Management of HER2 + Biliary Tract Cancers

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Disclosures

- Consulting or Advisory Role: Zymeworks, Ipsen ,Novartis, Janssen, Boehringer Ingelheim, Askgene Pharma, BPGBio, Jazz Pharmaceuticals, Astra Zeneca, US WorldMeds, Nihon Medi-Physics

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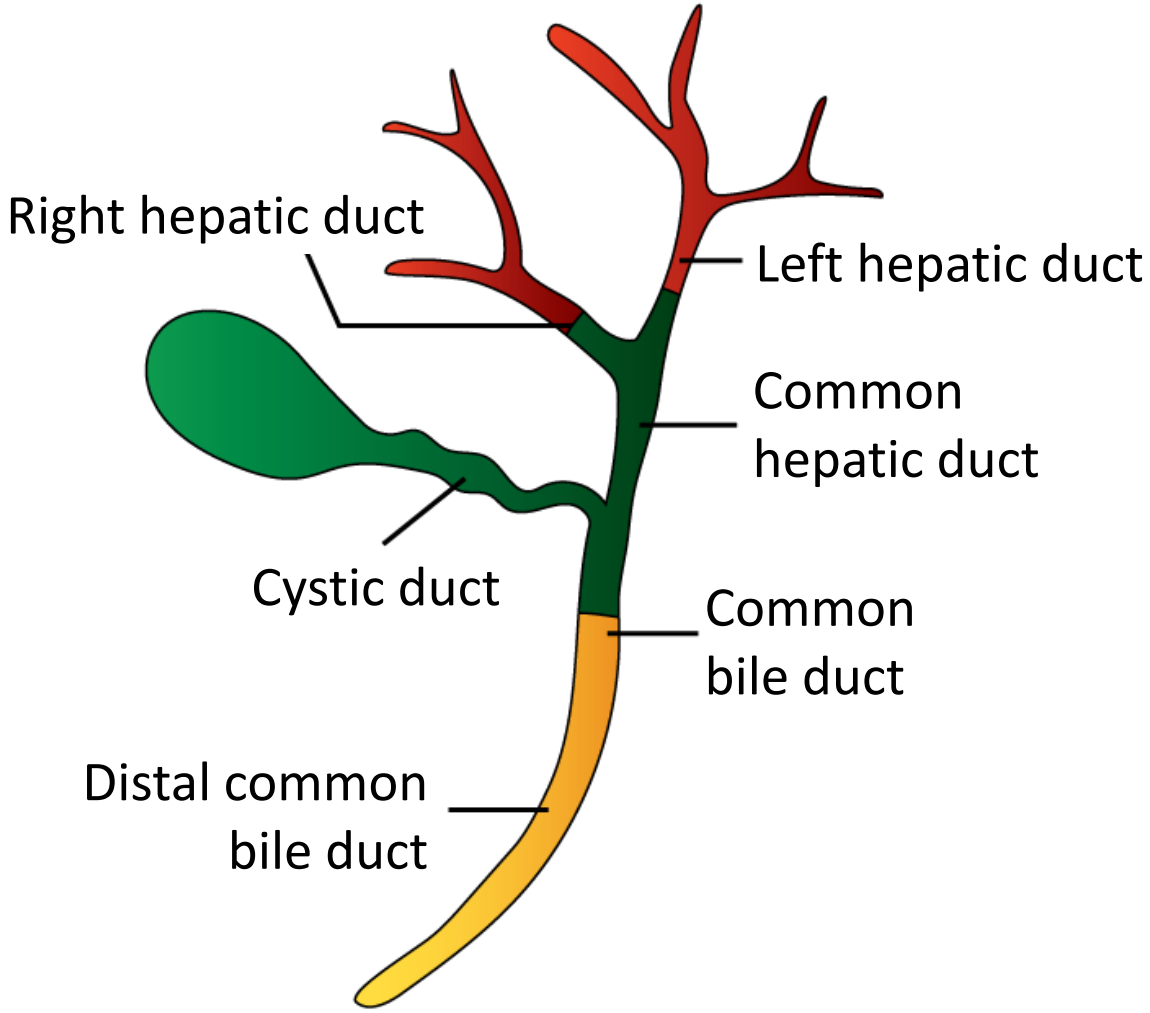
Biliary Cancers

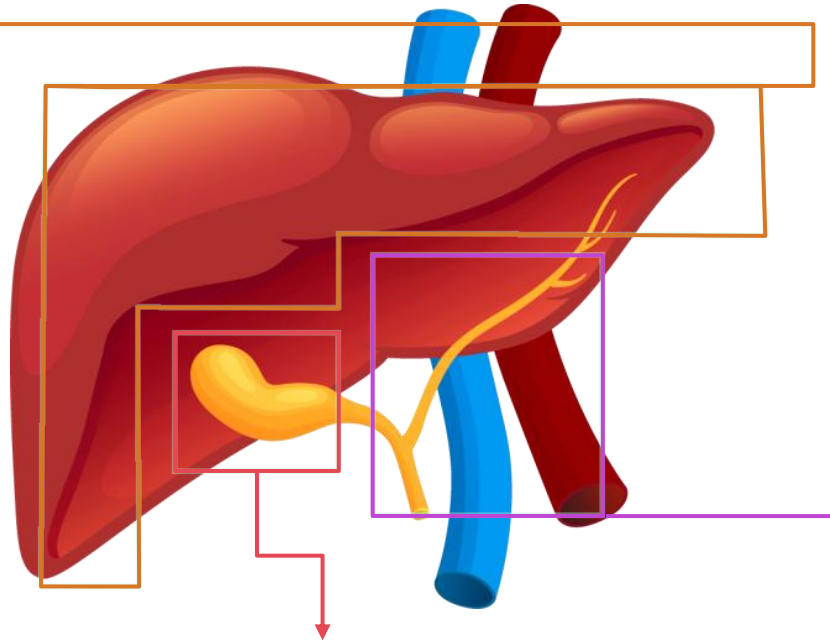


Intrahepatic—in the liver

Perihilar—near the hilum (where the bile ducts exit the liver)

Distal extrahepatic—outside the liver

Biliary Tract Cancers: Genomic Differences Based on Tumor Location[1]



ICC

- *FGFR 1-3* alterations
- *TP53* mutation
- *IDH1/2* mutations
- *ARID1A* mutation
- *CDKN2A/B* loss
- *KRAS* mutations
- *MCL1* amplification
- *SMAD4* mutations
- *BAP1* mutations
- *PTEN* mutations
- *PIK3CA* mutations
- *BRAF* mutations
- *ERBB3* amplifications
- *MET* amplifications
- *NRAS* mutations
- *CDK6* mutations
- *ERBB3* mutations
- *MET* mutations
- *BRCA1/2* mutations
- *NF1* mutations
- *EGFR* mutations

Large-duct ICC
KRAS mutations
(15% to 30%)
TP53 mutations
(10% to 40%)

Small-duct ICC
IDH1/2 mutations
(15% to 20%)
FGFR2 fusions
(10% to 20%)

Gallbladder carcinoma

- *TP53* mutation
- *ERBB2/3* amplification
- *CDKN2A/B* loss
- *ARID1A* mutation
- *PIK3CA* mutations
- *NRAS* mutations
- *AKAP11* mutation
- *FBXW7* mutation
- *GNAS* mutation
- *LAMA2* mutation
- *CSMD3* mutation
- *RNF43* mutation
- *DF3B1* mutation
- *BRCA1* mutation
- *SMARCB1* mutation
- *MAPP2K4* mutation
- *NF1* mutation
- *SMAD4* mutation
- *EGFR* mutation
- *FGFR 1-2* fusions, mutations, and amplification
- *IDH1/2* mutation

GBC and ECC
KRAS mutations
(30% to 45%)
Low frequency of
IDH and *FGFR*
alterations

ECC

- *KRAS* mutation
- *TP53* mutation
- *SMAD4* mutation
- *CDKN2A/B* loss
- *ARID1A* mutation
- *IDH* mutation
- *PIK3CA* mutation
- *MET* mutation
- *BRAF* mutation
- *MET* amplification

Biomarker-driven management to improve outcomes

Biospecimen sampling (tumor, blood, urine)

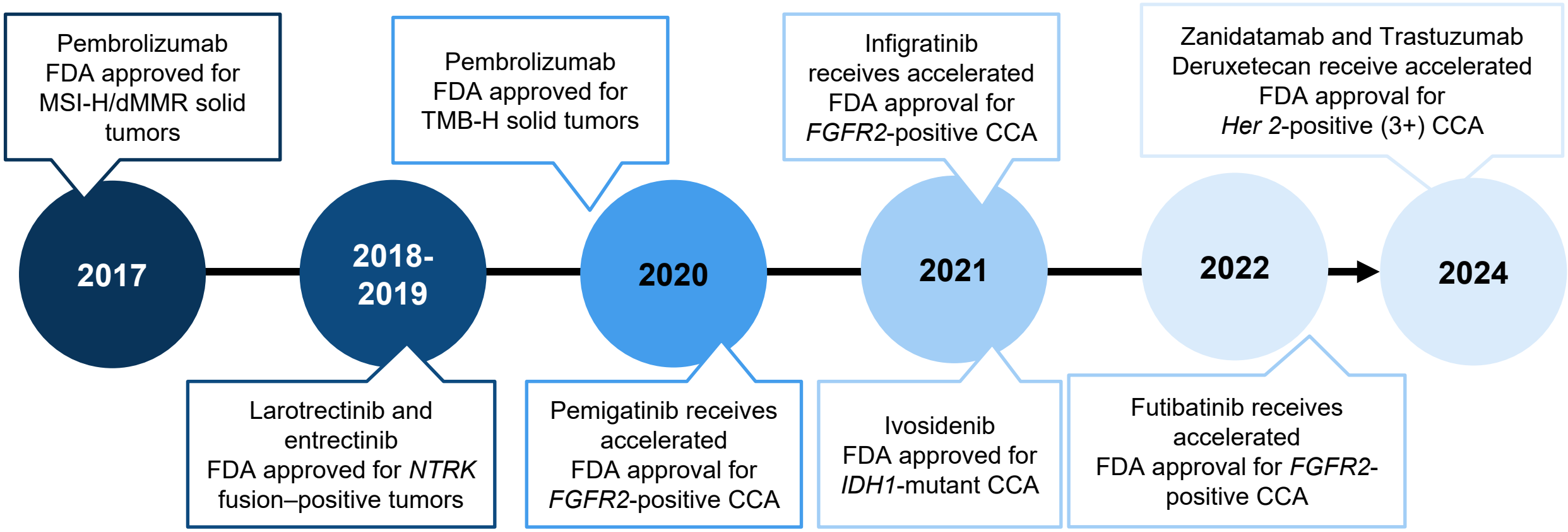
Immune (TME) profiling:
PD-L1 ligand expression
(10% to 70%)

Epigenetic profiling:
p16INK4A methylation
miRNA transcription inhibition
LncRNA

Genomic profiling:
NGS

1. Scott AJ et al. *J Clin Oncol*. 2022;40:2716-2734.

Precision Oncology Is Key For Optimal Management of Advanced Biliary Cancers[1-8]

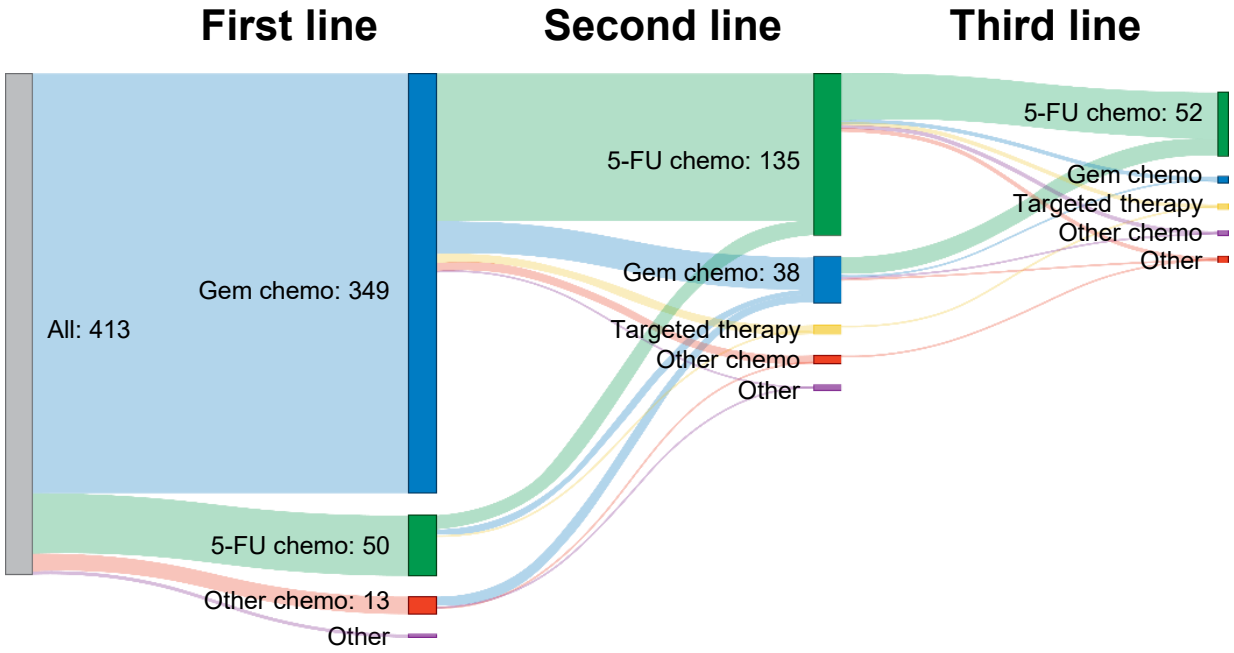


1. Keytruda (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s117,s118lbl.pdf.
2. Vitrakvi (larotrectinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211710s005lbl.pdf.
3. Rozlytrek (entrectinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf.
4. Pemazyre (pemigatinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213736s001lbl.pdf.
5. Truseltiq (infigratinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214622s000lbl.pdf.
6. Lytgobi (futibatinib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214801s000lbl.pdf.
7. Tibsovo (ivosidenib) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211192_s008lbl.pdf.
8. https://ir.zymeworks.com/news-releases/news-release-details/zymeworks-reports-last-patient-enrolled-pivotal-study.

Current Shortcomings in the Management of Advanced Biliary Cancers[1,2]

A recent assessment of 1,009 oncology providers treating patients with advanced CCA found that 81% were not confident in their ability to use targeted therapies in patients with advanced CCA

Moreover…

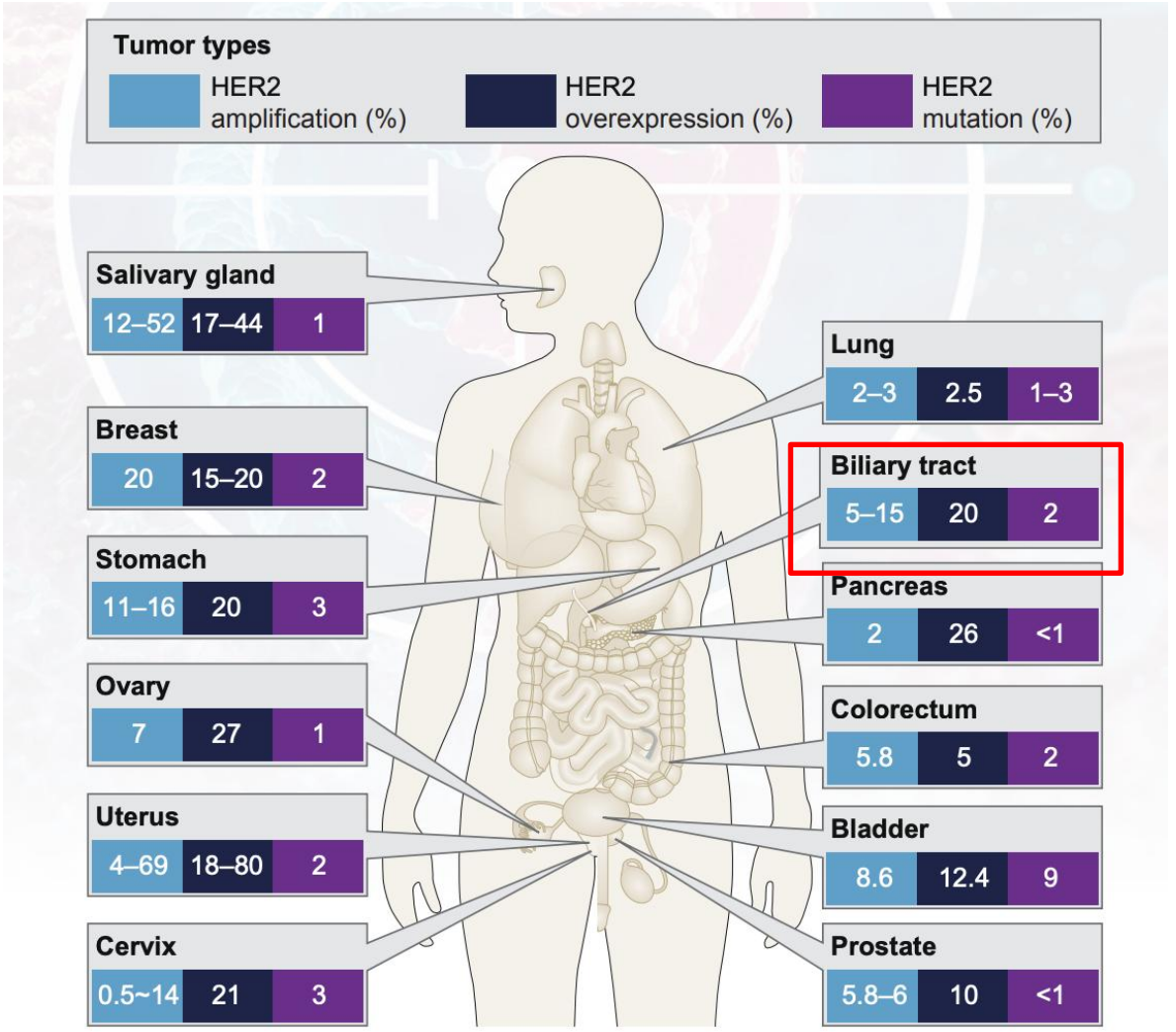


- 85% of patients initiated gemcitabine-based chemotherapy as their first-line treatment
- About 46% of patients initiated second-line treatments, which were predominantly 5-FU–based chemotherapies
- Few patients (17%) moved to the third line of treatment
- Median time on treatment in the first line was 3.2 months, and in both the second and third line median time was 2.7 months

1. Parikh K et al. ASCO GI 2021. Abstract 347. 2. Valderrama A et al. ASCO GI 2022. Abstract 398.

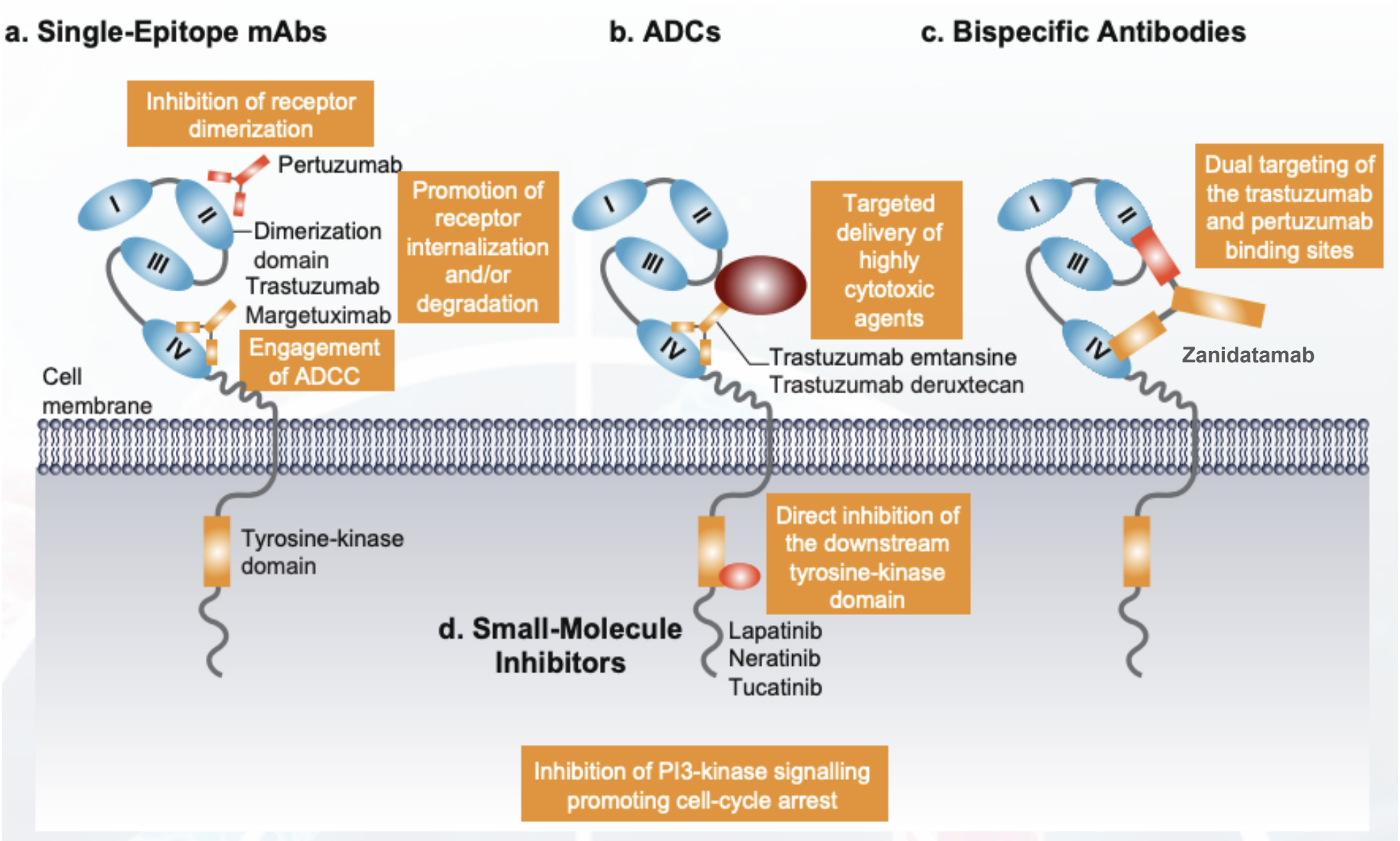
HER2 Aberrations: Clinical Role and Frequency Across Tumor Types[1]

- HER2 is an established therapeutic target in breast and gastric cancer, and these alterations are found across a variety of other solid tumors
- A number of novel HER2-targeted therapies are being evaluated in gastrointestinal cancers, indicating that the role and impact of these therapies will continue to expand, along with the need for broader HER2 testing

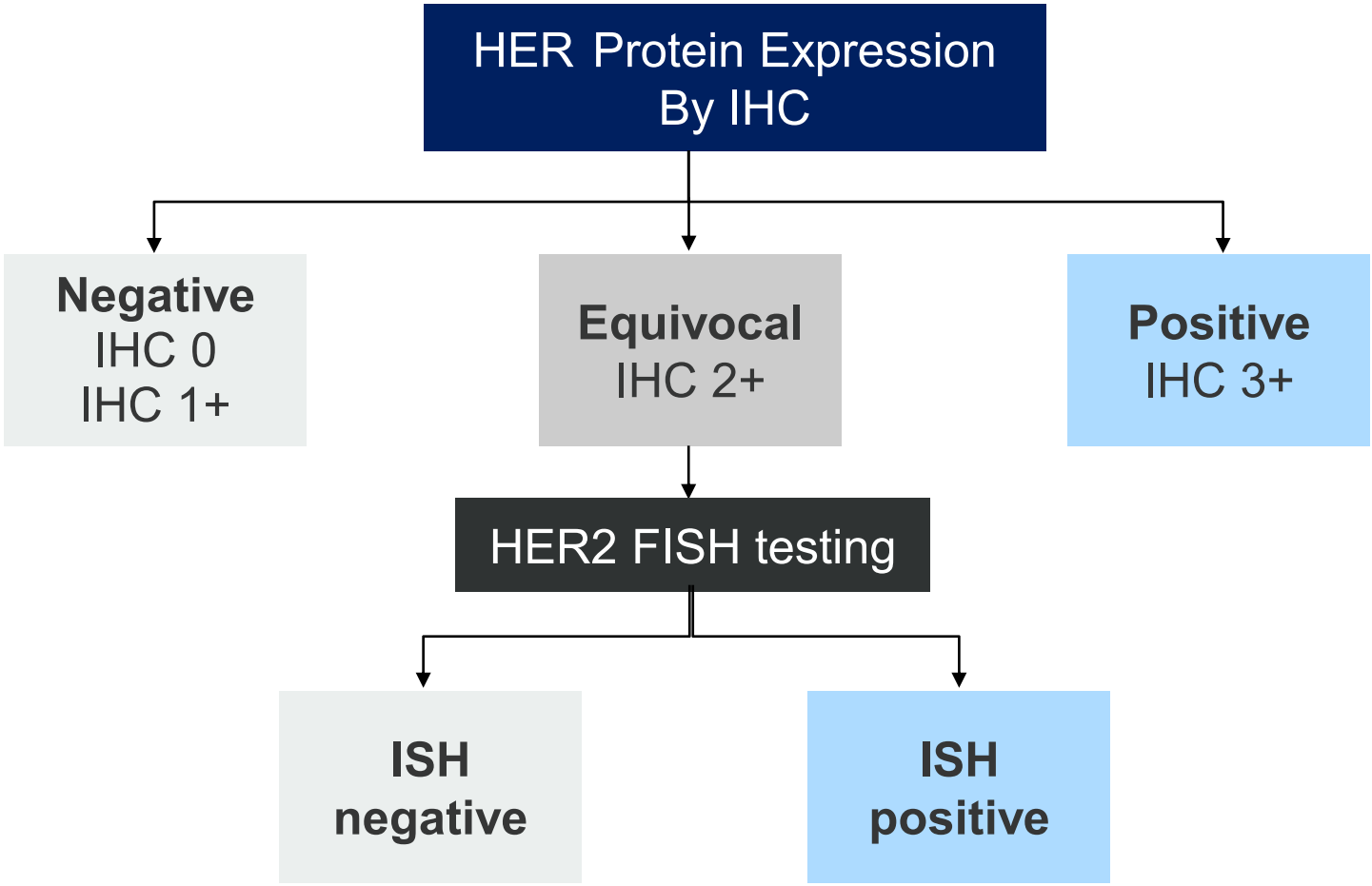


1. Oh D-Y, Bang Y-J. *Nat Rev Clin Oncol*. 2020;17:33-48.

Mechanism of Actions of Agents Targeting HER2[1]



HER2 Testing in BTC

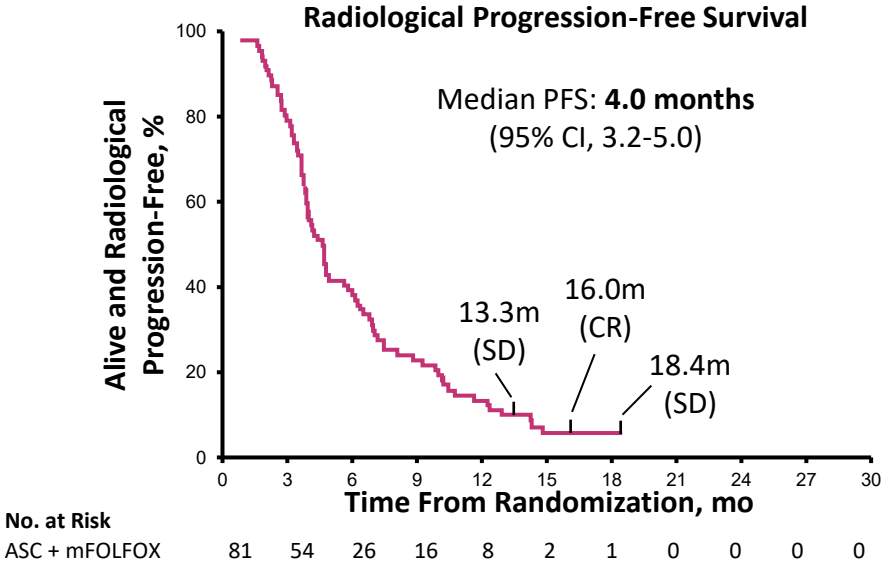


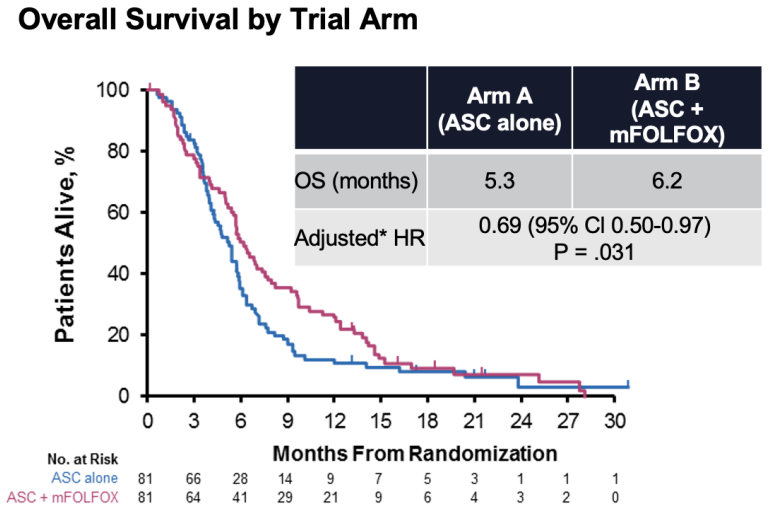
- ASCO, American Society of Clinical Oncology; ASCP, American Society for Clinical Pathology; CAP, College of American Pathologists; FNA, fine-needle aspiration.
- 1. NCCN. Biliary tract cancers (v6.2024). 2025. Accessed March 18, 2025. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf; 2. CAP. Accessed November 7, 2024. https://tinyurl.com/ywak5djp

Clinical Trials

Second-Line FOLFOX Chemotherapy vs Active Symptom Control for Advanced BTC (ABC-06): A Phase 3, Open-Label, RCT[1]

Best Response Rate (RECIST v 1.1)	Arm B (ASC + mFOLFOX), n = 81	
	n	%
Complete response (CR)	1	1
Partial response (PR)	3	4
Stable disease (SD)	23	28
Response rate (CR + PR)	4	5
Disease control rate (CR + PR + SD)	27	33
Progressive disease	30	37
Death	23	28
Not evaluable (nonmeasurable disease)	1	1

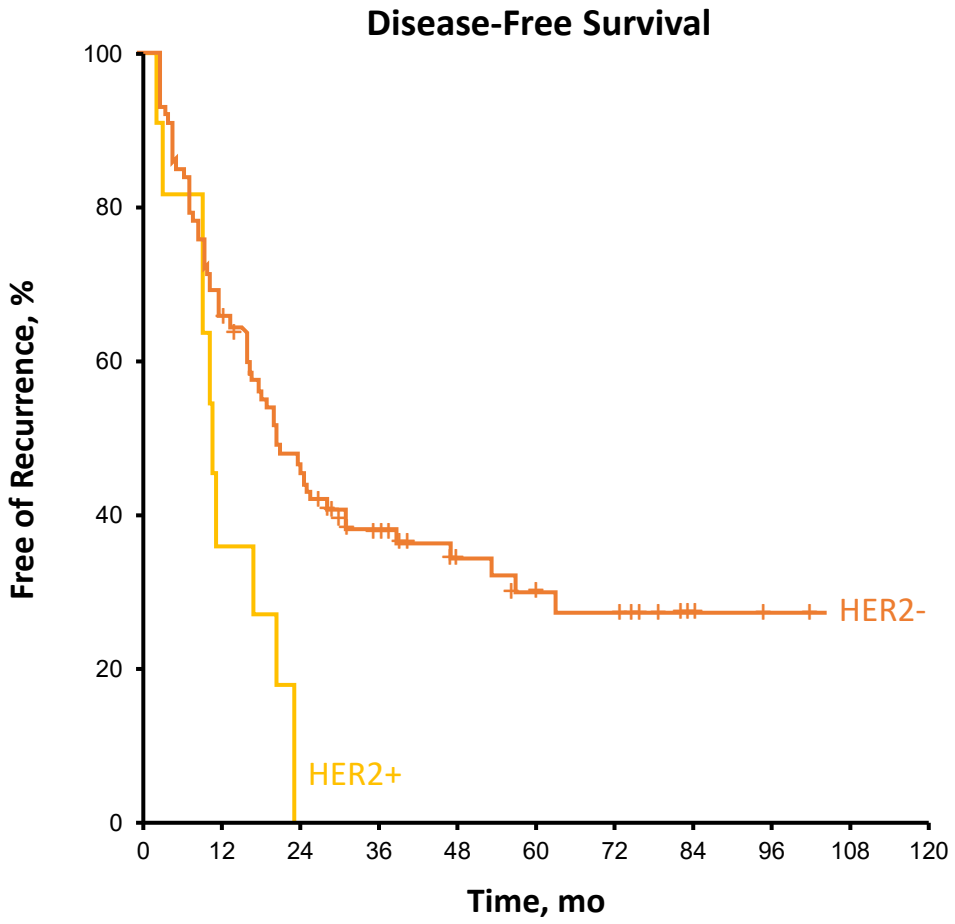




	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
OS (months)	5.3	6.2
Adjusted* HR	0.69 (95% CI 0.50-0.97) P = .031	

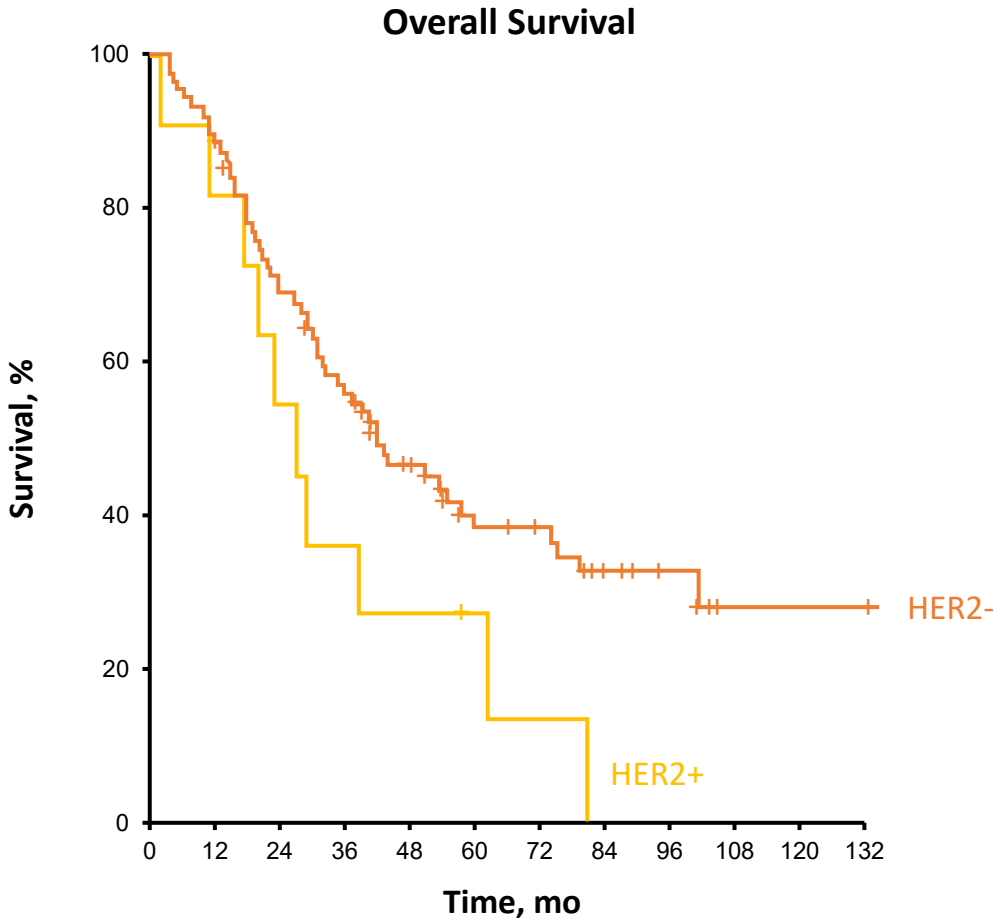
1. Lamarca et al. *Lancet Oncol*. 2021;22:690-701.

HER2 Overexpression and Prognosis[1]



Disease-free survival curves according to HER2 status

Median DFS 10.1 vs. 17.8 months, *P* = .04



Overall survival curves according to HER2 status

Median OS 23.5 vs. 36.1 months, *P* = .241

1. Vivaldi C et al. *The Oncologist*. 2020;25:886-893.

Impact of HER2-Positivity on Prognosis and Targeted Therapeutic Outcomes in Advanced Biliary Tract Cancer

Choong-kun Lee[1,2], Dong Hyun Seo[1,2], Daniel Fox[3], Jaime Ivan Haro-Silerio[3], Taek Chung[4], Chang Gon Kim[1,2], Deepak Bhamidipati[5], Funda Meric-Bernstam[6], Shubham Pant[7], Milind Javle[7], Hye Jin Choi[1,2], Sunyoung S. Lee[7]

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[5] Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX, USA.[6] Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA.[7] Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA.

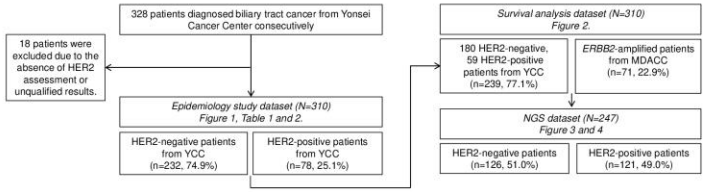
ASCO Gastrointestinal Cancers Symposium
#629

Background

- Biliary tract cancer (BTC): one of the most fatal cancers with limited treatment options
- HER2 positivity, defined as IHC 3+ or IHC 2+ with positive in situ hybridization (ISH), or *ERBB2* amplification, is observed in approximately 20% of patients with advanced BTC.
- The combination of gemcitabine and cisplatin with immune checkpoint inhibitors, as evaluated in the TOPAZ-1 and KEYNOTE-966 trials, represents the current standard first-line systemic therapy for advanced BTCs. However, therapeutic options remain limited after progression on first-line treatment.
- Anti-HER2 treatments evaluated in various phase II trials, including the MyPathway study (Javle *et al.*, Lancet Oncology, 2021), KCSG-HB19-14 trial (Lee *et al.*, Lancet Gastroenterology & Hepatology, 2023), and HERIZON-BTC-01 (Harding *et al.*, Lancet Oncology 2023) have demonstrated efficacy in pretreated HER2-positive BTC patients, with objective response rates (ORR) ranging from 23% to 40% and median progression-free survival (PFS) between 4.0 and 5.1 months.
- Recent advances in HER2-targeting agents have shown promising results in HER2-positive BTCs. However, data on the prevalence of HER2 positivity and its impact on prognosis in cholangiocarcinoma patients remains limited.

Methods

- A retrospective cohort study was conducted at Yonsei Cancer Center (YCC), Korea, and MD Anderson Cancer Center (MDACC), USA, including Stage IV BTC patients with known HER2 status diagnosed between 2009 and 2023.
- Patients were classified as HER2-positive based on immunohistochemistry (IHC 3+ or 2+/ISH+) or next-generation sequencing (*ERBB2* amplification).
- Among the enrolled patients, those who received palliative chemotherapy (at least two cycles) and whose survival events were not attributed to causes of death unrelated to BTC were included in the survival analysis.
- Tissue NGS results from targeted panel sequencing (Illumina TruSight Oncology 500, FoundationOne CDx, and MDA MAPP, MD Anderson Cancer Center's proprietary NGS platform) were included in this study.



Results

Table 1. Baseline patient characteristics from Yonsei Cancer Center (N=310)

	HER2-negative (N=232)	HER2-positive (N=78)	Overall (N=310)	P
Age				0.957
Mean (range)	63.5 (26-83)	63.2 (27-84)	63.5 (26-84)	
Gender				0.227
Female	92 (39.7%)	37 (47.4%)	129 (41.6%)	
Male	140 (60.3%)	41 (52.6%)	181 (58.4%)	
Cancer type				<0.01
Intrahepatic	105 (45.3%)	20 (25.6%)	125 (40.3%)	
Extrahepatic	59 (25.4%)	13 (16.7%)	72 (23.2%)	
Gallbladder	53 (22.8%)	43 (55.1%)	96 (31.0%)	
Ampulla of Vater	15 (6.5%)	2 (2.6%)	17 (5.5%)	
ECOG				0.444
0	134 (57.8%)	44 (56.4%)	178 (57.4%)	
1	80 (34.5%)	24 (30.8%)	104 (33.5%)	
2	10 (4.3%)	4 (5.1%)	14 (4.5%)	
3≤	8 (3.4%)	6 (7.7%)	14 (4.5%)	
Pathology				0.135
Adenocarcinoma moderately differentiated	131 (56.5%)	55 (70.5%)	186 (60.0%)	
Adenocarcinoma poorly differentiated	64 (27.6%)	10 (12.8%)	74 (23.9%)	
Adenocarcinoma well differentiated	14 (6.0%)	6 (7.7%)	20 (6.5%)	
Adenosquamous carcinoma	1 (0.4%)	1 (1.3%)	2 (0.6%)	
Others	22 (9.5%)	6 (7.7%)	28 (9.0%)	
History of surgery				0.467
No	127 (54.7%)	39 (50.0%)	166 (53.5%)	
Yes	105 (45.3%)	39 (50.0%)	144 (46.5%)	
History of radiotherapy				0.396
No	121 (52.2%)	45 (57.7%)	166 (53.5%)	
Yes	111 (47.8%)	33 (42.3%)	144 (46.5%)	

HER2 positivity, observed in approximately 25% of biliary tract cancers, is linked to poor prognosis. Targeting HER2 in these subgroups is essential for improving survival outcomes.

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Figure 1. Distribution of HER2-positive patients by overexpression (IHC) and amplification (NGS) status (N=310)

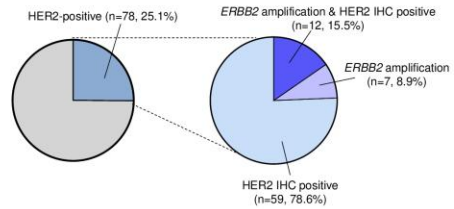


Table 2. Correlation of HER2 grading system measured using NGS and IHC (N=201)

	ERBB2 amplification in NGS		
	No (n=182)	Yes (n=19)	P-value
Immunohistochemistry			<0.0001
0	54 (29.6%)	0 (0.0%)	
1+	46 (25.3%)	2 (10.5%)	
2+	72 (39.6%)	11 (57.9%)	
3+	10 (5.5%)	6 (31.6%)	
HER2 IHC classification			<0.0001
HER2 negative	155 (85.1%)	3 (15.8%)	
HER2 positive	27 (14.9%)	12 (68.4%)	
N/A (2+, ISH not done)	0 (0.0%)	4 (21.0%)	

Figure 2. Survivals according to HER2 status and HER2 targeted therapy (N=310)

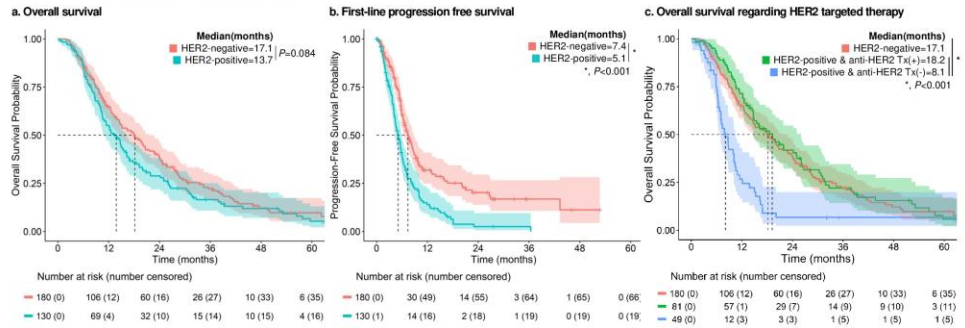


Figure 3. Oncoplot of BTC patients enrolled in survival analysis (N=247)

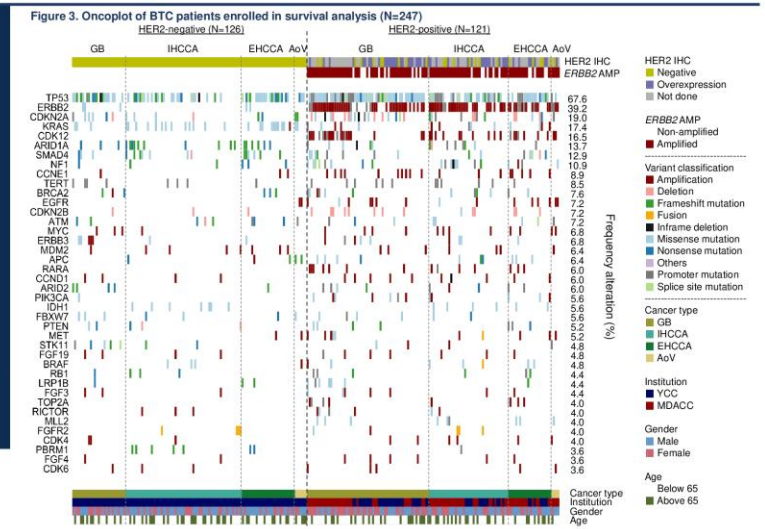
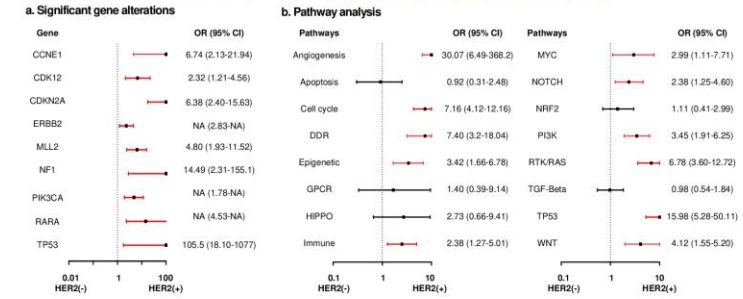


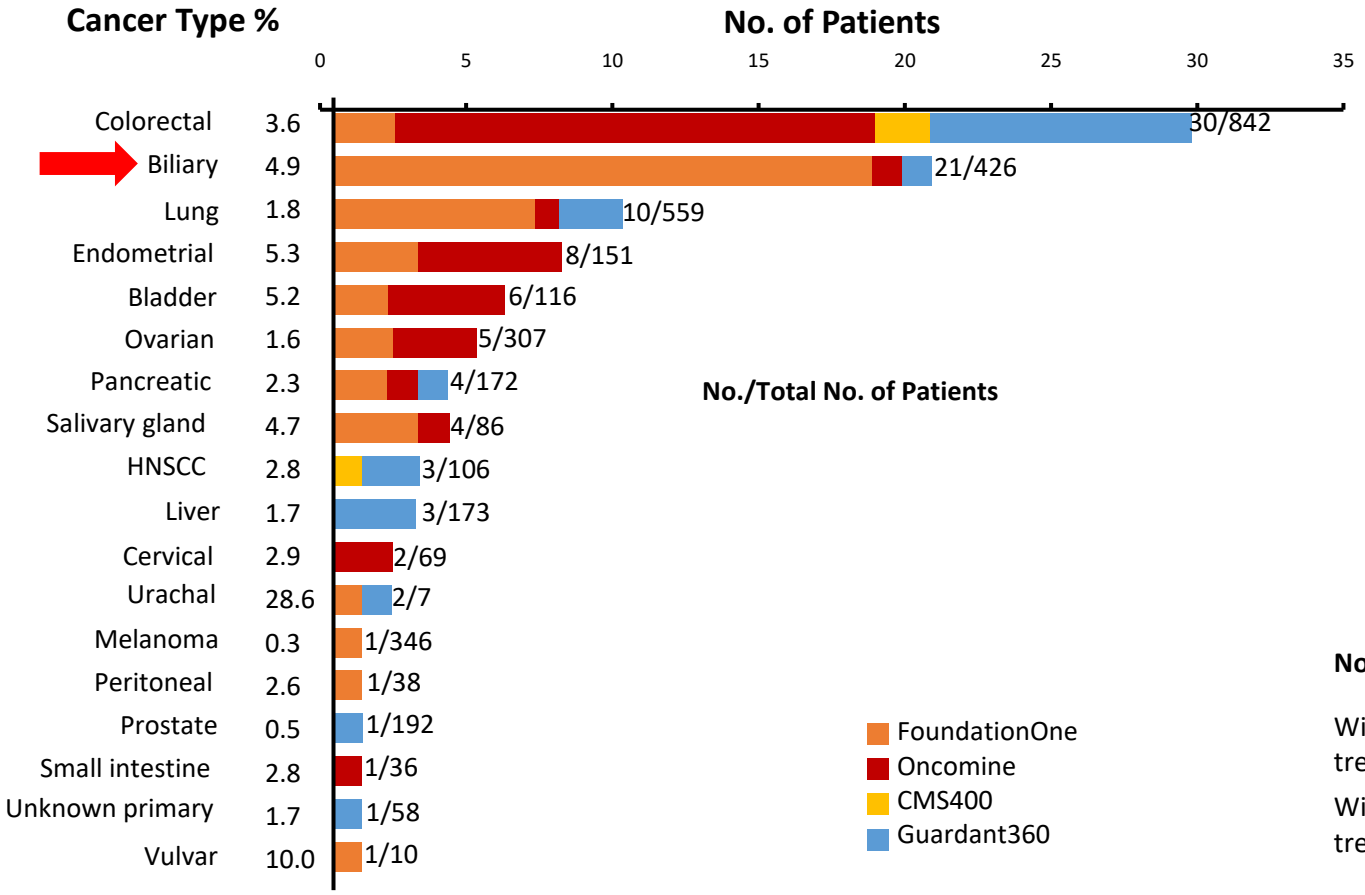
Figure 4. Significant Gene Alteration frequencies and oncogenic pathway analysis by HER2 Status (N=247)

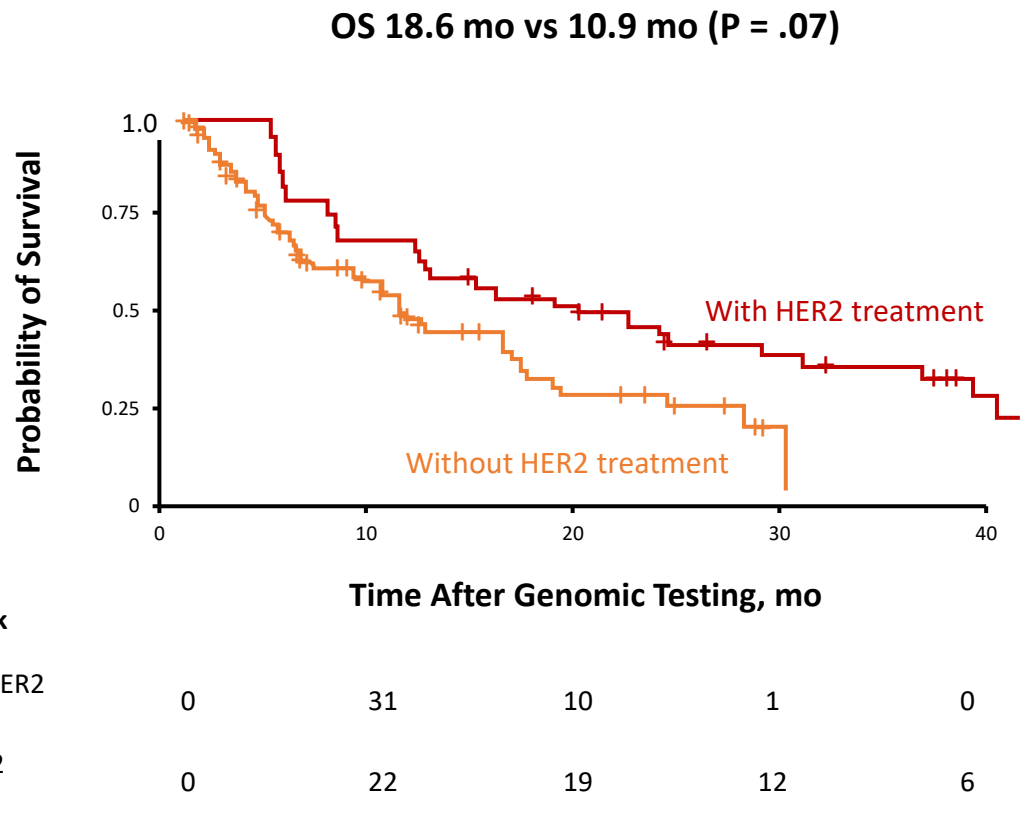


Conclusion

- HER2 positivity is associated with an unfavorable prognosis in advanced biliary tract cancer (BTC).
- The prevalence of HER2 positivity varies by primary tumor site, with the highest rates observed in gallbladder cancer.
- HER2-targeted therapies have demonstrated significant survival benefits in HER2-positive BTC, supporting their integrations into standard of care, and evaluation in the first-line treatment setting.
- Approximately 15% discordance between HER2 assessment by NGS and IHC highlights the need for optimizing the HER2 scoring system and supports the necessity of performing both NGS and IHC for accurate HER2 evaluation in BTC.
- HER2-positive BTC show distinct gene alterations and oncogenic pathway activations compared to HER2-negative BTC.

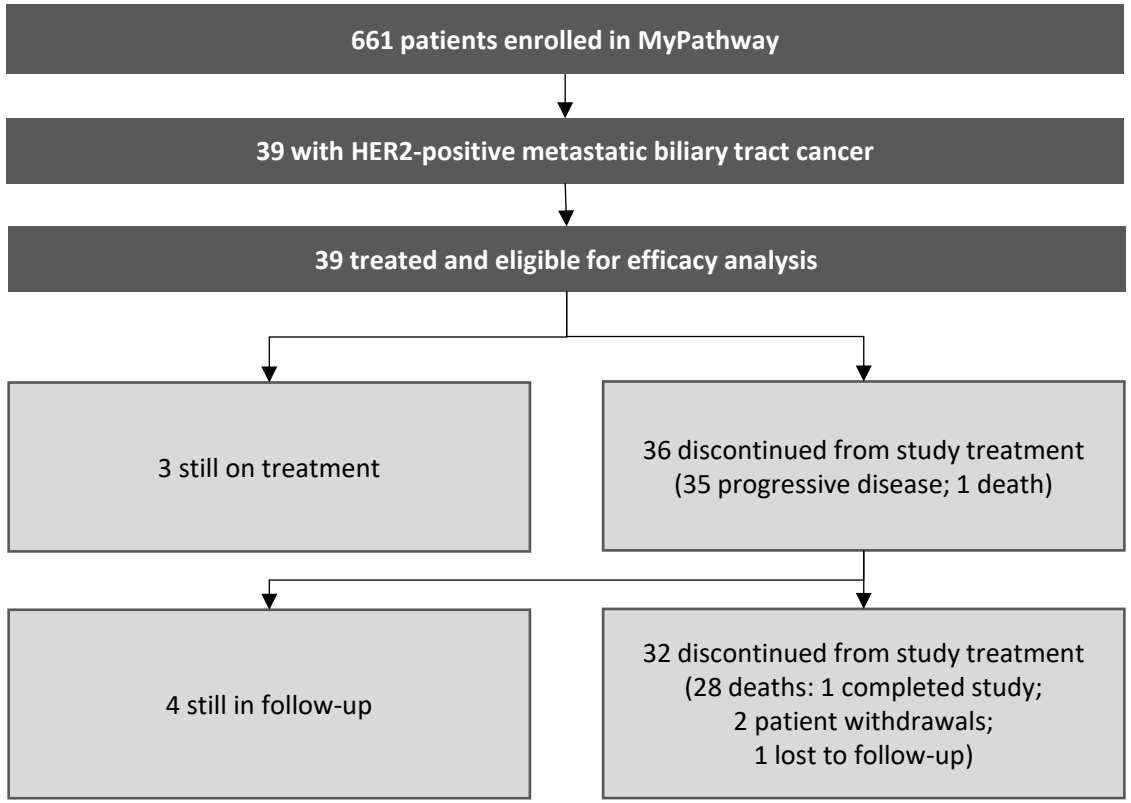
Targeting ERBB2 Amplification Identified by NGS for Advanced/Metastatic Solid Tumors Beyond Conventional Indications[1]





1. Dumbrava EEI et al. *JCO Precis Oncol*. 2019;3:PO.18.00345.

MyPathway Trial: Pertuzumab and Trastuzumab for HER2-Positive, Metastatic BTC[1]



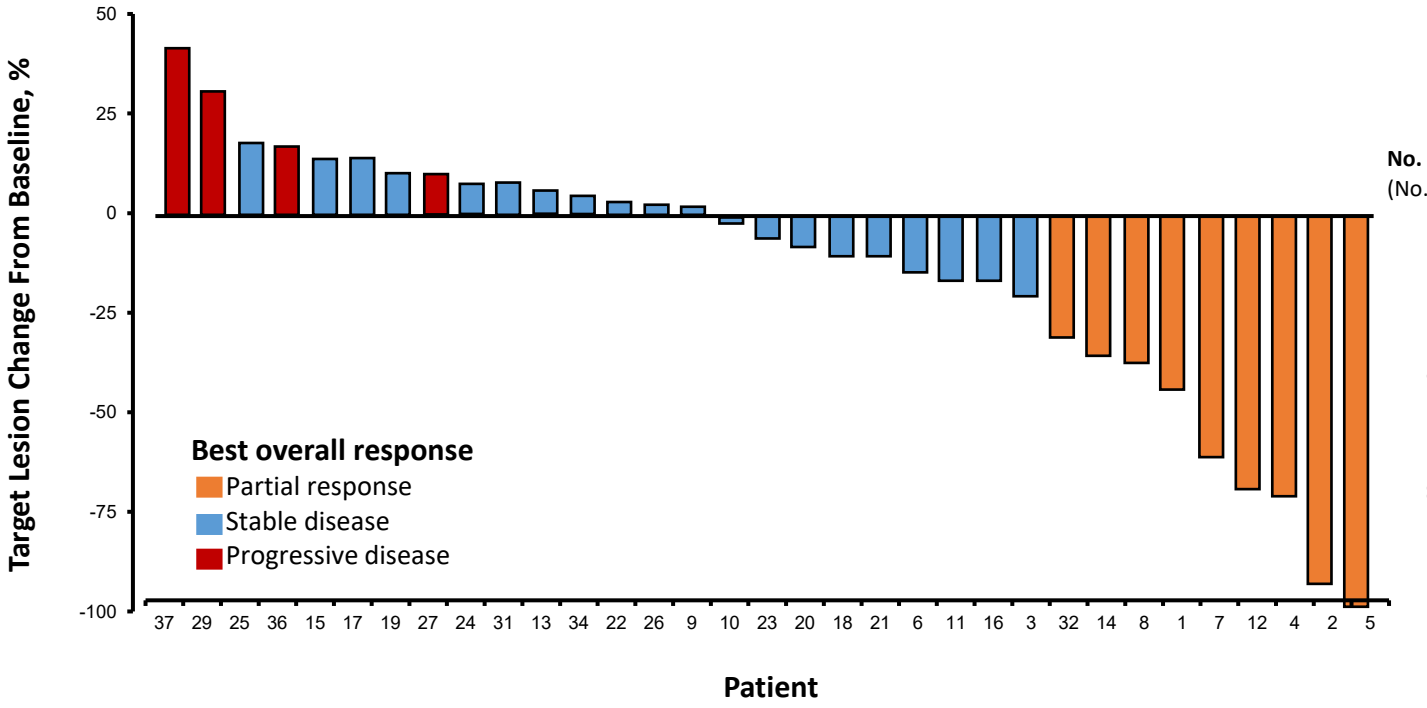
No. of Previous Regimens	2 (1-3)
1	16 (41%)
2	8 (21%)
3	9 (23%)
4	3 (8%)
Missing	3 (8%)

Previous Regimens	
Gemcitabine plus cisplatin	24 (62%)
Capecitabine	5 (13%)
FOLFOX	5 (13%)
Gemcitabine	4 (10%)
Gemcitabine plus capecitabine	4 (10%)
Gemcitabine plus nab-paclitaxel	4 (10%)
FOLFOXIRI	2 (5%)
Capecitabine plus oxaliplatin	2 (5%)
Fluorouracil plus oxaliplatin	2 (5%)

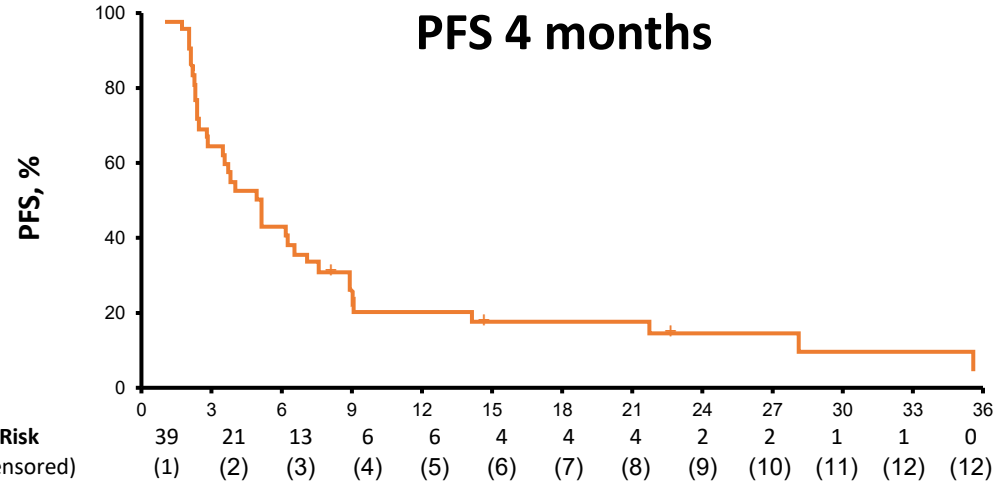
1. Javle M et al. *Lancet Oncol.* 2021;22:1290-1300.

MyPathway Trial: Pertuzumab and Trastuzumab for HER2-Positive, Metastatic BTC[1]

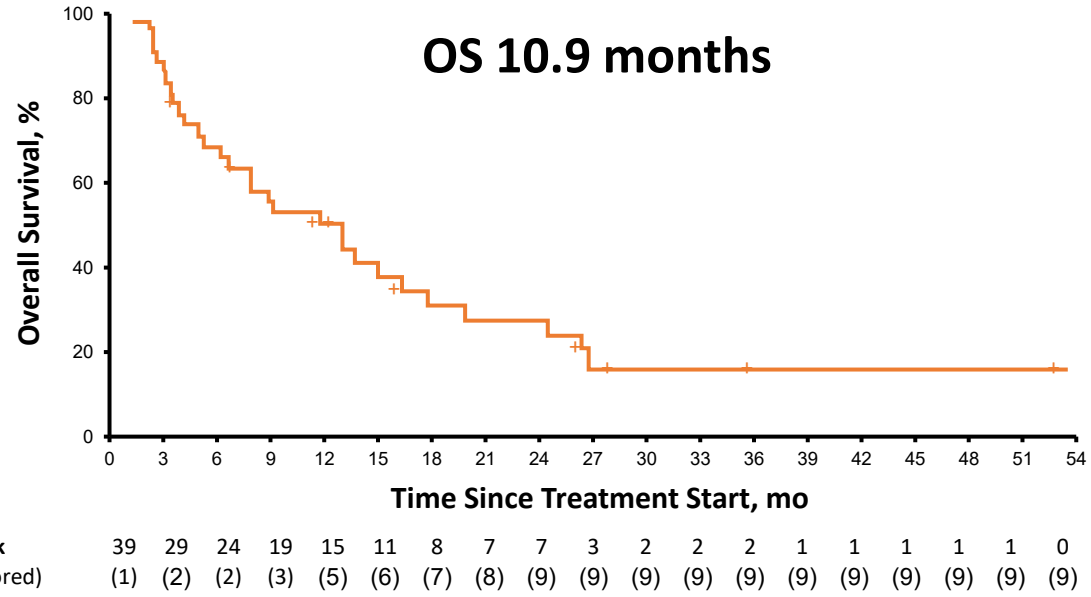
ORR 29%



PFS 4 months



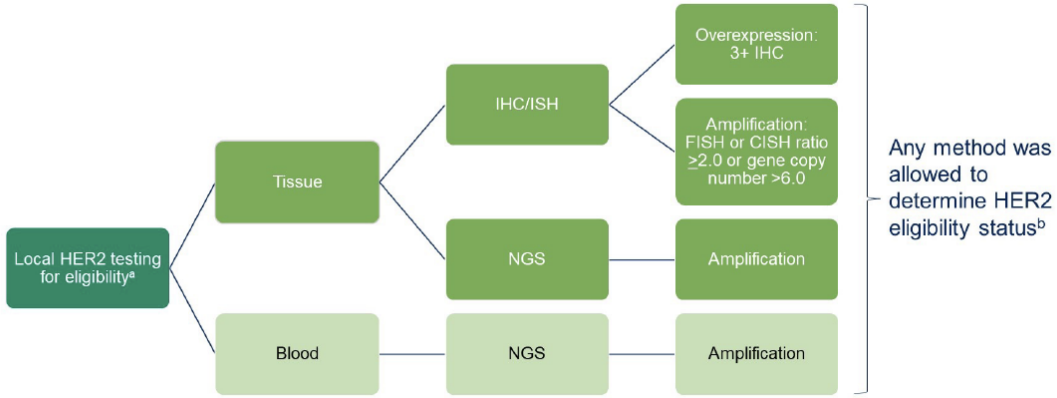
OS 10.9 months



1. Javle M et al. *Lancet Oncol.* 2021;22:1290-1300.

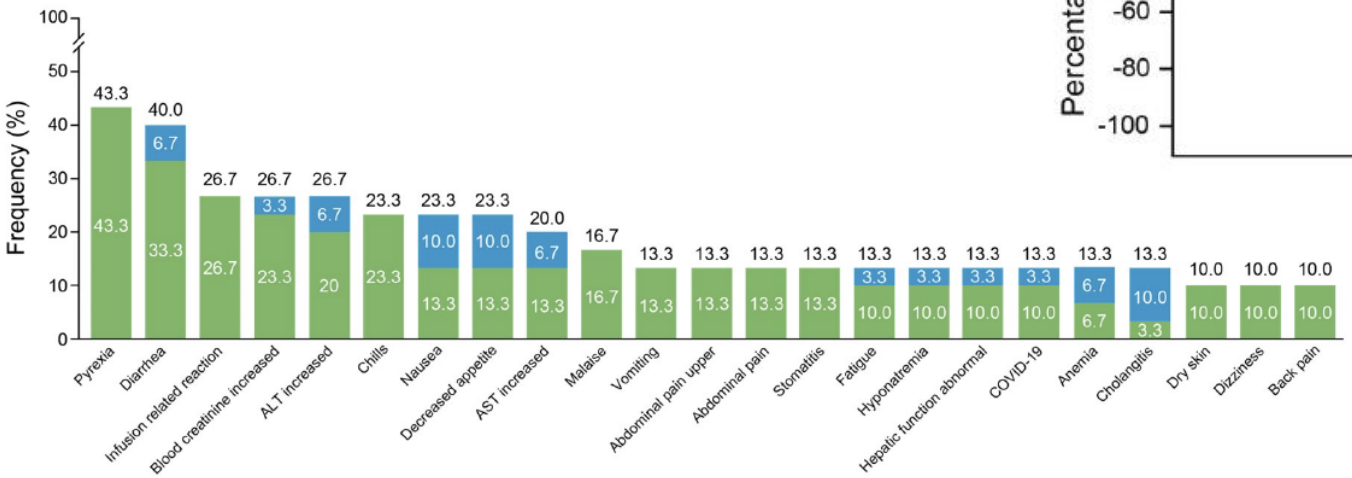
Tucatinib and Trastuzumab

HER2 Testing for Eligibility for BTC Cohort



a Processed locally in a CLIA- or ISO-accredited laboratory before enrollment in the study. b Patients deemed positive by any method were considered eligible.

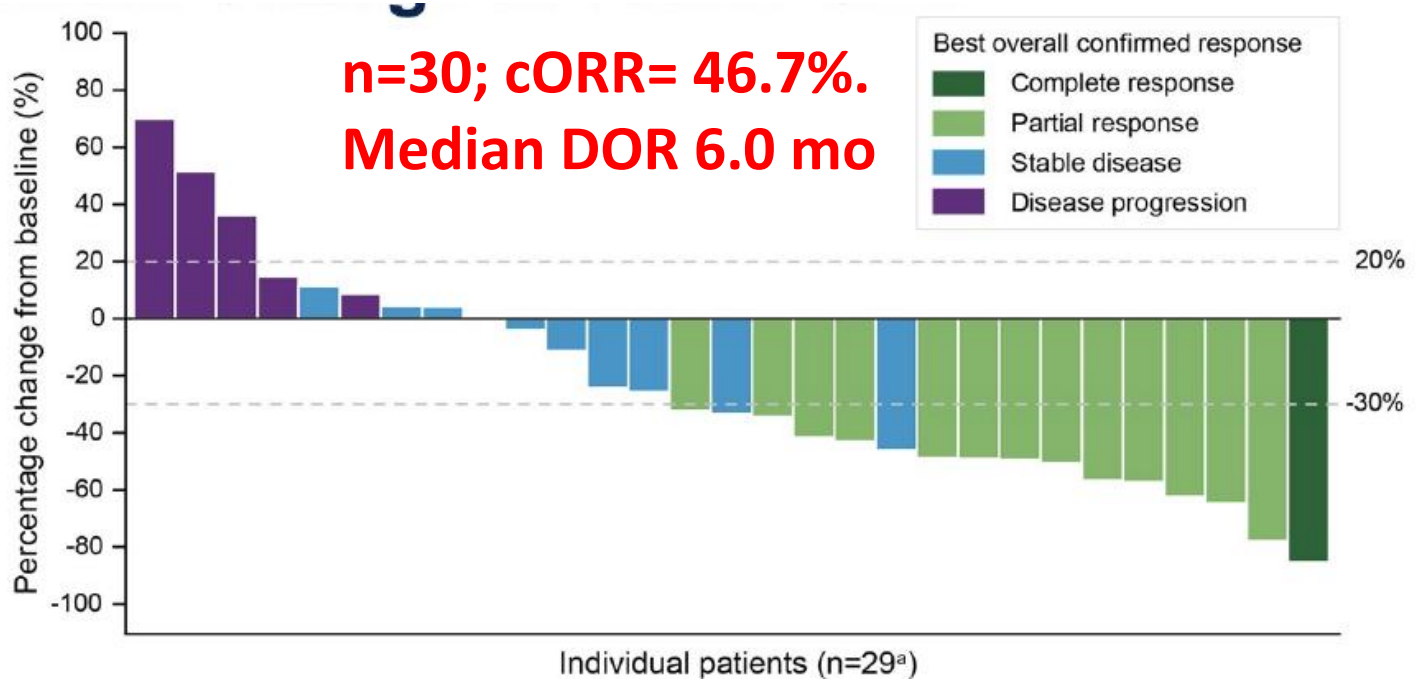
Most Common TEAEs (≥10%)[a]



Most common grade ≥3 TEAEs were nausea, decreased appetite, and cholangitis (each in 3 patients [10.0%])

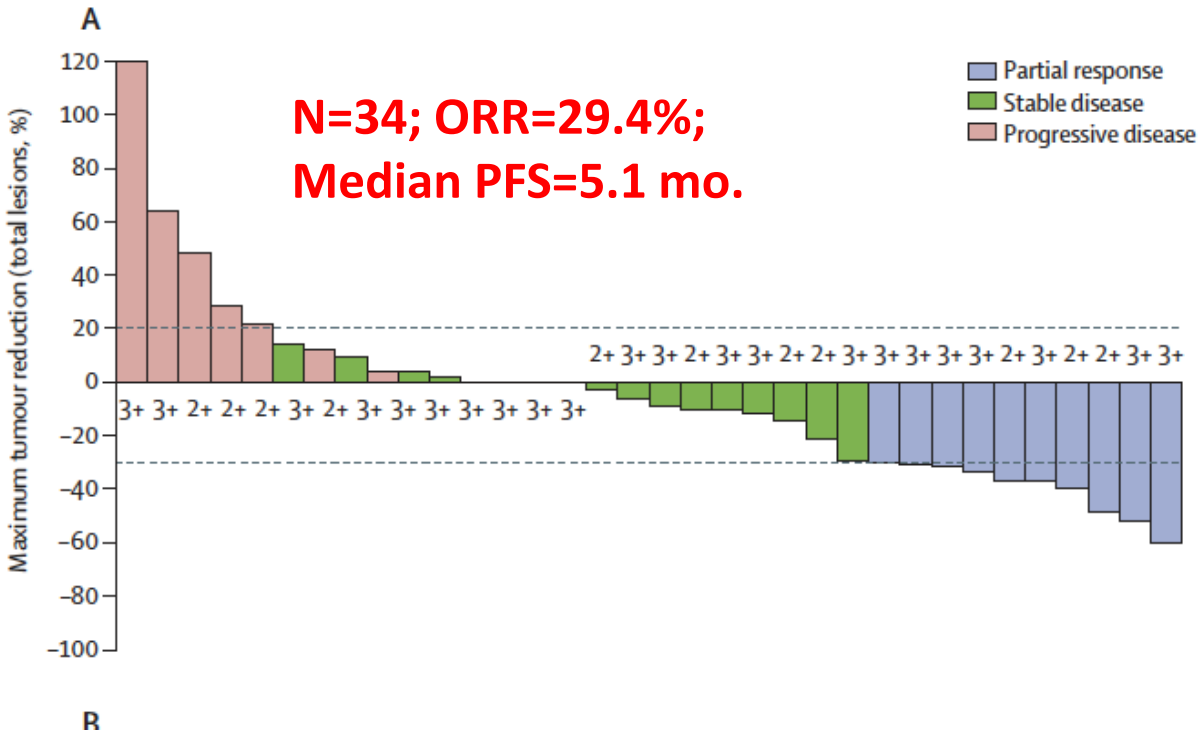
Data cutoff: Jan 30, 2023.
a Percentages may not add up to total due to rounding.

n=30; cORR= 46.7%.
Median DOR 6.0 mo



Courtesy. Nakamura,et al. ASCO 2023

Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19–14)



N=34; ORR=29.4%;
Median PFS=5.1 mo.

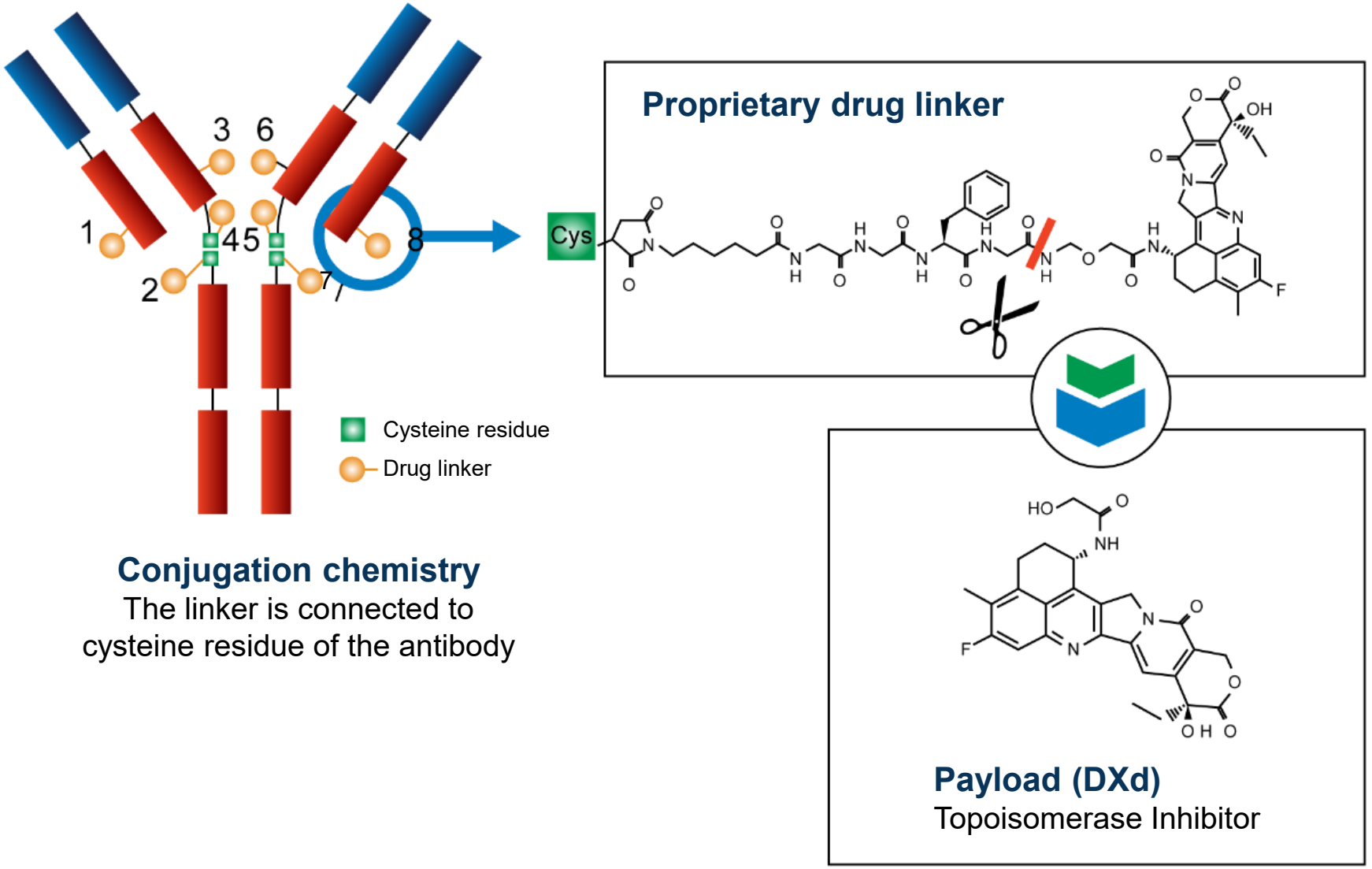
	Any grade	Grade 3	Grade 4
Haematological			
Neutrophil count decreased	21 (62%)	10 (29%)	9 (26%)
Anaemia	8 (24%)	5 (15%)	0
Platelet count decreased	5 (15%)	3 (9%)	0
Non-haematological			
Peripheral sensory neuropathy	17 (50%)	4 (12%)	0
General weakness	6 (18%)	3 (9%)	0
Diarrhoea	7 (21%)	2 (6%)	0
Abdominal pain	4 (12%)	1 (3%)	0
Fever	3 (9%)	1 (3%)	0
Biliary tract infection	1 (3%)	1 (3%)	0
Oral mucositis	7 (21%)	0	0
Anorexia	5 (15%)	0	0
Nausea	5 (15%)	0	0
Infusion-related reaction	4 (12%)	0	0
Dyspepsia	4 (12%)	0	0
Total	34	23 (68%)	9 (26%)

Data shown as n (%) of all participants (N=34). Any grade treatment-related adverse events with an incidence of more than 10% or any treatment-related adverse events that were grade 3 or worse are shown.

Table 2: **Treatment-related adverse events**

Choong-Kun Lee. Lancet Gastroenterol. 2023; 8;56-65

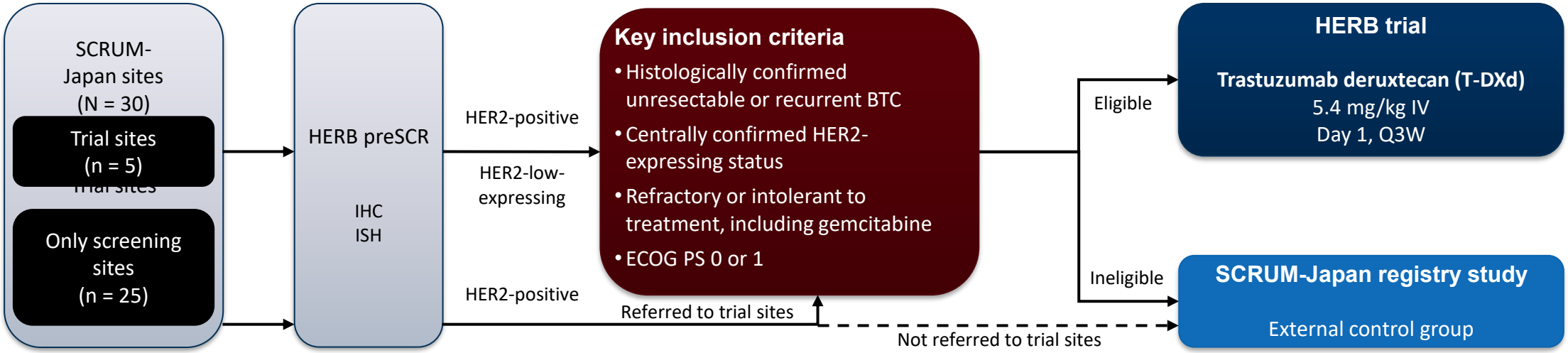
HERB Trial: T-DXd in Patients With HER2-Expressing Unresectable or Recurrent BTC[1-3]



Conjugation chemistry
The linker is connected to cysteine residue of the antibody

1. Enhertu (fam-trastuzumab deruxtecan-nxki) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf.
2. Iwata H et al. ASCO 2018. Abstract 2501. 3. Tsuruntani J et al. *Cancer Discov*. 2020;10:688-701.

HERB Trial: Study Design And Demographics[1]



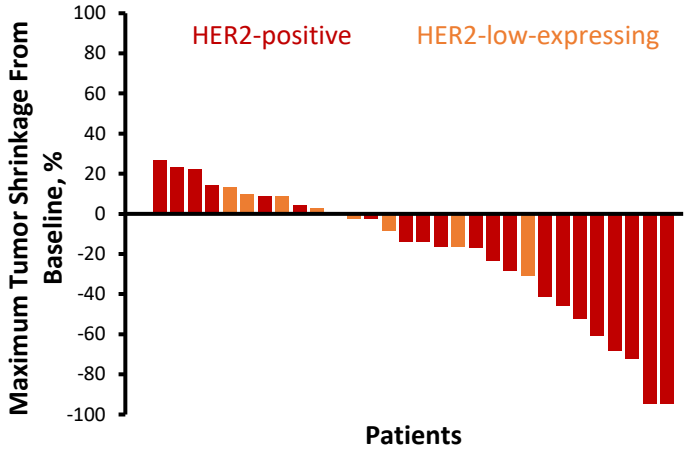
	HER2-Positive (n = 22)	HER2-Low-Expressing (n = 8)	All Patients (N = 30)
Median age (range), y	67.5 (39-78)	68 (43-80)	68 (39-80)
Sex, female, n (%)	9 (40.9)	3 (37.5)	12 (40.0)
ECOG PS 0, n (%)	15 (68.2)	6 (75.0)	21 (70.0)
Primary tumor location, n (%)			
Intrahepatic cholangiocarcinoma	3 (13.6)	3 (37.5)	6 (20.0)
Extrahepatic cholangiocarcinoma	6 (27.3)	2 (25.0)	8 (26.7)
Gallbladder cancer	11 (50.0)	2 (25.0)	13 (43.3)
Ampulla of Vater cancer	2 (9.1)	1 (12.5)	3 (10.0)
Disease status, n (%)			
Unresectable	13 (59.1)	4 (50.0)	17 (56.7)
Recurrent	9 (40.9)	4 (50.0)	13 (43.3)
Disease extent, n (%)			
Locally advanced	2 (9.1)	1 (12.5)	3 (10.0)
Metastatic	20 (90.9)	7 (87.5)	27 (90.0)
Number of prior regimens, n (%)			
1	6 (27.3)	3 (37.5)	9 (30.0)
≥2	16 (72.7)	5 (62.5)	21 (70.0)
HER2 expression, n (%)			
IHC 3+	10 (45.5)	0 (0.0)	10 (33.3)
IHC 2+	12 (54.5)	6 (75.0)	18 (60.0)
IHC 1+, 0	0 (0.0)	2 (25.0)	2 (6.7)

1. Ohba A et al. ASCO 2022. Abstract 4006.

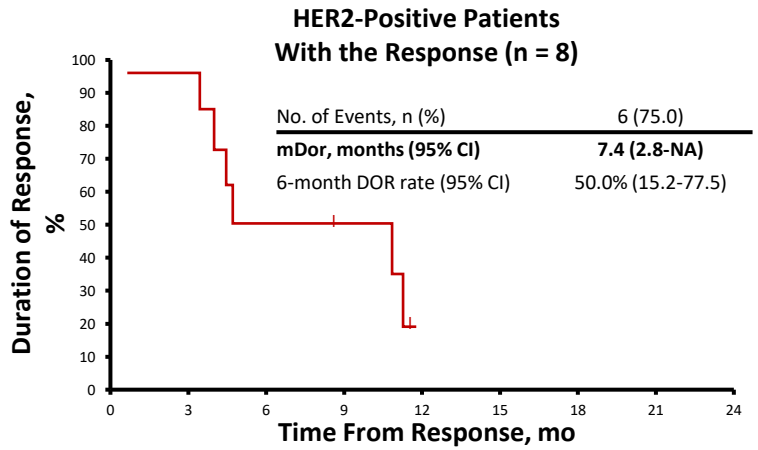
HERB Trial: T-DXd Shows Activity in Patients With HER2-Expressing BTCs[1]

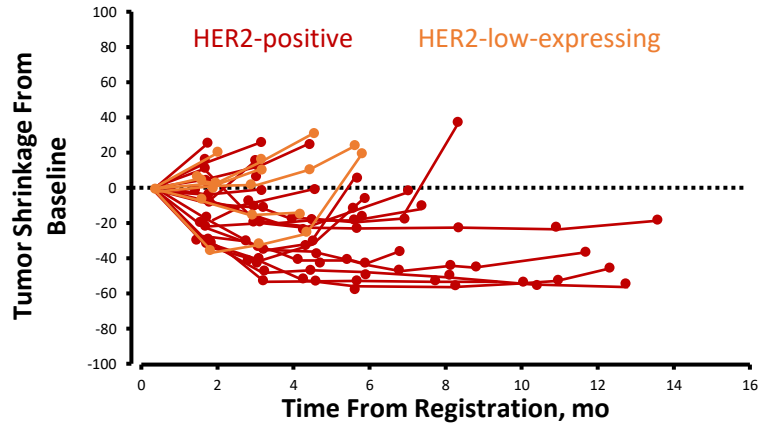
Confirmed ORR

	HER2-Positive (n = 22)	HER2-Low-Expressing (n = 8)	All Patients (N = 30)
Confirmed ORR (90% CI) (95% CI)	**36.4%** **(19.6-56.1)** (17.2-59.3)	12.5% – (0.3-52.7)	30.0% – (14.7-49.4)
Confirmed DCR (95% CI)	81.8% (59.7-94.8)	75.0% (34.9-96.8)	80.0% (61.4-92.3)
Confirmed best response, n (%)			
CR	2 (9.1)	0 (0)	2 (6.7)
PR	6 (27.3)	1 (12.5)	7 (23.3)
SD	10 (45.5)	5 (62.5)	15 (50.0)
PD	3 (13.6)	1 (12.5)	4 (13.3)
NE	1 (4.5)	1 (12.5)	2 (6.7)



Duration of Response (DOR)





1. Ohba A et al. ASCO 2022. Abstract 4006.

Open-Label, Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy
- ECOG/WHO PS 0–1 restricted in strenuous activity

T-DXd
5.4 mg/kg
Q3W

n = 40 per cohort planned
(*cohorts with no objective responses in first 15 patients were to be closed*)

Primary endpoint
- Confirmed ORR (INV)

Secondary endpoints
- DoR
- DCR
- PFS
- OS
- Safety

Data cutoff for analysis
- June 8, 2023

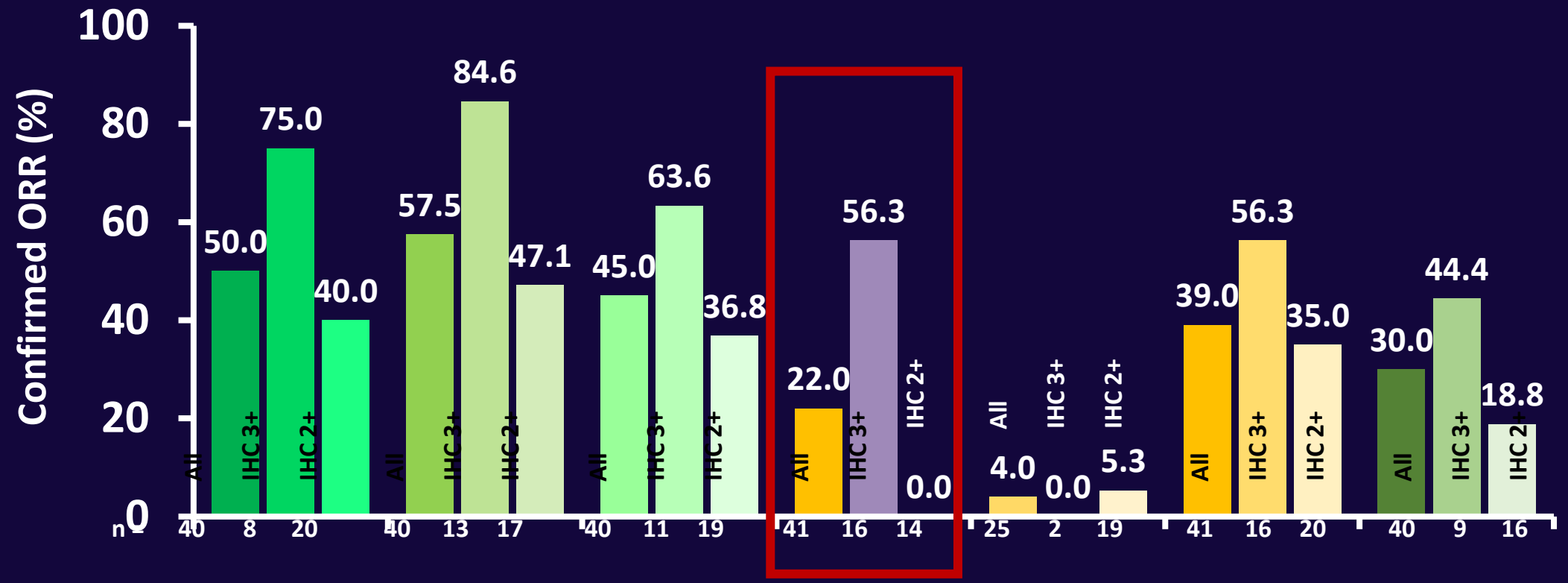
*Salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma (n = 1), head and neck cancer (n = 1), lip and/or oral cavity cancer (n = 1), esophageal adenocarcinoma (n = 1), intestinal adenocarcinoma (n = 1), appendiceal adenocarcinoma (n = 1), esophageal squamous cell carcinoma (n = 1), testicular cancer (n = 1), and vulvar carcinoma (n = 1).

2L+ = second-line or beyond; ASCO/CAP = American Society of Clinical Oncology/College of American Pathologists; ECOG = Eastern Cooperative Oncology Group; INV = investigator assessed; PS = performance status; WHO = World Health Organization.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58. NCT04482309 (https://clinicaltrials.gov/study/NCT04482309). Accessed 6/10/2024.

Phase 2 DESTINY-PanTumor02 Study: ORR by HER2 Status

Primary Analysis (N = 267)



	All patients	IHC 3+
Median DoR (95% CI)	11.3 mo (9.6–17.8); range = 5.7–22.1 mo	22.1 mo (9.6–NR)

Median follow-up = 12.75 months.

NR = not reached.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

Phase 2 DESTINY-PanTumor02 Study: Biliary Tract Cancer
PFS (INV) and OS by HER2 Expression Level

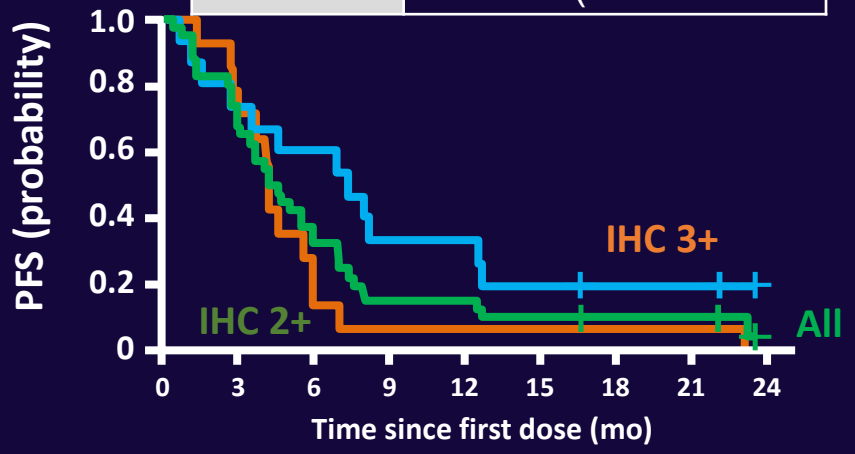
Findings for combination of all 7 tumor cohorts

- mPFS = 6.9 mo
- mOS = 13.4 mo
- Longest mOS in HER2 subgroups = 21.1 mo for IHC 3+

In April 2024, the FDA approved T-Dxd for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

Progression-free survival

	mPFS (95% CI)
IHC 3+	7.4 mo (2.8–12.5)
IHC 2+	4.2 mo (2.8–6.0)
Total	4.6 (3.1–6.0

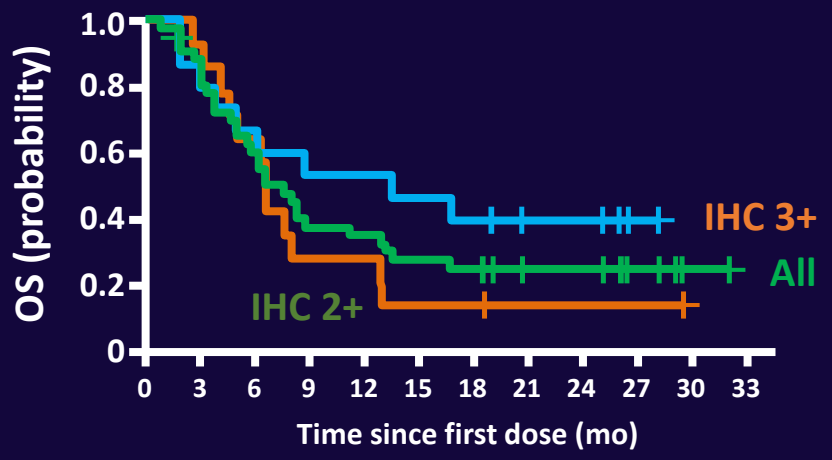


Number at risk for biliary tract cancer

IHC 3+	16	11	9	5	5	3	2	2	0
IHC 2+	14	10	3	1	1	1	1	1	0
Total	41	27	14	6	6	4	3	3	0

Overall survival

	mOS (95% CI)
IHC 3+	12.4 mo (2.8–NR)
IHC 2+	6.0 mo (3.7–11.7)
Total	7.0 (4.6–10.2)



Number at risk for biliary tract cancer

IHC 3+	16	12	9	8	8	7	5	4	1	0	
IHC 2+	14	12	7	4	2	2	1	1	1	0	
Total	41	32	21	16	12	11	8	7	4	1	0

m = median.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47-58.

DESTINY-PanTumor02 – BTC Cohort: AE's

Safety Summary n (%)	Biliary Tract Cancer (n=41)
Any drug-related TEAEs	33 (80.5)
Drug-related TEAEs Grade ≥3	19 (39.0)

The most common (>5%) Grade ≥3 drug-related TEAEs in the biliary tract cohort:

- **Neutropenia (9.8%)[a]**
- **Neutrophil count decrease (9.8%)[a]**
- **Nausea (7.3%)**
- **Fatigue (7.3%)**

ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Biliary Tract Cancer cohort (n=41)	0	5	1	0	1	7 (17.1)

The phase 3 DESTINY-BTC01 trial: T-DXd + rilvegostomig (PD-1/TIGIT bi-specific antibody) versus SoC for HER2-expressing biliary cancer in the 1L setting

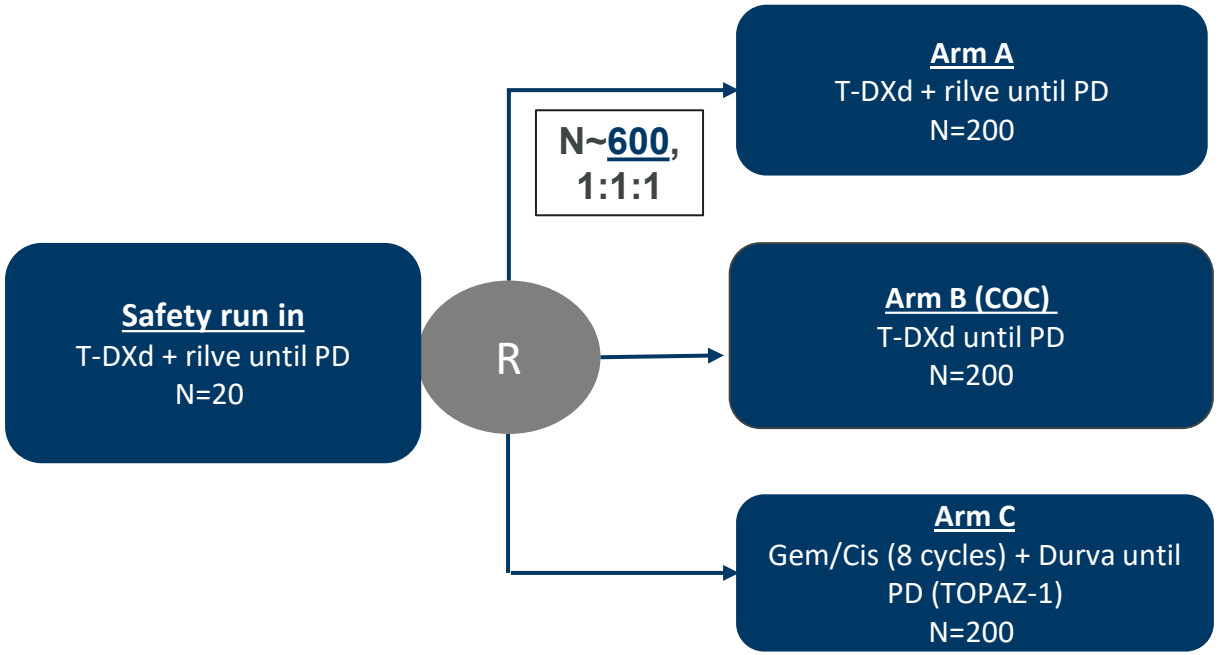
DESTINY-BTC01

Key eligibility criteria

- Advanced or metastatic BTC (cholangiocarcinoma [IHCC or EHCC] or gallbladder cancer [GBC])
- No prior treatment in advanced/metastatic setting. Recurrent dx >6 months after primary surgery or adjuvant therapy
- HER2+ (IHC 3+/2+)

- Measurable by RECIST v1.1

- ECOG 0-1



Endpoints

Primary:

- OS in IHC 3+ (Arm A vs Arm C)

Secondary:

- OS (ITT)
- PFS (INV)
- ORR (INV)
- DOR (INV)
- Safety
- PRO

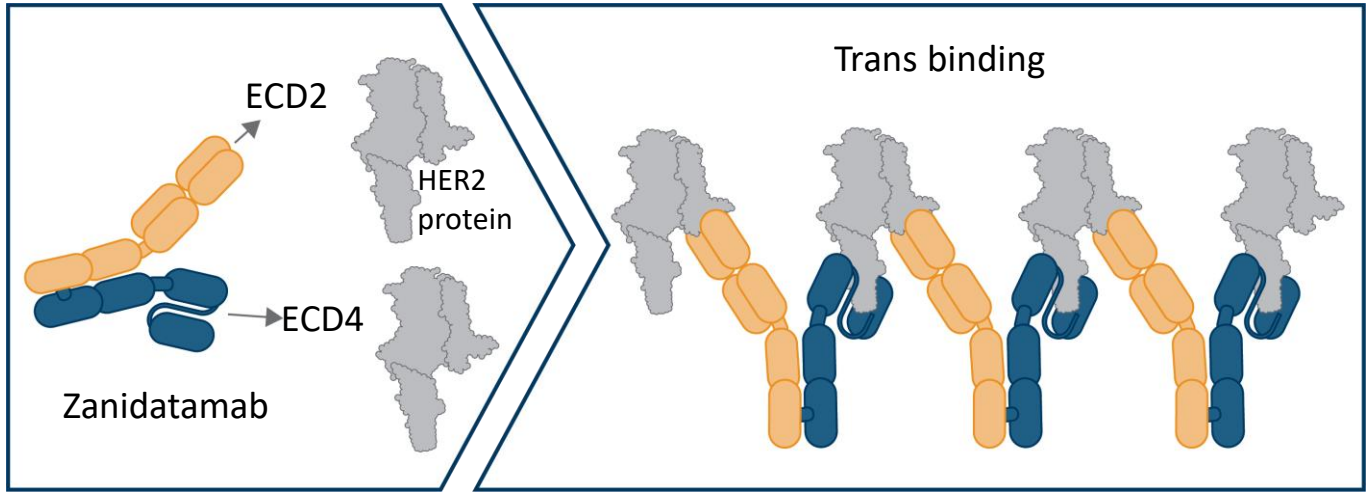
Patients from ARTEMIDE-Biliary01 can be recruited to DESTINY-BTC 01, but only from the control arm.

BTC, biliary tract cancer; COC, contribution of components; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; IHCC, intrahepatic cholangiocarcinoma; INV, investigator-assessed; ITT, intent-to-treat; NR, not reportable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, once every three weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SoC, standard of care; SR, safety run; TAP, tumour assessment percentage; TOPAZ, a combination of gemcitabine, cisplatin, and durvalumab.

Zanidatamab (ZW25), A Bispecific Antibody for HER2-Expressing Cancers[1]

Zanidatamab's unique binding geometry

- Biparatopic binding targets two distinct HER2 epitopes and results in HER2 binding across a range of expression levels (low to high)
  - The geometry of zanidatamab prevents it from binding to the same HER2 molecule
  - Binding occurs on 2 separate HER2 molecules in *trans*



Dual HER2-binding of zanidatamab drives unique MOA

- HER2-receptor cross-linking, clustering, internalization, and downregulation
  - Enhanced receptor clustering on cell surface (cluster internalization, receptor downregulation) compared to trastuzumab ± pertuzumab
  - Inhibition of cellular proliferation
- Fc-mediated cytotoxicity: ADCC, ADCP, CDC

1. Weisser NE et al. *Nature Commun*. 2023;14:1394.

Phase 1 Trial of Zanidatamab in Patients With Locally Advanced/Metastatic HER2-Expressing Cancers[1,]

Part 1 Dose Escalation (N = 46)						
Cohorts 1-3: Any cancer[a] (Any HER2 expression IHC1+, 2+, or 3+)			Cohort 4: Any cancer[b] (IHC3+ or IHC2+/FISH- or FISH+)	Cohorts 5-6: GEA (IHC3+ or IHC2+/FISH+)		Cohort 7: BC (IHC3+ or IHC2+/FISH+)
QW			Q2W	Q2W		Q3W
5 mg/kg n = 3	10 mg/kg n = 6	15 mg/kg n = 7	20 mg/kg n = 7	25 mg/kg n = 6	30 mg/kg n = 6	30 mg/kg n = 11

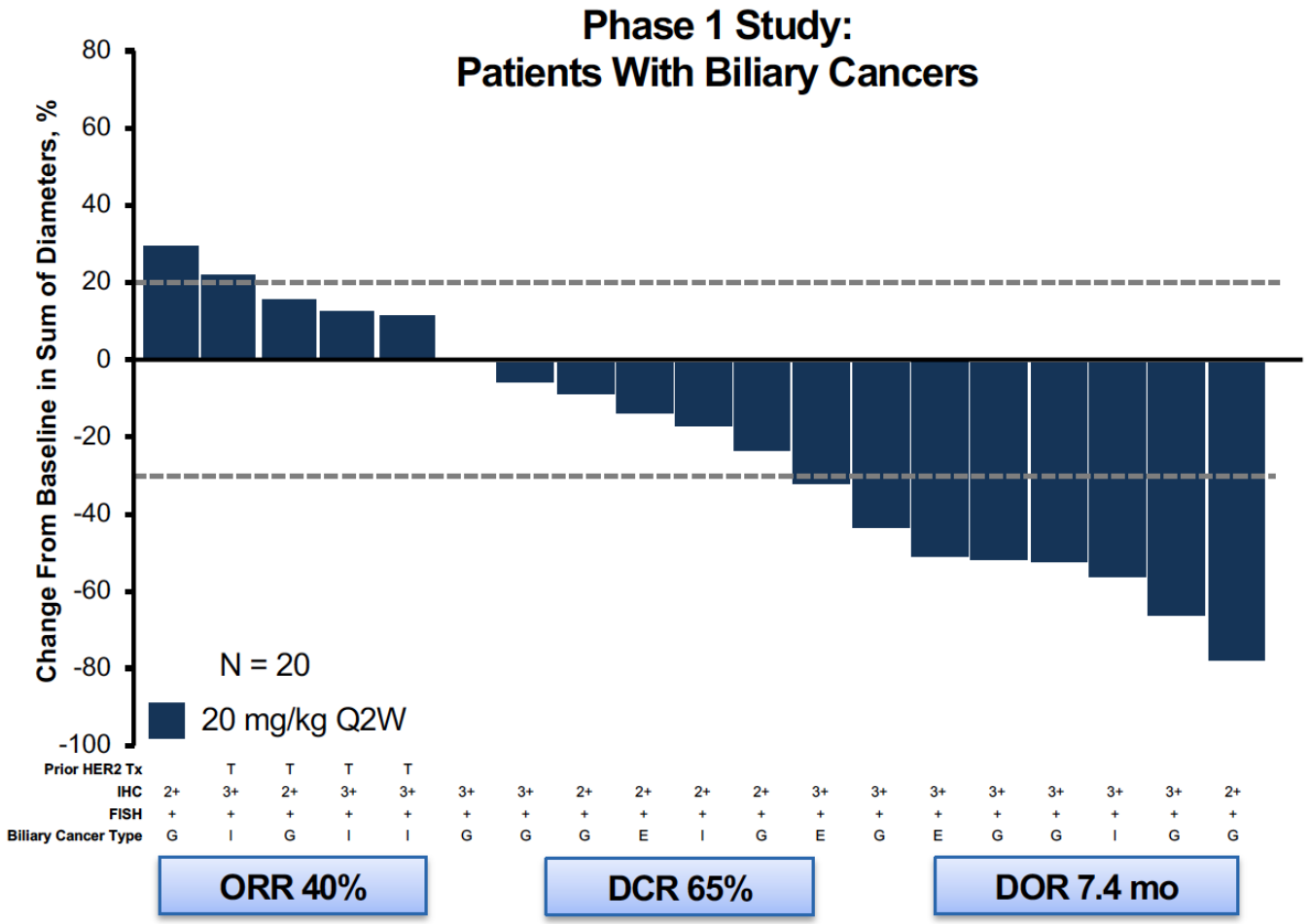
↓

Part 2 Dose Expansion (N = 86)		
Cohort 5: Any cancers other than BC or GEA IHC3+ or IHC2+/FISH+ 20 mg/kg Q2W[c]		
BTC n = 22	CRC n = 28	Other n = 36

[a] Includes BC (n = 8), gastric cancer (n = 5), CRC (n = 1), skin cancer (n = 1), and oesophageal cancer (n = 1). [b] Includes BC (n = 3), cervical cancer (n = 1), oesophageal cacner (n = 1), gastrooesophageal junction cancer (n = 1), and gastric cancer (n = 1). [c] One patient with CRC received 10 mg/kg QW and was pooled with the 20 mg/kg Q2W dose for analyses.

1. Meric-Bernstam F et al. *Lancet Oncol*. 2022;23:1558-1570.

Antitumor Activity in Patients With HER2-Expressing BTC Treated With Zanidatamab in Part 2 of Study[1,a]



Median DOR 8.5 mo.
Median PFS 3.5 mo.

[a] Dotted lines represent 20% increase or 30% decrease in tumor size. Waterfall plot of greatest percentage change in the sum of the longest diameters of measurable tumors in patients with biliary tract cancer. E=extrahepatic cholangiocarcinoma. FISH=fluorescence in situ hybridization. G=gallbladder cancer. I=intrahepatic cholangiocarcinoma. T=trastuzumab.

2023 ASCO® ANNUAL MEETING

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

Shubham Pant, MD[1]; Jia Fan, MD, PhD[2]; Do-Youn Oh, MD, PhD[3]; Hye Jin Choi, MD, PhD[4]; Jin Won Kim, MD, PhD[5]; Heung-Moon Chang, MD, PhD[6]; Lequn Bao, MD[7]; Sun Huichuan, MD, PhD[2]; Teresa Macarulla, MD, PhD[8]; Feng Xie, MD[9]; Jean-Philippe Metges, MD[10]; Jie'er Ying, MD[11]; John A Bridgewater, MD, PhD[12]; Myung-Ah Lee, MD, PhD[13]; Mohamedtaki A Tejani, MD[14]; Emerson Y Chen, MD, MCR[15]; Dong Uk Kim, MD[16]; Harpreet Wasan, MD, FRCP[17]; Michel Ducreux, MD, PhD[18]; Yuanyuan Bao, MS[19]; Lin Yang, PhD[20]; JiaFang Ma, MD[19]; Phillip M Garfin, MD[20]; James J Harding, MD[21]

[1]MD Anderson Cancer Center, Houston, Texas, US; [2]Affiliated Zhongshan Hospital of Fudan University, Shanghai, China; [3]Seoul National University Hospital, Seoul, Korea; [4]Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [5]Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [7]Hubei Cancer Hospital, Hubei, China; [8]Vall d'Hebrón University Hospital and Vall d'Hebrón Institute of Oncology, Barcelona, Spain; [9]The Third Affiliated Hospital of the Chinese PLA Naval Military Medical University, Shanghai, China; [10]CHRU de Brest-Hopital Morvan, ARPEGO Network, Brest, France; [11]Zhejiang Cancer Hospital, Hangzhou, China; [12]University College London Cancer Institute, London, UK; [13]The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, Korea; [14]AdventHealth, Orlando, Florida, US; [15]Oregon Health & Science University, Knight Cancer Institute, Portland, Oregon, US; [16]Pusan National University Hospital, Busan, Korea; [17]Hammersmith Hospital, Imperial College, London, UK; [18]Université Paris-Saclay, Gustave Roussy, Villejuif, France; [19]BeiGene (Beijing) Co., Ltd., Beijing, China; [20]Current Jazz Pharmaceuticals employee and former Zymeworks employee during the conduct of the study; [21]Memorial Sloan Kettering Cancer Center, New York, New York, US

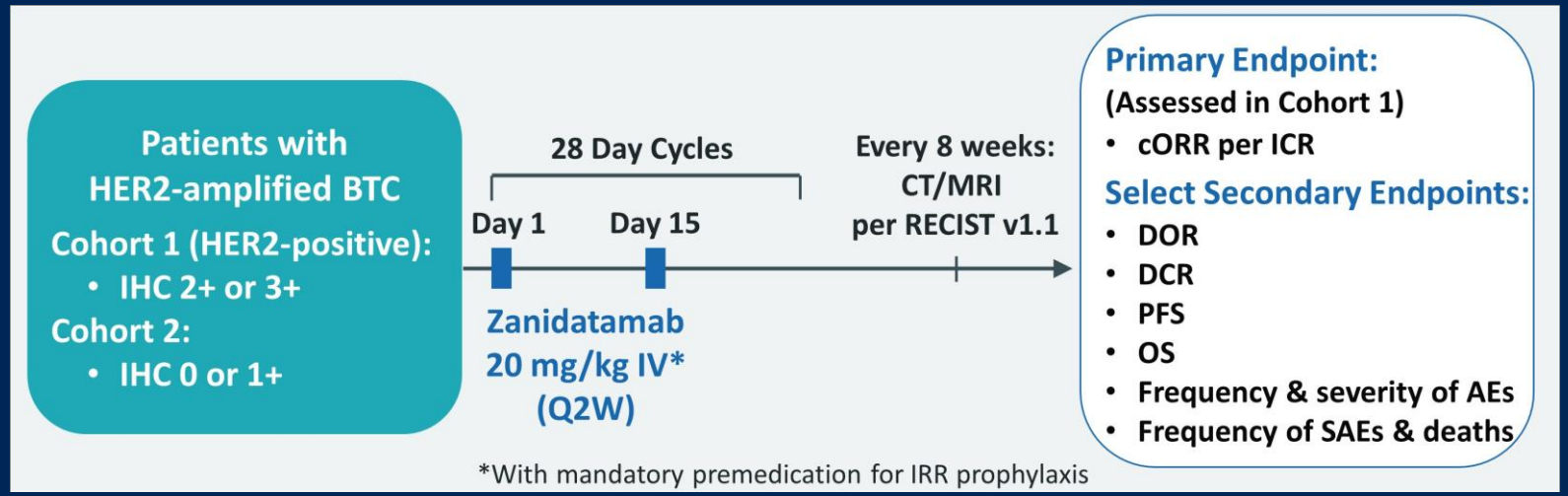
Corresponding Author: spant@mdanderson.org

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

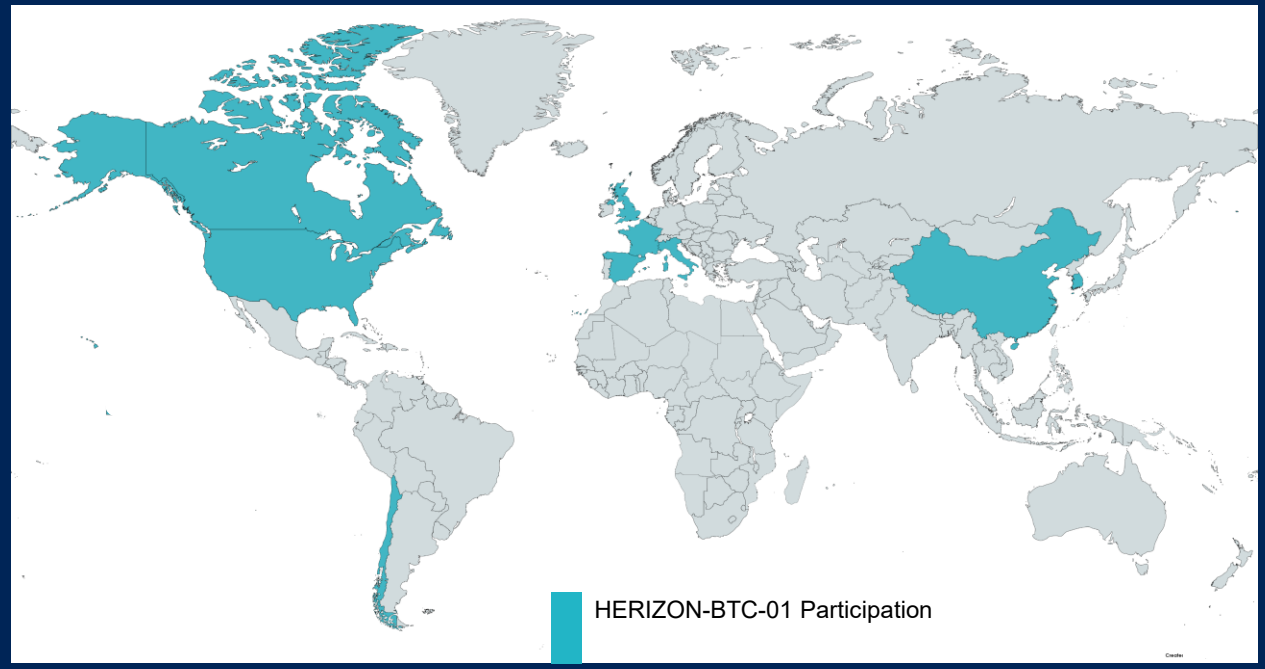


[1] Excludes ampullary

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)

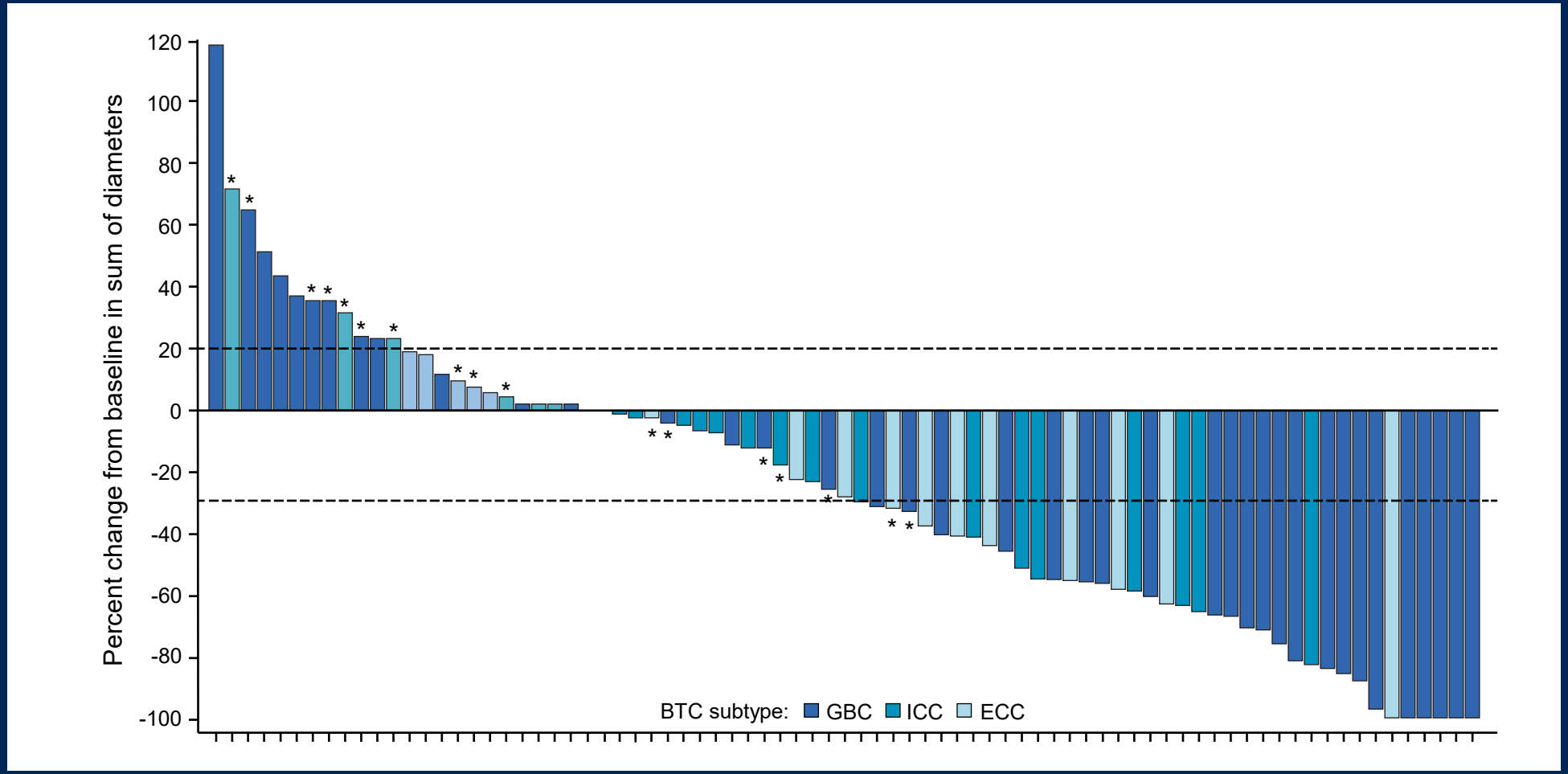
- 16 patients had ongoing responses at the time of data cutoff

		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.

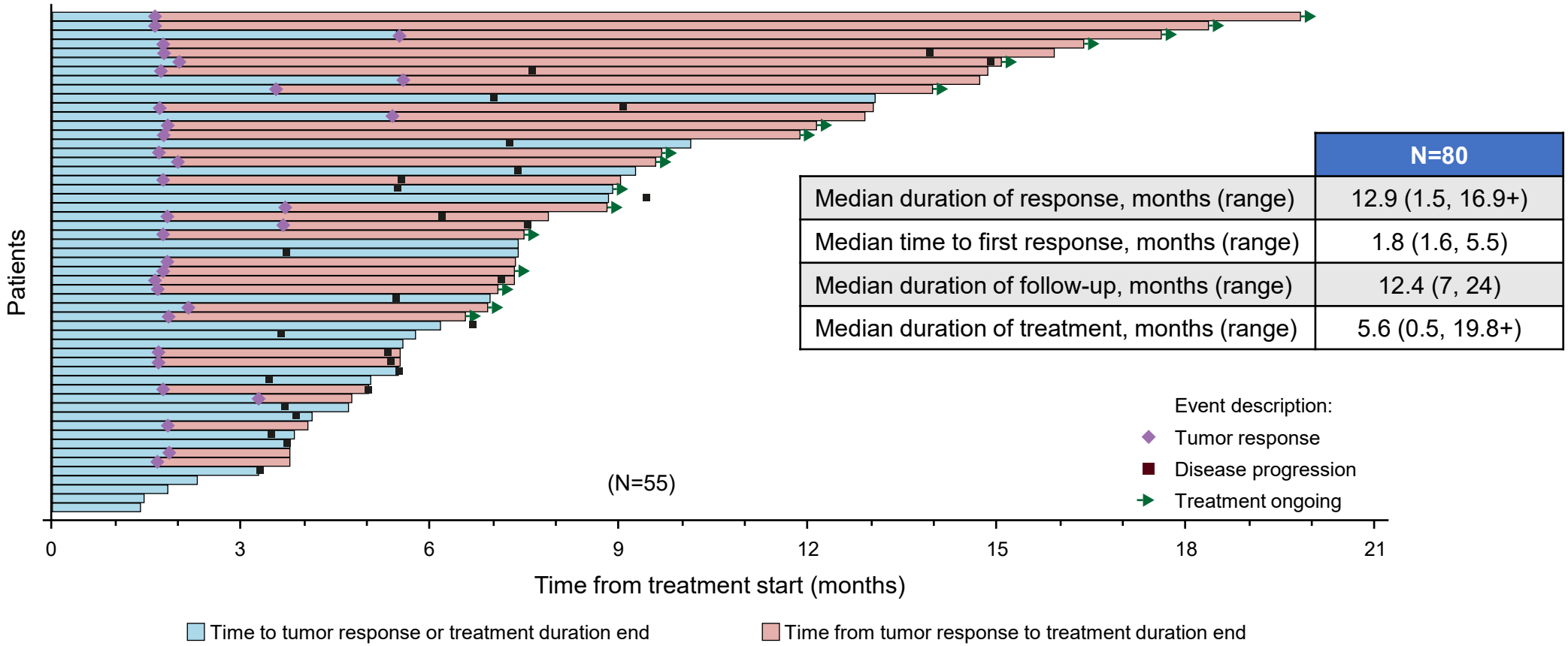
[1] NE = one patient died prior to first post-baseline tumor assessment.

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)

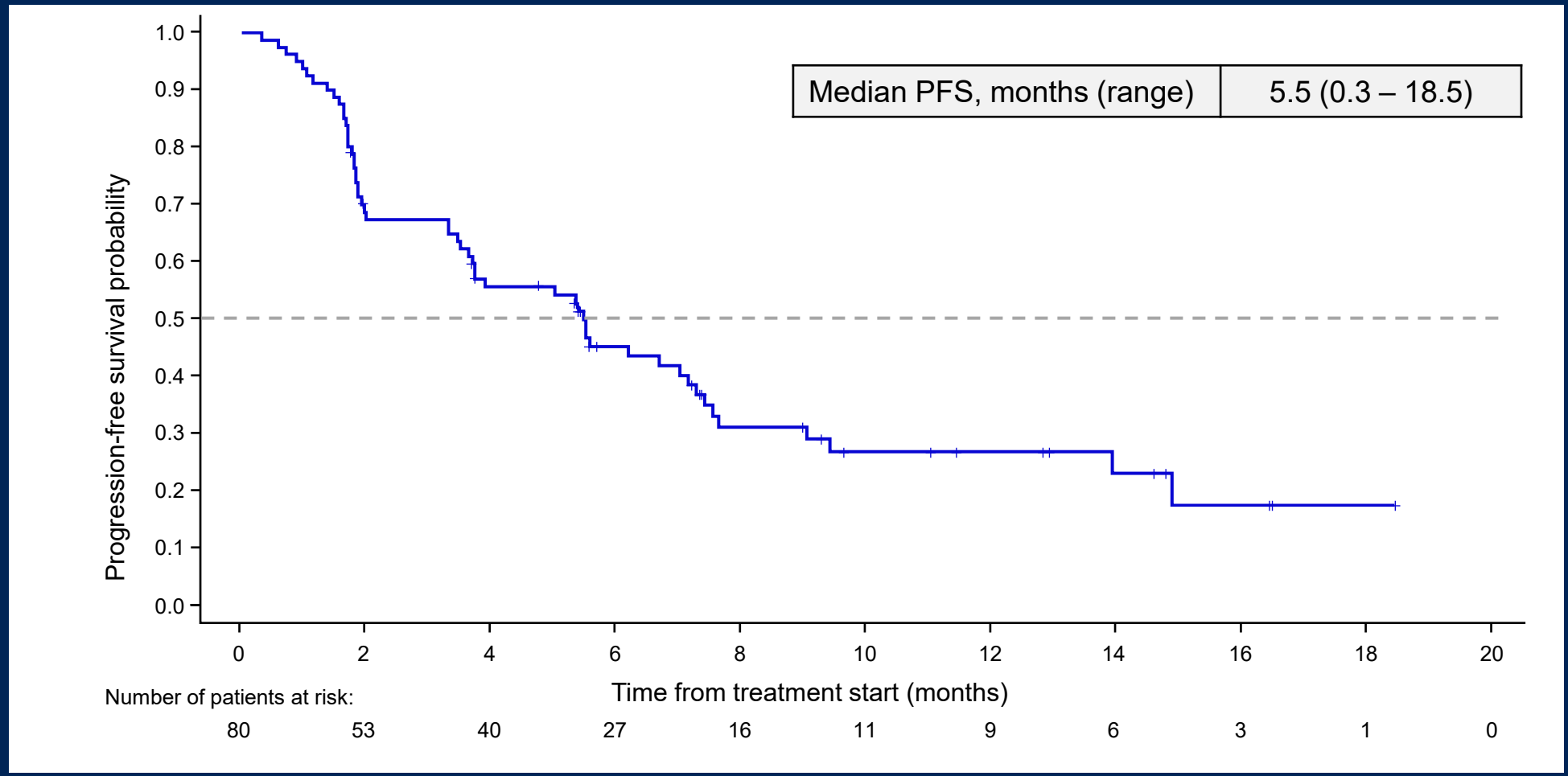


	N=80
Median duration of response, months (range)	12.9 (1.5, 16.9+)
Median time to first response, months (range)	1.8 (1.6, 5.5)
Median duration of follow-up, months (range)	12.4 (7, 24)
Median duration of treatment, months (range)	5.6 (0.5, 19.8+)

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



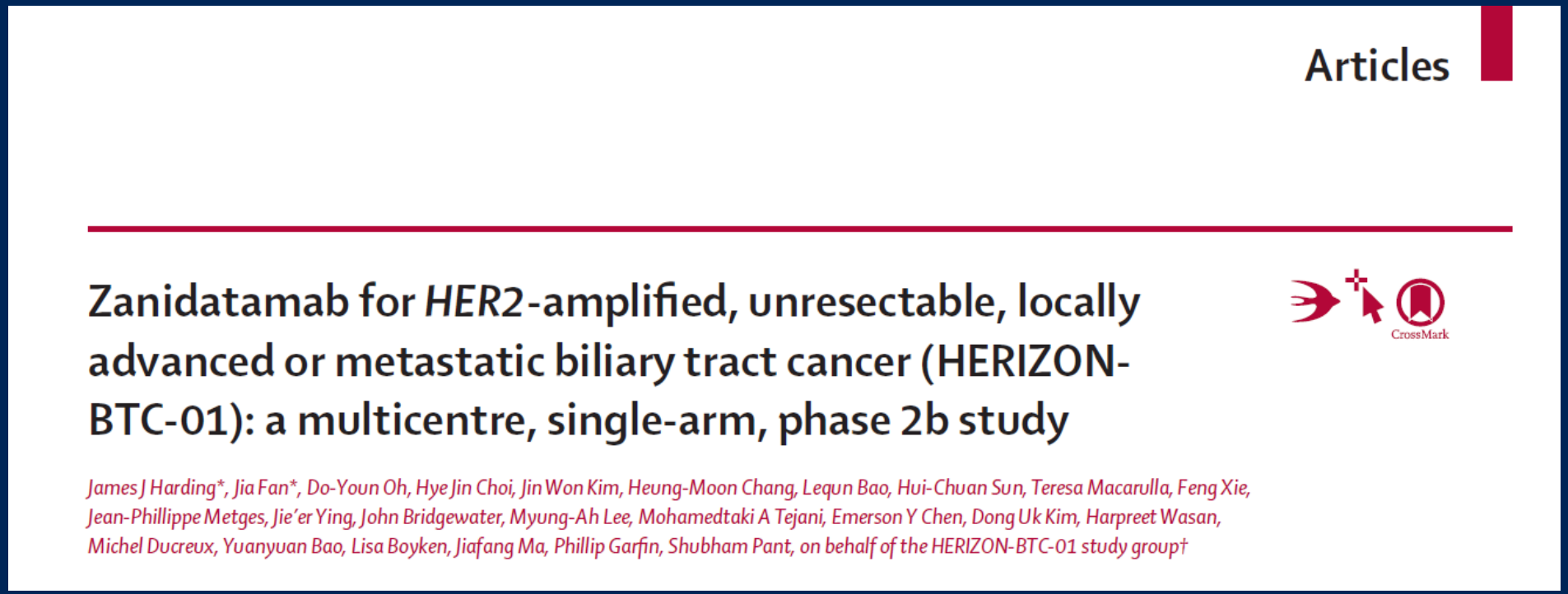
Adverse Events

	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

Full Publication – *The Lancet Oncology*


Articles

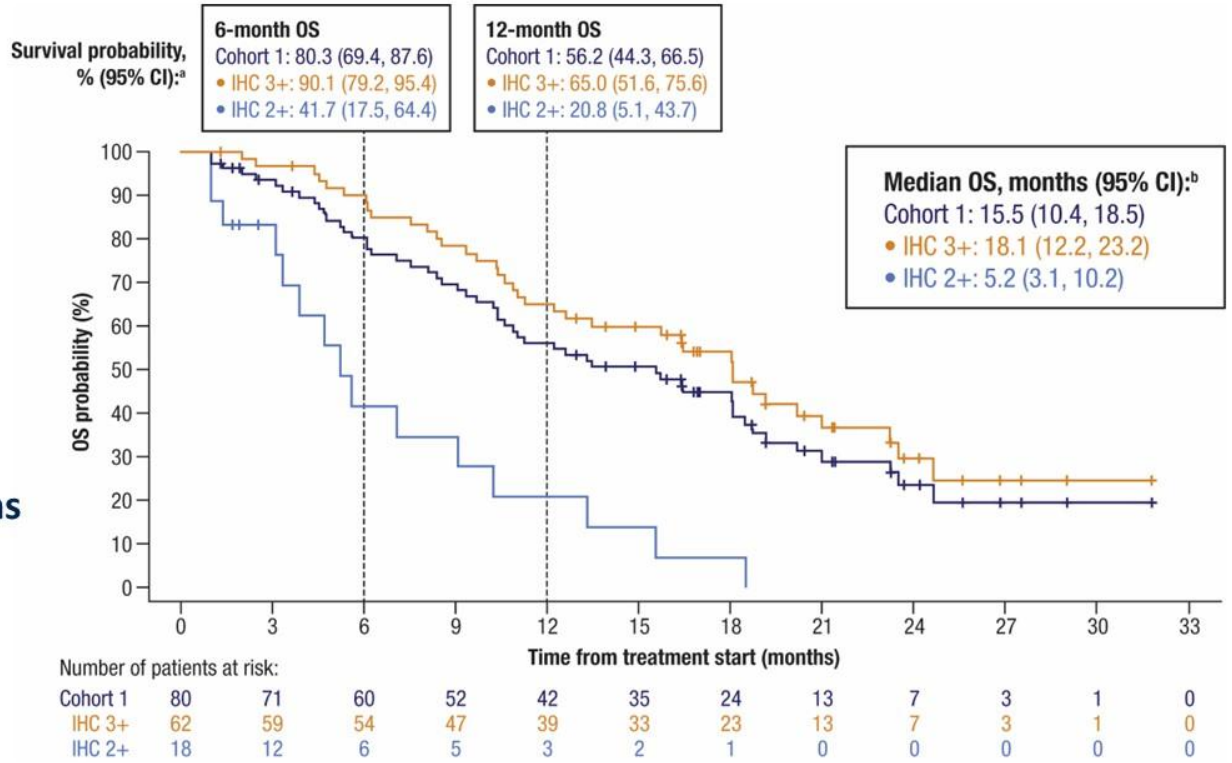
Zanidatamab for *HER2*-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study

James J Harding, Jia Fan*, Do-Youn Oh, Hye Jin Choi, Jin Won Kim, Heung-Moon Chang, Lequn Bao, Hui-Chuan Sun, Teresa Macarulla, Feng Xie, Jean-Phillippe Metges, Jie'er Ying, John Bridgewater, Myung-Ah Lee, Mohamedtaki A Tejani, Emerson Y Chen, Dong Uk Kim, Harpreet Wasan, Michel Ducreux, Yuanyuan Bao, Lisa Boyken, Jiafang Ma, Phillip Garfin, Shubham Pant, on behalf of the HERIZON-BTC-01 study group†*

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

Efficacy Outcomes With Long-Term Follow-Up in HER2-Positive BTC

- The median (range) duration of follow-up was 22 (16-34) months (data cutoff: July 28, 2023)
- **cORR (41.3%) and DCR (68.8%) were maintained from the primary analysis;[1] 1 additional patient achieved a CR**
  - In a pre-planned subgroup analysis of cORR by HER2 expression, responses were observed in both IHC 3+ (cORR: 51.6%) and IHC 2+ (cORR: 5.6%)
- **The median DOR (95% CI) increased to 14.9 (7.4, NR) months from the primary analysis[1]**
- **The median OS (95% CI) was 15.5 (10.4, 18.5) months**



[a]CIs for 6-month and 12-month OS based on the Greenwood method. [b]Estimates per Kaplan-Meier method; median OS CIs based on the Brookmeyer and Crowley method with log-log transformations.

Baseline characteristics were previously published.[1]

BTC, biliary tract cancer; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; OS, overall survival.

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

Phase 3 HERIZON-BTC-302 Study Design

Previously untreated unresectable, locally advanced or metastatic HER2+ BTC(N ≈ 286)

Exclusion Criteria:

- ECOG PS >1
- Prior HER2-targeted therapy[b]
- >2 cycles of a gemcitabine-based regimen ± pembrolizumab or durvalumab

R 1:1

21-day treatment cycles (≤8 cycles)

Active: Zanidatamab 1800 mg IV (<70 kg) or Zanidatamab 2400 mg IV (≥70 kg) plus CisGem ± PD1/L1 inhibitor[c]

SOC: CisGem ± PD1/L1 inhibitor[c]

Up to 52 months (primary endpoint)

Up to 68 months (secondary outcomes)

Primary endpoints

- PFS in patients with IHC 3+ tumors

Secondary endpoints include

- OS in patietns with IHC3+ tumors
- PFS for all participants
- OS for all participants
- cORR rate
- DOR
- TEAEs

cORR = complete overall response rate; CisGem = cisplatin and gemcitabine; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; IHC = immunohistochemistry; PFS = progression-free survival. PS = Performance Status; TEAE = treatment-emergent adverse events.

[a] IHC 3+ or IHC 2+/ISH+.

[b] Except for patients who completed it for breast cancer >5 years prior to BTC diagnosis.

[c] Pembrolizumab or durvalumab at physician's discretion if locally approved.

Harding J, et al. HERIZON-BTC-302: A phase 3 study of zanidatamab with standard-of-care (SOC) therapy vs SOC alone for first-line treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced/metastatic biliary tract cancer (BTC). (https://meetings.asco.org/abstracts-presentations/241684). Accessed 1/27/2025; https://clinicaltrials.gov/study/NCT06282575.

Key Takeaways: Advanced/Metastatic, HER2+ BTC

- BTC is uncommon (<1% of all adult cancers)[1,2]
- For patients with locally advanced/metastatic BTC, nontargeted second-line therapy with mFOLFOX offers limited clinical benefit: ORR 5%; median PFS 4.0 months[3]
- HER2 amplification/overexpression is observed in a subset of BTC (3.7% in IHCC, 3% in perihilar EHCC, 18.5% in distal EHCC, 31.3% in gallbladder carcinomas [GBC])[4]
- HER2-targeted therapies have demonstrated clinical benefit in a number of tumor types (eg, breast and gastric cancer); promising activity in BTC has been demonstrated with multiple HER2-directed agents
- HER2-directed agents approved for use in BTC are zanidatamab and T-DXd, which were granted accelerated approval by the FDA for the treatment of adult patients with previously treated, unresectable, or metastatic HER2-positive (IHC 3+) BTC.

BTC = biliary tract cancer; EHCC = extrahepatic cholangiocarcinoma; IHC = immunohistochemistry.

1. Siegel RL, et al. *CA Cancer J Clin*. 2022;72:7-33. 2. Valle JW, et al. *Lancet*. 2021;397:428-444. 3. Lamarca A, et al. *Lancet Oncol*. 2021;22:690-701. 4. Hiraoka N, et al. *Hum Pathol*. 2020;105:9-19. 5. FDA. News release 11/21/2024 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zanidatamab-hrii-previously-treated-unresectable-or-metastatic-her2). Accessed 1/12/2025.

Case

72 y/o female with stage 4 gallbladder cancer.

- Initial treatment 5/1/2024 with Cddp/Gem/Durva
- 3/1/2025 progressive disease on CT in liver.
  - 3 lesions < 1.5 cm - 2 in left and 1 in R lobe.
- Blood NGS Negative, Tissue IHC Her 3+

Questions:

Treatment options – What would people select as next line of therapy?

Has anyone used Zanidatamab?

Thank You