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.

Treatment Duration for Patients with Response (CR or PR) or Stable Disease per RECIST v1.1 by ICR (Cohort 1)

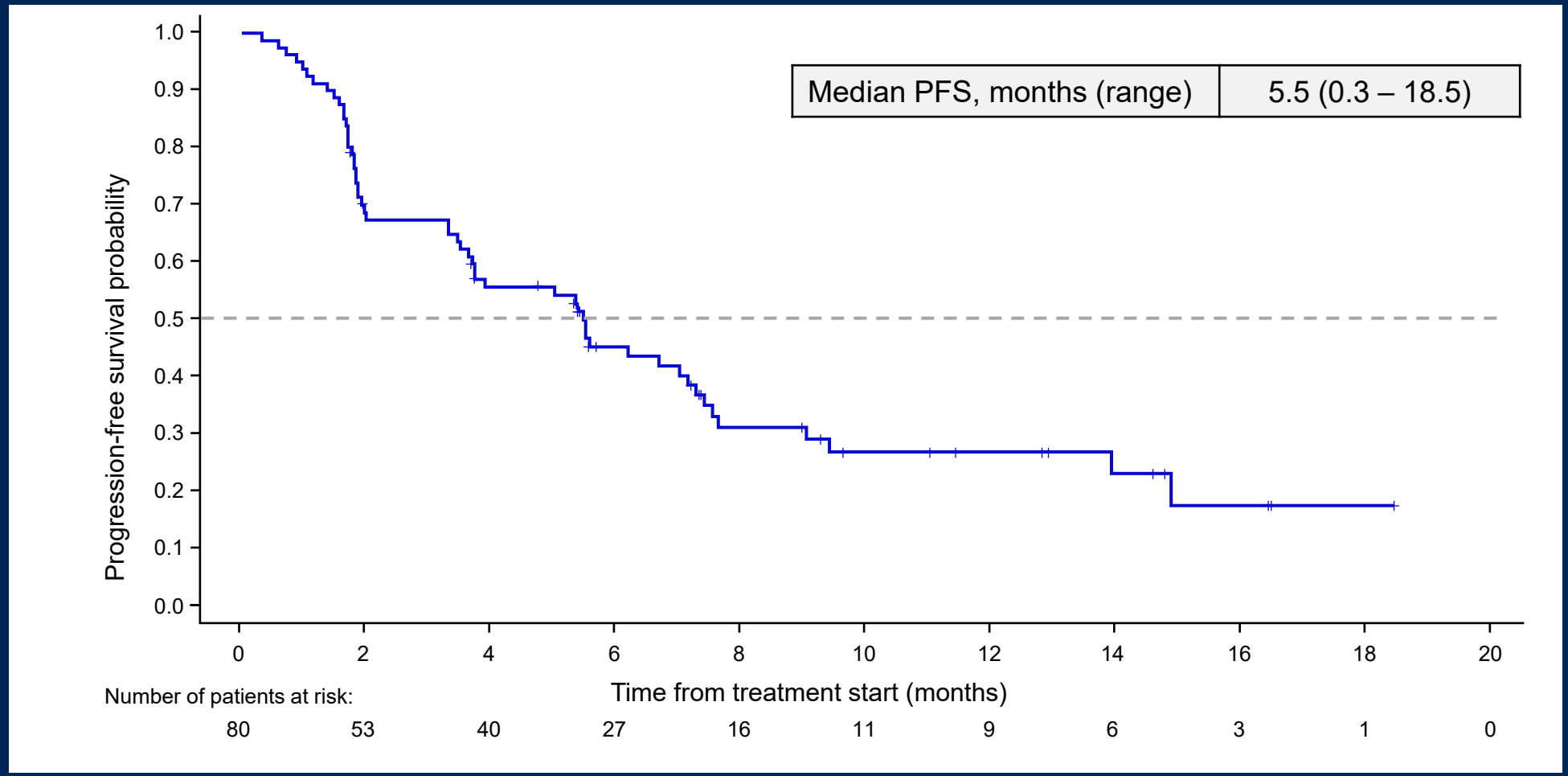


	N=80
Median duration of response, months (range)	12.9 (1.5, 16.9+)
Median time to first response, months (range)	1.8 (1.6, 5.5)
Median duration of follow-up, months (range)	12.4 (7, 24)
Median duration of treatment, months (range)	5.6 (0.5, 19.8+)

Note: Decisions to discontinue zanidatamab were based on investigator assessment. One patient with non-responding tumors was still on treatment.

Progression-free Survival in Patients with HER2-positive BTC (Cohort 1)

- OS data not yet mature



Adverse Events

	Cohort 1 (N = 80)		Total (N = 87)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TEAE, n (%)	78 (97.5)	46 (57.5)	84 (96.6)	52 (59.8)
Any TRAE, n (%)	61 (76.3)	15 (18.8)	63 (72.4)	16 (18.4)
Serious TRAE, n (%)	7 (8.8)	7 (8.8)	7 (8.0)	7 (8.0)
TRAEs leading to treatment discontinuation, n (%)	2 (2.5)	1 (1.3)	2 (2.3)	1 (1.1)
TRAEs leading to death, n (%)	0	0	0	0
TRAEs, any Grade occurring in ≥ 10% of patients or Grade ≥ 3 in ≥ 2 patients, n (%)				
Diarrhea	32 (40.0)	4 (5.0)	32 (36.8)	4 (4.6)
IRR	28 (35.0)	1 (1.3)	29 (33.3)	1 (1.1)
Ejection fraction decreased	8 (10.0)	3 (3.8)	8 (9.2)	3 (3.4)
Nausea	8 (10.0)	1 (1.3)	8 (9.2)	1 (1.1)
Anemia	4 (5.0)	2 (2.5)	4 (4.6)	2 (2.3)

TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event.

- 2 TRAEs led to zanidatamab discontinuation:
  - 1 Grade 2 ejection fraction decreased
  - 1 Grade 3 pneumonitis
- 3 patients had TRAES that led to dose reductions:
  - 1 Grade 3 diarrhea
  - 1 Grade 3 diarrhea and Grade 3 nausea
  - 1 Grade 2 weight decreased
- No serious TRAEs occurred in more than 1 patient
- No Grade 4 TRAES; no treatment-related deaths

Adverse Events of Special Interest (AESI)

		Cohort 1 (N = 80)		Total (N = 87)	
		Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
AESI, n (%)	IRR	28 (35.0)	1 (1.3)	29 (33.3)	1 (1.1)
	Confirmed cardiac events	5 (6.3)	3 (3.8)	5 (5.7)	3 (3.4)
	Non-infectious pulmonary toxicities	1 (1.3)	1 (1.3)	1 (1.1)	1 (1.1)
Select AE, n (%)[1]	Diarrhea	38 (47.5)	6 (7.5)	38 (43.7)	6 (6.9)

[1] AESIs that occurred in at least 1 patient

- IRR events: all events resolved, generally within 1 day; most occurred with the first cycle of treatment (26/29); most had no recurrence (26/29)
- Confirmed cardiac events: decreased LVEF in 5 patients (5.7%). Patients were clinically asymptomatic, and the events were confounded by pre-existing or concurrent conditions.
- Diarrhea: all but 2 events (both Grade 3) were managed in the outpatient setting, typically with loperamide; most events (87/99) were resolved at the time of data cutoff; median time to resolution of 2.0 days (range, 1 – 267)

Conclusions

- Zanidatamab demonstrated antitumor activity, including rapid and durable responses, in patients with treatment-refractory HER2-positive BTC
  - cORR per ICR of 41.3%; most responses were identified at first disease assessment
  - Median DOR: 12.9 months
- Zanidatamab demonstrated a manageable and tolerable safety profile
  - Few events led to treatment discontinuation
  - No Grade 4 TRAEs; no deaths were treatment-related
  - Most common AEs were IRRs and diarrhea; predominately low-grade and reversible
- These results support zanidatamab having meaningful clinical benefit and potential as a future treatment option in HER2-positive BTC
  - Additional studies are both planned and active, including zanidatamab in combination with CISGEM

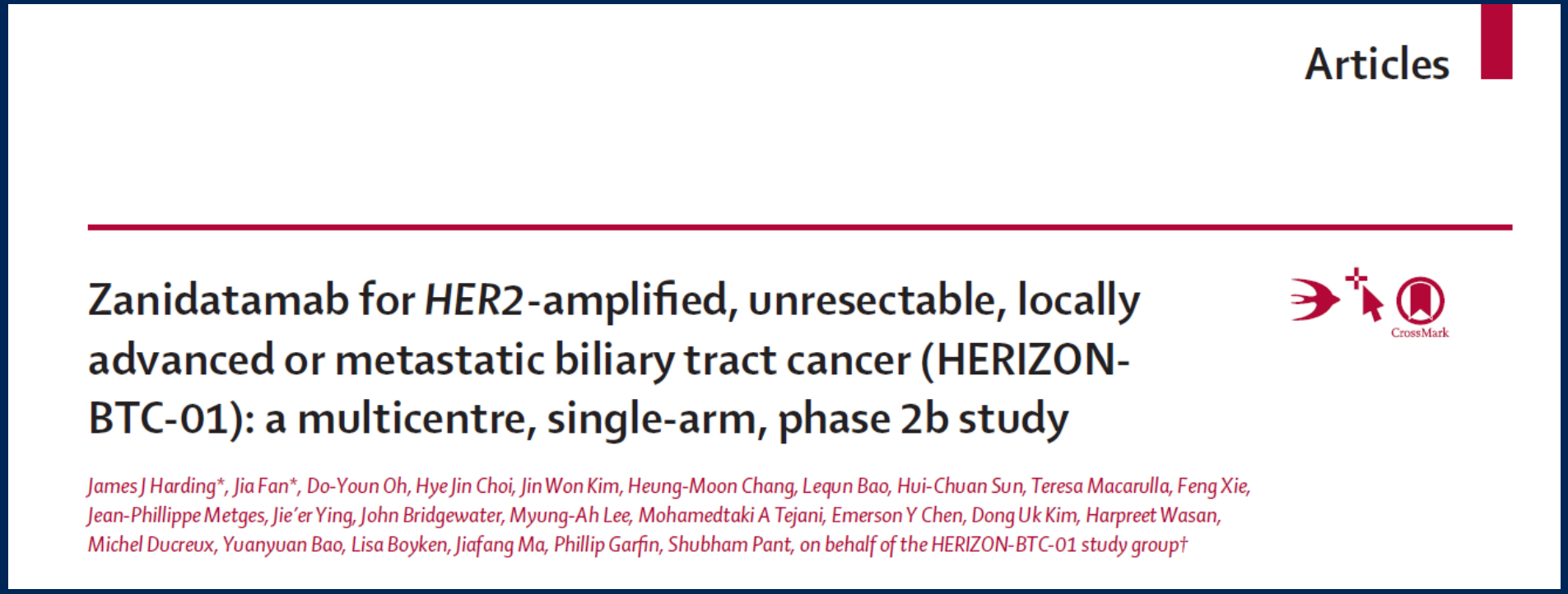
CISGEM = cisplatin and gemcitabine

Acknowledgement, Disclosure

We sincerely thank all patients and their caregivers. Thanks to all the investigators, clinical trial researchers, personnel and staff who contributed to the trial in any way.

The HERIZON-BTC-01 study is funded by Zymeworks BC Inc., Jazz Pharmaceuticals, Inc., and BeiGene Ltd.

Full Publication – *The Lancet Oncology*



Articles

Zanidatamab for *HER2*-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study

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- www.thelancet.com/oncology
- **Published online June 2, 2023 https://doi.org/10.1016/S1470-2045(23)00242-5**