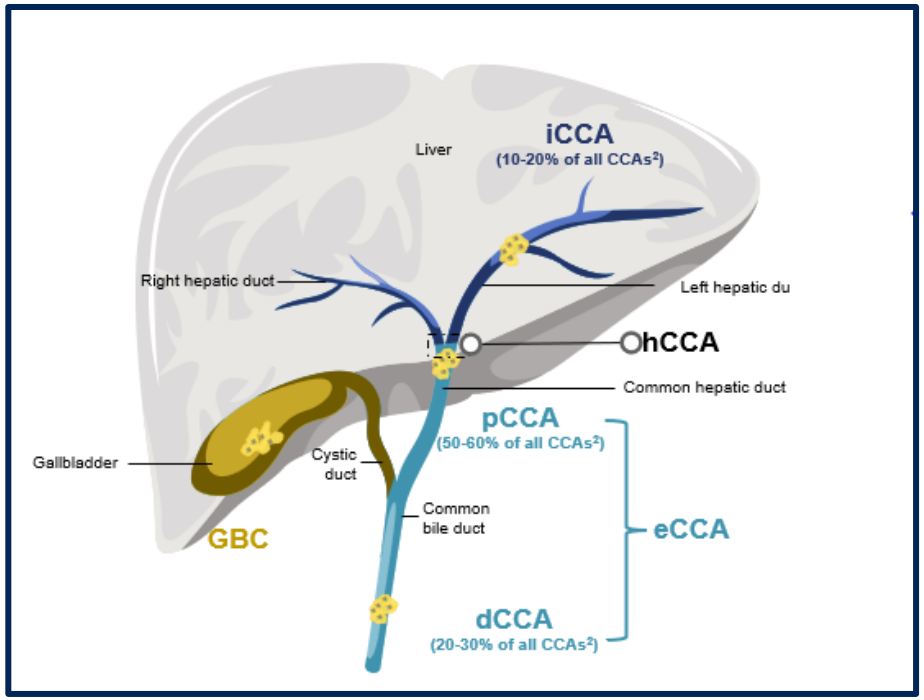
Administration of Zanidatamab Request for ICD-10-PCS Procedure Codes

ICD-10 Coordination & Maintenance Committee Meeting
March 2024

Zanidatamab is a Jazz Pharmaceuticals' investigational product and is not yet FDA approved.

Unmet Need in Patients with Biliary Tract Cancer (BTC)

BTC is a highly heterogeneous group of malignancies[1]; ~12,000 HER2-positive BTC cases annually[2]



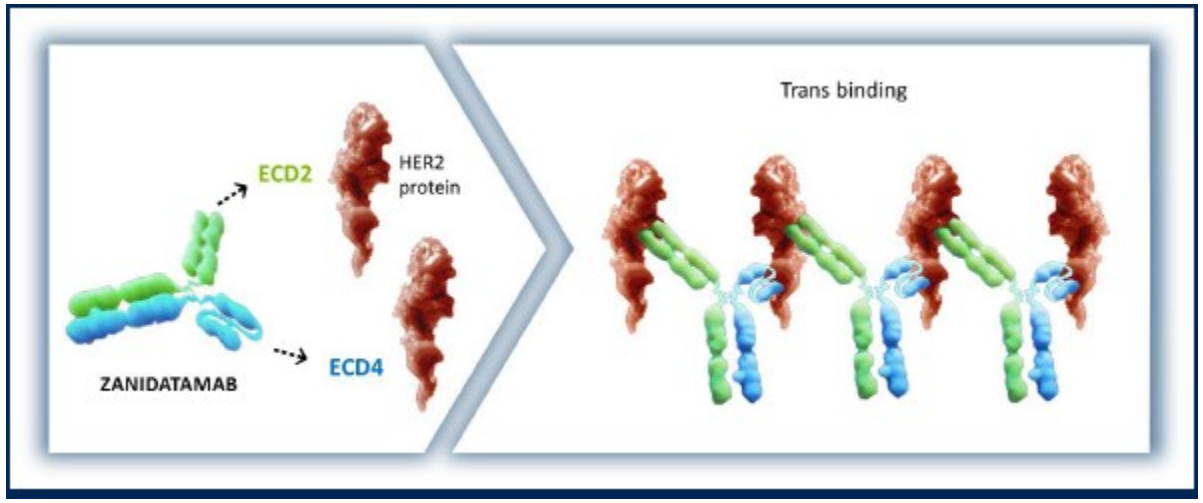
- Tumors of the biliary tract can be classified into two main types of cancer based on anatomical location[1]
  - Gallbladder cancer (GBC) arises from the gallbladder or cystic duct
  - Cholangiocarcinoma (CCA) arises along the biliary tree
- For patients with locally advanced/metastatic BTC, standard 2L+ offers limited clinical benefit
  - ORR 5-15%[3,4]; mPFS 4.0 months[3]; median OS <12 months[5]
- *HER2* amplification/overexpression is observed in a subset of BTC
  - 20% of GBC 15% of ECC, 7% of ICC[1]
- *HER2*-targeted therapies have demonstrated clinical benefit in breast, gastric cancer and lung cancer.
- There are no FDA-approved HER2-targeted therapies for BTC

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

1. Moeini A, et al. *JHEP Rep*. 2021;3(2):100226. 2. Incidence sources (US, Europe, Japan):Incidence sources: Kantar reports; ToGA surveillance report; SEER, cancer.gov ; ClearView Analysis; GLOBOCAN; data on file. Europe represents major markets, U.K., France, Germany, Spain, Italy. 3. Lamarca A, et al. *Lancet Oncol* 2021;22:690-701.4. Yoo C, et al. *Lancet Oncol* 2021; 22:1560-72. 5. Mirallas O, et al. *ESMO Open*. 2022;7(3):100503.

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

- Zanidatamab is a bispecific antibody that is also biparatopic[1]
  - It binds to two distinct epitopes of *HER2* (ECD4 and ECD2)
  - Binding occurs on two separate *HER2* molecules in a trans orientation
  - Its geometry prevents binding to the same *HER2* molecule
  - Zanidatamab binding prevents *HER2* dimerization
- Preclinical studies demonstrate greater activity than trastuzumab ± pertuzumab (targeted treatments for *HER2*-positive breast cancer)[1]
- Zanidatamab has shown a manageable safety profile and encouraging antitumor activity in patients with *HER2*-exressing 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.

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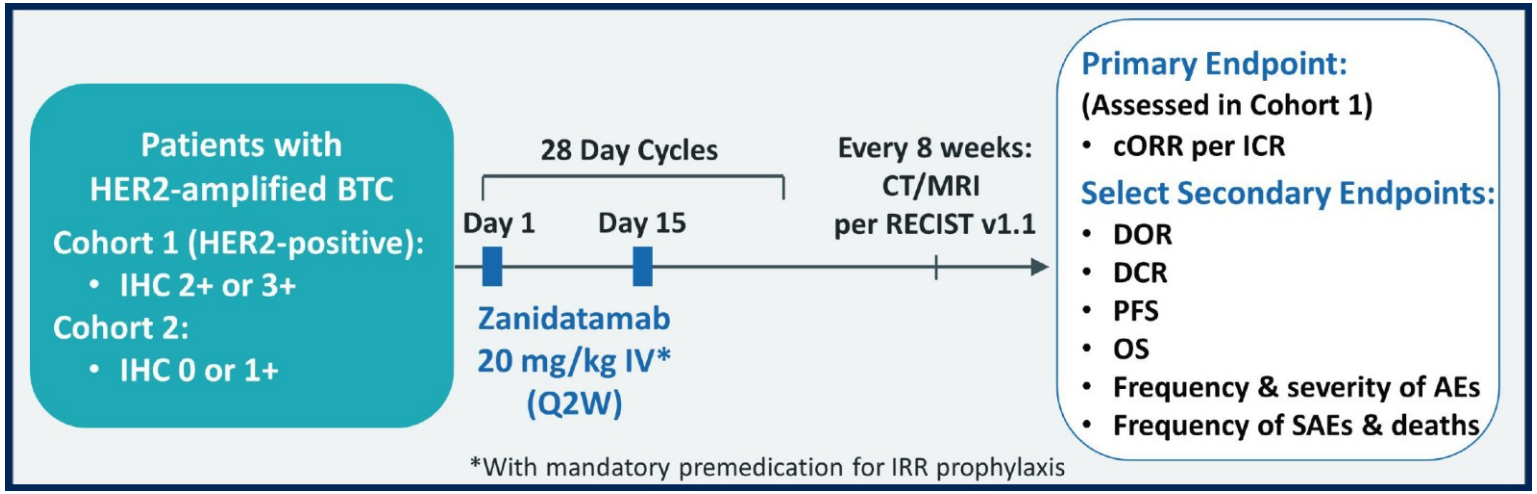
HERIZON-BTC-01 Study Design

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



- 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: Cohort 1 (n=80) and Cohort 2 (n=7)

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 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event..

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Demographics and Baseline Disease Characteristics (Cohort 1)[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

ECC, extrahepatic cholangiocacinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; IHC, immunohistochemistry

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.

1. Pant S, et al. J Clin Oncology 2023 41:16_suppl, 4008.

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Dosing & Administration of Zanidatamab

- **Single-use packaging:** Zanidatamab will be supplied as sterile, single-use, preservative-free, lyophilized powder in a glass vial containing 300 mg drug product
- **Weight-based dosing*:** 20 mg/kg every 2 weeks (Q2W) on Days 1 and 15 of each 28-day cycle
- **Administration:** Zanidatamab is administered by intravenous infusion in 0.9% normal saline over ~120 to 150 minutes during Cycle 1. If the first 2 doses are well tolerated, the infusion duration can be decreased to 90 minutes. If the next 2 doses are well tolerated, the infusion duration may be further decreased to less than 90 minutes; however, the infusion rate should not exceed 250 mL/hour
  - Not to be administered as an IV push or bolus; not to be mixed with other medications
- **Medical record:** Inpatient administration of zanidatamab will be documented in the medical record in the same manner as other therapies that are administered via intravenous infusion.
  - Outpatient administration of zanidatamab will follow standard practices in those settings.

*Final dosing will be based on the FDA-approved prescribing information.

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

1. Pant S, et al. J Clin Oncology 2023 41:16_suppl, 4008.

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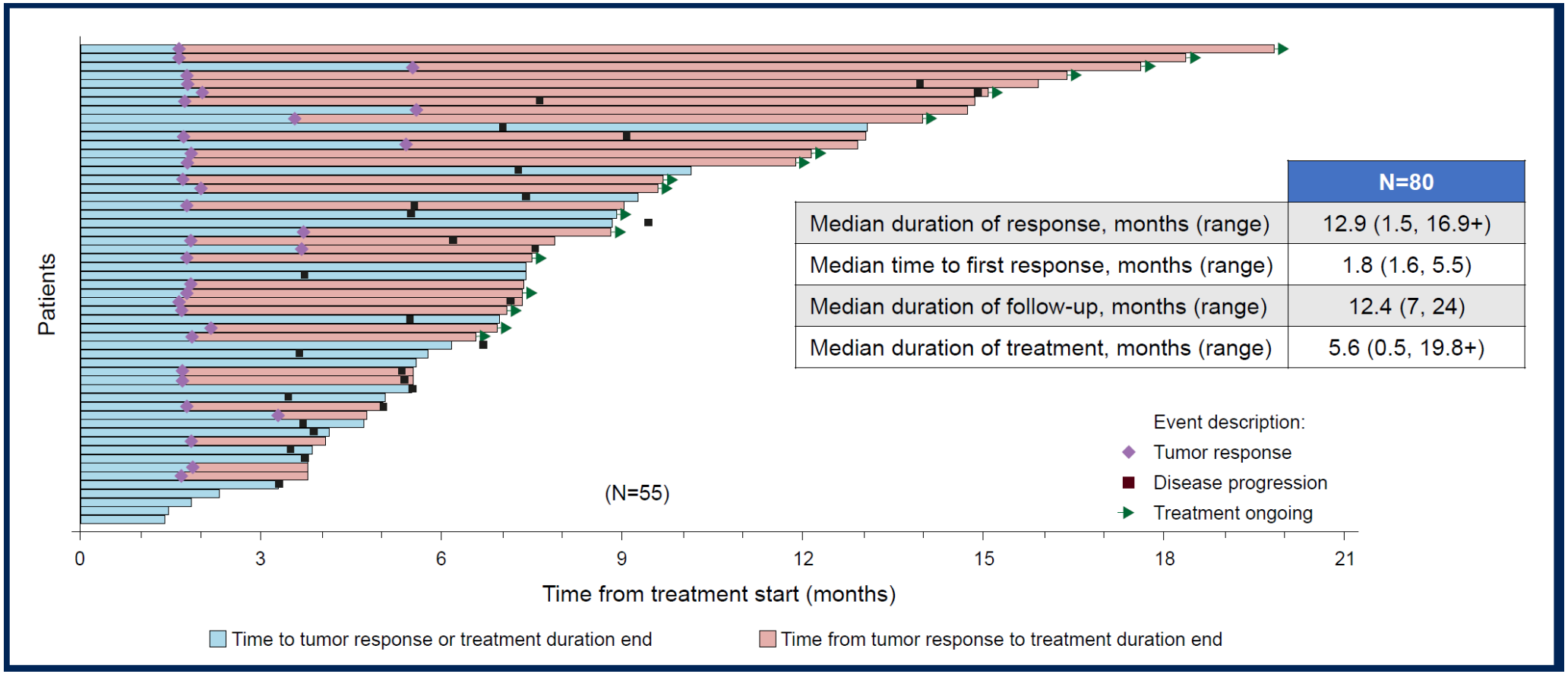
Treatment Duration for Patients with Response (CR or PR) or Stable Disease per RECIST v1.1 by ICR (Cohort 1)[1]



	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.

1. Pant S, et al. J Clin Oncology 2023 41:16_suppl, 4008.

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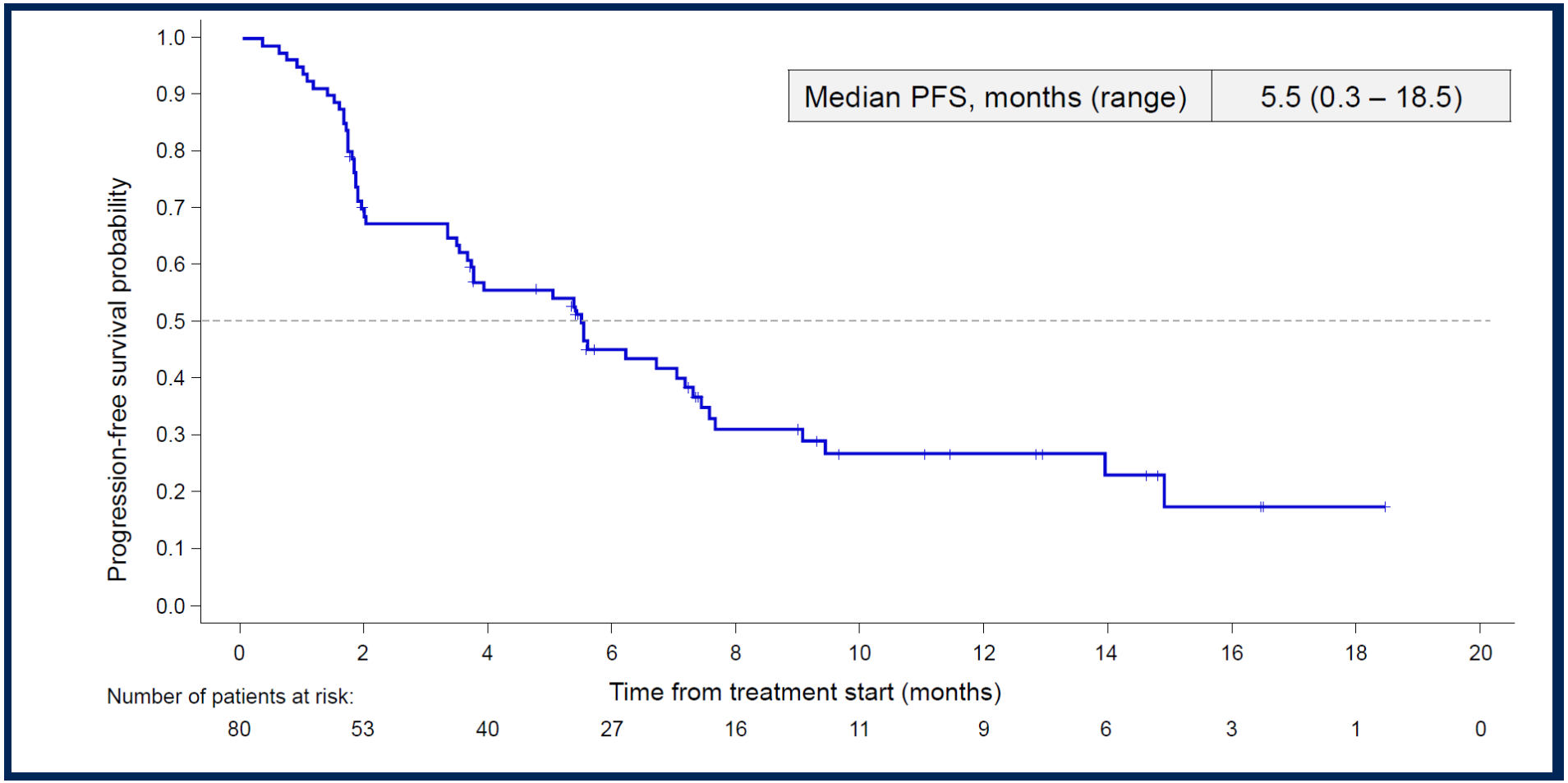
Progression-free Survival in Patients with *HER2*-positive BTC (Cohort 1)[1]

- Overall survival (OS) not yet mature



PFS, progression-free survival

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Adverse Events[1]

	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)

IRR = infusion-related reaction; 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

1. Pant S, et al. J Clin Oncology 2023 41:16_suppl, 4008.

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Upon FDA approval, Zanidatamab Will Fulfill an Unmet Need for Patients with *HER2*-positive BTC

- The prognosis of locally advanced (unresectable)/metastatic BTC is poor and standard 2L+ offers limited clinical benefit: ORR 5-15% and mPFS 4.0 months
- *HER2* amplification/overexpression is observed in a subset of BTC, but there are no approved *HER2*-targeted therapies for BTC
- Zanidatamab, a *HER2*-targeted bispecific antibody with a unique mechanism of action, demonstrated antitumor activity, including rapid and durable responses, in patients with previously-treated, locally advanced/metastatic *HER2*-positive BTC
- Zanidatamab demonstrated a manageable and tolerable safety profile
- In summary, zanidatamab demonstrated meaningful clinical benefit and has the potential to be a future treatment option in patients with previously-treated, locally advanced (unresectable)/metastatic *HER2*-positive BTC

2L+, second-line or later (treatment); BTC, biliary tract cancer; HER2, human epidermal growth factor receptor 2; mPFS, median progression-free survival; ORR, overall response rate
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