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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)

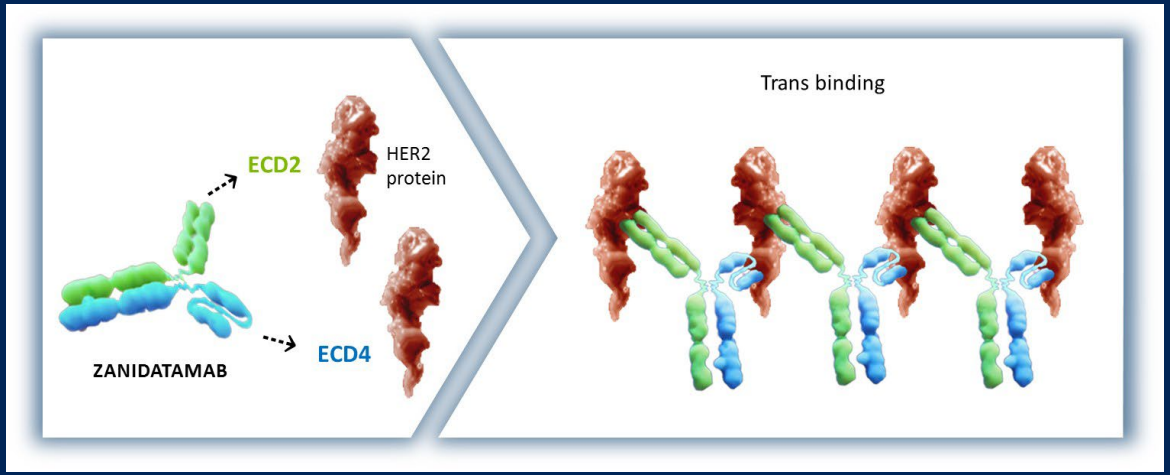
- BTC is uncommon (< 1% of all adult cancers)[1,2]
- For patients with locally advanced/metastatic BTC, standard 2L+ offers limited clinical benefit
  - ORR 5 – 15%[3,4]
  - mPFS 4.0 mo[3]
- HER2 amplification/overexpression is observed in a subset of BTC
  - 19 – 31% of GBC, 17 – 19% of ECC, 4 – 5% 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

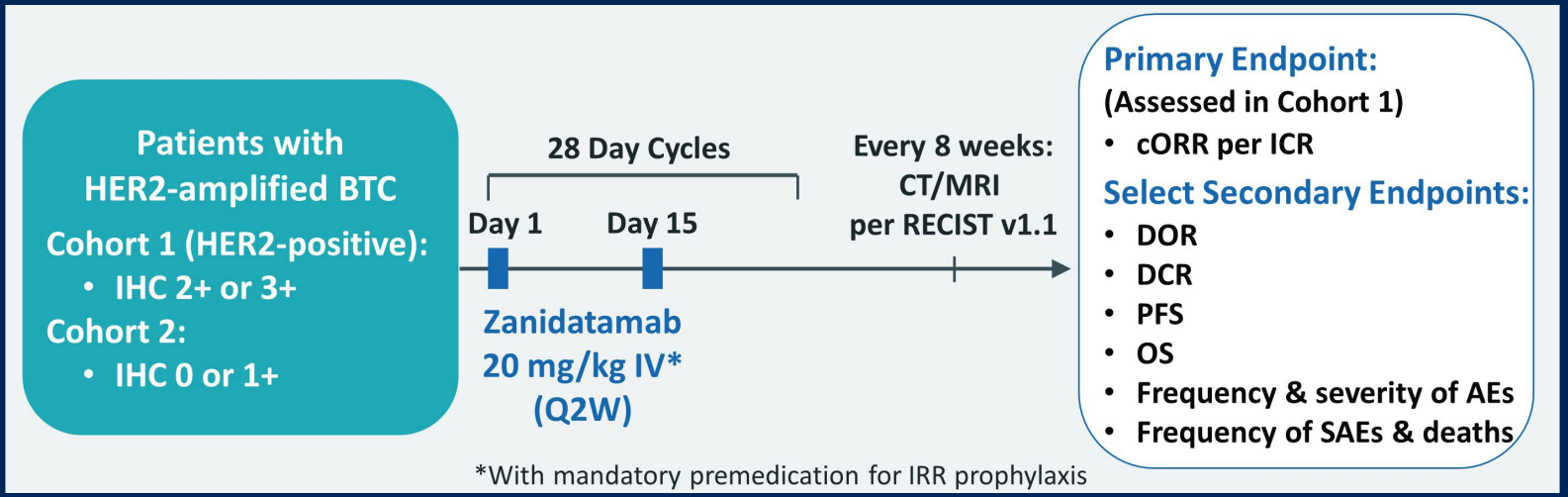
[1] Weisser NE, et al. Nature Commun 2023;14:1394. [2] Meric-Bernstam F, et al. Lancet Oncol 2022;23:1558–1570.

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

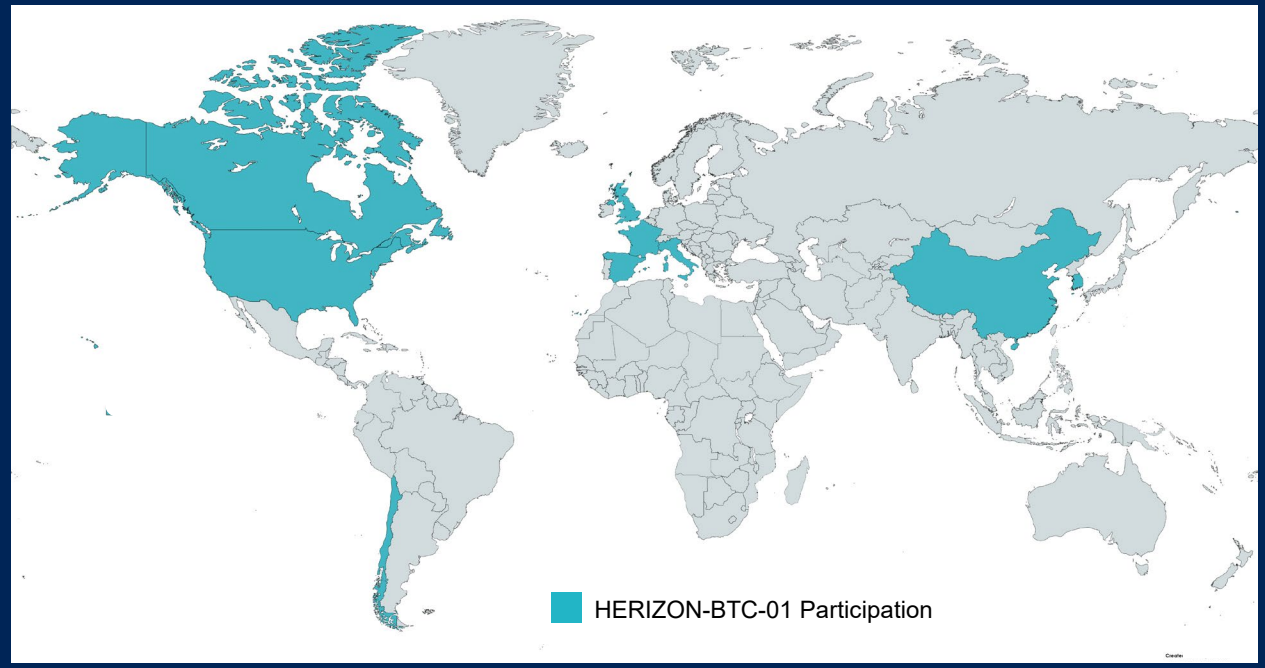


[1] Excludes ampullary

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)

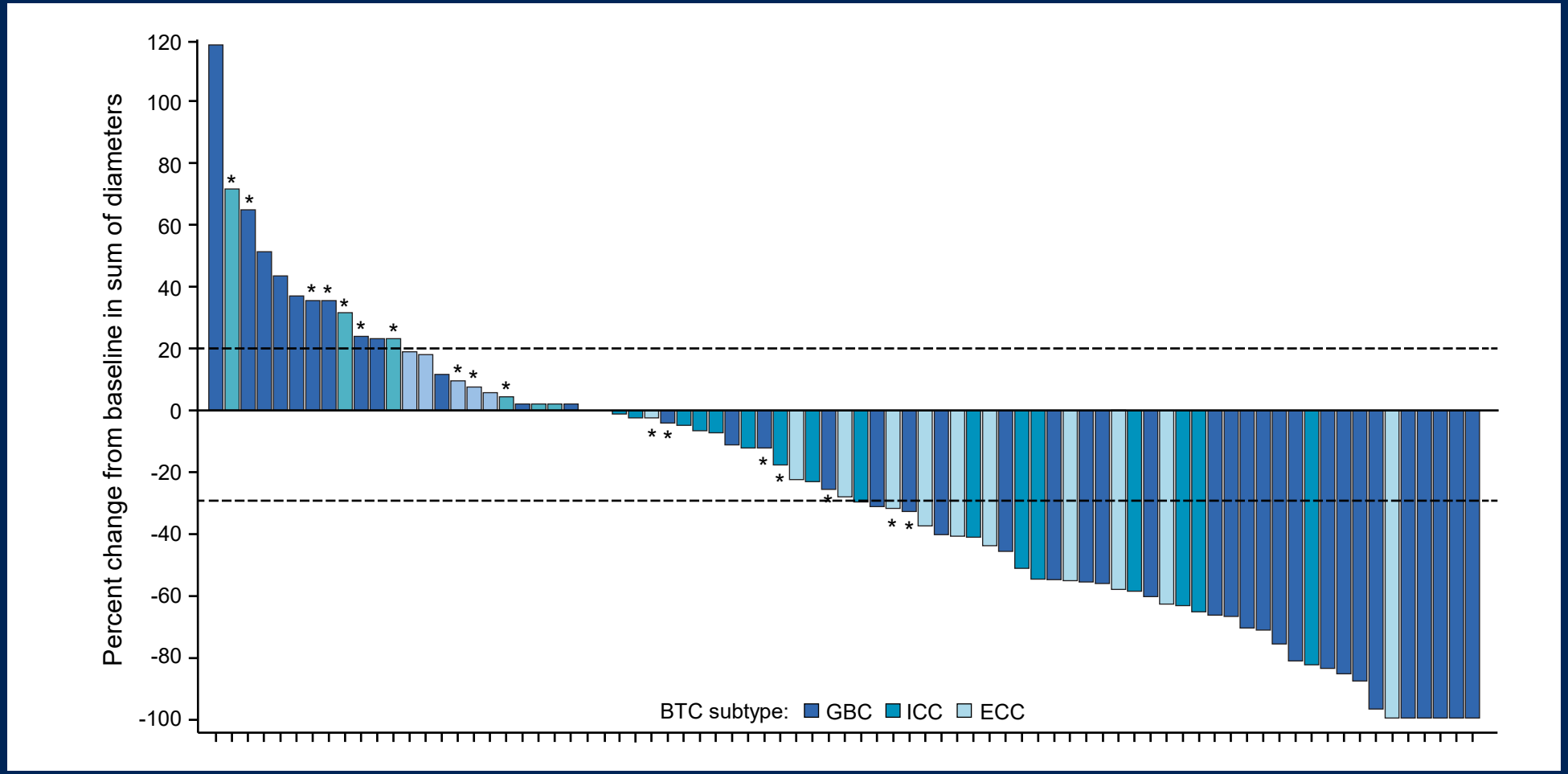
- 16 patients had ongoing responses at the time of data cutoff

		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.

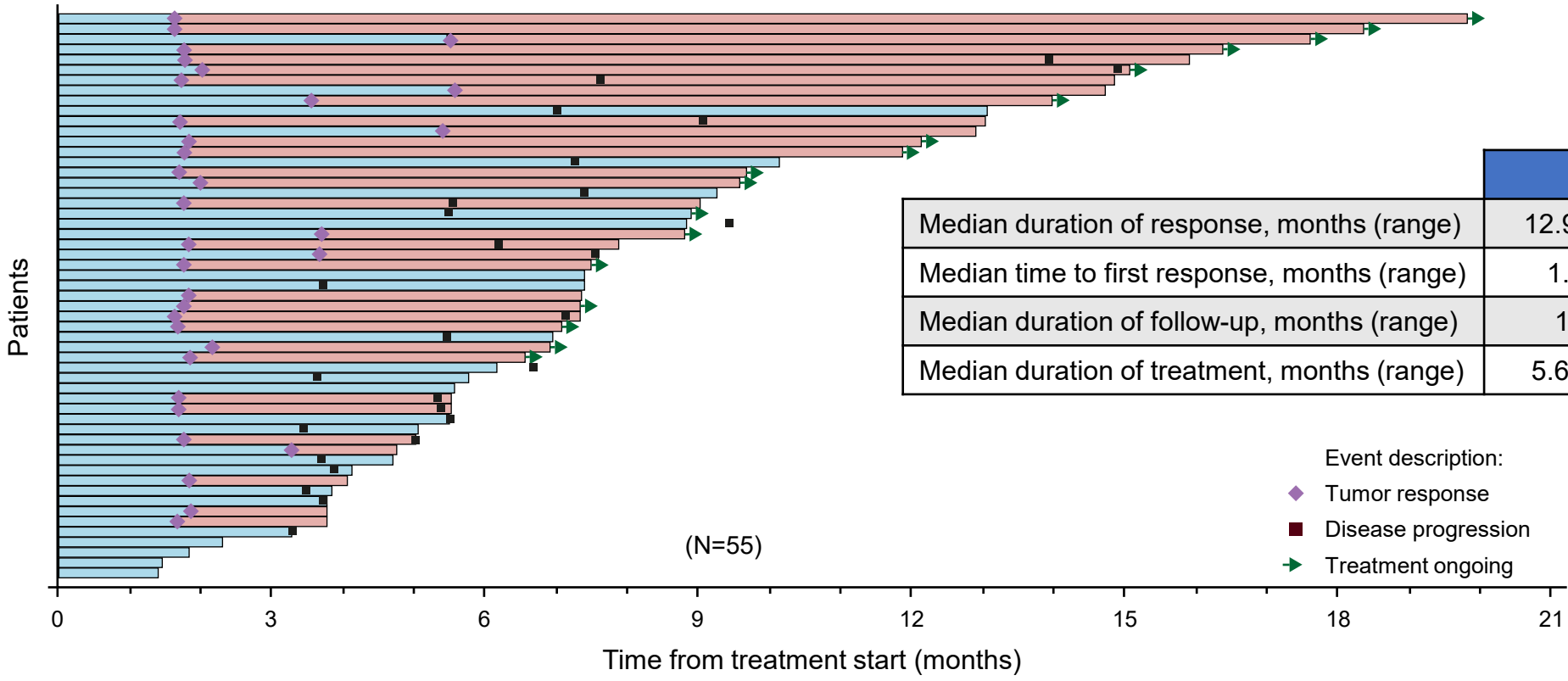
[1] NE = one patient died prior to first post-baseline tumor assessment.

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)

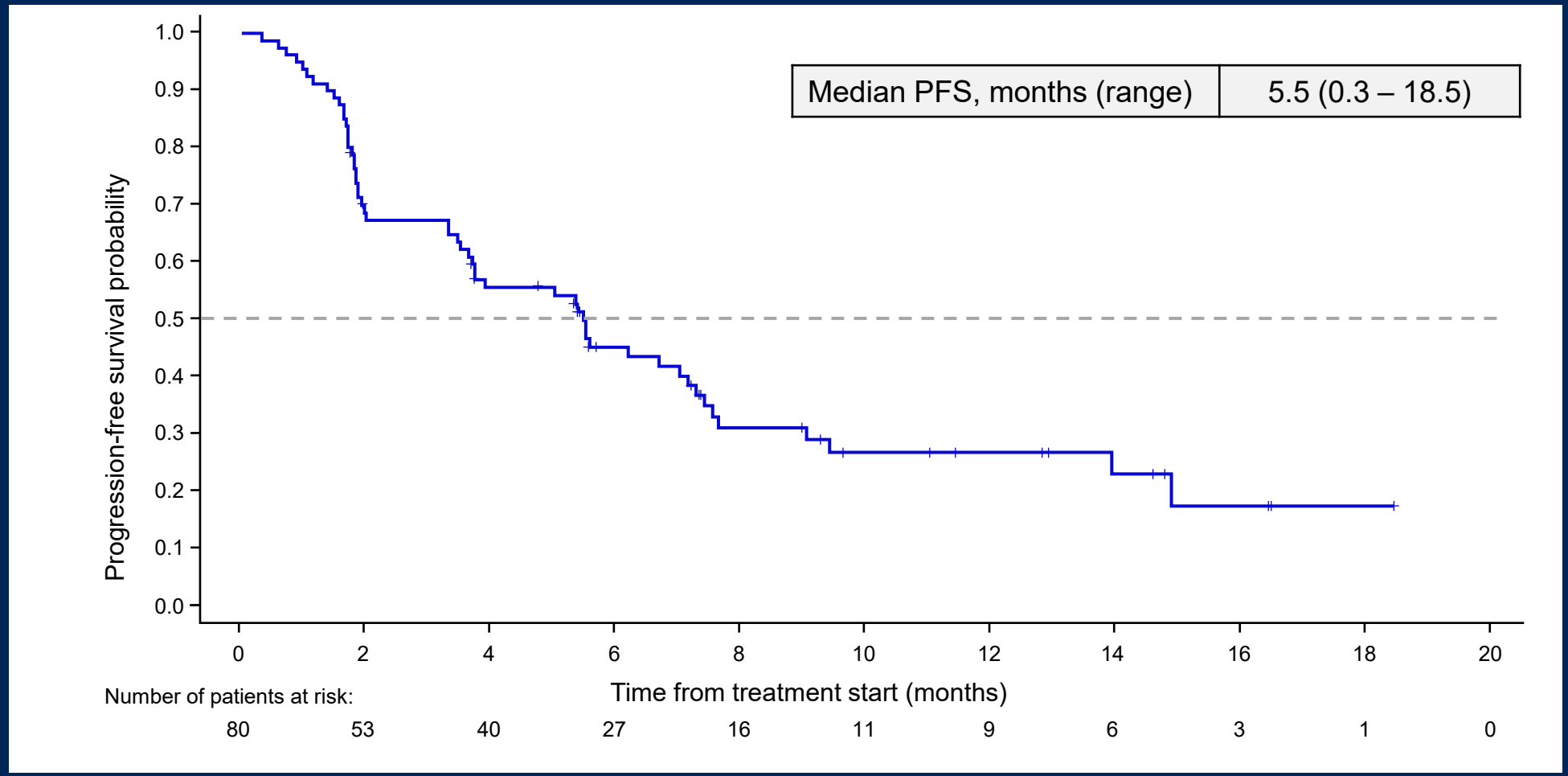


	N=80
Median duration of response, months (range)	12.9 (1.5, 16.9+)
Median time to first response, months (range)	1.8 (1.6, 5.5)
Median duration of follow-up, months (range)	12.4 (7, 24)
Median duration of treatment, months (range)	5.6 (0.5, 19.8+)

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

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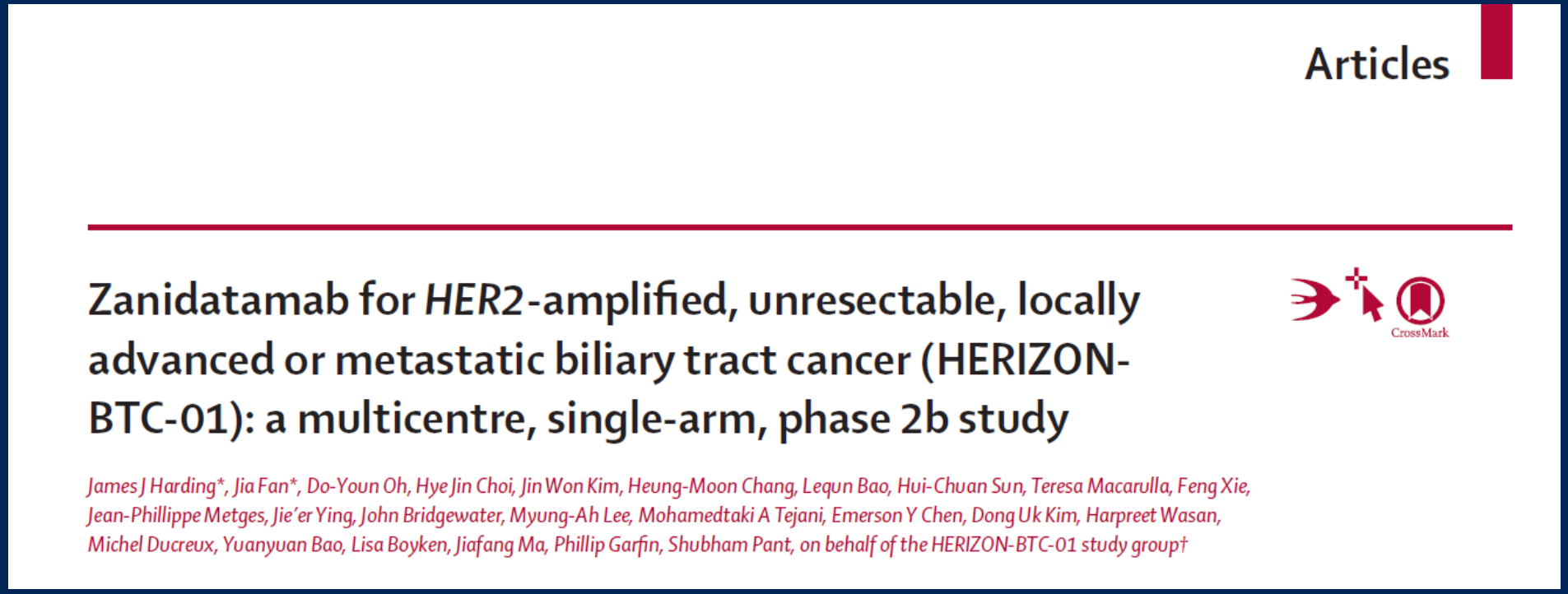
Full Publication – *The Lancet Oncology*



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