Expert Second Opinion: Investigators Discuss the Optimal Management of HER2-Positive Gastrointestinal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Thursday, January 8, 2026

7:15 PM – 8:45 PM PT

Faculty

Haley Ellis, MD

Eric Van Cutsem, MD, PhD

Zev Wainberg, MD, MSc

Moderator

Lionel A Kankeu Fonkoua, MD

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Faculty

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Moderator

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Rochester, Minnesota

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Dr Ellis — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Cogent Biosciences, Jazz Pharmaceuticals Inc
Honoraria	Incyte Corporation, Jazz Pharmaceuticals Inc
Nonrelevant Financial Relationships	Medscape, OncLive, The Jackson Laboratory

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Prof Van Cutsem — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Agenus Inc, ALX Oncology, Amgen Inc, Arcus Biosciences, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeOne, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Cantargia, Daiichi Sankyo Inc, Debiopharm, Eisai Inc, ElmediX, Fosun Pharma, Galapagos NV, GSK, Incyte Corporation, Ipsen Biopharmaceuticals Inc, iTeos Therapeutics, Jazz Pharmaceuticals Inc, Johnson & Johnson, Lilly, Merck KGaA, Microbial Machines, Mirati Therapeutics Inc, MSD, Nordic Pharma, Novartis, Novocure Inc, Pfizer Inc, Pierre Fabre, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, Simcere, Taiho Oncology Inc, Takeda Pharmaceutical Company Limited, Trishula Therapeutics, Zymeworks Inc

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Dr Wainberg — Disclosures
Faculty

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Data and Safety Monitoring Boards/Committees	AstraZeneca Pharmaceuticals LP, Pfizer Inc

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Dr Kankeu Fonkoua — Disclosures
Moderator

No relevant conflicts of interest to disclose.

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

A CME Symposium Held Adjunct to the 2026 ASCO® Gastrointestinal Cancers Symposium

Friday, January 9, 2026

6:00 PM – 8:00 PM PT

Faculty

Jaffer A Ajani, MD

David H Ilson, MD, PhD

Rutika Mehta, MD, MPH

Moderator

Samuel J Klempner, MD

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

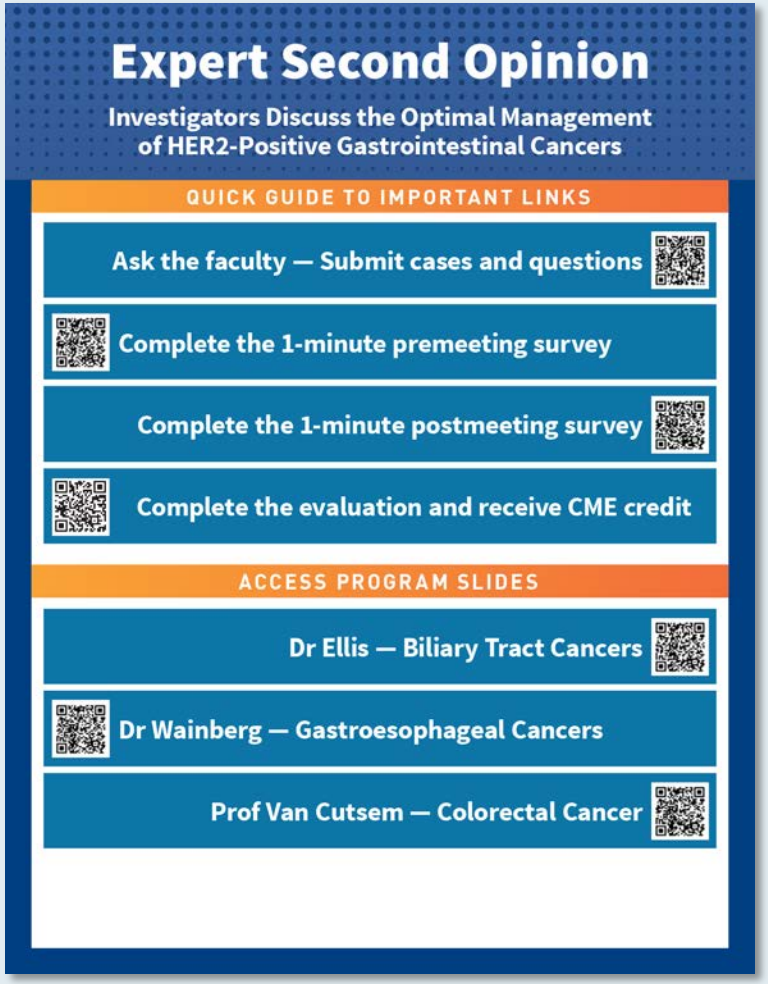
Please refer to the printed handout provided with your meeting syllabus, and scan the corresponding QR code to

Review and Download Program Slides.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: We will aim to address as many questions as possible during the program.

Get CME Credit: Complete the course evaluation.



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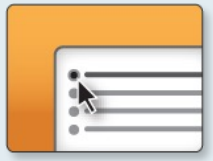
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Agenda

Module 1: Biliary Tract Cancers — Dr Ellis

Module 2: Gastroesophageal Cancers — Dr Wainberg

Module 3: Colorectal Cancer — Prof Van Cutsem

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Survey of 50 Community-Based General Medical Oncologists

December 22, 2025 – January 7, 2026

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Agenda

Module 1: Biliary Tract Cancers — Dr Ellis

Module 2: Gastroesophageal Cancers — Dr Wainberg

Module 3: Colorectal Cancer — Prof Van Cutsem

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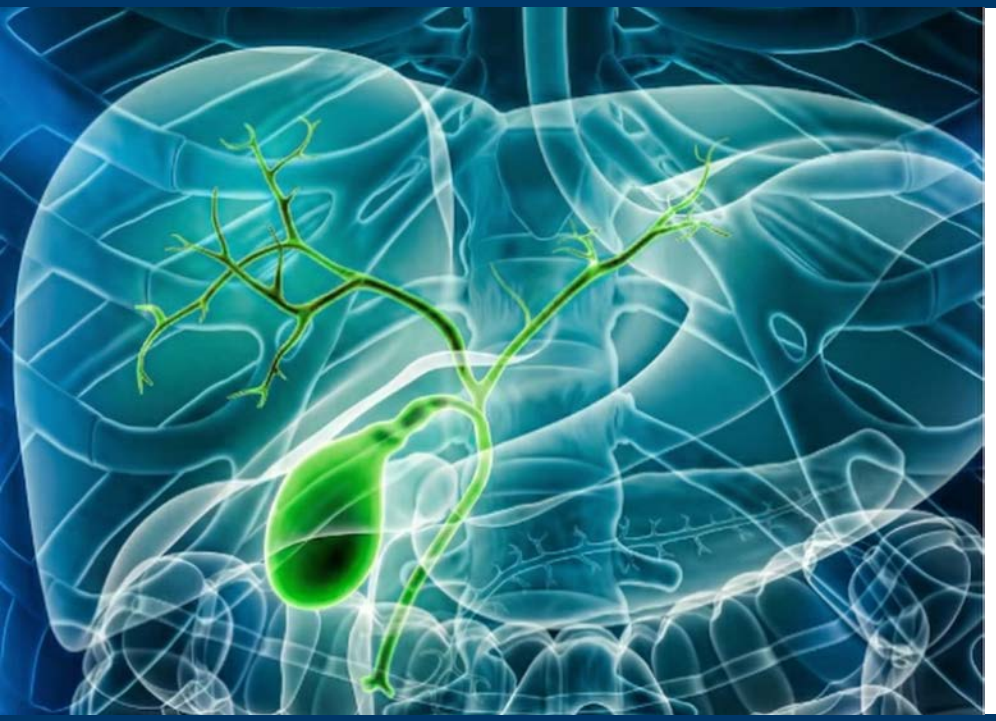

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HER2-Positive Biliary Tract Cancers

Dr. Haley Ellis

Mass General Brigham Cancer Institute, Attending Physician | Harvard Medical School, Instructor of Medicine

Tucker Gosnell Center for GI Cancers | Termeer Center for Targeted Therapies & Investigational Cancer Therapeutics

Mass General Brigham Cancer Institute

HARVARD MEDICAL SCHOOL

Overview

Biliary tract cancer (BTC) therapeutic landscape and prevalence of HER2

Clinical indications and methods for HER2 testing

Efficacy and safety of HER2-targeted therapies in BTC

- Trastuzumab deruxtecan (DESTINY-PanTumor02 and HERB trials)
- Zanidatamab (HERIZON-BTC-01 trial)
- Ongoing phase 3 trials for treatment-naïve patients

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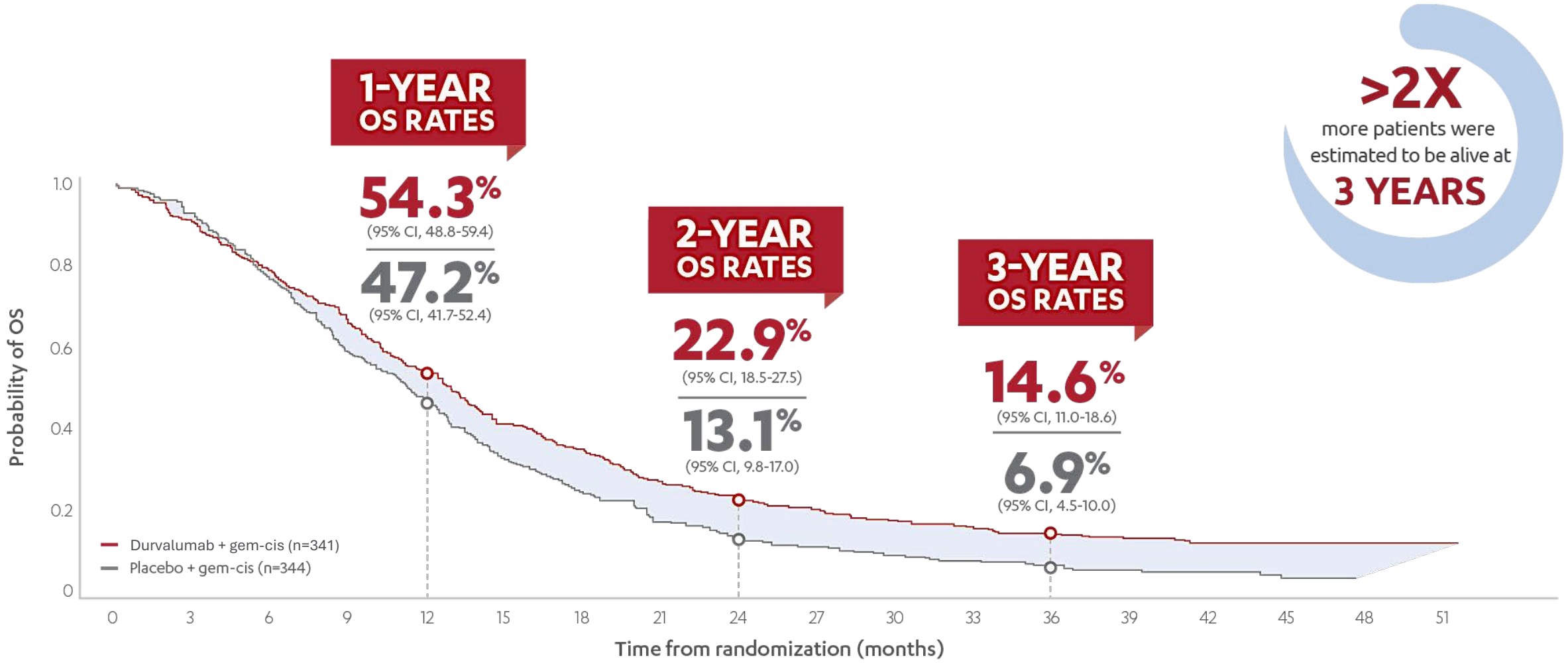
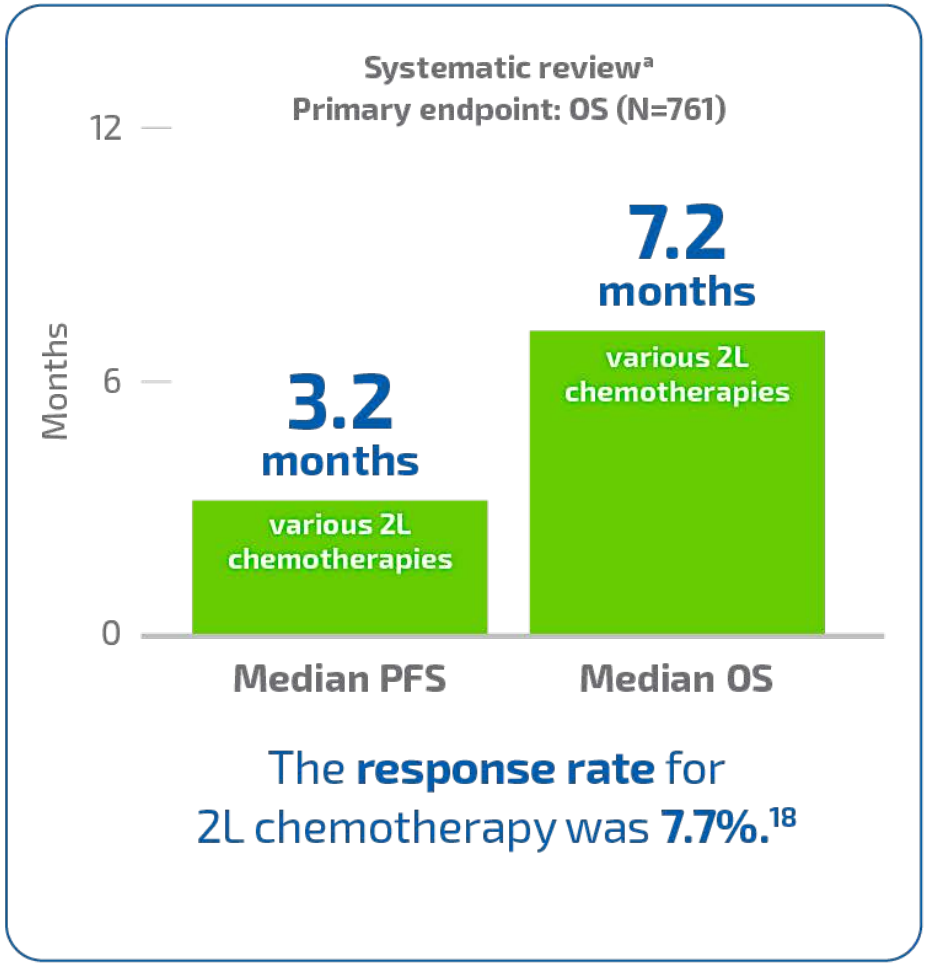
Chemotherapy plus immunotherapy is the first-line standard in advanced BTC

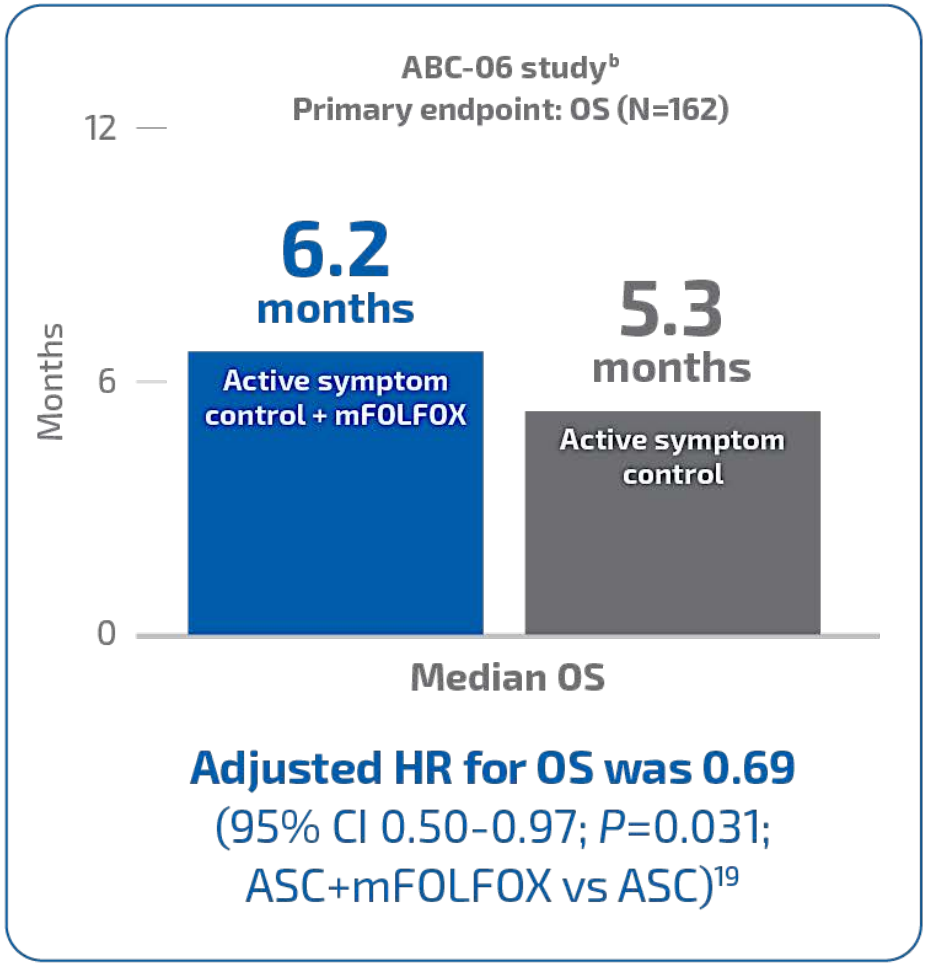


TOPAZ-1: Oh et al. NEJM Evid 2022 | Oh et al. J Hepatol 2025

Limited benefit with second-line chemotherapy in BTC



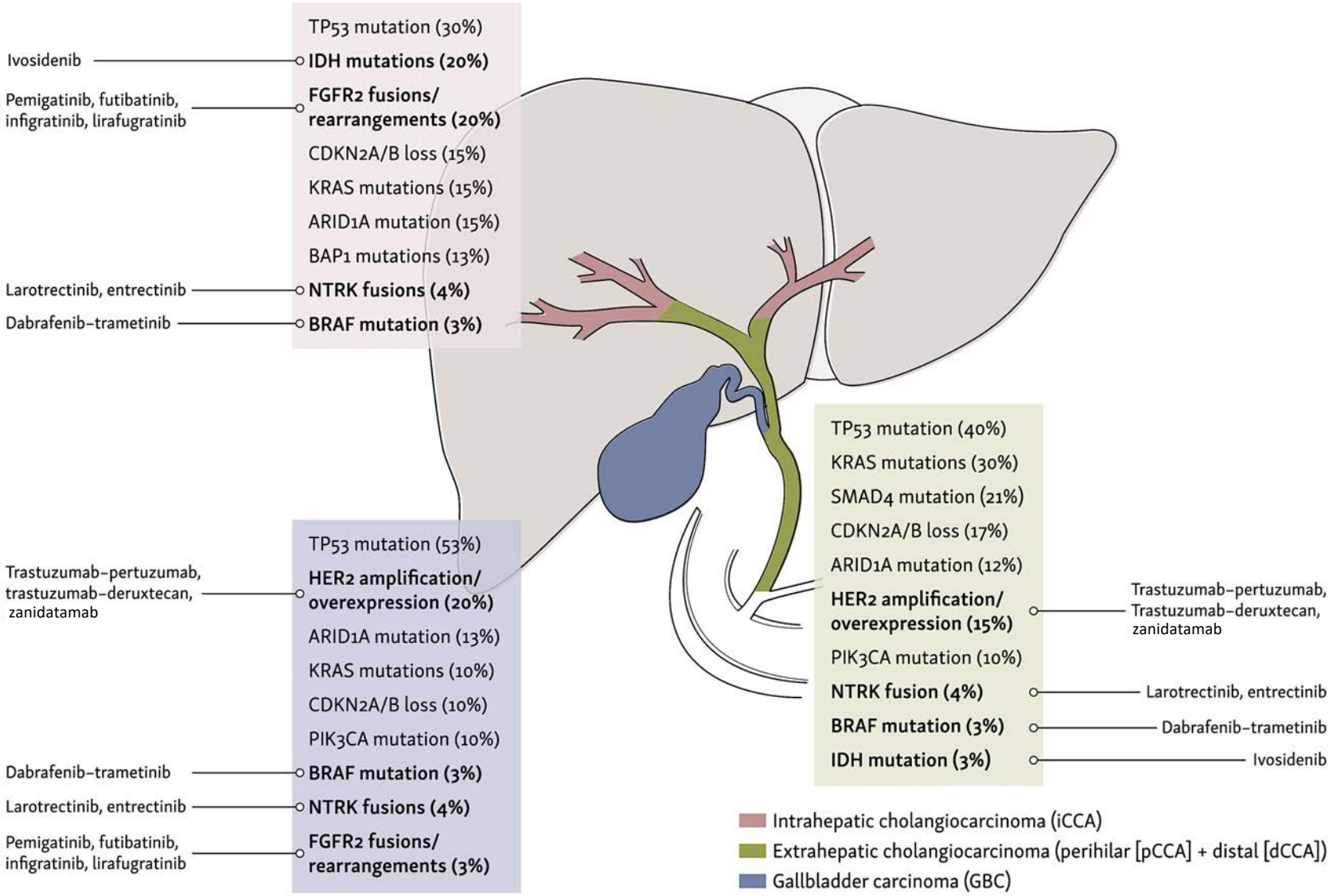
The **response rate** for 2L chemotherapy was **7.7%.**[18]



Adjusted HR for OS was 0.69 (95% CI 0.50-0.97; *P*=0.031; ASC+mFOLFOX vs ASC)[19]

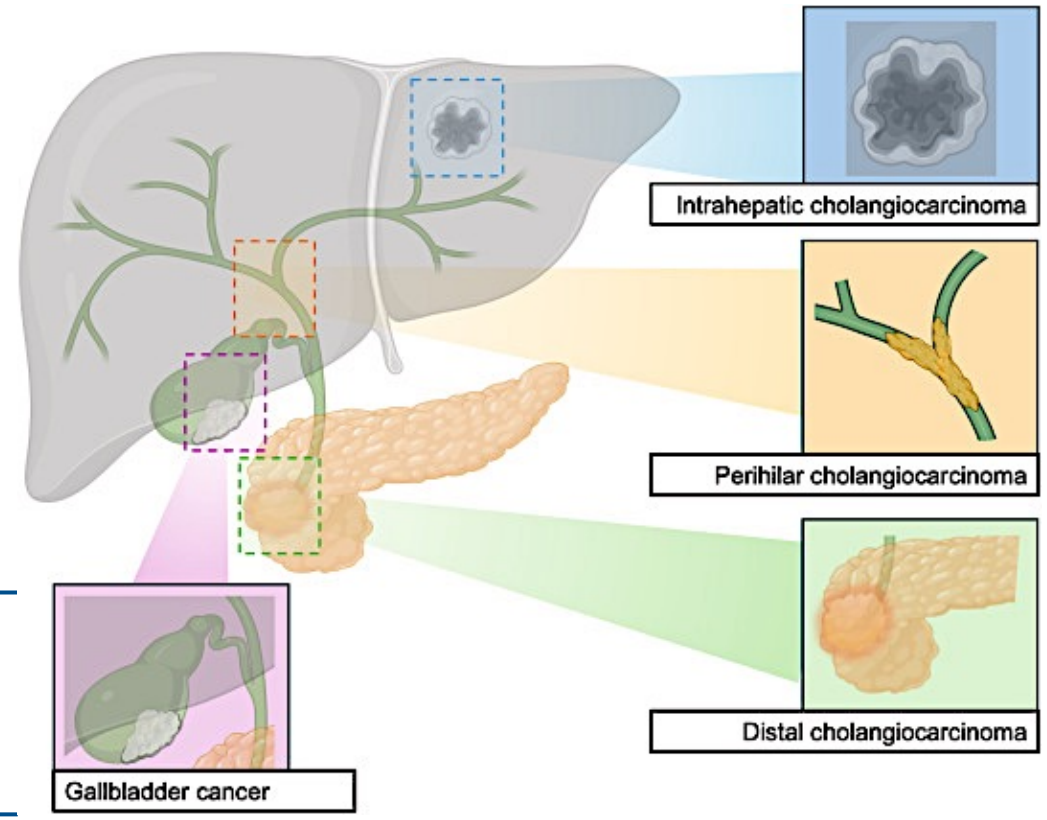
Lamarca et al. Ann Oncol 2014 | ABC-06: Lamarca et al. Lancet Oncol 2021

BTC has multiple actionable genomic targets



Kehmann et al. ESMO Open 2024

HER2 amplification/overexpression spans BTC subtypes



Intrahepatic cholangiocarcinoma (iCCA)
~3-5%

Extrahepatic cholangiocarcinoma (eCCA)
~10-20%

Gallbladder cancer (GBC)
~15-35%

Galdy et al. Cancer Metastasis Rev 2017 | Ayasun et al. Cancers 2023 | Soreide et al. Eur J Surg Oncol 2025

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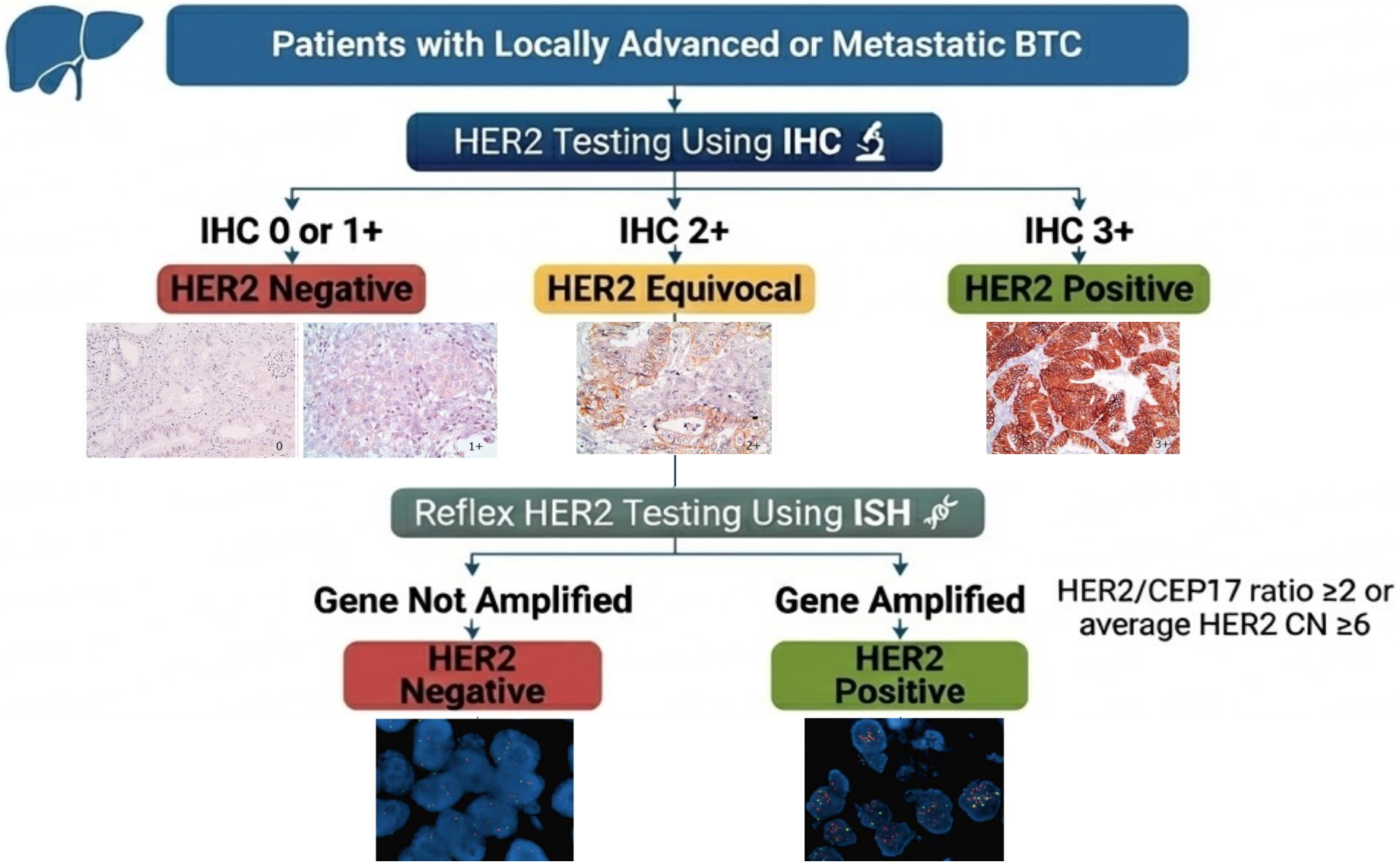
HER2 testing in BTC: who, when, and how

- **WHO:** All patients with unresectable or metastatic BTC, across subtypes
- **WHEN:** At diagnosis and/or repeat at progression
- **HOW:**

	Immunohistochemistry (IHC)	In Situ Hybridization (ISH)	Next-Generation Sequencing (NGS)
Target	HER2 Protein	*ERBB2* DNA	*ERBB2* DNA
Alteration	HER2 Overexpression	*ERBB2* Amplification	*ERBB2* Amplification + Mutations
Sample Type			

Javle et al. Cancer 2016 | Jacobi et al. Oncol Res Treat 2021 | Inoue et al. JCO Precis Oncol 2025 | NCCN Guidelines 2025

Defining HER2 positivity in BTC using gastric cancer scoring



Grillo et al. World J Gastroenterol 2016 | Bartley et al. J Clin Oncol 2017 | NCCN Guidelines 2025

HER2 testing in BTC: use both IHC and NGS

Correlation of HER2 grading using NGS and IHC	NGS result	
	HER2 not amplified* (n=182)	*HER2* amplified* (n=19)
IHC score		
0	30%	0%
1+	25%	11%
2+	40%	58%
3+	5%	32%
HER2 IHC classification		
HER2 negative	85%	**16%**
HER2 positive	**15%**	68%
N/A (2+, ISH not done)	0%	21%

~15% discordance between IHC and NGS in BTC

Lee et al. ASCO GI 2025

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- **Zanidatamab (HERIZON-BTC-01 trial)**
- **Ongoing phase 3 trials for treatment-naïve patients**

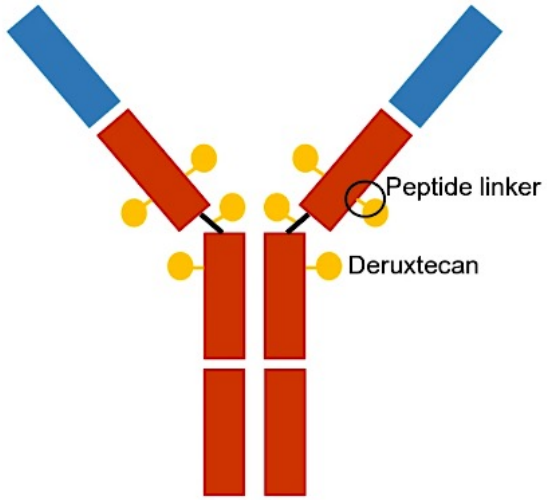
Second-line HER2-targeted therapy landscape in BTC

Trial	Treatment	Design	# BTC Pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
ABC-06[1] 2021	**FOLFOX**	Phase 3 *UK*	162	--	--	5%	33%	--	4.0	6.2
MyPathway[2] 2021	**Trastuzumab + Pertuzumab**	Phase 2 *Basket, US*	39	No	IHC 3+, ISH+, or NGS Amp	23%	51%	10.8	4.0	10.9
KCSG-HB19-14[3] 2023	**Trastuzumab + FOLFOX**	Phase 2 *Korea*	34	No	IHC 3+ (68%), IHC 2+/ISH+ (32%), or NGS Amp	29%	79%	4.9	5.1	10.7
SGNTUC-019[4] 2023	**Trastuzumab + Tucatinib**	Phase 2 *Basket*	30	No	IHC 3+, ISH+, or NGS Amp	47%	77%	6.0	5.5	15.5
HERIZON-BTC-01[5] 2023	**Zanidatamab**	Phase 2 *Global*	62 80 18	No	**IHC 3+** IHC 3+ or IHC 2+/ISH+ IHC 2+/ISH+	**52%** 41% 6%	**79%** 69% 33%	**14.9** 14.9 NE	**7.2** 5.5 1.7	**18.1** 15.5 5.2
DESTINY-PanTumor02[6] 2024	**Trastuzumab Deruxtecan**	Phase 2 *Basket, Global*	16 41 14	**Yes (17%)**	**IHC 3+** IHC 3+ or 2+ IHC 2+	**56%** 22% 0%	-- 78% --	-- 8.6 --	**7.4** 4.6 4.2	**12.4** 7.0 6.0
HERB[7] 2024	**Trastuzumab Deruxtecan**	Phase 2 *Japan*	22 8	Yes (*n* = 0)	**IHC 3+** **IHC 3+ or IHC 2+/ISH+** IHC 2+/ISH-, IHC 1+/ISH-, IHC 0/ISH+	**40%** **36%** 13%	-- **82%** 75%	-- **7.4** --	-- **5.1** 3.5	-- **7.1** 8.9
SUMMIT[8] 2023	**Neratinib**	Phase 2 *Basket*	25	No	**HER2 mutant**	16%	28%	3.7	2.8	5.4

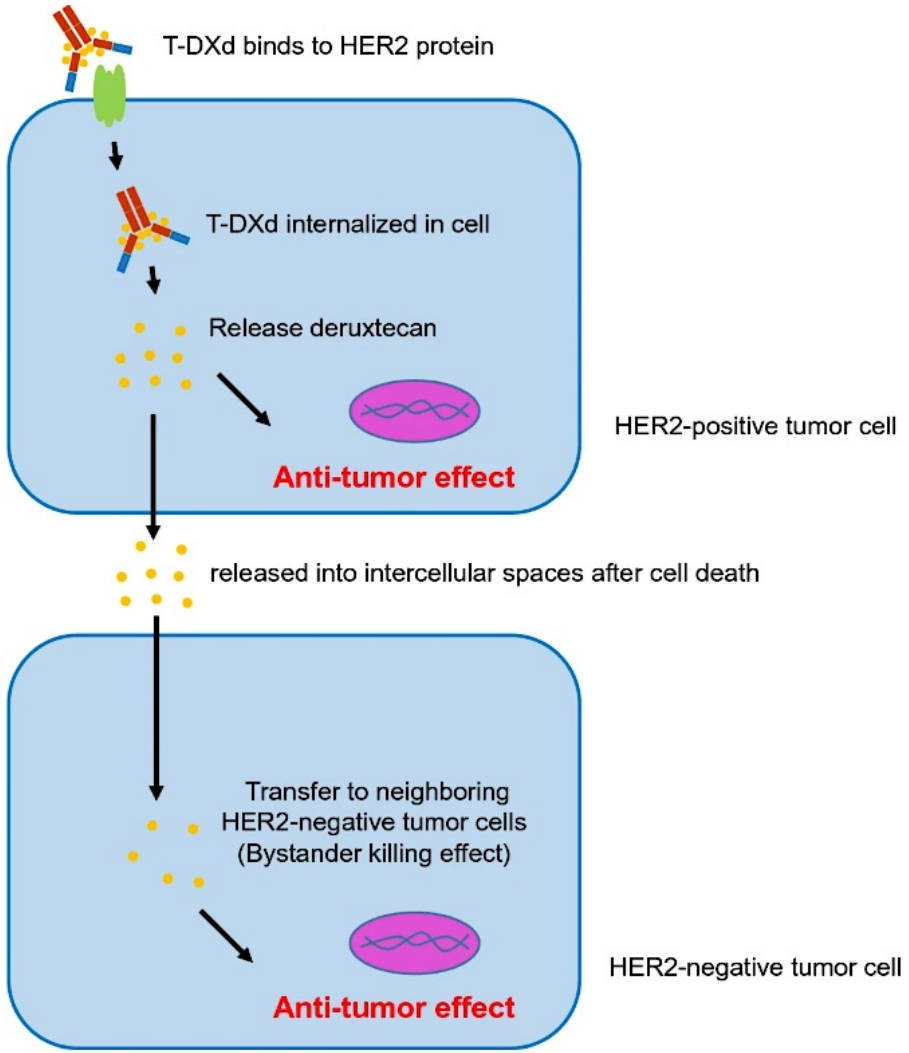
[1]Lamarca et al. Lancet Oncol 2021 | [2]Javle et al. Lancet Oncol 2021 | [3]Lee et al. Lancet Gastroenterol Hepatol 2023 | [4]Nakamura et al. J Clin Oncol 2023 | [5]Harding, Fan et al. Lancet Oncol 2023 | [6]Meric-Bernstam et al. J Clin Oncol 2024 | [7]Ohba et al. J Clin Oncol 2024 | [8]Harding et al. Nat Comm 2023

Trastuzumab deruxtecan (T-DXd): *HER2 antibody-drug conjugate*

FDA approved for previously treated, unresectable or metastatic HER2 ***IHC 3+*** *solid tumors*



Trastuzumab deruxtecan (T-DXd)

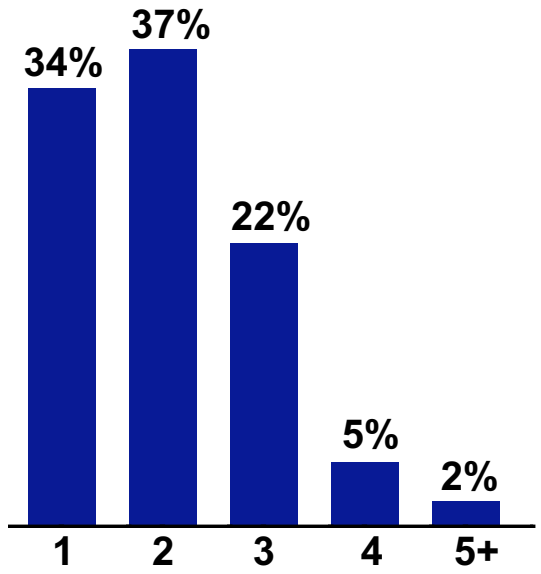


Aoki et al. Gastric Cancer 2021 | Ogitani et al. Cancer Sci 2016 | Ogitani et al. Clin Cancer Res 2016 | Nakada et al. Chem Pharm Bull (Tokyo) 2019 | Trastuzumab deruxtecan package insert

DESTINY-PanTumor02 trial of T-DXd: *eligibility and baseline*

- Locally advanced, unresectable, or metastatic HER2-expressing BTC, including AOV
- Progressed after ≥ 1 systemic therapy or without alternative treatment options, including HER2 therapy
- **HER2 IHC 3+ or 2+** by central (17%) or local (83%) testing

Prior Lines of Therapy (Median 2)



Prior HER2 Therapy (17%)

- Trastuzumab (*n* = 6)
- Pertuzumab (*n* = 1)
- Zanidatamab (*n* = 1)

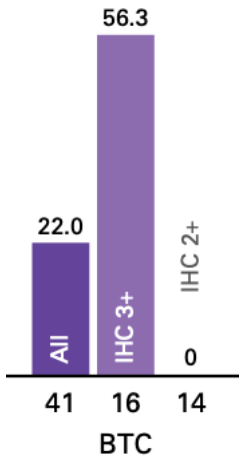
Meric-Bernstam et al. J Clin Oncol 2024

DESTINY-PanTumor02 trial of T-DXd: *efficacy*

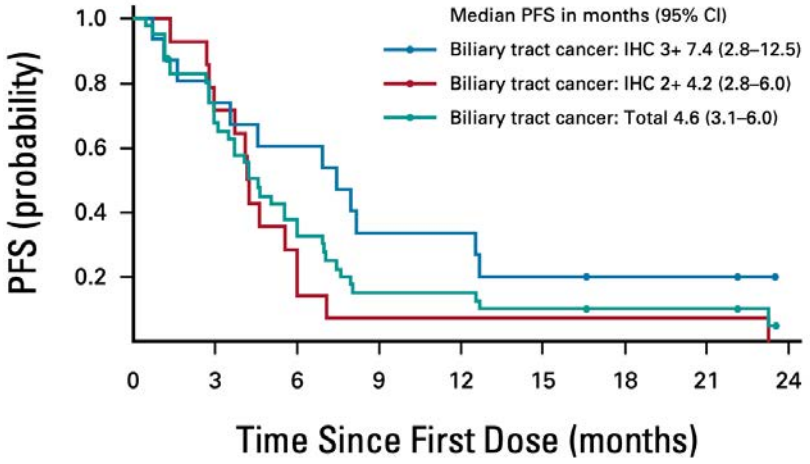
Design	# BTC Pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
Phase 2	16	**Yes (17%)**	**IHC 3+**	**56%**	--	--	**7.4**	**12.4**
Basket,	41		IHC 3+ or 2+	22%	78%	8.6	4.6	7.0
Global	14		IHC 2+	0%	--	--	4.2	6.0

IHC 3+ Outcomes

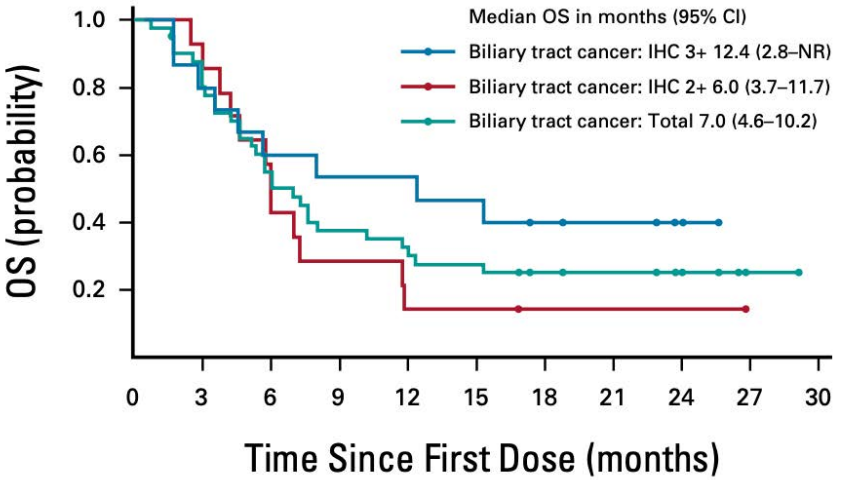
ORR: 56%



mPFS: 7.4 months



mOS: 12.4 months



Meric-Bernstam et al. J Clin Oncol 2024

DESTINY-PanTumor02 trial of T-DXd: *safety*

- **Treatment-Related Adverse Events (TRAEs)**
  - **39%** Grade 3+
  - **12%** Discontinued
  - **32%** Dose reduced

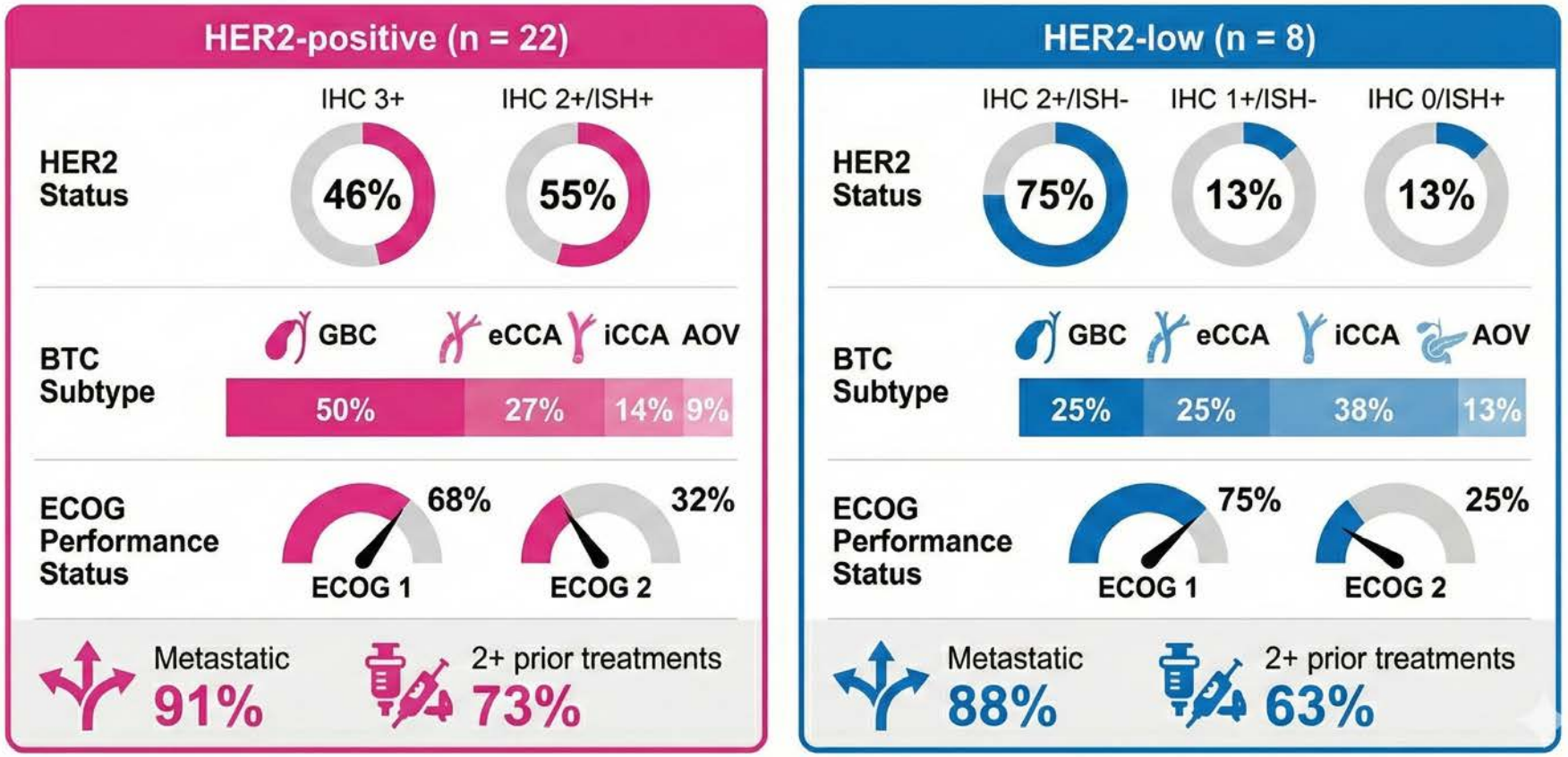
- **Common TRAEs**
  - **Nausea** (46%), **Vomiting** (22%), **Diarrhea** (20%)
  - **Anemia** (24%), **Neutropenia** (22%), **Fatigue** (22%)

- **ILD/Pneumonitis** (11%) – *across 267 patients in 7 cancer cohorts*
  - **9.0%** Grade 1-2
  - **0.4%** Grade 3
  - **1.1%** Grade 5 (1/3 patients with BTC)

Meric-Bernstam et al. J Clin Oncol 2024

HERB trial of T-DXd: *eligibility and baseline characteristics*

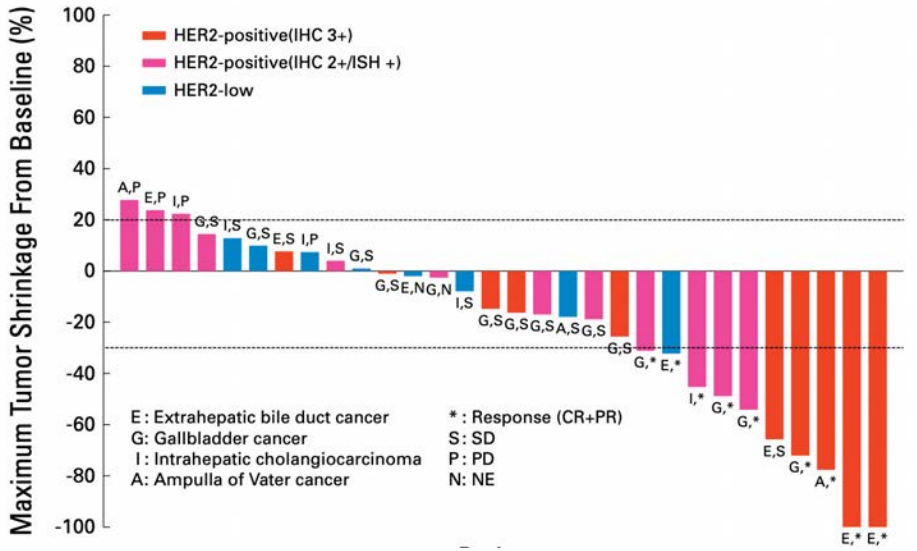
- Unresectable or recurrent HER2-expressing BTC
- Refractory or intolerant to gemcitabine-containing regimen
  - Prior HER2 therapy (*n* = 0)
- HER2 status centrally confirmed

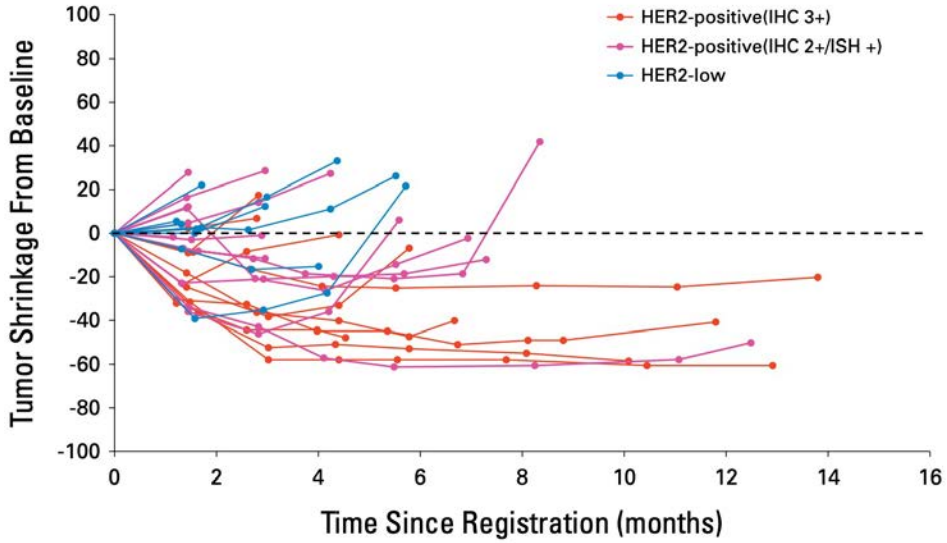


Ohba et al. J Clin Oncol 2024

HERB trial of T-DXd: *efficacy*

Design	# BTC Pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
Phase 2 *Japan*	**22**	Yes (*n* = 0)	**HER2 positive**	**36%**	**82%**	**7.4**	**5.1**	**7.1**
	10		IHC 3+/ISH+	40%				
	12		IHC 2+/ISH+	33%				
	8		**HER2 low**	**13%**	**75%**	**--**	**3.5**	**8.9**
	6		IHC 2+/ISH-					
	1		IHC 1+/ISH-					
	1		IHC 0/ISH+					





Ohba et al. J Clin Oncol 2024

HERB trial of T-DXd: *safety*

- **Treatment-Related Adverse Events (TRAEs)**
  - **82%** Grade 3+
  - **25%** Discontinued
  - **19%** Dose reduced

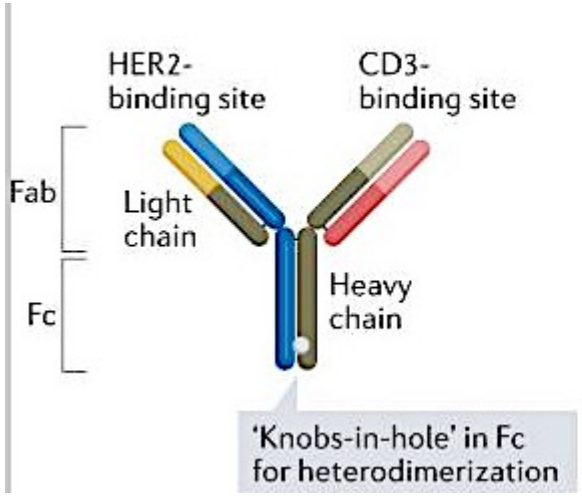
- **Common Grade 3+ TRAEs**
  - **Anemia** (53%), **Neutropenia** (31%), **Leukopenia** (31%), **Lymphopenia** (22%)

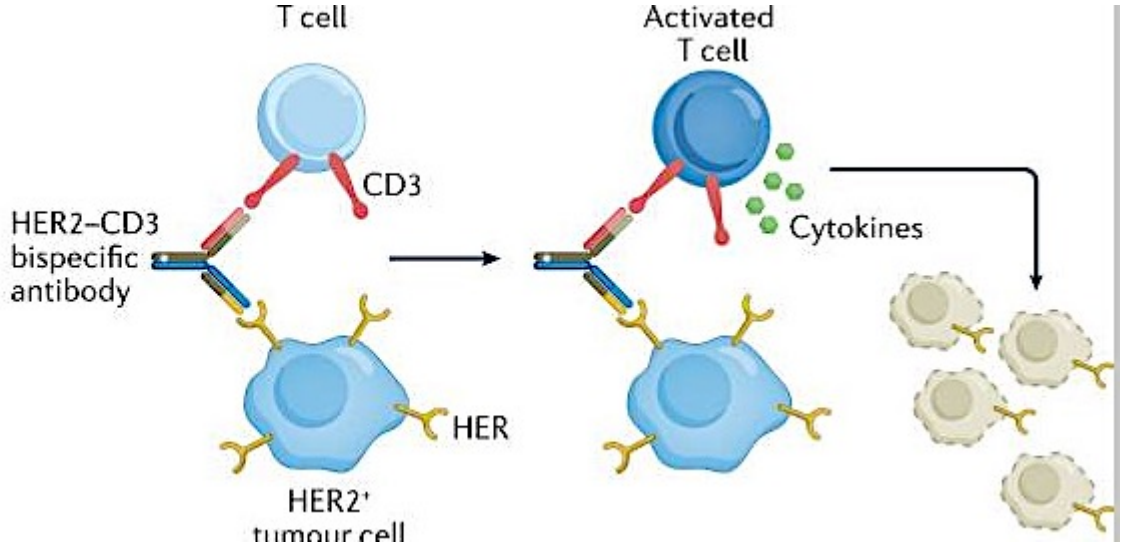
- **ILD/Pneumonitis** (25%)
  - **13%** Grade 3+
  - **6%** Grade 5 (1/3 patients with BTC)

Ohba et al. J Clin Oncol 2024

Zanidatamab: *HER2 bispecific antibody*

- **Simultaneously binds 2 distinct sites on HER2**, facilitating unique mechanisms of action:
  - Enhanced cross-linking and receptor clustering
  - Increased receptor internalization and downregulation
  - Inhibition of downstream signaling pathways
  - Activation of ADCC, ADCP, CDC





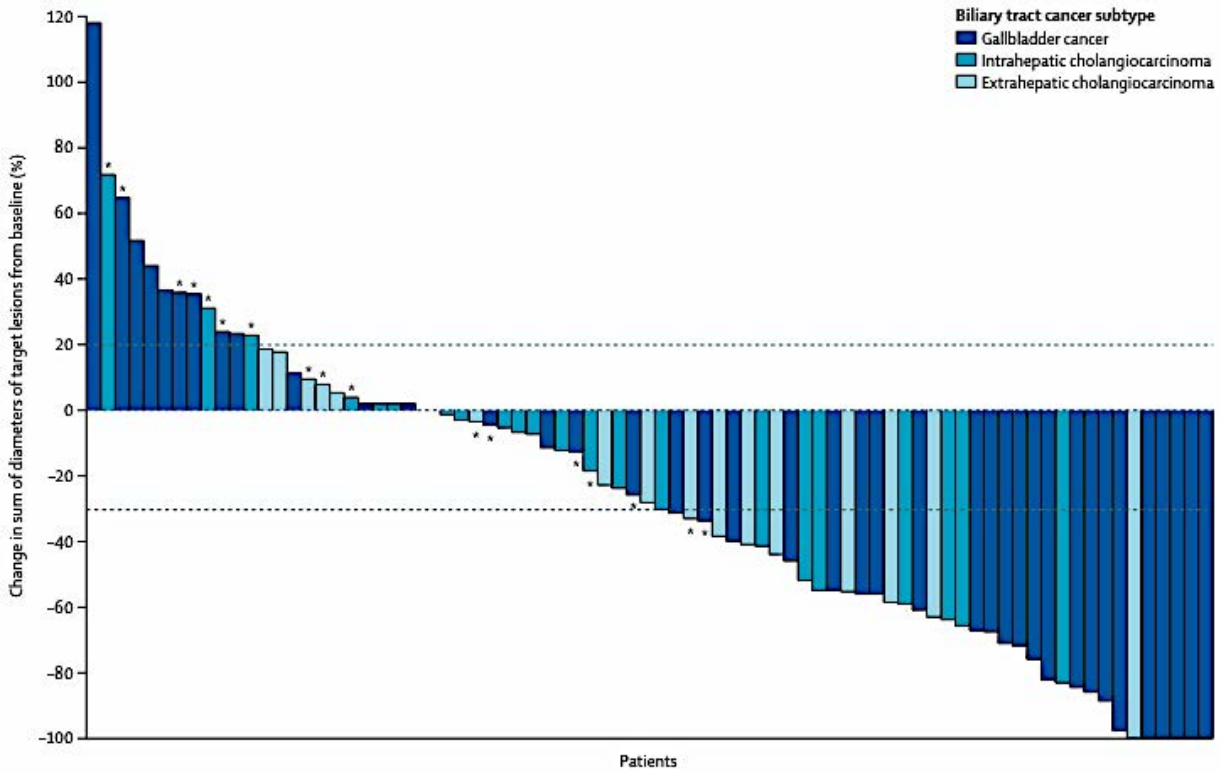
FDA approved for previously treated, unresectable or metastatic HER2 ***IHC 3+*** *BTC*

Swain et al. Nat Rev Drug Discov. 2022; Tabernero et al. Future Oncology 2022

HERIZON-BTC-01 trial of zanidatamab: *efficacy*

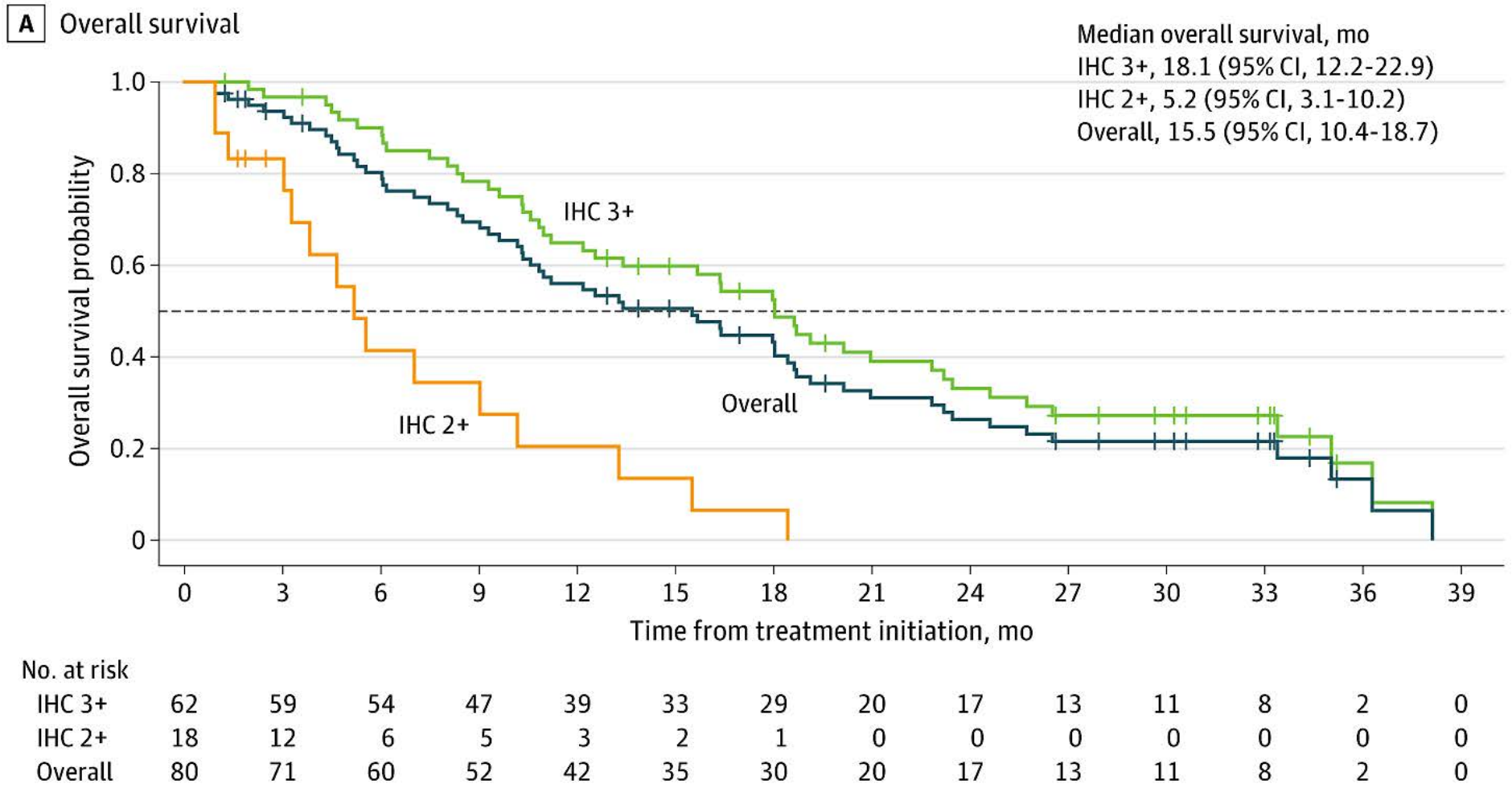
Design	# BTC Pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
Phase 2b *Global*	62 80 18	No	**IHC 3+** IHC 3+ or IHC 2+/ISH+ IHC 2+/ISH+	**52%** 41% 6%	**79%** 69% 33%	**14.9** 14.9 NE	**7.2** 5.5 1.7	**18.1** 15.5 5.2

- Previously treated unresectable, locally advanced, or metastatic BTC
- HER2 amplification confirmed by ISH per central testing
- **51%** GBC, **29%** iCCA, **20%** eCCA



Harding, Fan et al. Lancet Oncol 2023 | Pant et al. JAMA Oncol 2025

HERIZON-BTC-01 trial of zanidatamab: *long-term follow-up*

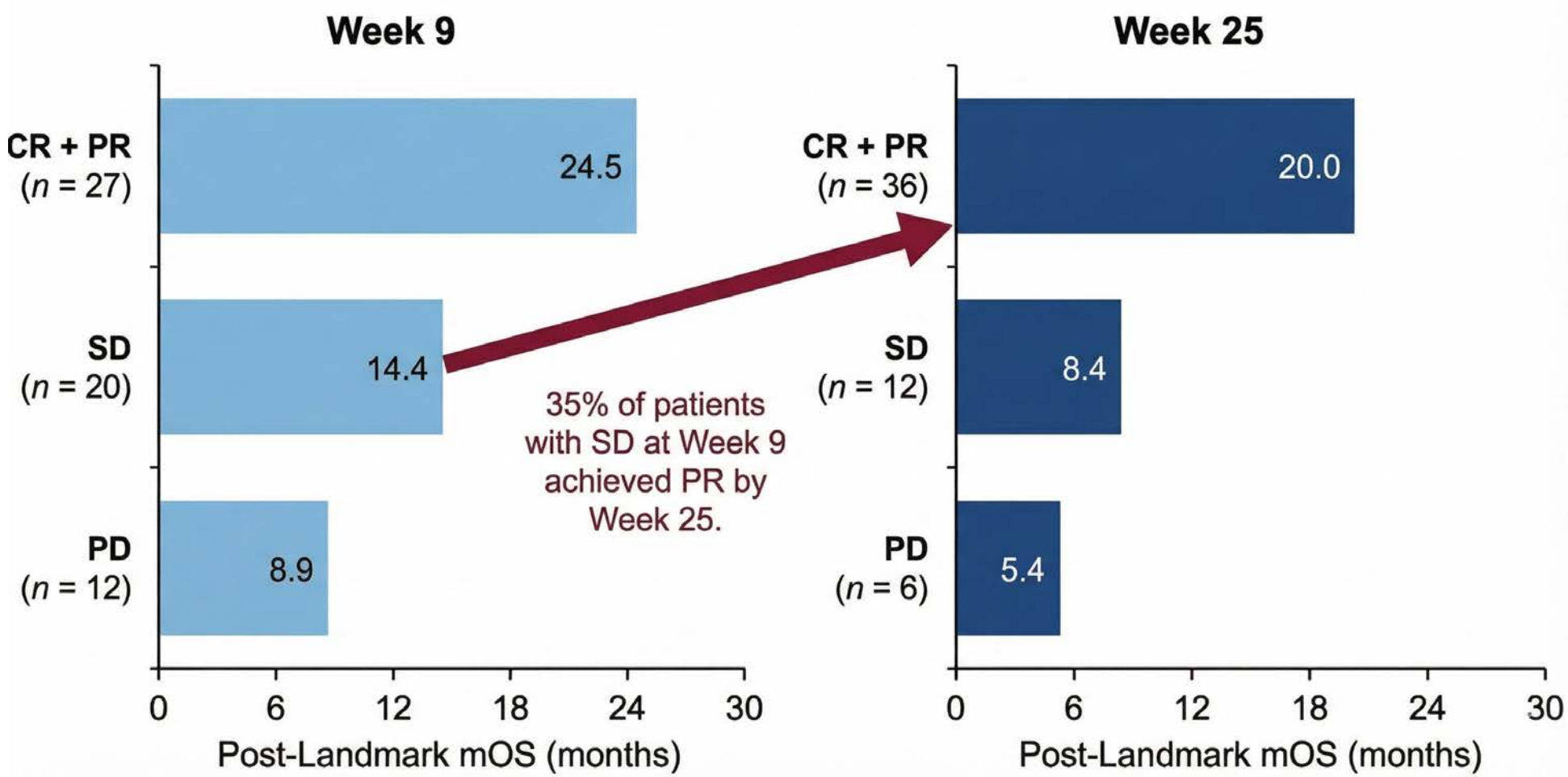


33-month follow-up

Pant et al. JAMA Oncol 2025

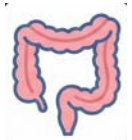
HERIZON-BTC-01 trial of zanidatamab: *post hoc analysis*

HER2 IHC 3+ patients (*n* = 62)



Harding et al. ASCO GI 2026, Abstr 545

HERIZON-BTC-01 trial of zanidatamab: *safety*



Diarrhea (50%) – *mostly grade 1-2*

- Supportive care with antidiarrheals and hydration
- Grade 1-2: resume at same dose or consider dose reduction
- Grade 3: hold until grade ≤1, then resume at reduced dose (15 mg/kg)

Infusion-related reactions (35%) – *mostly grade 1-2*

- Premedicate 30-60 min prior (acetaminophen, antihistamine, corticosteroid)
- Shorten infusion duration from 120-150 min to 60 min, if well-tolerated
- *Permanent discontinuation* (0.4%)

Left ventricular dysfunction (4%) → *resolved* (70%); *permanent discontinuation* (0.9%)

No cytokine release syndrome – *not a T-cell engager*

Harding, Fan et al. Lancet Oncol 2023; Zanidatamab package insert

Ongoing phase 3 studies of HER2 therapies for *treatment-naïve* HER2+ advanced BTC

	DESTINY-BTC-01 NCT06467357	**HERIZON-BTC-302** NCT06282575
Trial Design	Global, randomized phase 3 trial	Global, randomized phase 3 trial
Target # Pts	620	286
HER2 Status	IHC 3+ or IHC 2+	IHC 3+ or IHC 2+/ISH+
Treatments	**T-DXd + Rilvegostomig** (PD-1/TIGIT bispecific) vs **T-DXd** vs **Gem/Cis/Durva** (SOC)	**Gem/Cis +/- PD-(L)1 inhibitor + Zanidatamab** vs **Gem/Cis +/- PD-(L)1 inhibitor** (SOC)
Prior Tx		May have received ≤ 2 cycles of chemo +/- ICI
1º Endpoint	OS in IHC 3+ with T-DXd + Rilve vs SOC	PFS in IHC 3+
2º Endpoints	OS in IHC 3+/2+ T-DXd + Rilve vs SOC OS in IHC 3+ and 3+/2+ T-DXd vs SOC PFS in IHC 3+ and 3+/2+ T-DXd +/- Rilve vs SOC ORR, DOR Safety, tolerability	OS in IHC 3+ and overall population PFS in overall population ORR Adverse events PROs

Ikeda et al. ESMO 2024 | Harding et al. ASCO GI 2025

Take Home Messages

📌 HER2 amplification/overexpression occurs across all BTC subtypes **(~5-35%)**

📌 Early, comprehensive HER2 testing using **NGS and IHC** recommended for all patients with locally advanced or metastatic BTC, when feasible

📌 HER2-targeted treatments are rapidly advancing in BTC

- **T-DXd** and **Zanidatamab** are approved and effective for previously treated HER2 IHC 3+ BTC
- Consider first-line trials in HER2-driven BTC
- Therapy sequencing should be individualized, taking into account comorbidities, side effect profile, mechanism of action, prior treatments, etc.

Questions from General Medical Oncologists — Biliary Tract Cancers

78-year-old woman with HER2-amplified BTC s/p gemcitabine + cisplatin + pembrolizumab now with PD in the liver and rising TBili = 3.7, unstentable. Approach to HER2-positive disease in the setting of elevated TBili?

72 yo F with HER2-positive metastatic biliary cancer, history of CHF with EF 40%. Role of T-DXd or zanidatamab in patients with reduced EF? How to manage the toxicity of zanidatamab?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Biliary Tract Cancers

62 yo male with node-positive gallbladder cancer, HER2-positive. He was treated per BILCAP trial with capecitabine adjuvantly and a year later developed liver mets. He wants to be aggressive. Would you give trastuzumab deruxtecan or zanidatamab first line and skip cis/gem/durva since he has had "a previous chemotherapy"?

93 yr old female diagnosed with Stage IV gallbladder cancer with HER2 IHC 3+. Baseline ECOG 2 due to generalized frailty. Would you consider treating an elderly frail pt with anti-HER2 therapy in the front line, and if so, what would be your preferred treatment?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Biliary Tract Cancers

70 yo man with advanced BTC post 1st-line chemoimmunotherapy. Progressing now, HER2-positive and FGFR fusion. How to choose between anti-HER2 and anti-FGFR therapy? Is there a better sequence?

81 yo with CKD and metastatic cholangiocarcinoma, NGS noted IDH2 mutation, HER2 IHC 2+. Disease progressed on durva/carbo/gem. Would you target HER2 or IDH2 in the 2nd line?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Biliary Tract Cancers

61 yo male with HER2 IHC 3+ cholangiocarcinoma with h/o kidney transplantation 3 yrs prior. Would you plan to give anti-HER2 tx up front? In such a case, can I use either T-DXd or zanidatamab first to bypass using front-line gemicitabine + cisplatin chemo alone?

67 yo male with HER2 IHC 3+ cholangiocarcinoma treated with cis/gem/durva and developed Grade 2 pneumonitis on durva, which resolved quickly with steroids. Now has disease progression 11 months later. Would you give trastuzumab deruxtecan to this patient with previous pneumonitis, although completely and quickly resolved, on durva?

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Biliary Tract Cancers — Dr Ellis

Module 2: Gastroesophageal Cancers — Dr Wainberg

Module 3: Colorectal Cancer — Prof Van Cutsem

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HER 2+ Gastric/GEJ Cancers

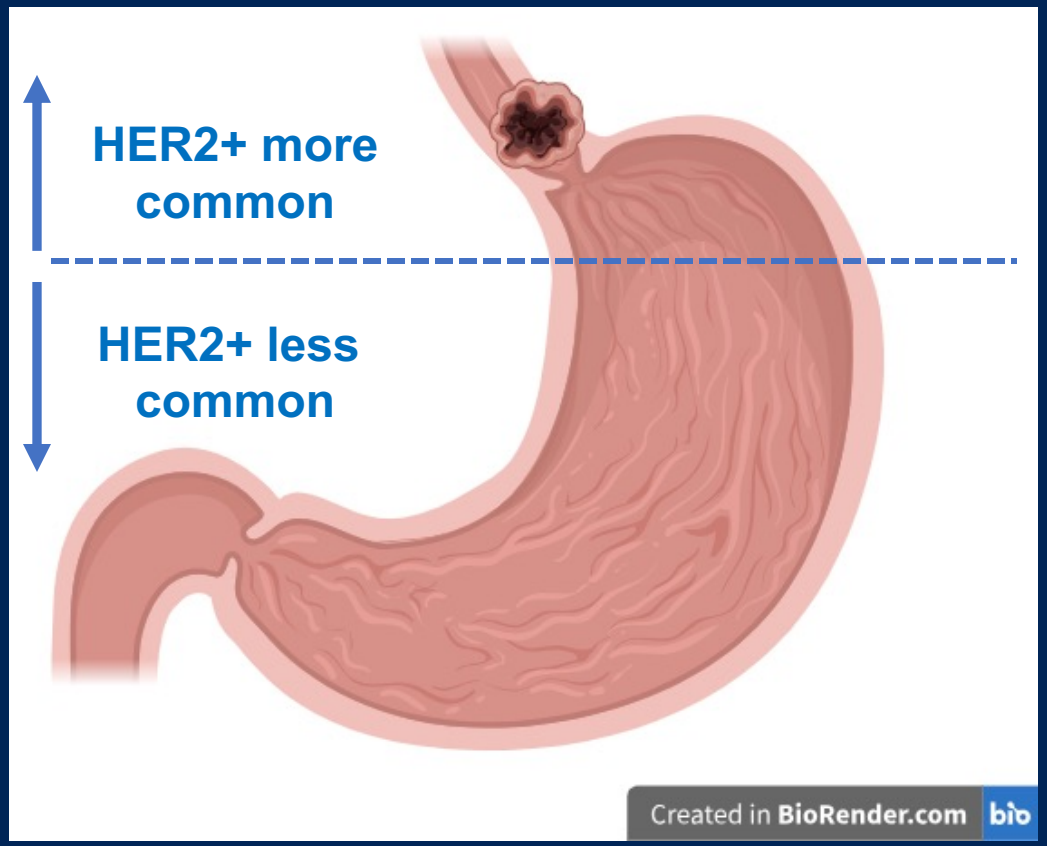
Zev Wainberg, MD

Co-Director, UCLA Gastrointestinal Oncology Program

Director, Early Phase Clinical Research Program, Jonsson Comprehensive Cancer Center

Professor of Medicine and Surgery, David Geffen School of Medicine at UCLA

HER2 biology in gastroesophageal adenocarcinoma



- ~15-20% of gastric/ GE adenocarcinoma
- Member of the HER family of receptors (HER1/EGFR, HER3, HER4)
- HER2 heterodimerization activates downstream RAS/MAPK and PI3K signaling pathways
- Intestinal type > diffuse type
- Typical anatomical location: GE jxn/ esophagus
- Associated with PDL1 co-expression and a favorable tumor immune microenvironment

Koopman et al., J Cancer Research and Clin Oncol 2021;39(Suppl 15):4045.
Yang et al., Lancet 2024;404(10466):1991-2005.
Bartley et al., J Clin Oncol 2017;35(4):446-464.

HER2 testing: IHC +/- FISH is the gold standard, but there are other options

Diagnostic test	Diagnostic Criteria for Positive Result	Advantages	Disadvantages
IHC +/- FISH*	• IHC 3+ OR • IHC 2+ and FISH+	• **GOLD STANDARD** • Cost effective • Rapid	• Requires tissue • Intra- and inter-lesional heterogeneity
Tissue NGS	• copy number ≥5 with >80% of exons amplified • ≥2.5-fold change in copy number	• High concordance with IHC/FISH • Multiple targets tested simultaneously	• Cost • Longer turn around time
Blood NGS	• "Amplification" • Variable copy number cutoffs	• Speed • Convenience • Detects intra-and inter-lesional heterogeneity	• Cost • Requires high shedding • Lower sensitivity

* Immunohistochemistry (IHC) score of 3+ (showing strong complete or basolateral membranous staining in > 10% of the tumor cells [surgical specimen] or in a tumor cell cluster [≥ 5 cells] irrespective of percentage of tumor cells stained [biopsy]) or IHC score of 2+ (moderate/weak complete basolateral or lateral membranous reactivity in > 10% of the neoplastic cells [surgical specimen] or in a tumor cluster [≥ 5 tumor cells {biopsy}]). Gene amplification by *in situ* hybridization (ISH+) (chromosome enumeration probe [CEP] 17 ratio ≥ 2 or average HER2 copy number ≥6 signals/cell.

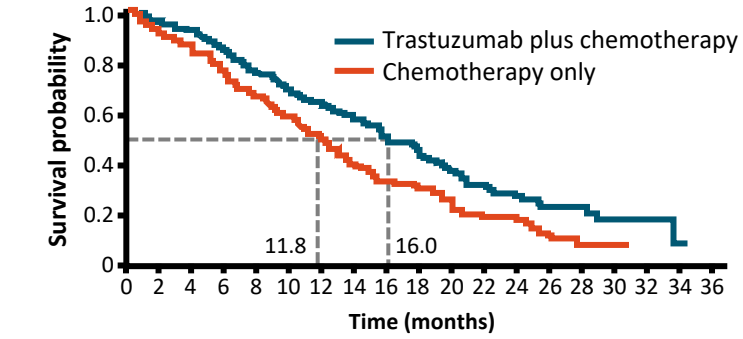
Klempner et al., J Clin Oncol 2021;39(Suppl 15):4045.
Ross et al., J Mol Diagnostics 2017;19(2):244-254.
Bartley et al., J Clin Oncol 2017;35(4):446-464.

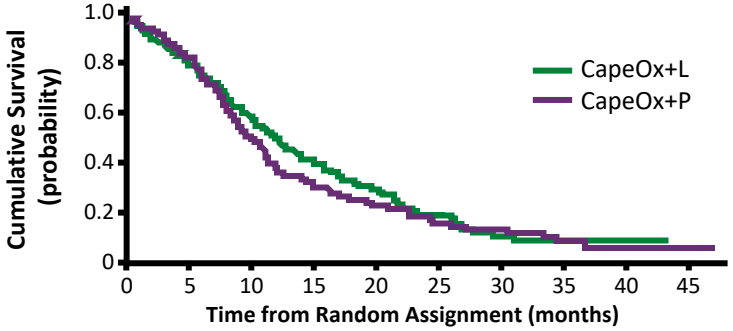
HER2-Targeting Agents as First-Line Treatment: Esophagogastric Cancer is Not Breast Cancer

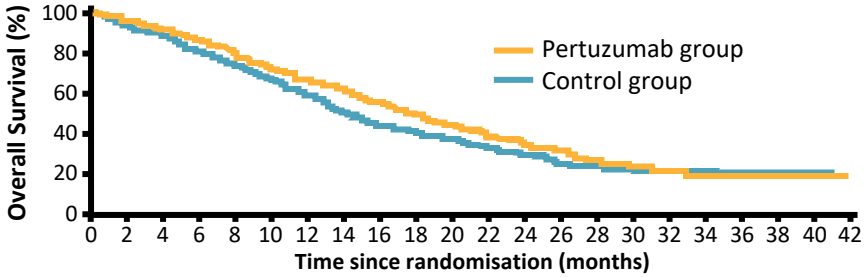
- **Trastuzumab approved first line**
  - ToGA: Cape-Cis + trastuzumab improved RR, PFS, OS
  - mOS in IHC2+/FISH or IHC3+ for trastuzumab + CT vs CT: 16.0 vs 11.8; HR (95% CI): 0.65 (0.51-0.83)

- **First-line lapatinib + cape/oxaliplatin**
  - No difference in OS
  - mOs for lapatinib + cape/oxaliplatin vs cape/oxaliplatin: 12.2 vs 10.5 (HR: 0.91: 0.73-1.12; *P* = .3492)

- **First-line pertuzumab + trastuzumab/Cis+ FU**
  - No difference in OS
  - mOS for pertuzumab vs control: 17.5 vs 14.2 mos (HR (95% CI): 0.84 (0.71-1.00), *P* = .057)







Bang. Lancet. 2010;376: 687. Hecht. JCO. 2016;34:443. Tabernero. Lancet Oncol. 2018;19: 1372.

KEYNOTE-811: Final OS Analysis

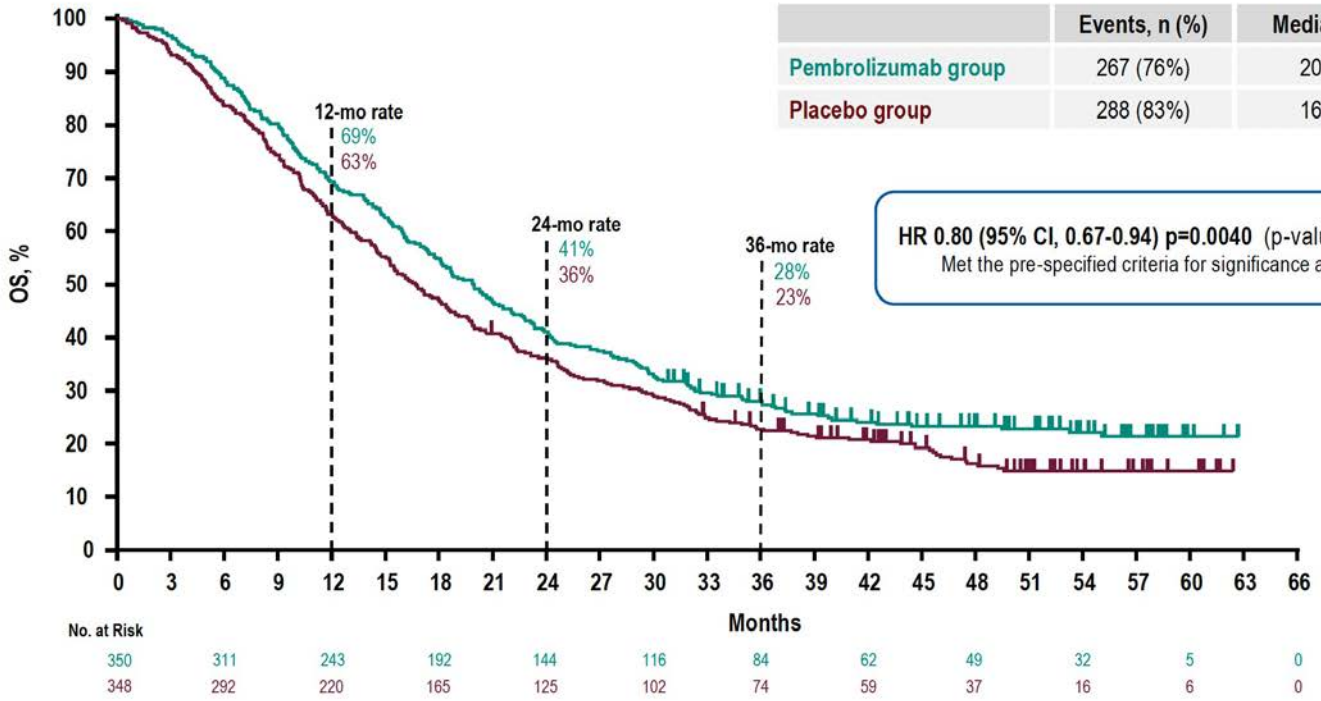
Key Eligibility Criteria
- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a] (Pembrolizumab Group)

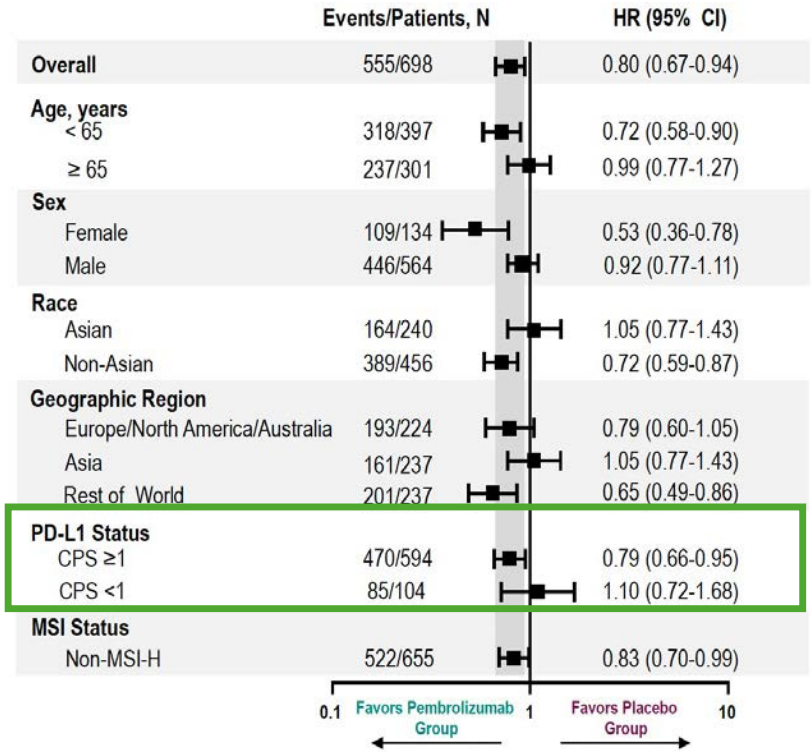
Placebo IV Q3W + Trastuzumab and FP or CAPOX[a] (Placebo Group)

Treated until unacceptable toxicity, progression, or withdrawal, or a maximum of 35 cycles



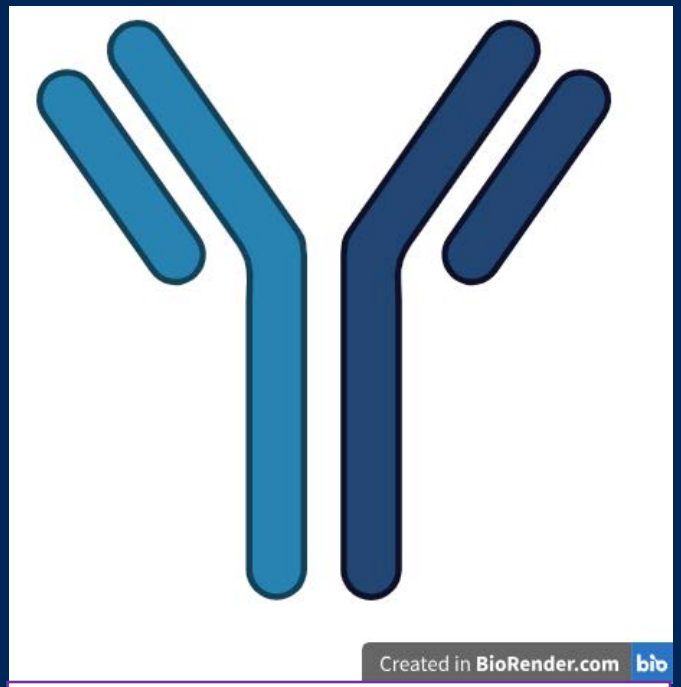
	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	267 (76%)	20.0 (17.8-22.1)
Placebo group	288 (83%)	16.8 (14.9-18.7)

HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis



Janjigian YY et al. ESMO 2024;Abstract 1400O.

Emerging 1L option for HER2+ GEA: Zanidatamab



- HER2-targeted, humanized, bispecific monoclonal antibody
- Binds to the HER2 juxtamembrane domain (ECD4) and dimerization domain (ECD2)
- FDA-approved for HER2+ BTC (IHC=3+, previously treated)

Study design

- Phase 2, multi-center, open-label, two-part study
- Enrolled patients with previous untreated metastatic/ advanced HER2+ GEA (HER2 IHC 3+ or 2+/FISH+)
- Treatment with zanidatamab + chemotherapy (CAPOX, mFOLFOX6, or 5FU/cis)

Key outcomes

- ORR= 76%, median DOR= 18.7 months (N= 42)
- Median PFS= 12.5 months (N=46)
- Median OS= 36.5 months

Toxicity management

- 24/25 patients (96%) experienced diarrhea
- Protocol amendment: Mandatory anti-diarrheal prophylaxis and omission of 5FU bolus (part 2)
- Post-implementation ORR= 95%

Elimova et al., Lancet Oncol 2025; 26: 847-859.

HERIZON
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HERIZON-GEA-01 Study Design

Global phase 3 trial of zanidatamab + chemotherapy ± tislelizumab vs trastuzumab + chemotherapy in previously untreated patients with HER2+ mGEA

Key Eligibility Criteria

- Age ≥18 years
- Unresectable, locally advanced, recurrent or metastatic GEA
- HER2 IHC 3+ or IHC 2+/ISH+ per central testing
- ECOG PS 0 or 1
- No prior treatment for locally advanced or metastatic disease
- No prior HER2-targeted agents or immunotherapy in any setting

Stratification Factors

- Geographic region
- HER2 status
- ECOG PS

R 1:1:1

Arm A: Trastuzumab + chemotherapy[a]

Arm B: Zanidatamab
1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W
+ chemotherapy[a]

Arm C: Zanidatamab
1800 mg (<70 kg)/2400 mg (≥70 kg) IV Q3W
+ tislelizumab[b] + chemotherapy[a]

Prophylaxis to prevent IRR and diarrhea was mandatory in the zanidatamab-containing arms

CT/MRI[c] Q6W

Dual Primary Endpoints

- PFS (per BICR)
- OS

Select Secondary Endpoints

- cORR (per BICR)
- Frequency and severity of AEs

ClinicalTrials.gov: NCT05152147

Treatment until disease progression/death/unacceptable toxicity
Chemotherapy could be discontinued after 6 cycles

[a]Physician's choice of capecitabine plus oxaliplatin or 5-fluorouracil plus cisplatin. Chemotherapy was administered for at least 6 cycles or until disease progression, unacceptable toxicity, or another criterion for treatment discontinuation was met.
[b]Tislelizumab 200 mg was administered IV Q3W. [c]CT/MRI scans were performed every 6 weeks for the first 54 weeks, then every 9 weeks.
AE, adverse event; BICR, blinded independent central review; cORR, confirmed objective response rate; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; GEA, gastroesophageal adenocarcinoma; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRR, infusion-related reaction; ISH, in situ hybridization; IV, intravenously; mGEA, advanced or metastatic GEA; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomization.

Patient Disposition

A total of 914 patients were randomized, and median follow-up was >2 years

Randomized
N = 914

Zanidatamab + CT	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
n = 304; 300 patients treated[a]	n = 302; 299 patients treated[a]	n = 308; 302 patients treated
Ongoing treatment, n = 69 (23%)	**Ongoing treatment**, n = 88 (29%)	**Ongoing treatment**, n = 37 (12%)
Discontinued treatment, n = 231 (76%)	**Discontinued treatment**, n = 211 (70%)	**Discontinued treatment**, n = 265 (86%)
• Progressive disease, n = 132	• Progressive disease, n = 117	• Progressive disease, n = 200
• Adverse event, n = 25	• Adverse event, n = 27	• Adverse event, n = 10
• Death, n = 27	• Death, n = 26	• Death, n = 17
• Withdrawal by patient, n = 23	• Withdrawal by patient, n = 26	• Withdrawal by patient, n = 20
• Physician decision, n = 19	• Physician decision, n = 13	• Physician decision, n = 13
• Other, n = 5[b]	• Other, n = 2[b]	• Other, n = 5[b]
Survival follow-up, n = 69 (23%)	**Survival follow-up**, n = 58 (19%)	**Survival follow-up**, n = 81 (26%)
Median (range) follow-up 26.0 (7.6–46.0) months	**Median (range) follow-up** 25.9 (7.9–45.5) months	**Median (range) follow-up** 25.8 (7.5–45.6) months

[a]Treated includes all randomized patients who received any amount of any study treatment and does not necessarily reflect the safety analysis set. Five patients assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab and are included in the safety analysis set for the zanidatamab-chemotherapy arm. [b]Includes protocol violations and "other" reasons.
CT, chemotherapy.

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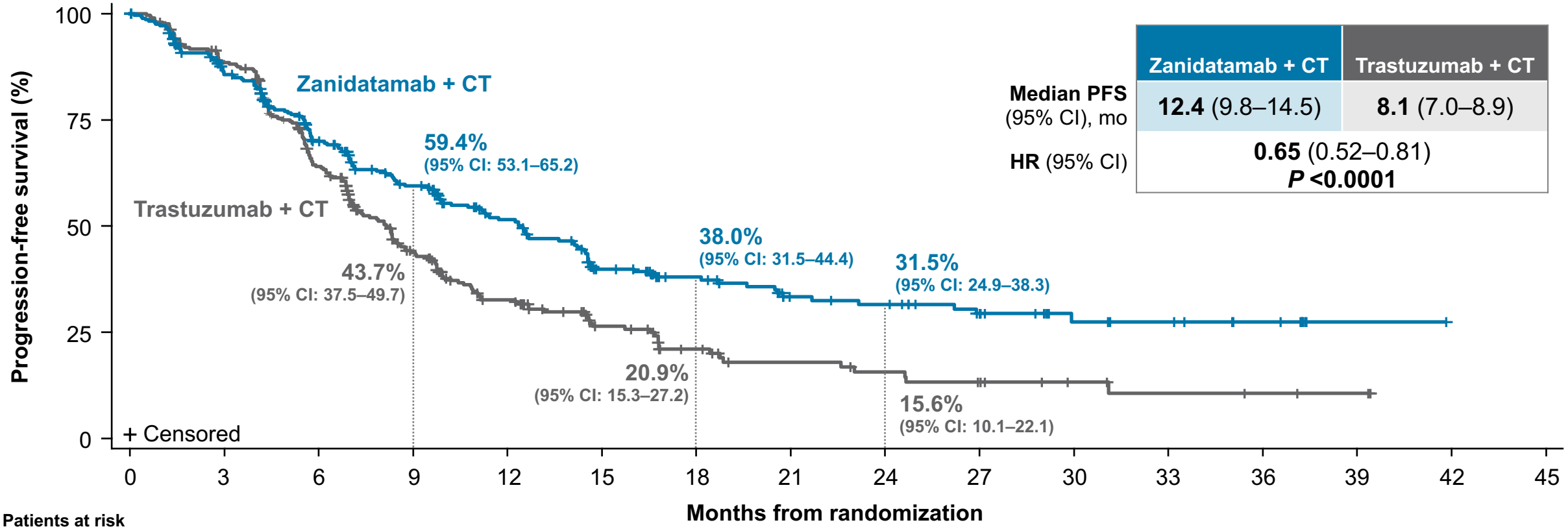
Primary Endpoint: PFS per BICR

Statistically significant and clinically meaningful improvement in PFS with zanidatamab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



	Zanidatamab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–14.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.65** (0.52–0.81) ***P* <0.0001**	

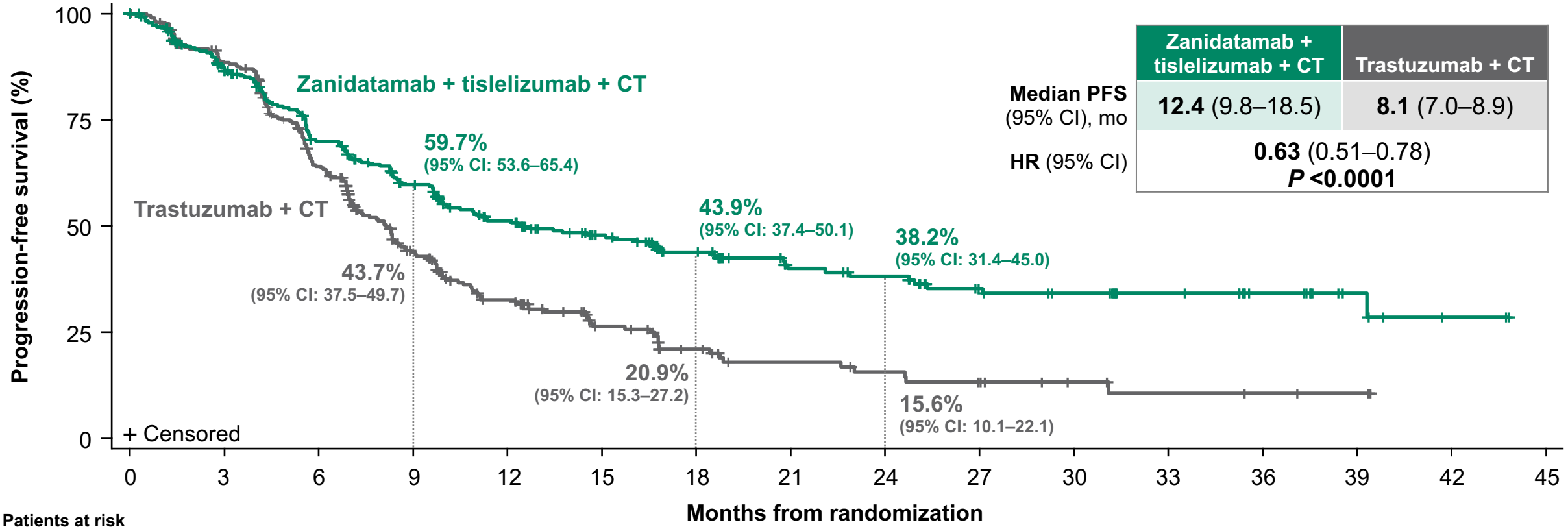
Patients at risk

Zani + CT	304	231	175	137	105	70	53	37	34	26	14	12	8	1	0	
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: PFS per BICR

Statistically significant and clinically meaningful improvement in PFS with zanidatamab + tislelizumab + CT vs trastuzumab + CT (>4-month prolongation in median PFS)



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median PFS (95% CI), mo	**12.4** (9.8–18.5)	**8.1** (7.0–8.9)
HR (95% CI)	**0.63** (0.51–0.78) ***P* <0.0001**	

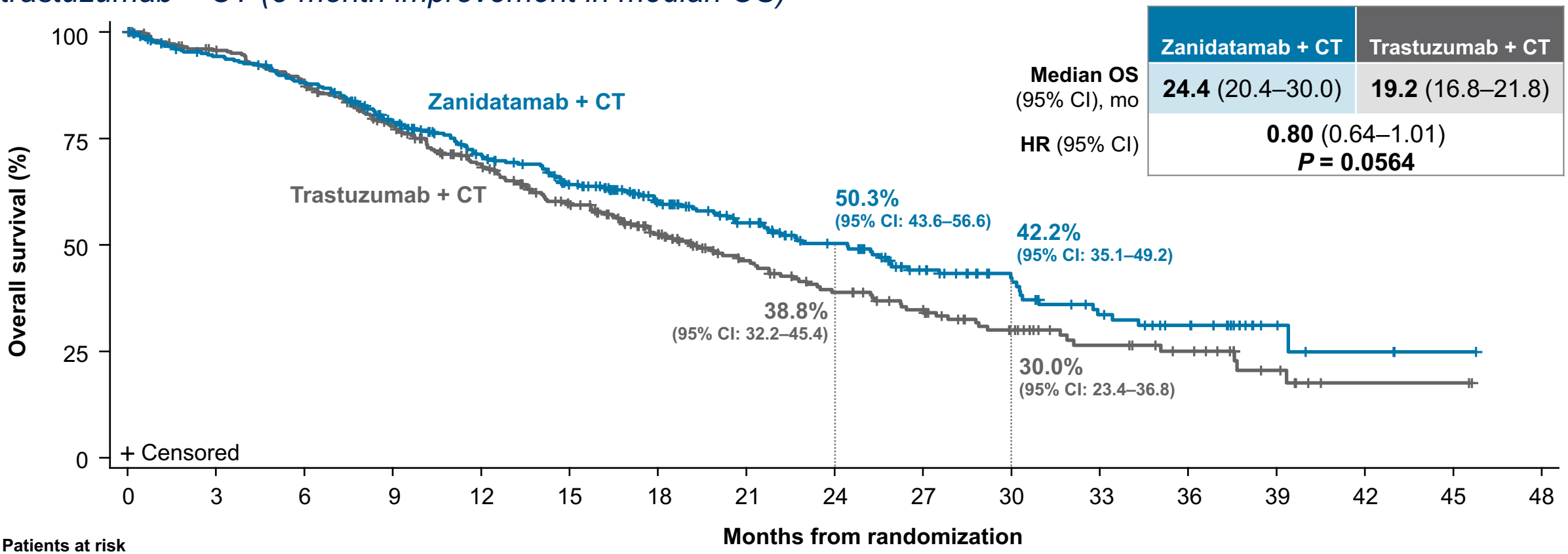
Patients at risk

Zani + TIS + CT	302	240	183	147	113	90	65	46	42	30	27	20	13	6	2	0
Tras + CT	308	247	168	97	63	37	23	16	13	10	6	4	3	2	0	

BICR, blinded independent central review; CT, chemotherapy; HR, hazard ratio; PFS, progression-free survival; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: Overall Survival

At this interim analysis, there was a strong trend toward significance for OS favoring zanidatamab + CT vs trastuzumab + CT (5-month improvement in median OS)



	Zanidatamab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**24.4** (20.4–30.0)	**19.2** (16.8–21.8)
HR (95% CI)	**0.80** (0.64–1.01)	
	***P* = 0.0564**	

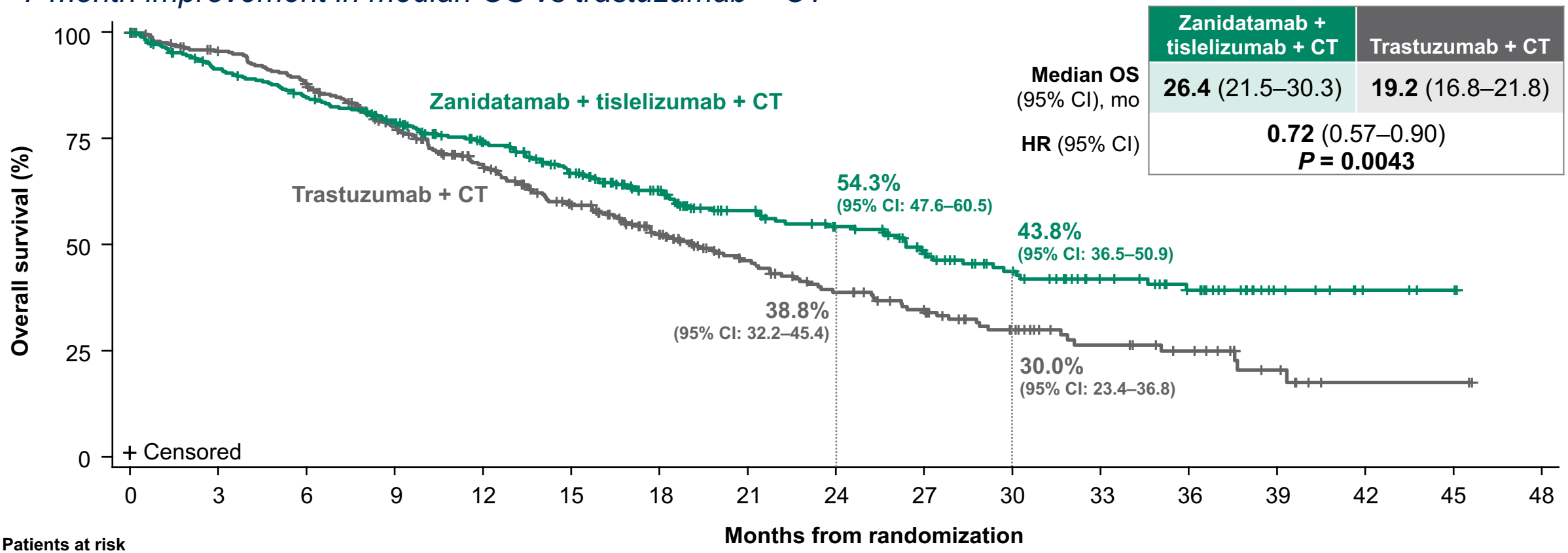
Patients at risk

Zani + CT	304	277	257	222	187	156	121	98	78	56	41	28	21	6	3	1	0
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; Tras, trastuzumab; Zani, zanidatamab.

Primary Endpoint: Overall Survival

Zanidatamab + tislelizumab + CT demonstrated a statistically significant and clinically meaningful OS benefit with a >7-month improvement in median OS vs trastuzumab + CT



	Zanidatamab + tislelizumab + CT	Trastuzumab + CT
Median OS (95% CI), mo	**26.4** (21.5–30.3)	**19.2** (16.8–21.8)
HR (95% CI)	**0.72** (0.57–0.90)	
	***P* = 0.0043**	

Patients at risk

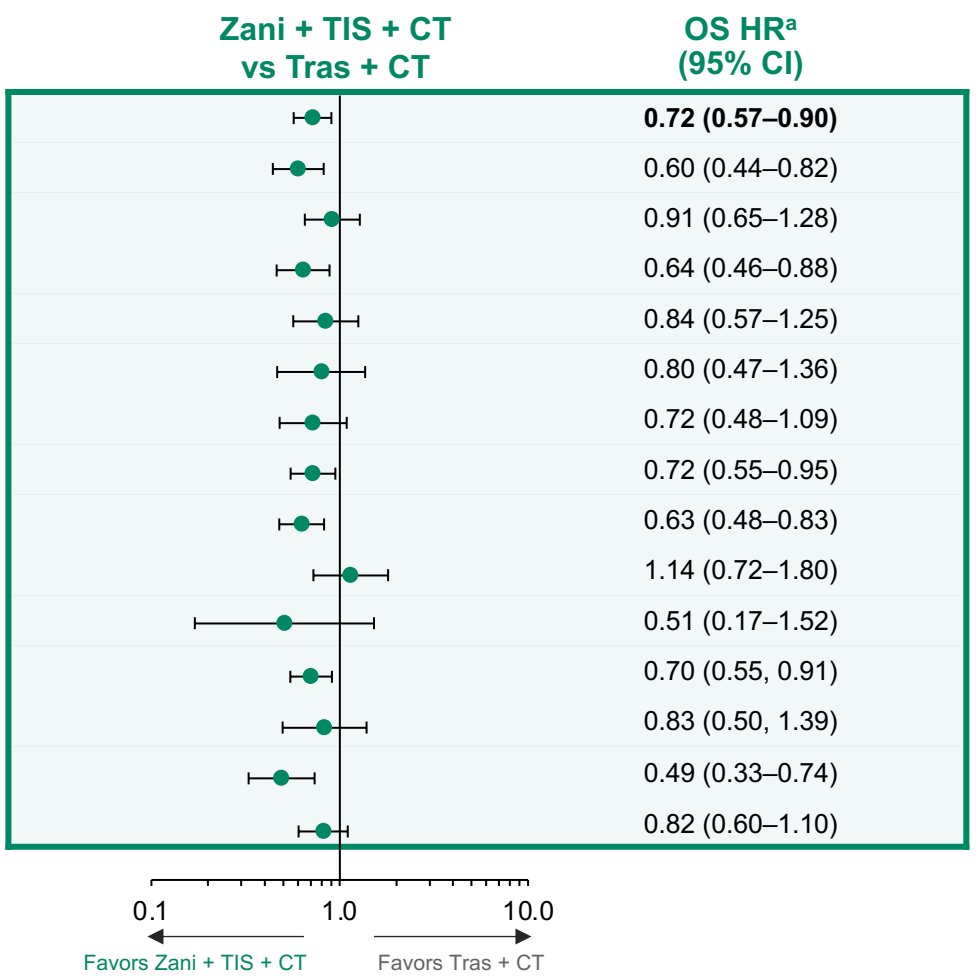
Zani + TIS + CT	302	267	246	222	190	157	125	96	82	64	49	36	27	10	4	2	0
Tras + CT	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0

CT, chemotherapy; HR, hazard ratio; OS, overall survival; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

OS in Key Prespecified Subgroups

Improvements in OS occurred across major prespecified subgroups, including regions and PD-L1 TAP scores

Subgroup	Category	Events/patients: Zanidatamab + tislelizumab + CT	Events/patients: Trastuzumab + CT
All patients		**134/302**	**170/308**
Age, years	<65	68/163	99/162
	≥65	66/139	71/146
Geographic region	Asia	63/159	89/165
	EU/NA	46/95	52/93
	ROW	25/48	29/50
ECOG PS	0	41/121	52/120
	1	92/180	118/188
Anatomical subtype	Gastric	87/208	127/226
	GEJ	42/74	33/60
	Esophageal	5/20	10/22
HER2 status	IHC 3+	106/251	138/255
	IHC 2+/ISH+	28/51	31/52
PD-L1 status	TAP <1%	38/90	65/98
	TAP ≥1%	79/187	92/188



[a]The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer treatment effects.
CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; NA, North America; OS, overall survival; PD-L1, programmed death-ligand 1; ROW, rest of world; TAP, tumor area positivity; TIS, tislelizumab; Tras, trastuzumab; Zani, zanidatamab.

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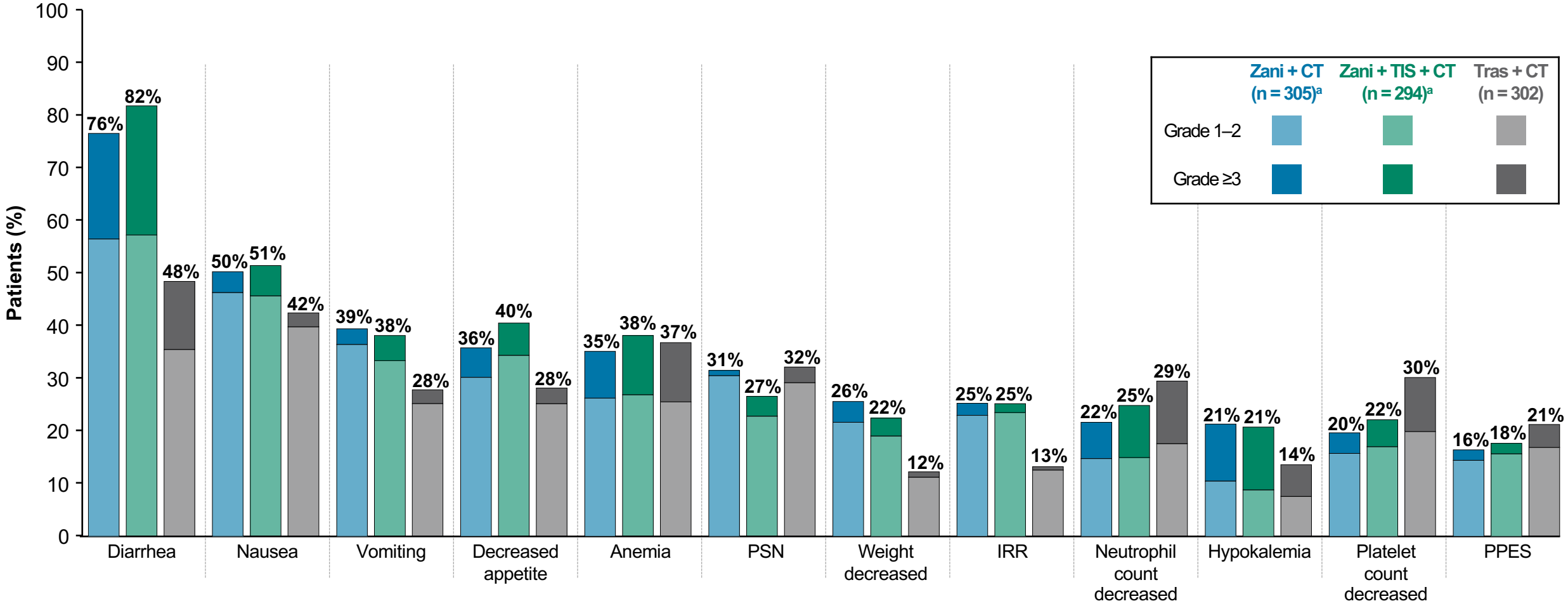
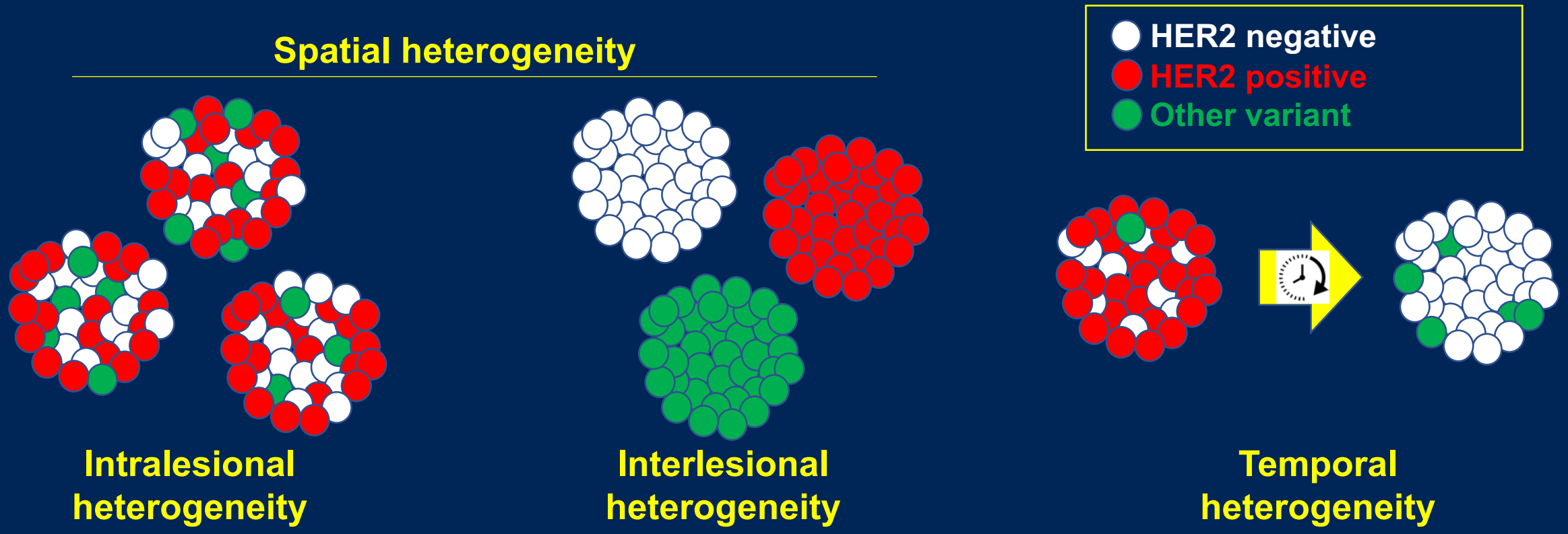
Common TRAEs (≥20% of Patients in Any Arm)

Diarrhea was the most common TRAE in all treatment arms



[a]Five patients who were assigned to the zanidatamab-tislelizumab-chemotherapy arm did not receive tislelizumab. Data from these patients are summarized in the zanidatamab-chemotherapy arm.
CT, chemotherapy; IRR, infusion-related reaction; PPES, palmar-plantar erythrodysesthesia syndrome; PSN, peripheral sensory neuropathy; TIS, tislelizumab; TRAE, treatment-related adverse event; Tras, trastuzumab; Zani, zanidatamab.

Heterogeneity may drive loss of HER2 expression

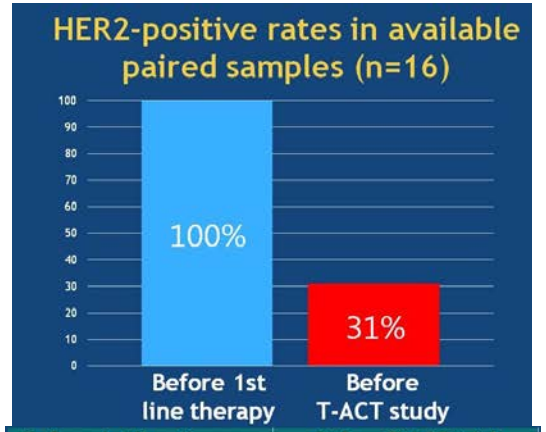


- Heterogeneous protein expression found in ~30% of HER2+ GEA cases
- Loss of HER2 expression reported in ~30-70% of cases post-progression on trastuzumab-based therapy

Bang et al., Gastric Cancer 2022; 25(4): 794-803.
Cammarota et al., Drugs 2025; 85:361-383.

“Loss” of HER2 Expression After Trastuzumab

T-ACT Trial



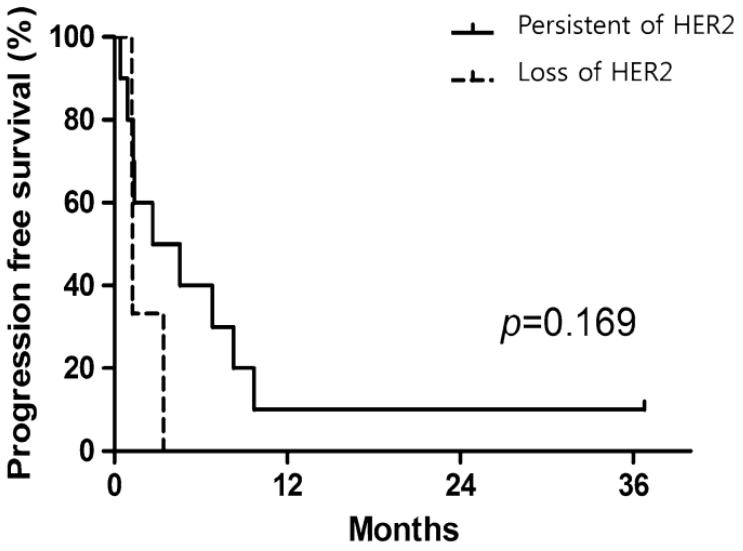
Before 1st line therapy			Before T-ACT trial		
HER2 status	IHC	FISH	HER2 status	IHC	FISH
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	2	+
+	3	-	+	2	+
+	3	-	-	1	+
+	3	-	-	1	-
+	3	-	-	1	+
+	3	-	-	1	-
+	2	+	-	1	+
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	2	+	-	0	-
+	2	+	-	0	-

HER2 positivity defined as IHC3+ or IHC2+ with FISH positive

GASTHER3

14/43 patients with loss of HER2 expression after trastuzumab

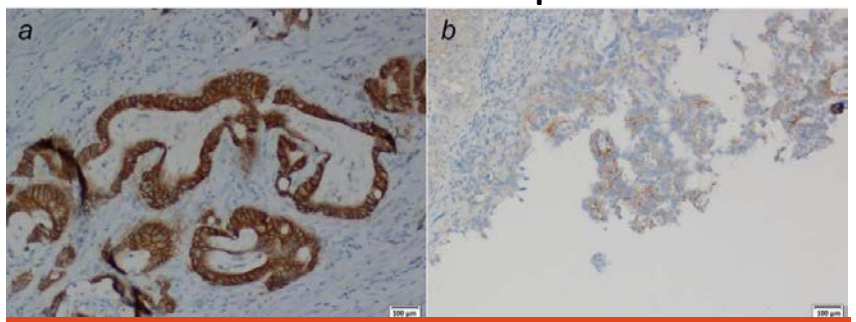
Impact of HER2 status on PFS



HER2 Expression Post Trastuzumab

Baseline

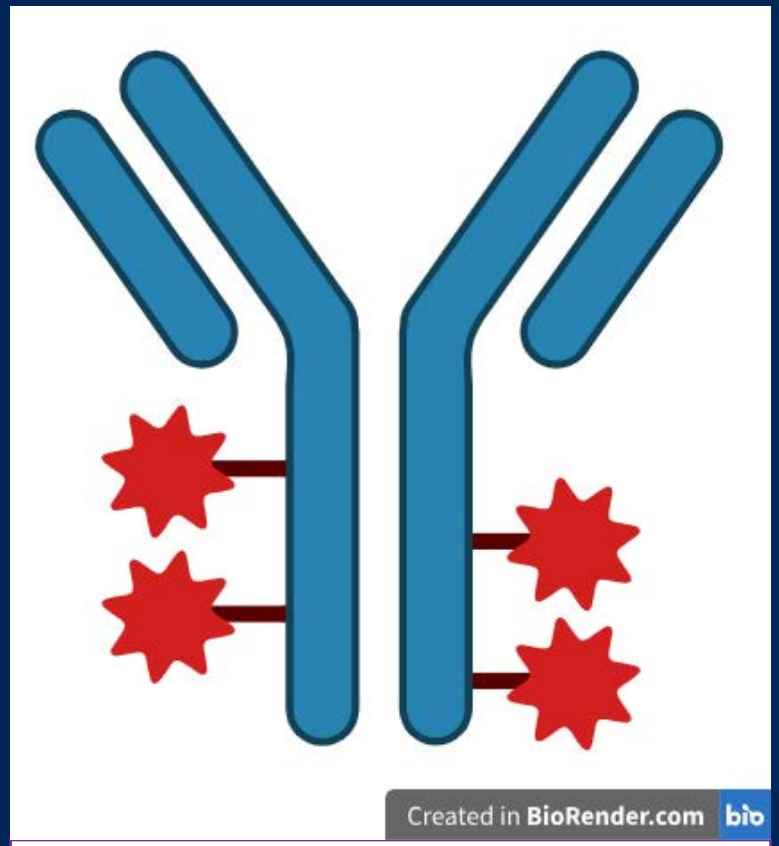
Post trastuzumab + cisplatin + 5FU



Tumor HER2 Status, %	Pretreatment (N = 22)	Post-treatment (N = 22)
Positive	100	59
Negative	-	27
Not assessable	-	14
Overexpressed	100	68
Loss of expression	-	32

Makiyama. ASCO 2018. Abstr 4011. Seo. Gastric Cancer. 2019;22:527. Pietrantonio. Int J of Cancer. 2016; 139: 2859.

Trastuzumab deruxtecan (T-DXd): Know your DESTINY



- Composed of an anti-HER2 mAb, cleavable linker, and a topo I inhibitor payload
- High DAR (8:1)
- Significant bystander effect

	Phase	Line	Regimen	Key Outcomes
DESTINY-Gastric01 (HER2+)	2	≥3L	**T-DXd** vs Investigator's choice Conducted in Japan and South Korea	**ORR**: 51% vs 14% p<0.001 **PFS**: 5.6 vs 3.5 mo HR= 0.47; 95% CI, 0.31–0.71 **OS**: 12.5 vs 8.4 mo HR= 0.59; 95% CI, 0.39–0.88
DESTINY-Gastric02	2	≥2L	**T-DXd** Conducted in US and EU	**ORR= 42%** 95% CI 30.8–53.4 **PFS:** 5.6 mo 95% CI 4.2–8.3 **OS:** 12.1 mo 95% CI 9·4–15·4

Shitara et al., NEJM 2020; 382: 2419-2430.
Van Cutsem et al., Lancet Oncol 2023; 24(7):744-756.

Blood-based biomarkers predict benefit from T-DXd

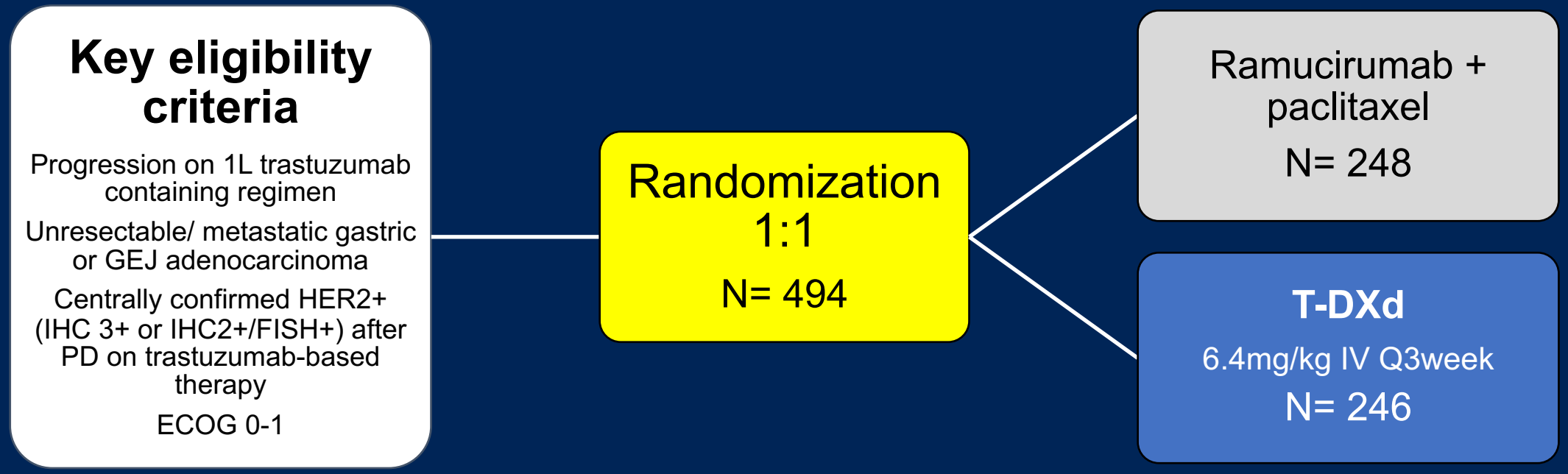
Exploratory biomarker analysis of the randomized, phase 2 DESTINY-Gastric01 trial

	Subgroup	N	ORR, % (95% CI)
Plasma HER2 amplification	No amplification	38	34.2 (19.6–51.4)
	Amplification	71	60.6 (48.3–72.0)
Plasma HER2 copy number	Low/ below median	53	39.6 (26.5–54.0)
	High/ above median	56	62.5 (48.5–75.1)
HER2 apCN	Low or no amp. (<median)	52	30.8 (18.7–45.1)
	High (≥median)	57	70.2 (56.8–81.6)
Serum HER2 ECD	Low (<median)	56	42.9 (29.7–56.8)
	High (≥median)	62	59.7 (46.4–71.9)

Shitara et al., Nature Medicine (2024) 30:1933-1942.

DESTINY-Gastric04: 2L T-DXd versus ramucirumab + paclitaxel

Phase 3, randomized, open-label, global multicenter study for 2L treatment of unresectable/ metastatic HER2+ GEA

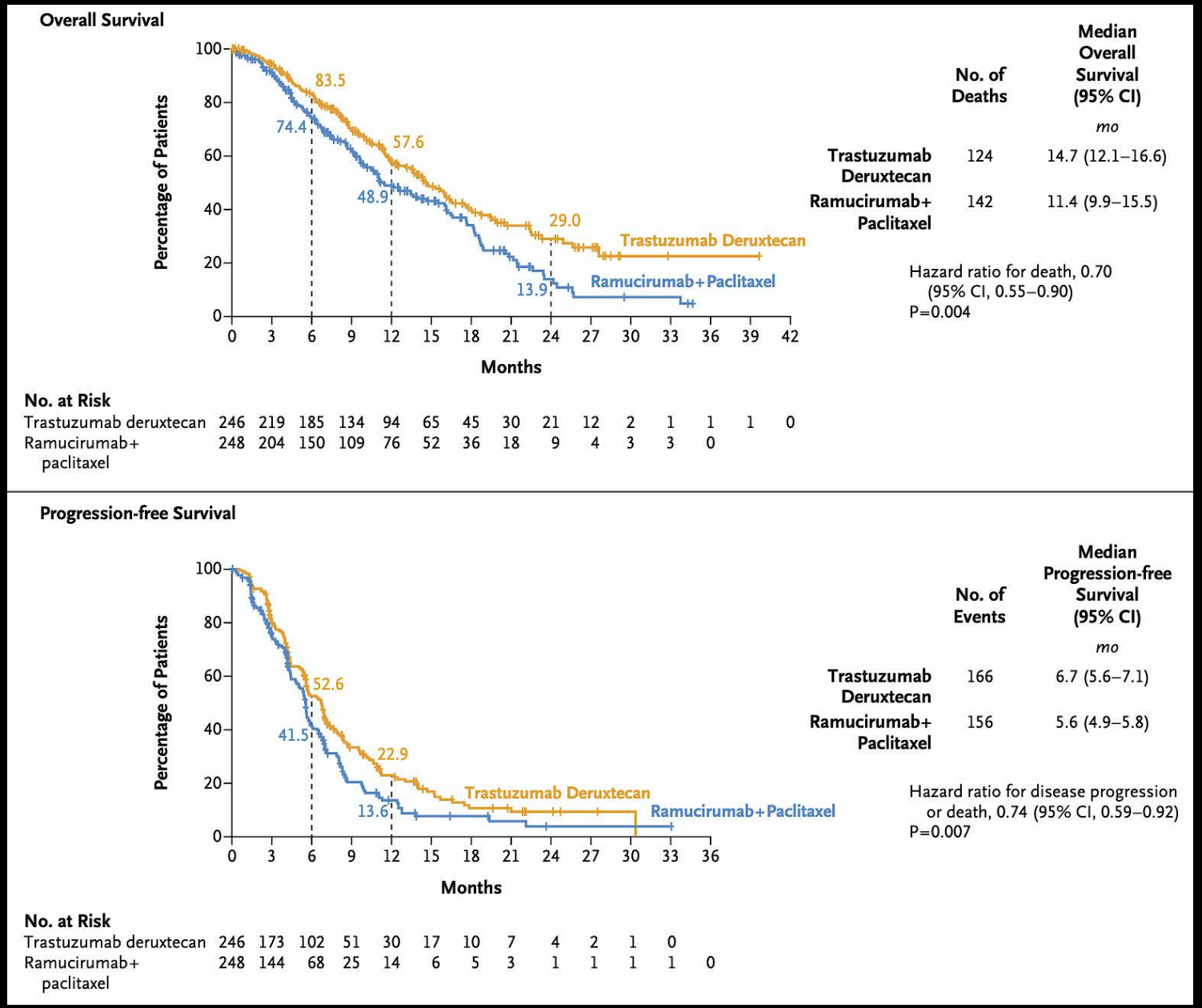


Stratification factors: HER2 status (IHC3+ vs IHC2+/FISH+), region (Asia vs EU vs China vs ROW), 1L TTP (< 6 mo vs >6mo)

Primary endpoint: Overall survival
Secondary endpoints: PFS, ORR, DOR, DCR

Shitara et al., N Engl J Med 2025;393:336-48..

Overall Survival and Progression-free Survival



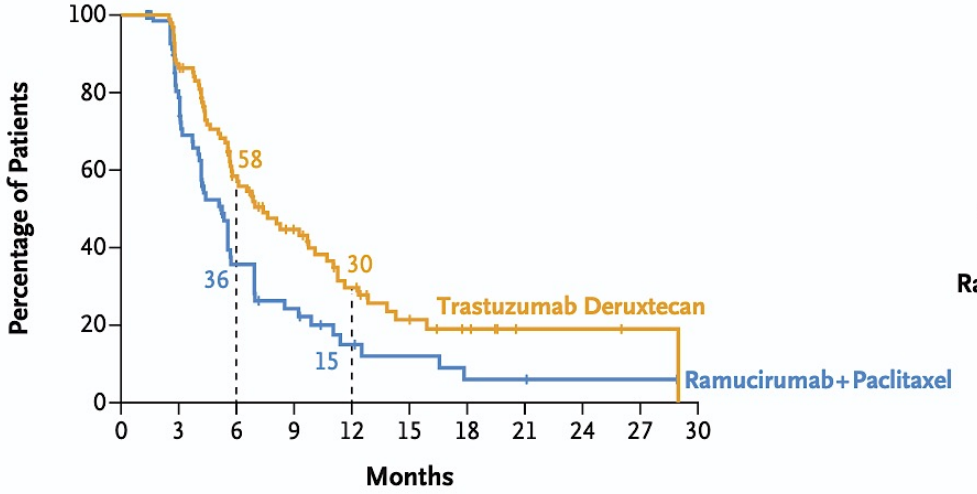
	T-DXd	Ram + paclitaxel	HR
OS, months (95% CI)	**14.7 (12.1-16.6)**	**11.4 (9.9-15.5)**	**0.70 (0.55-0.9) P= 0.004**
PFS, months (95% CI)	6.7 (5.6-7.1)	5.6 (4.9-6.8)	0.74 (0.59-0.92) P= 0.007

Shitara K et al. N Engl J Med 2025;393:336-348.

The NEW ENGLAND JOURNAL of MEDICINE

Duration of Response

C Duration of Response



	No. of Events	Median Duration of Response (95% CI)
		mo
Trastuzumab Deruxtecan	62	7.4 (5.7–10.1)
Ramucirumab+ Paclitaxel	52	5.3 (4.1–5.7)

No. at Risk

Trastuzumab deruxtecan	104	81	45	29	17	10	6	2	2	1	0
Ramucirumab+ paclitaxel	69	50	19	12	6	4	2	2	1	1	0

	T-DXd	Ram + paclitaxel
ORR (95% CI)	44.3% (37.8-50.9)	29.1% (23.4-35.3)

Shitara K et al. N Engl J Med 2025;393:336-348.

The NEW ENGLAND JOURNAL of MEDICINE

What is the Right Dose?

Safety

	T-DXd	Ramucirumab + paclitaxel
TRAEs	93.0%	91.4%
Treatment related SAEs	18.4%	17.6%
Grade ≥ 3 TRAEs	50.0%	54.1%
TRAE leading to discontinuation	11.5%	13.3%
Drug-related ILD/ Pneumonitis	13.9%	1.3%

-Destiny CRC02 showed no efficacy advantage of T-DXd 6.4 mg/kg > 5.4 mg/kg
-5.4 mg/kg had much less toxicity

Shitara et al., N Engl J Med 2025;393:336-48..

How to optimize real world efficacy and tolerability of T-DXd

- Retrospective, observational, study of 101 patients with metastatic GEA treated with T-DXd
- Single institution study in Japan
- All patients had HER2+ disease (IHC 3 + or IHC 2 + /ISH-positive)
- All patients had prior treatment with trastuzumab-containing regimen
  - HER2 status assessable in 33 pts
  - HER2 status converted to negative in 39% of patients

Question	Findings
What is the impact on efficacy when HER2 converts to negative?	ORR lower in pts who lose HER2 prior to treatment (31% vs 56%)
What is the impact of using a lower dose (5.4mg/kg) on efficacy?	No apparent loss of efficacy, possible improved tolerability in frail patients
What features might predict ILD/ pneumonitis?	ILD more frequent in patients treated at 6.4mg/kg, primary tumor removed, lower tumor burden

- **HER2 retesting advised if safe/ feasible**
- **Consider a lower dose of T-DXd in elderly/ frail patients**

Jubashi et al., Gastric Cancer (2025) 28:63–73.

Is there a role for T-DXd for HER2-intermediate or HER2-low metastatic GEA?

DESTINY-Gastric01 Exploratory Cohorts

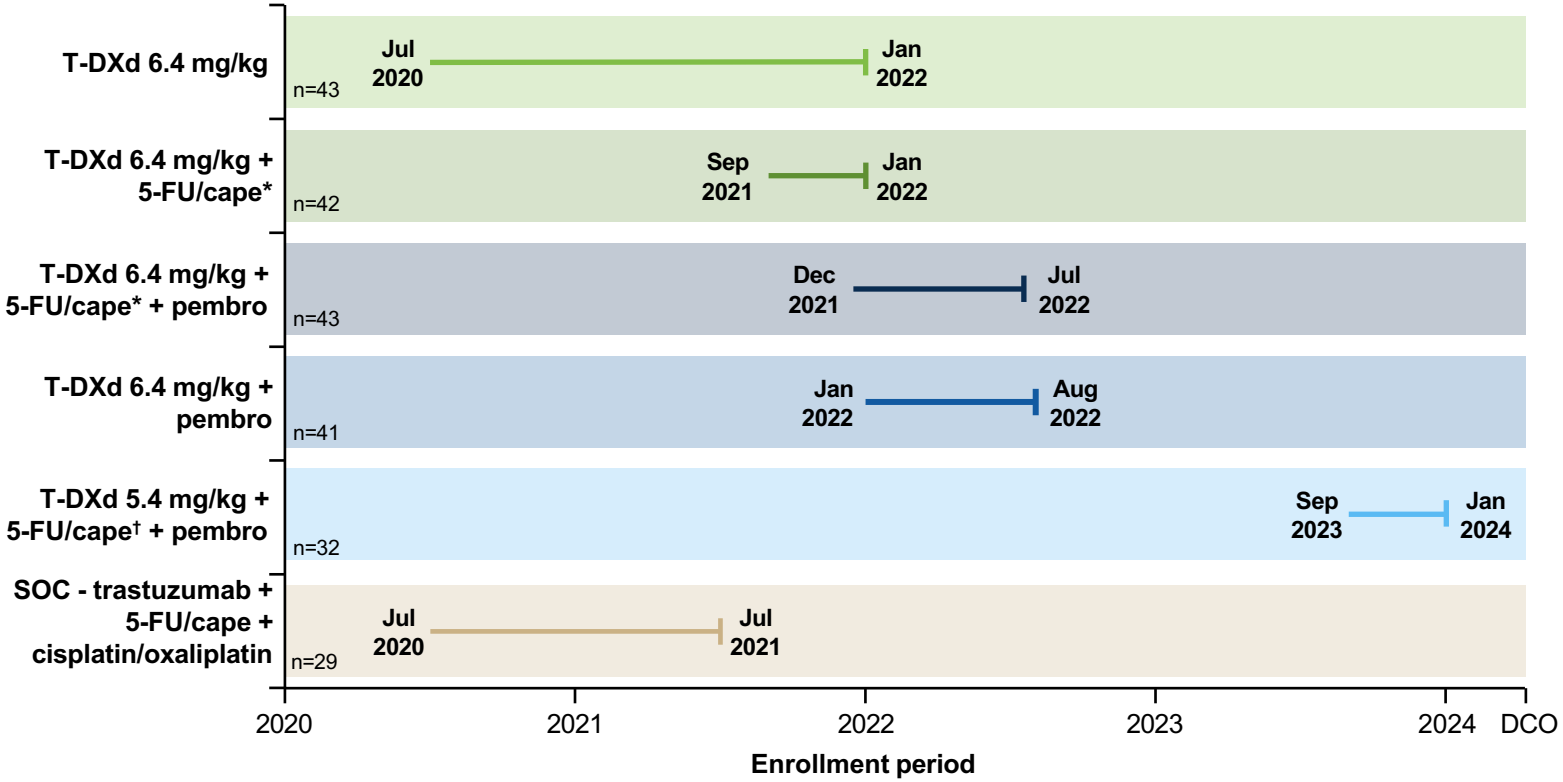
	Cohort 1: Intermediate IHC2+ and FISH- N= 21	Cohort 2: Low IHC 1+ N= 24
ORR (95% CI)	26.3% (9.1-51.2)	9.5% (1.2 to 30.4)
PFS (95% CI)	4.4 months (2.7-7.1)	2.8 months (1.5-4.3)
Overall survival (95% CI)	7.8 months (4.7-NE)	8.5 months (4.3-10.9)

- **T-DXd appears active in patients with HER2 intermediate/ low disease**
- **But… additional randomized controlled trials vs SOC needed**

Yamaguchi et al., J Clin Oncol (2023) 41(4):816-825.

DESTINY Gastric-03 (T-Dxd combinations)

Part 2 of DESTINY-Gastric03, a Phase 1b/2 trial (NCT04379596), with **non-contemporaneous and non-randomized arms**



Patient population

- Adults ≥18 years
- Unresectable, locally advanced or metastatic esophageal adenocarcinoma/GC/GEJA
- HER2+ (IHC 3+ or IHC 2+/ISH+ per local assessment)
- Treatment naïve for metastatic disease
- ECOG PS of 0 or 1

Part 2 endpoints

Primary

Confirmed ORR by investigator assessment

Secondary

- ORR, DOR, and PFS by investigator assessment, and OS
- Safety and tolerability

Exploratory

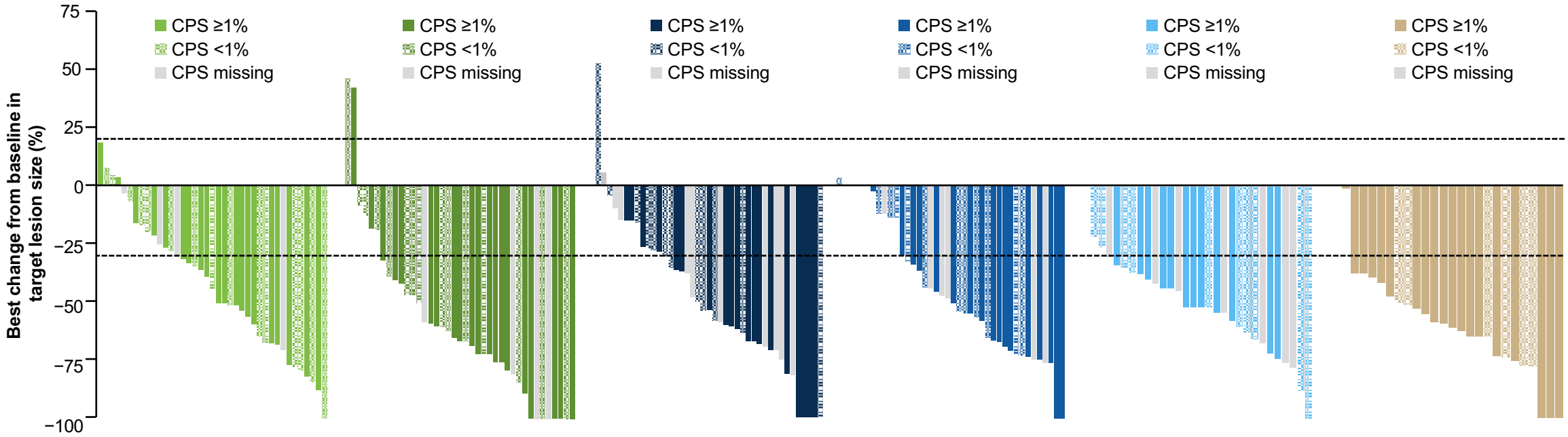
Antitumor activity by PD-L1 status

At DCO of **May 6, 2024**, median follow up: T-DXd 6.4 mg/kg = 17 months, T-DXd 6.4 mg/kg + 5-FU/cape = 21 months, T-DXd 6.4 mg/kg + 5-FU/cape + pembro = 17 months, T-DXd 6.4 mg/kg + pembro = 15 months, T-DXd 5.4 mg/kg + 5-FU/cape + pembro = 5 months, and SOC = 18 months

T-DXd: IV Q3W. Pembro: 200 mg IV Q3W. SOC: trastuzumab 6 mg/kg IV Q3W, investigator choice of 5-FU 800 mg/m² CIV infusion or cape 1000 mg/kg² BD, and investigator choice of cisplatin 80 mg/m² IV or oxaliplatin 130 mg/m² IV at SOC dose. *Investigator choice of 5-FU 600 mg/m² CIV infusion or cape 1000 mg/m² BD at dose established in Part 1; †investigator choice of 5-FU 600 mg/m² CIV infusion or cape 750 mg/m² BD

Objective response rate and best percentage change from baseline in target lesion size

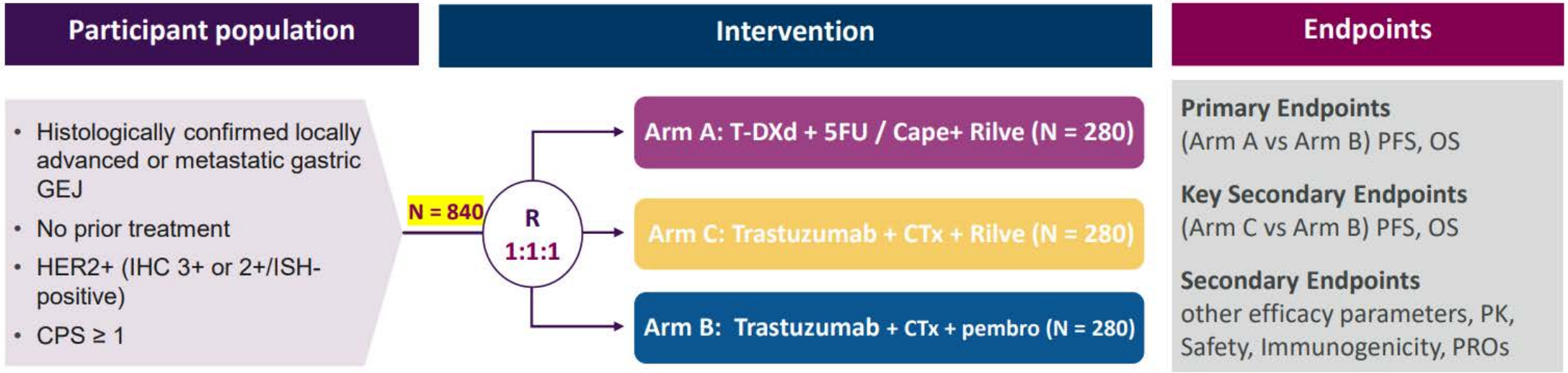
	T-DXd 6.4 mg/kg n=43	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² n=41	T-DXd 6.4 mg/kg + 5-FU/cape 1000 mg/m² + pembro n=43	T-DXd 6.4 mg/kg + pembro n=41	T-DXd 5.4 mg/kg + 5-FU/cape 750 mg/m² + pembro n=32	SOC - trastuzumab + 5-FU/cape + cisplatin/oxaliplatin n=29
mFollow up, months	17	21	17	15	5	18
mDOR, months (95% CI)	18 (6, 30)	20 (12, 28)	17 (8, NE)	18 (5, 21)	NE (2, NE)	14 (5, 20)
Confirmed ORR, % (95% CI)	49 (33, 65)	78 (62, 90)	58 (42, 73)	63 (46, 78)	59 (40, 77)	76 (56, 90)
CPS ≥1%	57	77	70	78	62	85
CPS <1%	53	73	39	44	46	71



Assessments were by Investigator using RECIST 1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively.

ARTEMIDE-Gastric01 Study

Study Design



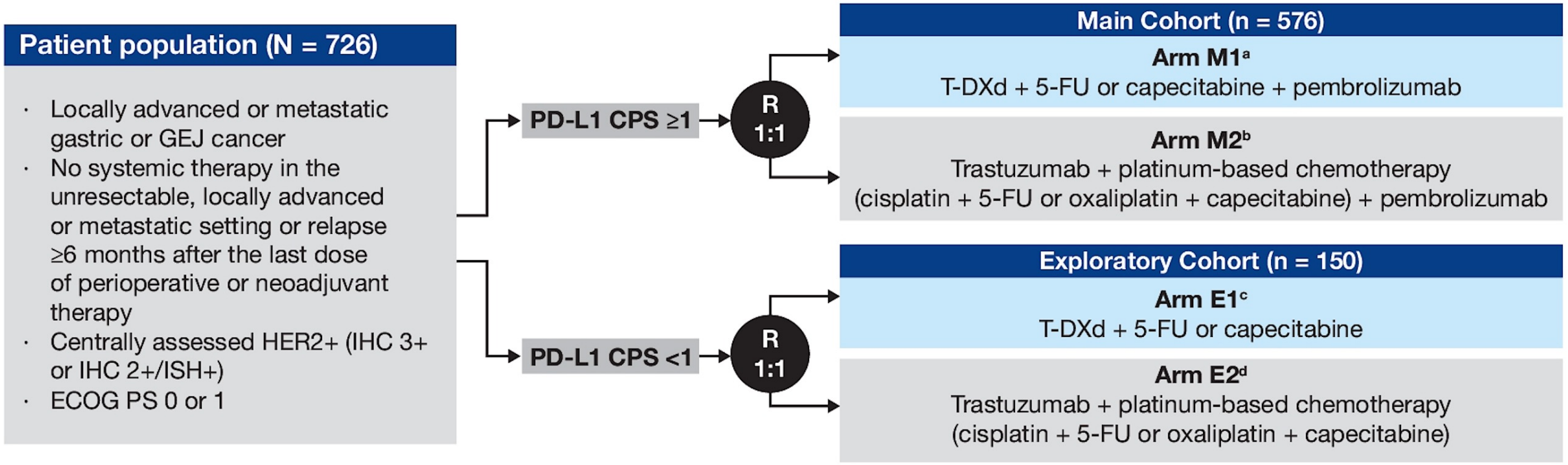
Stratification Factors

- HER2 status (IHC 3+ vs IHC 2+ plus ISH-positive)
- Geographic region (Japan/South Korea vs Rest of Asia [including China] vs North America/EU/ROW)
- PD L1 expression (CPS ≥ 10 vs CPS < 10).

Treatment arms

Arm A (treatment arm): T-DXd (dosed at 5.4 mg/kg), fluoropyrimidine (capecitabine [Investigators Choice of 750 mg/m2 twice-daily (BD) for 14 days] or 5-FU [600 mg/m2/day over 5 days]), and Rilvegostomig (dosed at 750 mg);
Arm B (control arm): Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg for subsequent cycles), with Investigators Choice of either cisplatin/5-FU (cisplatin dosed at 80 mg/m2 and 5-FU dosed at 800 mg/m2/day over 5 days) or CapeOx (capecitabine dosed at 1000 mg/m2 BD for 14 days and oxaliplatin dosed at 130 mg/m2) and pembrolizumab (dosed at 200 mg).
Arm C (CoC arm): Trastuzumab and chemotherapy the same as control arm, Rilvegostomig (dosed at 750mg)

DESTINY-Gastric05 (Open)



[a]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14 plus pembrolizumab 200 mg IV Q3W on day 1.

[b]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14) plus pembrolizumab 200 mg IV Q3W on day 1.

[c]T-DXd 5.4 mg/kg IV Q3W on day 1 plus 5-FU 600 mg/m^2/day IV on days 1 to 5 or capecitabine 750 mg/m^2 PO BID on days 1 to 14.

[d]Trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV Q3W plus platinum-based chemotherapy (cisplatin 80 mg/m^2/day IV on day 1 plus 5-FU 800 mg/m^2/day IV on days 1 to 5 or oxaliplatin 130 mg/m^2/day IV on day 1 plus capecitabine 1000 mg/m^2 PO BID on days 1 to 14).

Shitara K et al. ASCO 2025; Abstract TPS4207.

Questions from General Medical Oncologists — Gastroesophageal Cancers

69 yr old male with a hx of Stage II GE cancer treated with the CROSS regimen. Had local recurrence at the GE junction 15 months post-esophagectomy. Tumor was PD-L1-positive (CPS 10) and HER2-positive. Local recurrence resolved after treatment with FOLFOX/trastuzumab/ pembrolizumab. However, he then developed an isolated brain met, which has been resected. Would you give "adjuvant" T-DXd and for how long?

58 yo male with a HER2+ GE junction tumor treated with FOLFOX6, trastuzumab and nivolumab, progressed with supraclavicular adenopathy and brain mets. Now on second-line treatment with T-DXd. Is there a role for zanidatamab third line?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Gastroesophageal Cancers

56 yo male with Stage IV GEJ cancer with liver mets, PD-L1 CPS 1, HER2 IHC 3+. Quickly progressed on pembrolizumab + trastuzumab + FOLFOX. We planned to give T-DXd as 2nd-line tx. Unfortunately, the repeat bx shows HER2 IHC 2+, FISH-negative, but NGS is positive for an ERBB2 activating mutation. Can I now proceed with T-DXd? What anticipated ORR and PFS should be conveyed to this pt and their family?

53 yo M with HER2-amplified metastatic GEJ adenocarcinoma, PD-L1-positive. Progressed on FOLFOX + pembro + trastuzumab. Before considering HER2-targeted options in the 2nd line, how important is it to rebiopsy? Is there any role for HER2-targeted therapy in HER2 IHC 1+ or 2+ disease?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Gastroesophageal Cancers

73-year-old female with 6-month history of dysphagia, found on endoscopy to have semi-obstructive GEJ adenocarcinoma, HER2+ by IHC and FISH, no nodal or distant spread on imaging. What neoadjuvant approach would you recommend?

RTP
RESEARCH
TO PRACTICE

Questions from General Medical Oncologists — Gastroesophageal Cancers

56 yo male w/metastatic GEJ cancer. Progressed on FLOT + nivolumab. New liver lesion noted. Biopsy is HER2-positive, PD-L1 CPS >1. Should I consider 5-FU + oxaliplatin + trastuzumab + pembrolizumab? Is durvalumab better? What about T-DXd for this patient?

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1: Biliary Tract Cancers — Dr Ellis

Module 2: Gastroesophageal Cancers — Dr Wainberg

Module 3: Colorectal Cancer — Prof Van Cutsem

RTP
RESEARCH
TO PRACTICE

UZ LEUVEN

Integrating Therapies Targeting HER2 in mCRC

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HER2 Positivity in mCRC and Detection Methods

- **NCCN & ESMO Living guidelines** recommend HER2 testing according to the HERACLES criteria or through next-generation sequencing (NGS) in mCRC
  - ✓ HER2 positivity is defined by intense circumferential, basolateral, or lateral immunohistochemical staining (IHC 3+) in ≥ 50% of tumor cells. If the staining is observed in > 10% but < 50% of cells, a positive in situ hybridization (ISH) result (HER2/CEP17 ratio ≥ 2 in ≥ 50% of cells) is required to confirm HER2 positivity
  - ✓ moderate circumferential, basolateral, or lateral staining (IHC 2+) in ≥ 50% of cells also require a positive ISH result to be considered HER2 positive

- **Unlike in breast and gastric cancer, HER2 positivity in CRC lacks a standardized definition**.
  - ✓ compared with breast and gastric cancer, the HERACLES classification demands a higher proportion of tumor cells to exhibit staining (≥ 50% versus ≥ 10%) and it allows a broader range of staining patterns.

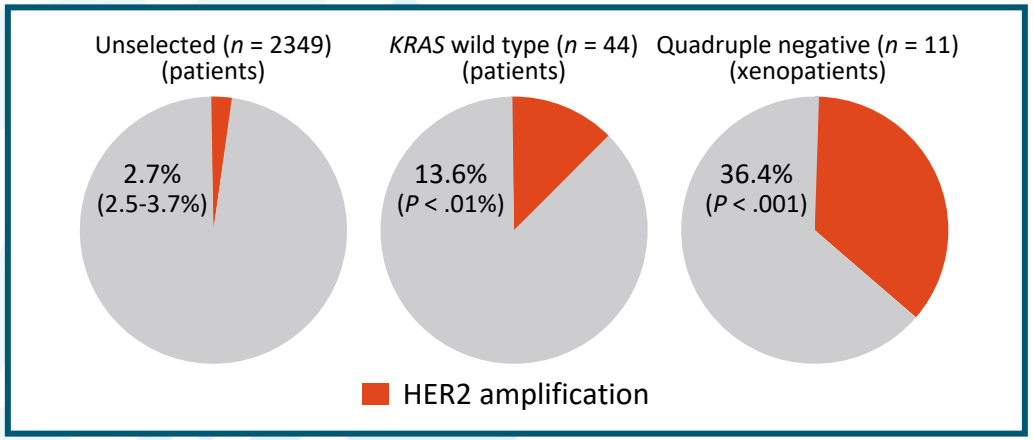
- A key challenge in HER2 detection in **mCRC is intratumoral heterogeneity**

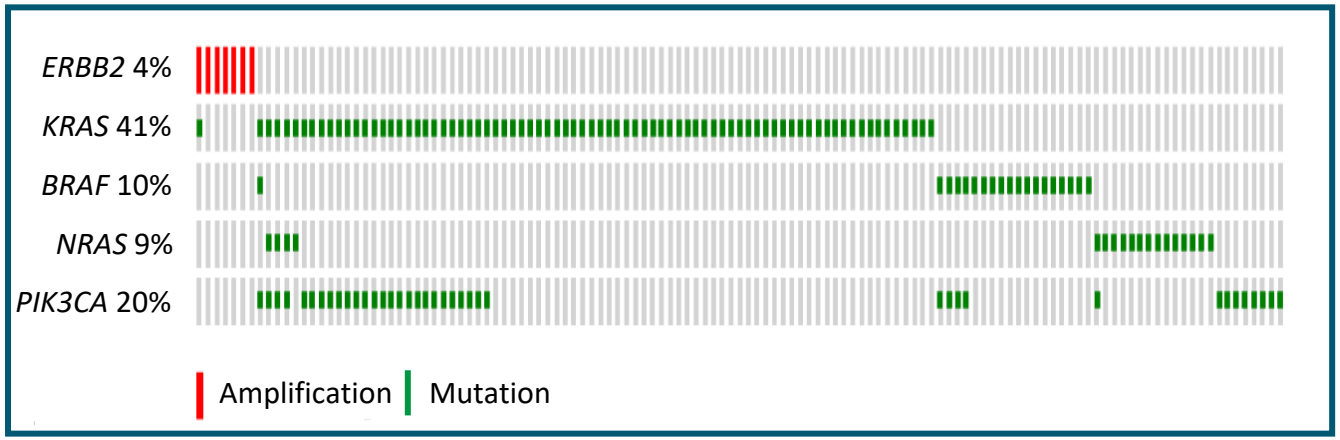
- **SO: multiple methodologies** can be used for HER2 assessment in mCRC.
  Notably, **gene-based approaches** may offer advantages overcoming intratumoral heterogeneity and **ctDNA** can potentially overcome heterogeneity between primary and metastasis and increase detection rates.
  As a result, **incorporating NGS and liquid biopsy** into diagnostic workflows could further refine patient selection for HER2- targeted therapies

Vaghi C et al, Drugs 2025, Nov 17. doi: 10.1007/s40265-025-02253-2

HER2 Amplification in Patients With Colorectal Cancer

Study	N	Positive Rate	IHC 2+ (Borderline)	IHC 3+ (Positive)	IHC/FISH Concordance
Nathanson[1]	139	IHC: 5 (3.6%) FISH: 4 (2.4%)	2	3	K = 0.89
Ooi[2]	244	IHC: 8 (3%) FISH: 8 (3%)	2	6	100%
Marx[3]	1439	IHC: 39 (3%) FISH: 36 (3%)	12	27	100%
Summary	1822		16	36	Good





- 5% HER2 amplification seen in HERACLES Study (screened = 914)[4]
- HER2 amplification enriched in *KRAS*, *NRAS*, *BRAF*, and *PIK3CA* WT tumors and in left sided tumors[5,6]

1. Nathanson et al. Int J Cancer. 2003; 105:796. 2. Ooi et al. Mod Pathol. 2004;17:895 3. Marx A et al. Human Path. 2010;41:1577. 4. Sartore-Bianchi A…Siena S . Lancet Oncol 2016. 5. Bertott A et al, Cancer Discovery 2011;1:508. 6. Kuwada et al . Int J Cancer. 2004;109:291.

HER2 Amplification in Patients With Colorectal Cancer

- HER2 overexpression/amplification:
  - ✓ 3% (unselected) to 5% (RAS and BRAF wild-type molecular profiles) of mCRCs
  - ✓ predominantly in left-sided colon and rectal adenocarcinomas
  - ✓ associated with metastases in the central nervous system.
- HER2 mutations: 1-2% of CRC

- Prognostic impact of HER2 amplification: controversial results
  However the largest combined analysis of 1604 patients in 8 trials: TRIBE2, TRIPLETE, VALENTINO, ATEZOTRIBE, PANDA, PANAMA, PARADIGM, CALGB/SWOG80405
  - ✓ HER2-positivity and mutation
    - negative prognostic factors in pMMR/MSS, RAS/BRAF wild-type mCRC
    - do not predict benefit from bev/anti-EGFRs in pMMR/MSS, RAS/BRAF wild-type mCRC

Impact of HER2 in Patients With mCRC Treated With CT + Bevacizumab or Anti-EGFRs: HER2 expression/amplification

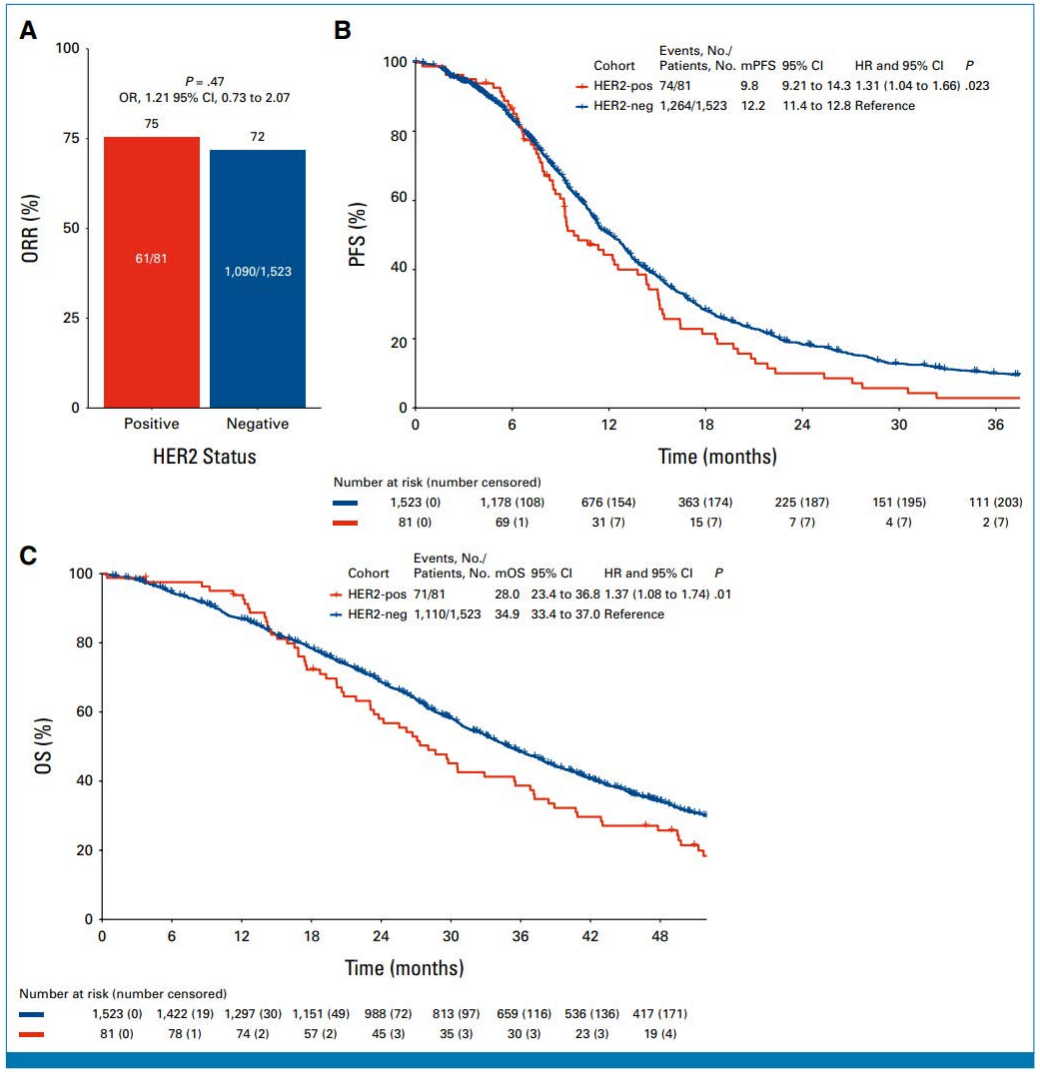


FIG 2. (A) ORR, (B) PFS, and (C) OS according to HER2 expression/amplification status. HER2-neg, human epidermal growth factor receptor 2–negative; HER2-pos, human epidermal growth factor receptor 2–positive; HR, hazard ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; OR, odds ratio; ORR, objective response rate; pop, population.

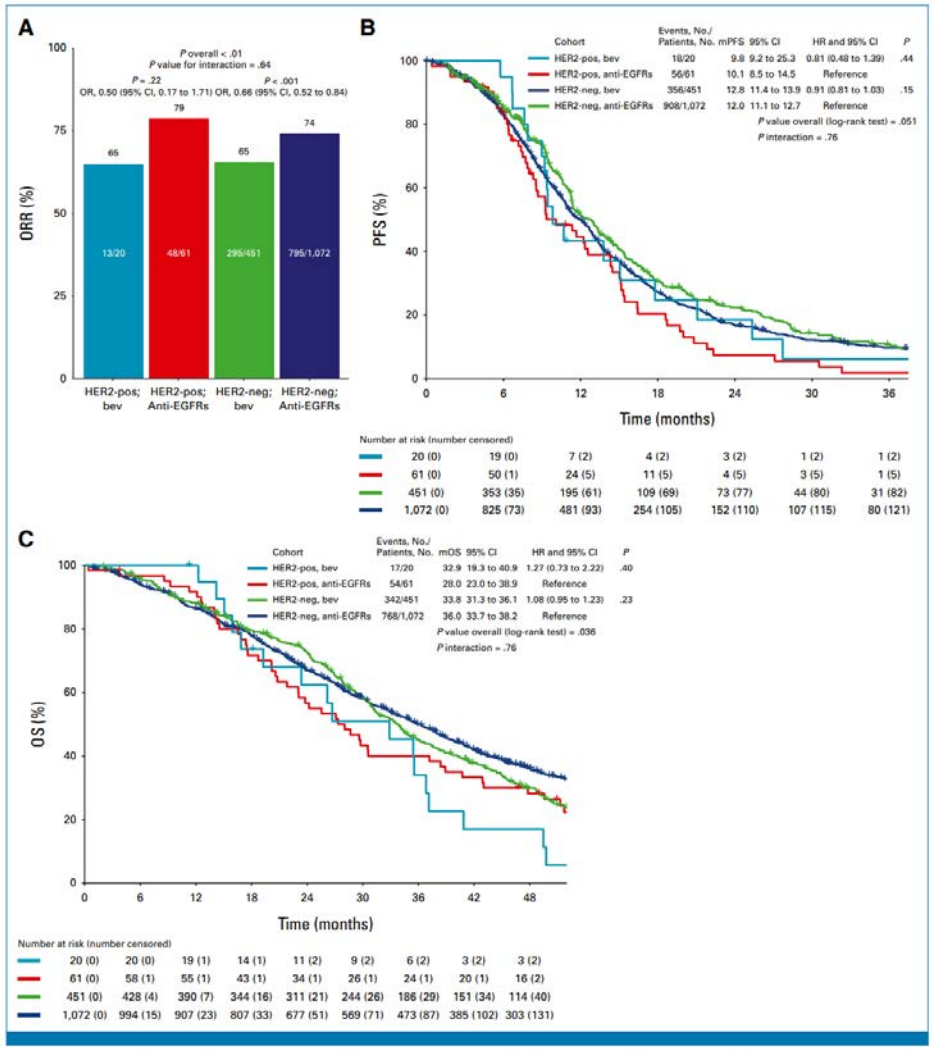


FIG 3. (A) ORR, (B) PFS, and (C) OS according to HER2 expression/amplification status and monoclonal antibody received. Anti-EGFRs, antiepidermal growth factor receptors; bev, bevacizumab; HER2-neg, human epidermal growth factor receptor 2–negative; HER2-pos, human epidermal growth factor receptor 2–positive; HR, hazard ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; OR, odds ratio; ORR, objective response rate; pop, population.

Germani M et al, J Clin Onc 2025, 43:3184-3197

Impact of HER2 in Patients With mCRC Treated With CT + Bevacizumab or Anti-EGFRs: HER2 mutation

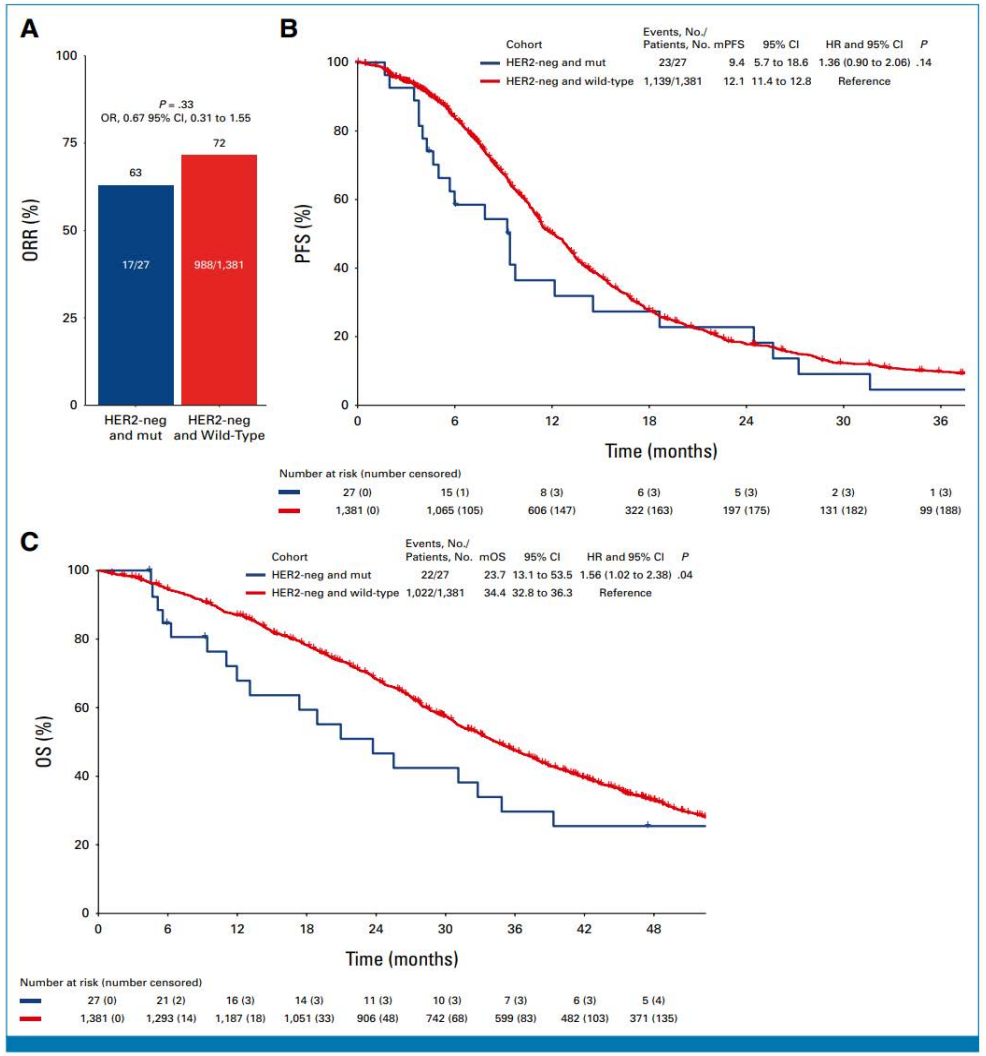


FIG 4. (A) ORR, (B) PFS, and (C) OS according to *HER2* mutational status in HER2-negative tumors. HER2-neg, human epidermal growth factor receptor 2–negative; HR, hazard ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; mut, mutant; OR, odds ratio; ORR, objective response rate; pop, population.

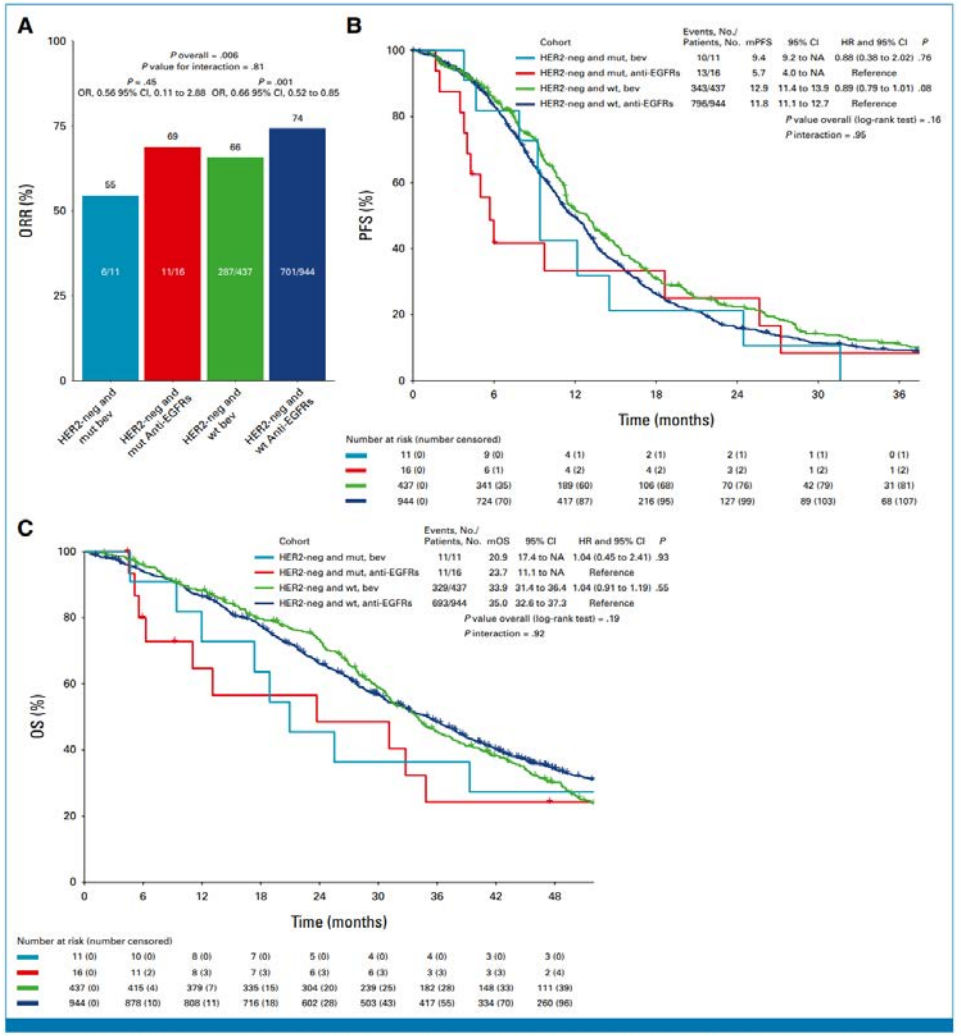
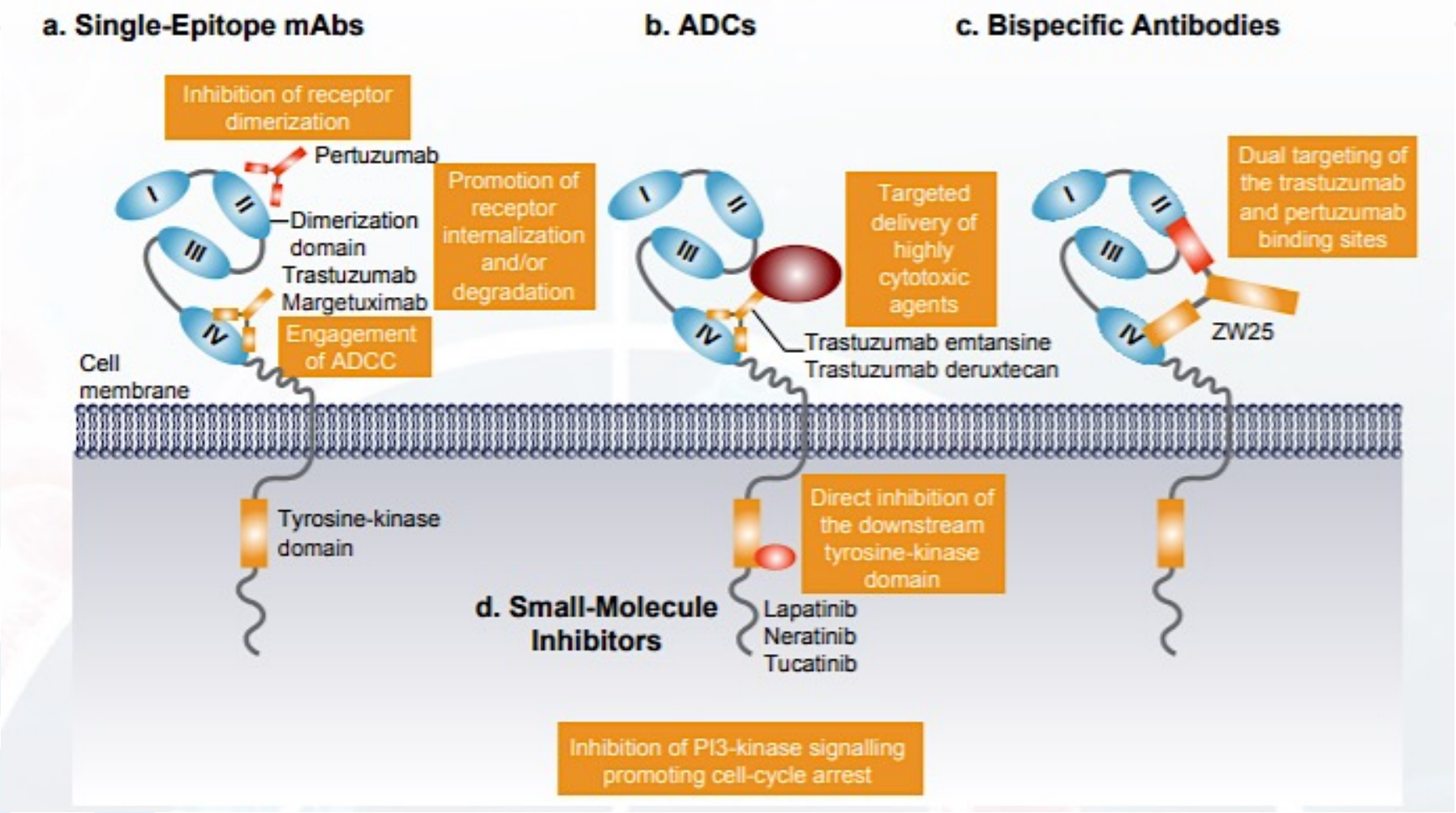


FIG 5. (A) ORR, (B) PFS, and (C) OS according to *HER2* mutational status in HER2-negative tumors and monoclonal antibody received. Anti-EGFRs, antiepidermal growth factor receptors; bev, bevacizumab; HER2-neg, human epidermal growth factor receptor 2–negative; HR, hazard ratio; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; mut, mutant; NA, not assessable; OR, odds ratio; ORR, objective response rate; pop, population; wt, wild-type.

Germani M et al, J Clin Onc 2025, 43:3184-3197

Mechanism of Action of HER2-Targeting Therapies



Oh DY et al Nat Rev Clin Oncol. 2020;17:33-48.

HER2-targeted therapies in mCRC

Table 1. HER2-targeted therapies in HER2+ mCRC.

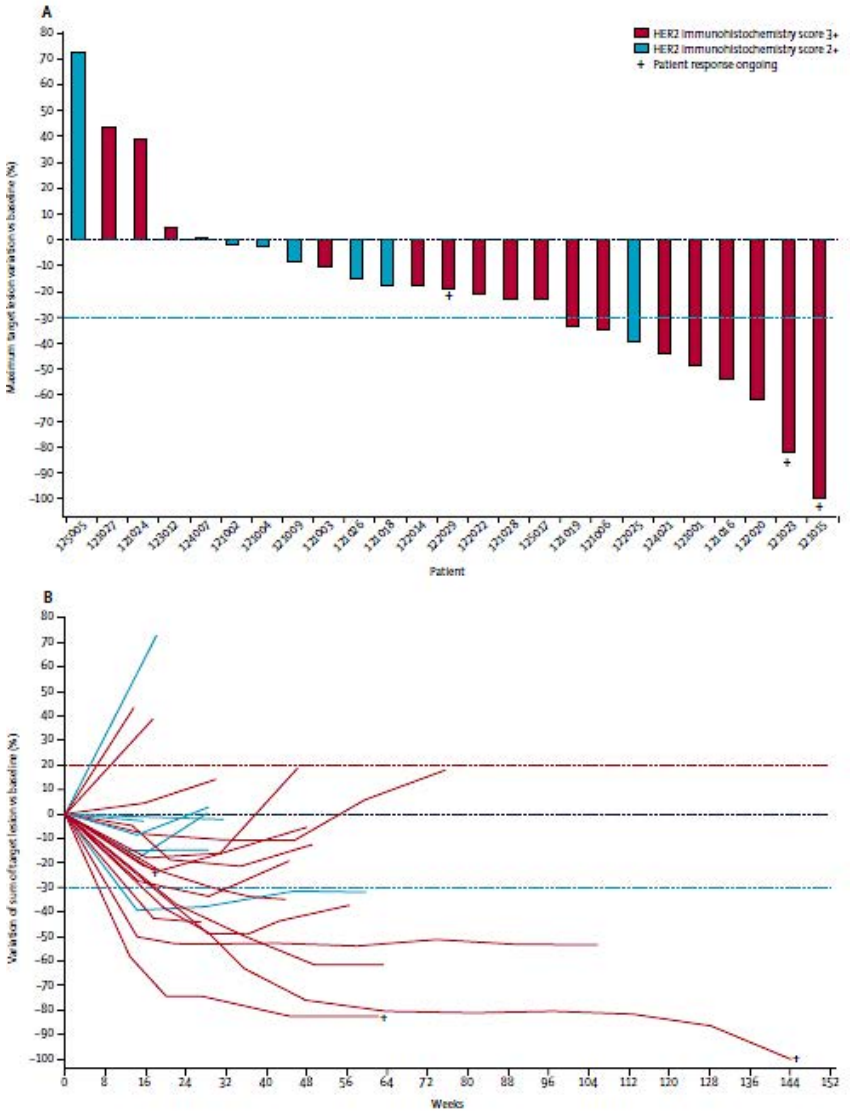
Clinical trial	Therapies	Patients, N	ORR, % (95% CI)	PFS, months
HERACLES-A [17]	Lapatinib + trastuzumab	32 (response evaluable)	28	4.7
MyPathway [18]	Pertuzumab + trastuzumab	57[†] (all patients)	32[†] (20–45)	2.9
		43 (HER2+, *KRAS* WT)	40 (25–56)	5.3
		13 (HER2+, *KRAS* mutated)	8 (0.2–36)	1.4
HERACLES-B [19]	Pertuzumab + T-DM1	31	9.7	4.1
TAPUR [20]	Trastuzumab + pertuzumab	38	25	17.2 weeks
TRIUMPH [21]	Pertuzumab + trastuzumab	30	30 (14–50) in tissue-positive patients	4.0 in tissue-positive patients
			28 (12–49) in ctDNA-positive patients	3.1 in ctDNA-positive patients
DESTINY-CRC01 [22]	Trastuzumab deruxtecan	53	45.3[‡]	6.9
MOUNTAINEER [23]	Tucatinib + trastuzumab	84 (HER2+, *RAS* WT)	38.1[‡] (27.7–49.3)[§]	8.2
HER2-FUSCC-G [24]	Trastuzumab + pyrotinib	11 (ongoing)	45.5	7.8

[†]Confirmation was not required; 56/57 patients were tested for *KRAS* status.
[‡]Confirmed ORR.
[§]Two-sided 95% exact CI, computed using the Clopper – Pearson method (1934).
CI: confidence interval; ctDNA: circulating tumor DNA; HER2: human epidermal growth factor receptor 2; ORR: objective response rate; PFS: progression-free survival; T-DM1: ado-trastuzumab emtansine; WT: wild type.

Strickler J ....Van Cutsem E et al, Future Oncol 2025

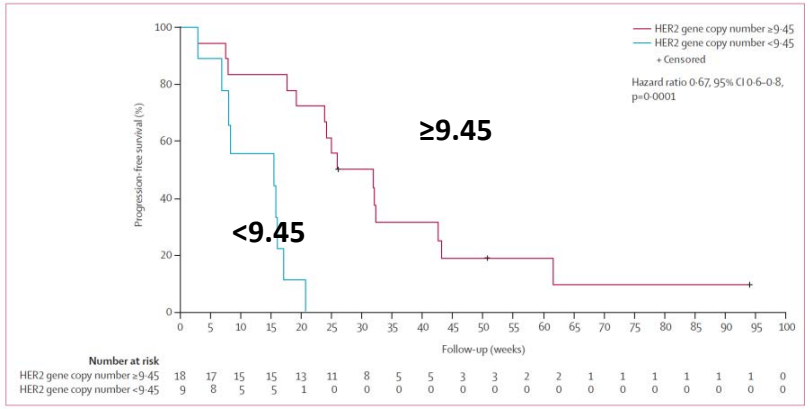
HER2-targeted therapy in mCRC: HERACLES-A

	Patients given trastuzumab and lapatinib (n=27)
Age (years)	62 (50–68)
Sex	
Men	23 (85%)
Women	4 (15%)
ECOG performance status 0–1	27 (100%)
HER2 expression by immunohistochemistry score	
3+	20 (74%)
2+	7 (26%)
Site of primary tumour	
Rectum	7 (26%)
Colon	20 (74%)
Proximal*	4 (20%)
Distal†	16 (80%)
Metastatic disease in multiple sites	26 (96%)
Number of previous lines of therapy	5 (4–6)
Patients with ≥4 previous lines of therapy	20 (74%)
Previous anti-angiogenesis treatment	20 (74%)
Previous therapy with panitumumab or cetuximab	27 (100%)
Patients eligible to be assessed for sensitivity to panitumumab or cetuximab‡	15 (56%)
Previous response to panitumumab or cetuximab	0
Time on previous treatment (total; months)§	20 (16–24)
By primary site	
Proximal	15 (13–19)
Distal	19 (15–24)
Rectum	23 (20–25)



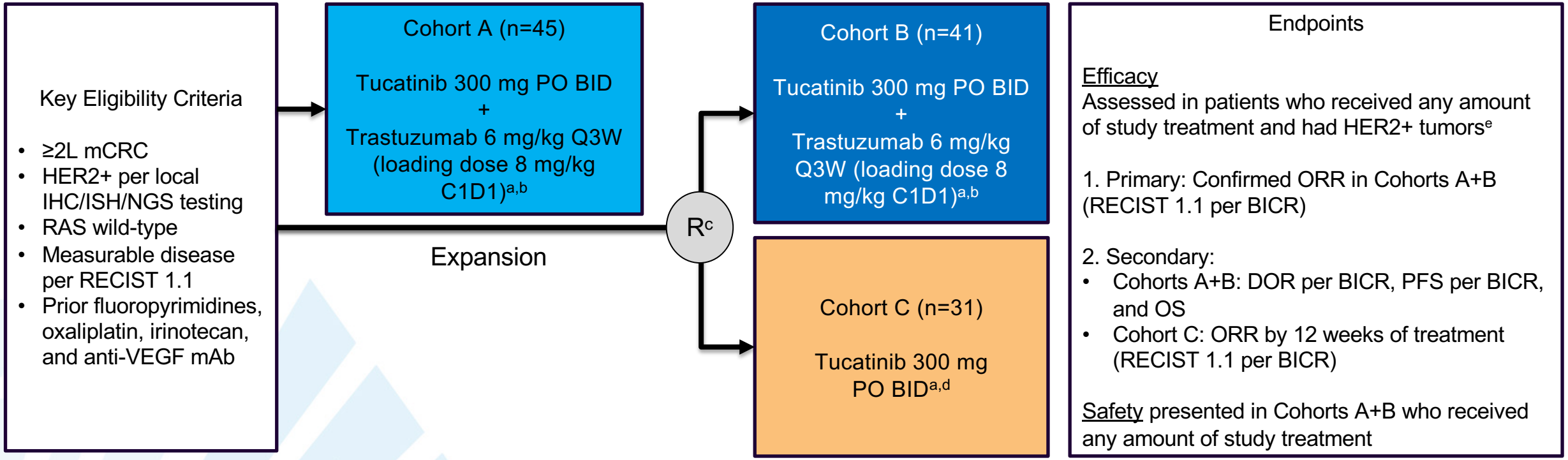
Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)

PFS according to HER2 GCN



Sartore-Bianchi A … Siena S, Lancet Oncol 2016

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC



MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Data cut-off for current analysis, March 28, 2022

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumor primary vs other; d Patients were allowed to cross over and receive tucatinib and trastuzumab if they experienced radiographic progression at any time point or if they had not achieved a PR or CR by week 12; e Patients had HER2+ tumors as defined by one or more protocol required local tests: IHC 3+ (n=46), amplification by ISH (n=36), or amplification by NGS (n=69)

https://clinicaltrials.gov/ct2/show/NCT03043313

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH… Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC

	Tucatinib plus trastuzumab (cohorts A and B; n=84)
Confirmed objective response rate (95% CI)*	38·1% (27·7–49·3)
Complete response†	3 (4%)
Partial response†	29 (35%)
Stable disease†‡	28 (33%)
Progressive disease†	22 (26%)
Not available§	2 (2%)
Disease control rate (post hoc)¶	60 (71%)
Median duration of response, months (IQR)	12·4 (8·3–25·5)

Data are n (%) unless specified otherwise. Percentages might not total 100 due to rounding. *Confirmed disease response and progression were assessed according to Response Evaluation Criteria in Solid Tumours, version 1.1, by blinded independent central review. †Best overall response. ‡Includes stable disease and non-complete response or non-progressive disease. §Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable. ¶Defined as the sum of the complete response, partial response, and stable disease.

Table 2: **Response to treatment in patients treated with tucatinib plus trastuzumab (n=84)**

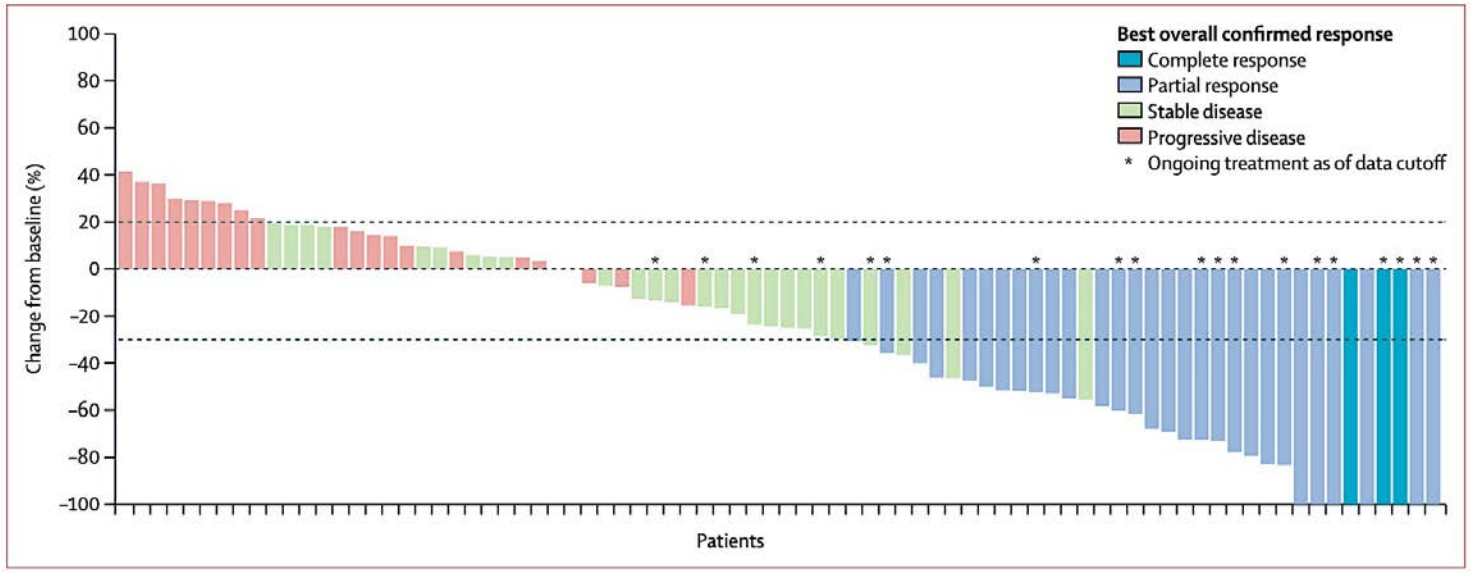


Figure 2: **Anti-tumour activity in patients treated with tucatinib plus trastuzumab with available baseline and post-baseline lesion measurements (n=80)**
Shown are the maximum percentage changes in the sum of the diameters of target lesions per blinded independent central review for all patients treated with combination therapy who had baseline and post-baseline target lesion measurements. Four patients who did not have these measurements were excluded. Six patients had 100% reductions and a best overall confirmed response of partial response due to non-target lesions that had not completely resolved. Similarly, four patients with greater than 30% reduction were classified as having stable disease on the basis of failure to confirm the response due to progression. The upper dashed horizontal line indicates a 20% increase in tumour size, and the lower dashed line indicates a 30% decrease in tumour size (corresponding to the RECIST definitions for progressive disease and partial response).

Post-hoc subgroup analysis by HER2 status according to immunohistochemistry: confirmed ORR by BICR

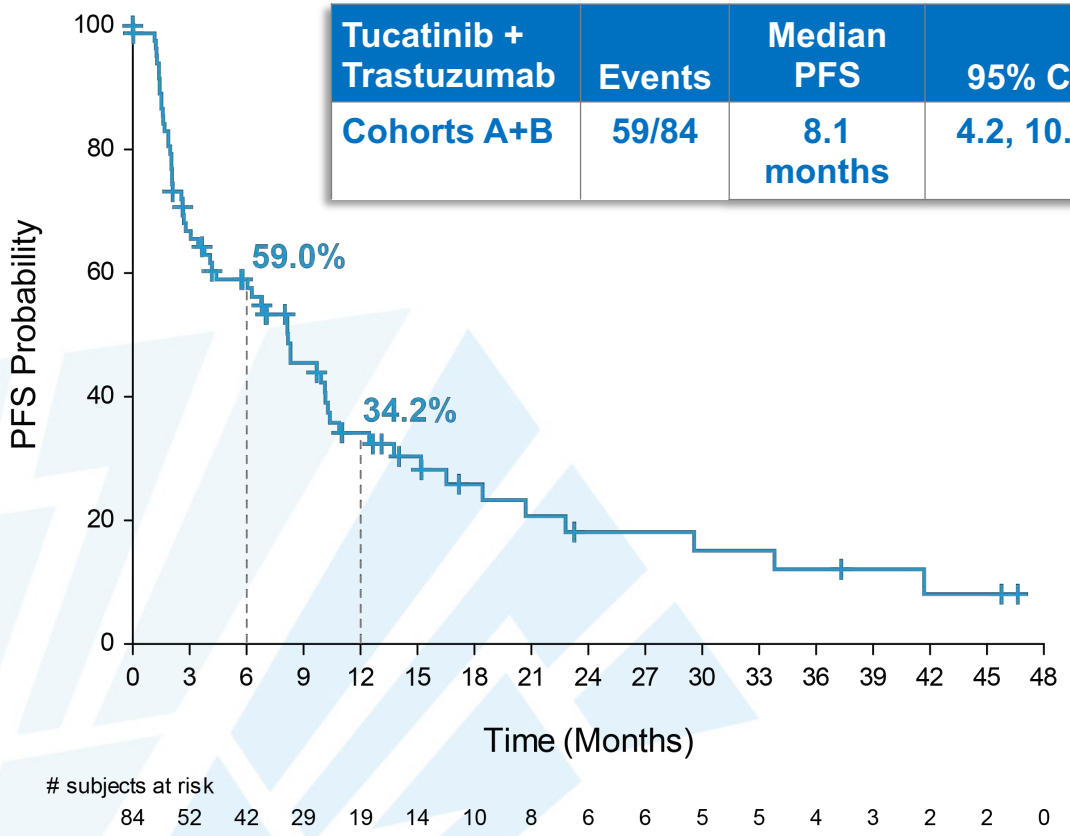
- ✓ **46·7% (95% CI 31·7–62·1; 21 of 45 patients) in those with IHC 3+ tumours,**
- ✓ **20·0% (4·3–48·1; three of 15 patients) in those with IHC 2+ and in-situ hybridisation-positive tumours**
- ✓ **10·0% (0·3–44·5; one of ten patients) in those with HER2-negative tumours**

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH… Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial of Tucatinib and Trastuzumab in HER2+ mCRC

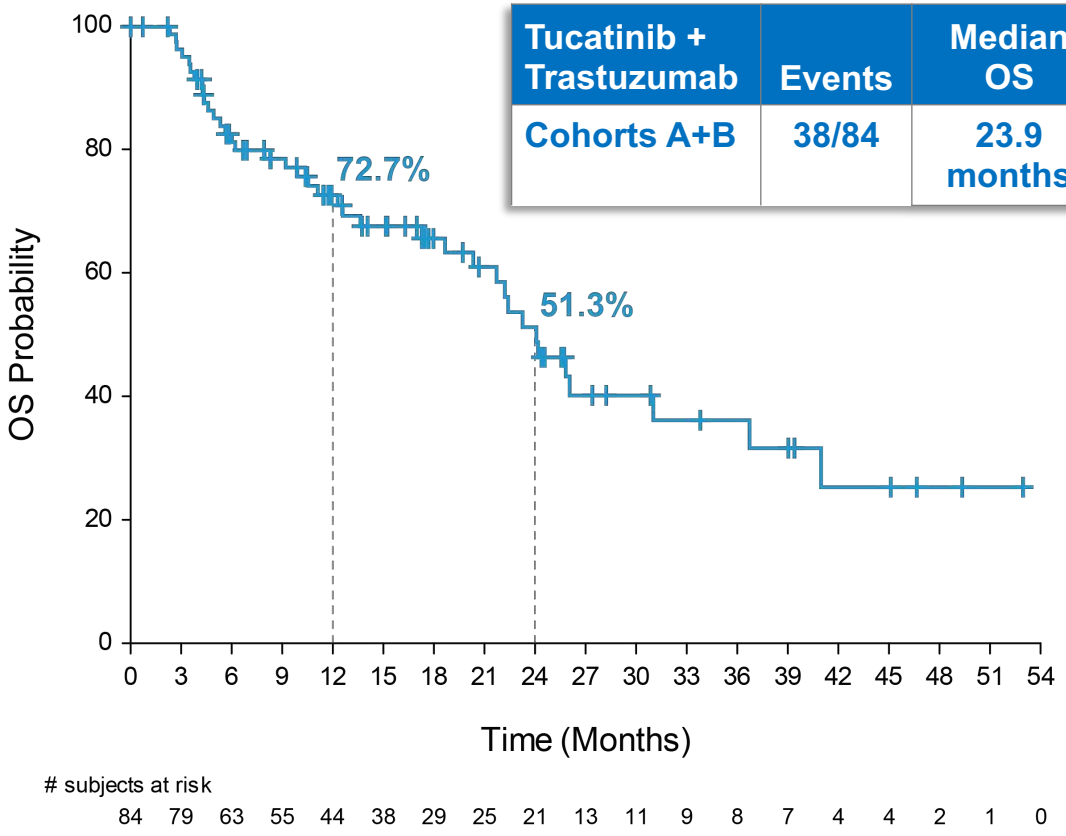
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.1 months	4.2, 10.2



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	23.9 months	18.7, 28.3



Median follow-up for Cohorts A+B in final analysis was 32.4 months.

BICR, blinded independent central review; IQR, interquartile range; OS, overall survival; PFS, progressive-free survival.

Data cutoff: 28 Mar 2022

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER: Efficacy by Central HER2 Testing Methods

- Clinical efficacy was similar across all 3 central HER2 testing methods

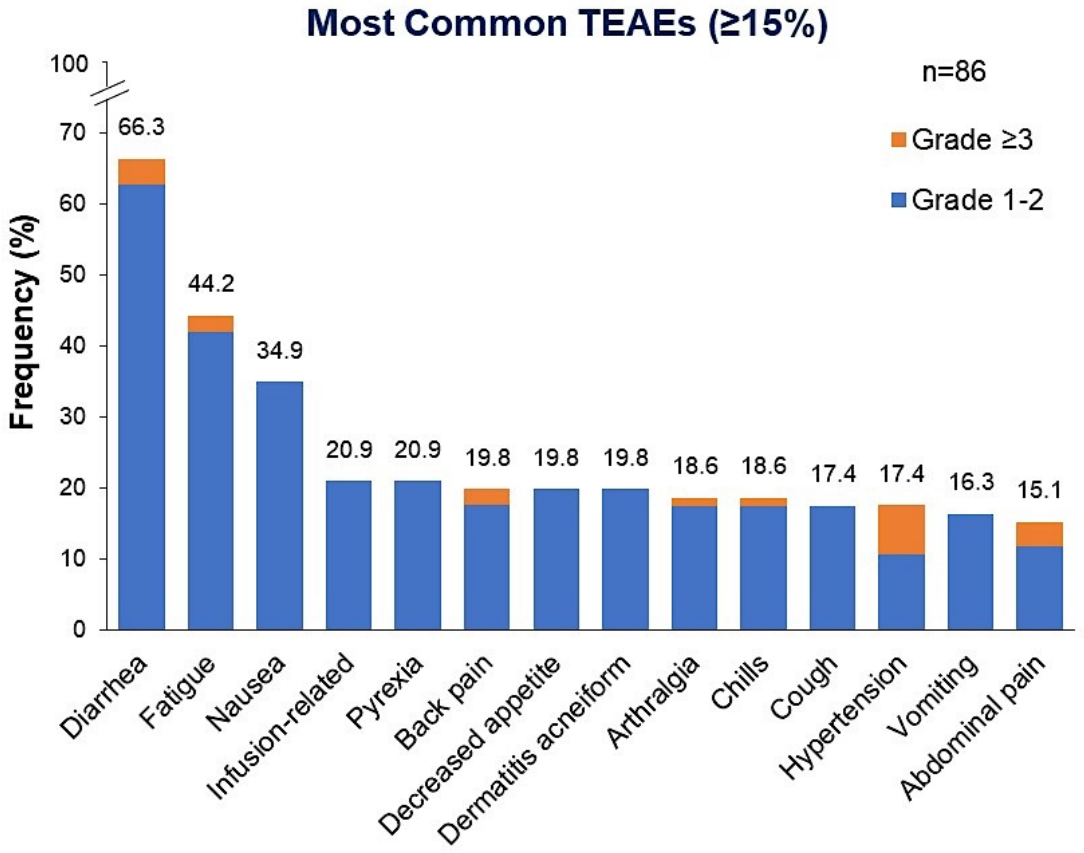
HER2 results	Tissue IHC/FISH		Tissue NGS (PGDx)		Blood NGS (G360)	
	+ (n=60)	– (n=10)	+ (n=44)	– (n=6)	+ (n=59)	ND (n=16)
cORR, % (95% CI)	41.7 (29.1–55.1)	10.0 (0.3–44.5)	50.0 (34.6–65.4)	0 (0–45.9)	42.4 (29.6–55.9)	25.0 (7.3–52.4)
Median DOR, mo (95% CI)	16.6 (11.4–25.5)	–	16.6 (10.6–18.8)	–	16.6 (8.3–18.8)	15.2 (11.4–NE)
Median PFS, mo (95% CI)	10.1 (4.2–14.5)	2.8 (1.2–6.3)	10.9 (6.8–20.0)	2.1 (1.3–NE)	8.1 (3.1–10.3)	6.3 (2.0–25.5)

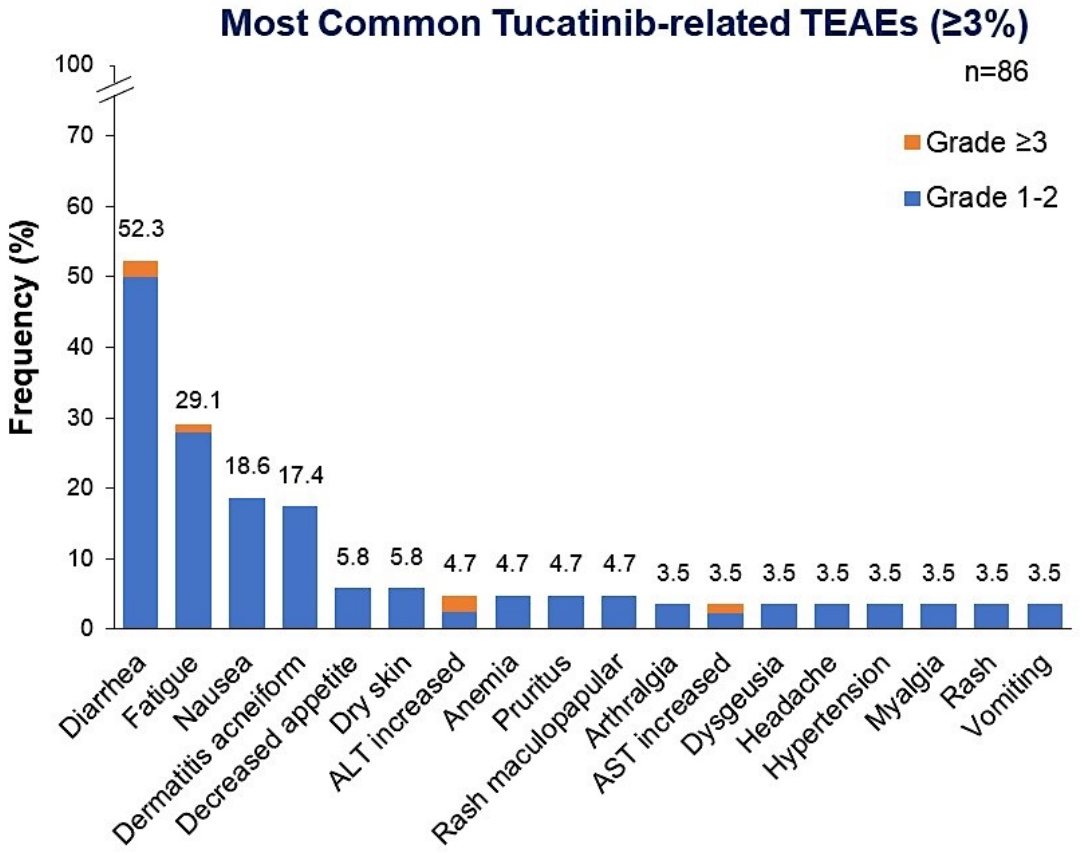
Note: To be included in this analysis, a patient had to have a local HER2+ test and ≥1 central HER2+ test from IHC/FISH, tissue-based NGS, and/or blood-based NGS.

CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescent in situ hybridization; G360, Guardant360® CDx test; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mo, months; ND, not detected; NE, not estimable; NGS, next-generation sequencing; PFS, progression-free survival; PGDx, PGDx elio tissue complete.

Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

Most Common TEAEs for Tucatinib + Trastuzumab





AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

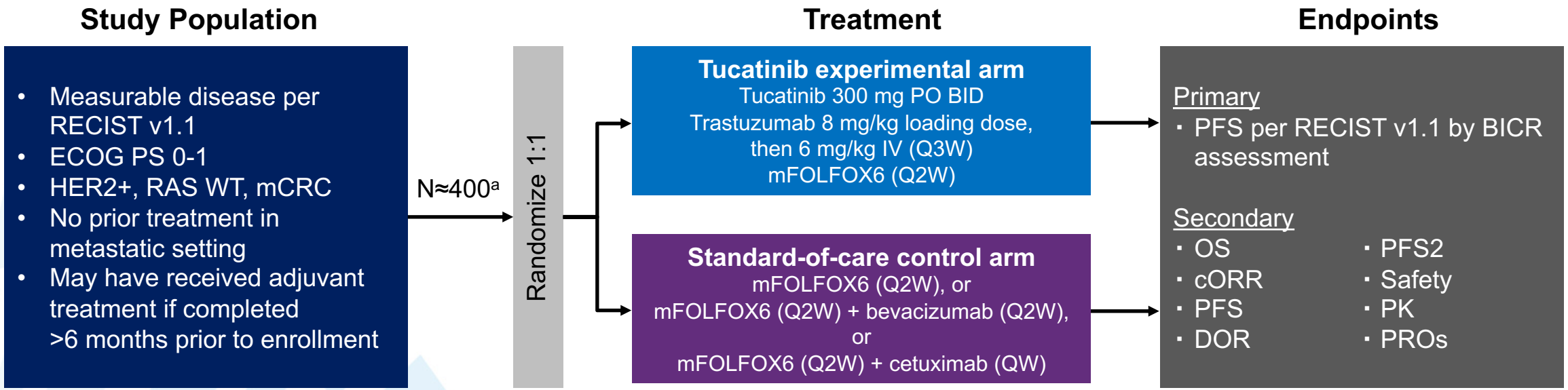
- Most common tucatinib-related AEs: diarrhoea (52.3%), fatigue (29.1%), nausea (18.6%), and dermatitis acneiform (17.4%)
  - Grade ≥3 tucatinib-related AEs (≥3%): alanine aminotransferase increase (2.3%) and diarrhoea (2.3%)

Data cutoff: 28 Mar 2022

Strickler JH…Van Cutsem E et al. *Lancet Oncol.* 2023; Strickler JH…Van Cutsem E et al. ASCO 2024; Abstract 3509.

MOUNTAINEER-03 trial in first line mCRC

- MOUNTAINEER-03 (NCT05253651) is a global, open-label, randomized, phase 3 study of tucatinib with trastuzumab and mFOLFOX6 versus standard of care for the first-line treatment of HER2+ and *RAS* wild-type mCRC



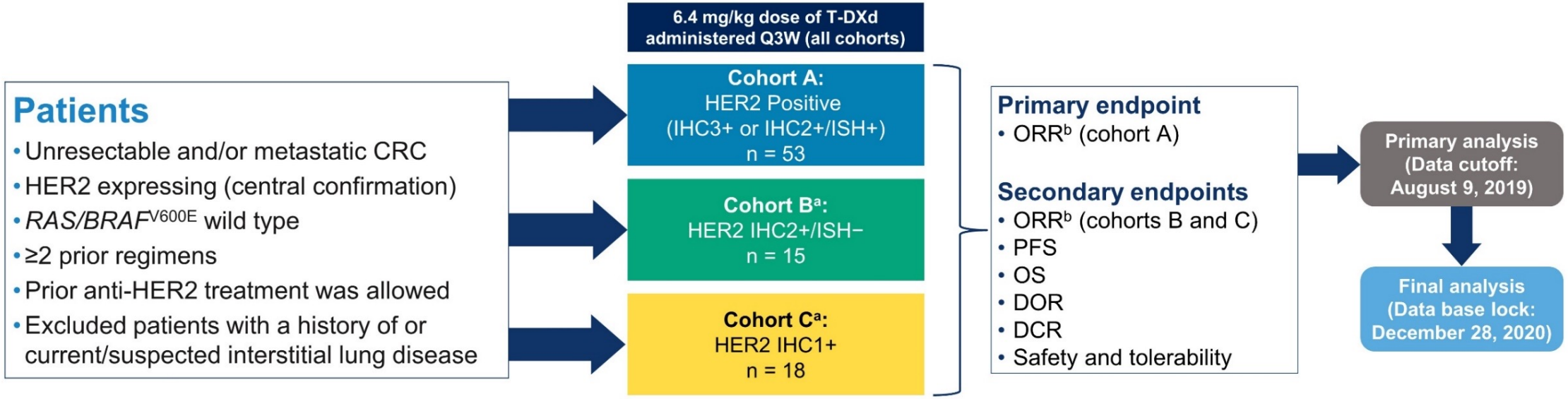
a Stratification by both primary tumor location (left-sided versus all other) and liver metastases (presence or absence)

BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IV, intravenously; mCRC, metastatic colorectal cancer; mFOLFOX6, modified 5-fluorouracil, leucovorin, and oxaliplatin; OS, overall survival; PFS, progression-free survival; PFS2, time from randomization to disease progression on next-line treatment or death from any cause; PK, pharmacokinetics; PO, by mouth; PROs, patient-reported outcomes; Q, each; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; W, week; WT, wild-type.

Strickler J ....Van Cutsem E et al, Future Oncol 2025

DESTINY-CRC01 Study Design

An open-label, multicenter, phase 2 study (NCT03384940)



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.

[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Siena S et al, Lancet Oncol 2021
Yoshino T et al, Nat Comm 2023

DESTINY-CRC01 trial

Table 3 | Key efficacy endpoints

	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A *n* = 53	HER2 IHC 2+/ISH− Cohort B *n* = 15	HER2 IHC 1+ Cohort C *n* = 18
Confirmed ORR by ICR	24 (45.3) [95% CI, 31.6–59.6]	0 [95% CI, 0.0–21.8]	0 [95% CI, 0.0–18.5]
Complete response	0	0	0
Partial response	24 (45.3)	0	0
Stable disease	20 (37.7)	9 (60.0)	4 (22.2)
Progressive disease	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
DCR	83.0 (70.2–91.9)	60.0 (32.3–83.7)	22.2 (6.4–47.6)
Median DoR, months	7.0 (5.8–9.5)	NE (NE–NE)	NE (NE–NE)
Median treatment duration, months	5.1 (3.9–7.6)	2.1 (1.4–2.6)	1.4 (1.3–1.5)

Data are presented as *n* (%), % (95% CI), or medians (95% CI).
DCR disease control rate, *DoR* duration of response, *ICR* independent central review, *IHC* immunohistochemistry, *ISH* in situ hybridization, *NE* not evaluable, *ORR* objective response rate.
[a]Patients were missing postbaseline scans.

Yoshino T et al, Nat Comm 2023

DESTINY-CRC01 trial: analysis according to IHC of HER2

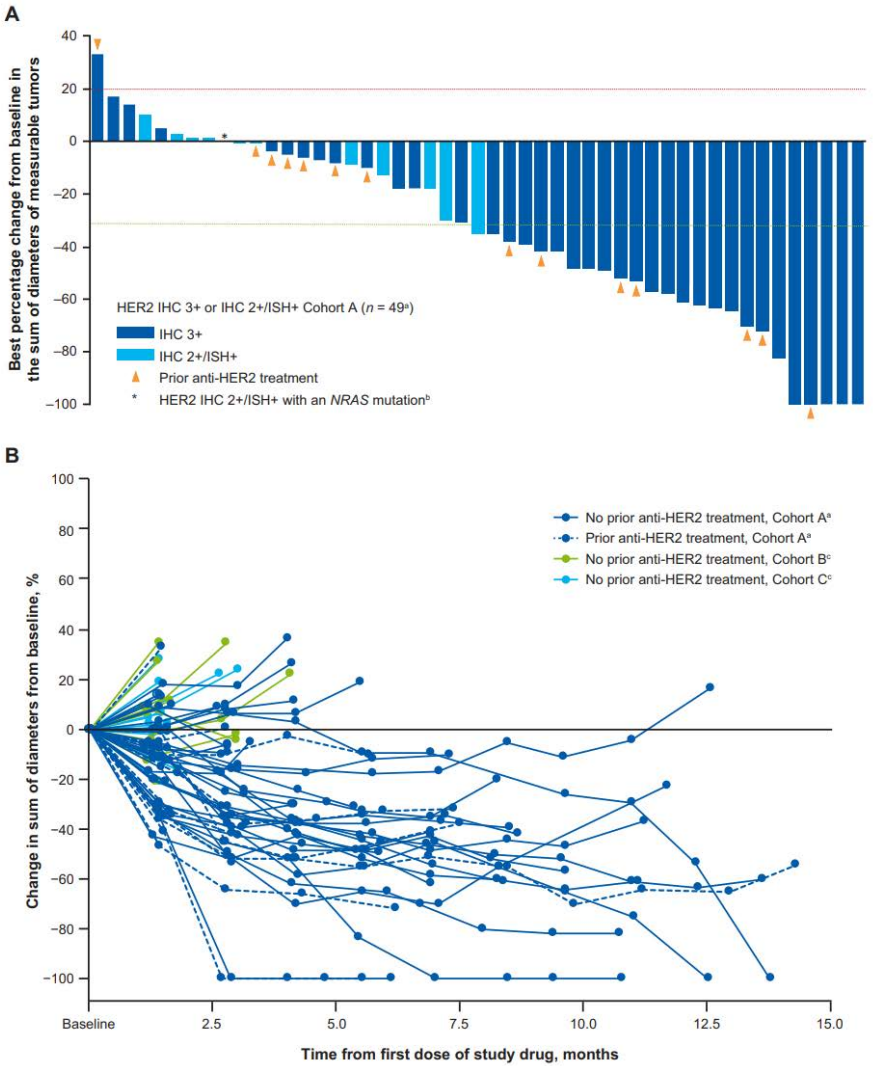
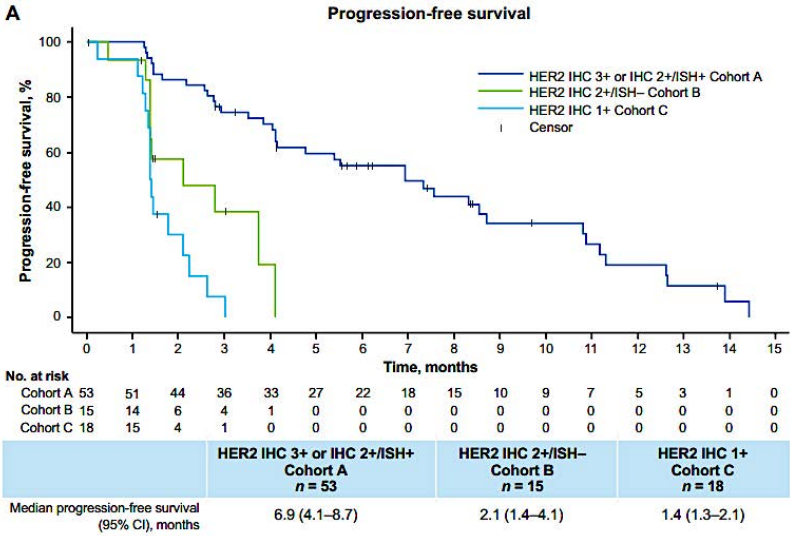
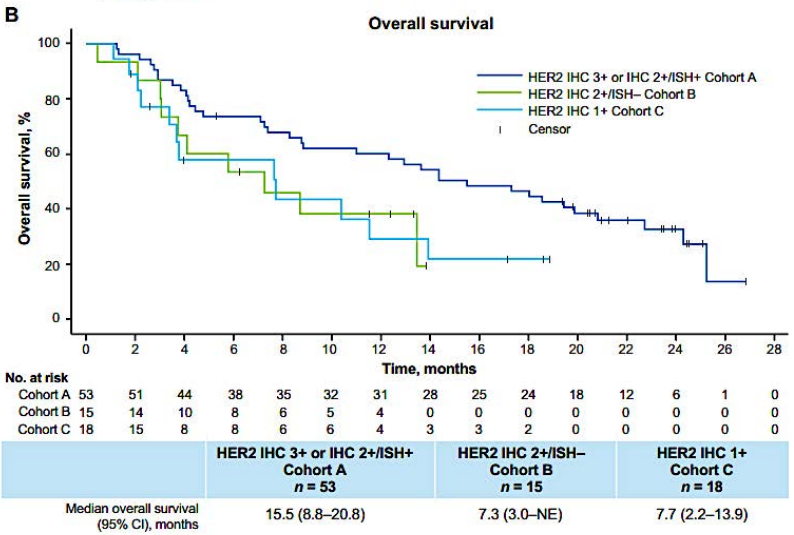


Fig. 1 | Antitumor activity of trastuzumab deruxtecan. A Waterfall plot showing the greatest percentage change from baseline in the sum of diameters of measurable tumors in patients with HER2-positive mCRC (cohort A). Each bar represents a patient. The line at 20% indicates progressive disease. The line at −30% indicates partial response. **B** Spider plot showing change over time from baseline in the sum of diameters of measurable tumors in cohorts A, B, and C. [a]Four patients from the full analysis set were excluded; 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment. [c]One patient from cohort B and 5 patients from cohort C had missing postbaseline data. HER2 human epidermal growth factor receptor 2, IHC immunohistochemistry, ISH in situ hybridization.



	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53	HER2 IHC 2+/ISH– Cohort B n = 15	HER2 IHC 1+ Cohort C n = 18
Median progression-free survival (95% CI), months	6.9 (4.1–8.7)	2.1 (1.4–4.1)	1.4 (1.3–2.1)



	HER2 IHC 3+ or IHC 2+/ISH+ Cohort A n = 53	HER2 IHC 2+/ISH– Cohort B n = 15	HER2 IHC 1+ Cohort C n = 18
Median overall survival (95% CI), months	15.5 (8.8–20.8)	7.3 (3.0–NE)	7.7 (2.2–13.9)

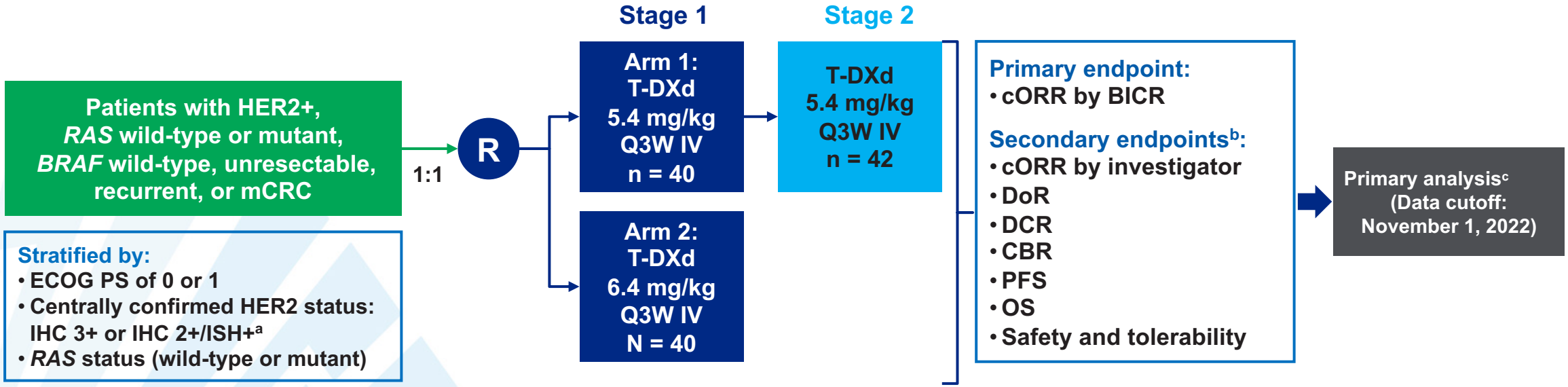
Fig. 2 | Progression-free survival and overall survival in patients with HER2-positive and HER2-low mCRC receiving trastuzumab deruxtecan. Kaplan–Meier curves representing (**A**) progression-free survival and (**B**) overall survival. Marks indicate where data were censored. HER2 human epidermal growth factor receptor 2, IHC immunohistochemistry, ISH in situ hybridization, NE not evaluable.

Yoshino T et al, Nat Comm 2023

DESTINY-CRC02 Study Design

A randomized, blinded, 2-stage, 2-arm, multicenter, global, phase 2 study (NCT04744831)

- Stage 1 (randomized) was followed by Stage 2 (nonrandomized), which enrolled an additional 42 patients



This study was not powered to statistically compare the two arms.

BICR, blinded independent central review; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; CBR, clinical benefit rate; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Both investigators and patients were blind to treatments.
[a]HER2 status was assessed with the Roche VENTANA HER2 Dual ISH DNA probe cocktail assay (IUO). [b]Exploratory endpoints included best percent change in the sum of diameters of measurable tumors based on BICR and investigator. [c]Primary analysis occurred ≥6 months after the last patient had been enrolled or when all patients discontinued from the study, whichever was earlier.

Raghav K... Yoshino T. Lancet Oncol 2024.

DESTINY-CRC02: efficacy results

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	**Stage 2 n = 42**	**Total N = 82**	**Stage 1 N = 40**
cORR, n (%) [95% CI]	**18 (45.0) [29.3-61.5]**	**13 (31.0) [17.6-47.1]**	**31 (37.8) [27.3-49.2]**	**11 (27.5) [14.6-43.9]**
CR	0	0	0	0
PR	18 (45.0)	13 (31.0)	31 (37.8)	11 (27.5)
SD	20 (50.0)	20 (47.6)	40 (48.8)	23 (57.5)
PD	2 (5.0)	6 (14.3)	8 (9.8)	4 (10.0)
NE	0	3 (7.1)	3 (3.7)	2 (5.0)
Confirmed DCR, n (%) [95% CI]	38 (95.0) [83.1-99.4]	33 (78.6) [63.2-89.7]	71 (86.6) [77.3-93.1]	34 (85.0) [70.2-94.3]
Median DoR, mo (95% CI)	8.1 (4.2-NE)	4.6 (4.1-7.0)	5.5 (4.2-8.1)	5.5 (3.7-NE)
Median follow-up, mo (range)	10.6 (2.9-17.1)	7.7 (0.5-10.3)	8.9 (0.5-17.1)	10.3 (0.7-16.4)
Median treatment duration, mo (range)	5.5 (1.4-13.2)	4.8 (0.7-10.8)	5.5 (0.7-13.2)	4.9 (0.7-13.8)
Median total dose, mg/kg (range)	39.6 (10.5-96.8)	37.4 (5.4-81.3)	37.8 (5.4-96.8)	40.8 (6.4-128.4)
Median number of cycles initiated (range)	8.0 (2-19)	7.0 (1-15)	7.0 (1-19)	7.0 (1-20)

cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; mo, month; NE, not evaluable; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; SD, stable disease; T-DXd, trastuzumab deruxtecan.

Raghav K... Yoshino T. Lancet Oncol 2024.

DESTINY-CRC02: efficacy results in subgroups

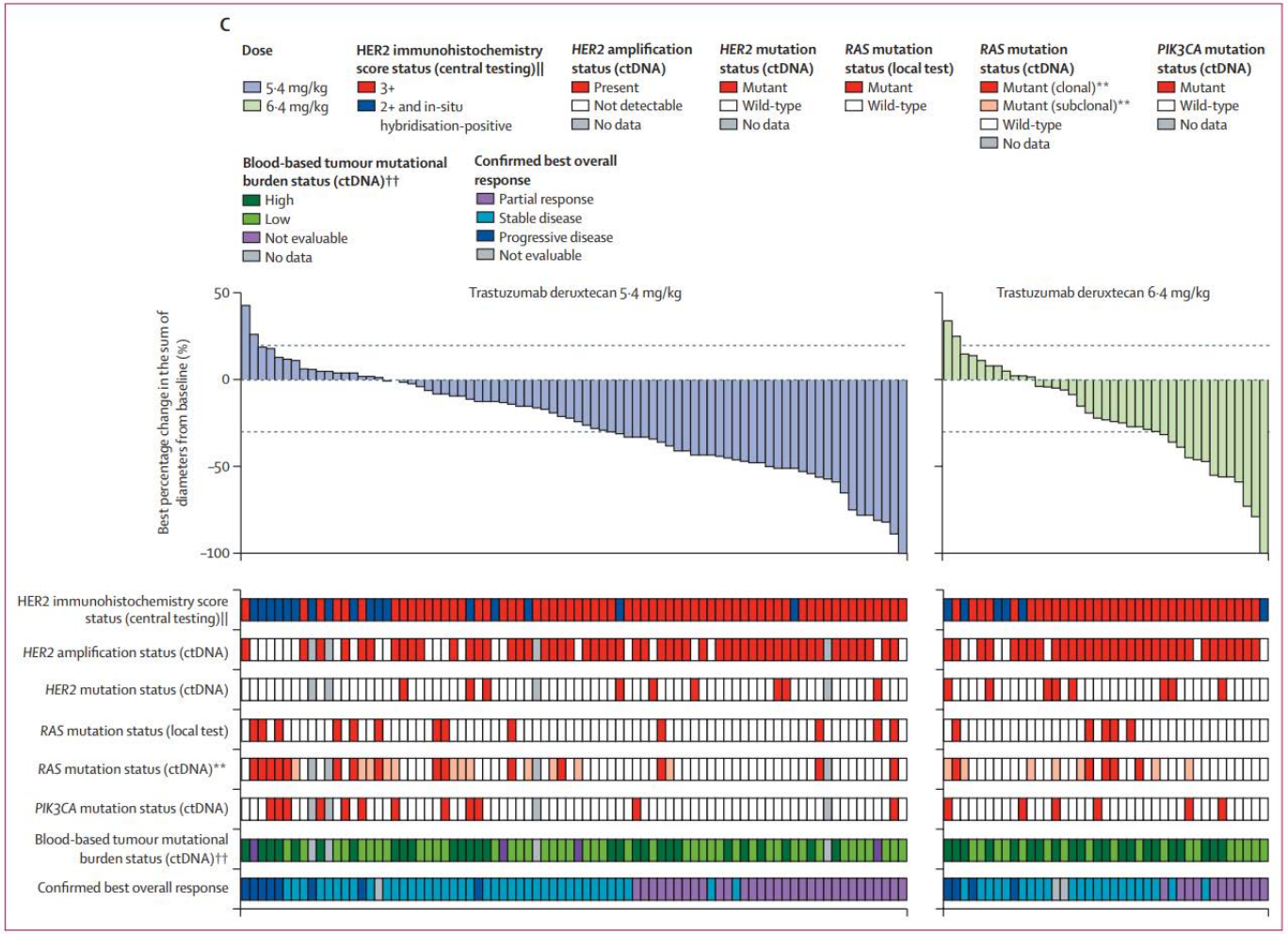


Figure 2: **Subgroup analyses of confirmed objective response rate and best percentage change in the sum of the diameters of all target lesions**
(A) Subgroup analyses of confirmed objective response rate in patients in the trastuzumab deruxtecan 5·4 mg/kg group. (B) Subgroup analyses of confirmed objective response rate in patients in the trastuzumab deruxtecan 6·4 mg/kg group. (C) Percentage change in the sum of diameters by blinded independent central review. Only patients with measurable disease at baseline and at least one post-baseline tumour assessment were included in the figure. Three patients with evaluable ctDNA were not evaluable per Response Evaluation Criteria in Solid Tumours version 1.1 and are not included in the figure. The dashed line at 20% denotes progressive disease and the dashed line at −30% denotes partial response, per Response Evaluation Criteria in Solid Tumours version 1.1. ctDNA=circulating tumour DNA. ECOG=Eastern Cooperative Oncology Group. NA=not applicable. *Based on the exact Clopper-Pearson method for binomial distribution. †Subgroups with fewer than ten patients are reported as NA. ‡Includes rectum, sigmoid, and descending. §Includes caecum, ascending, and transverse. ¶All *RAS*-mutant responders were immunohistochemistry score 3+. ||HER2 status was assessed by central laboratory. ***RAS* mutations were considered clonal if clonality score was ≥0·3 and subclonal if clonality score was <0·3. ††Blood-based tumour mutational burden cutoff was 20 mutations per Mb.

Raghav K... Yoshino T. Lancet Oncol 2024.

DESTINY-CRC01 and DESTINY-CRC02: adverse events

	Trastuzumab deruxtecan 5·4 mg/kg group (n=83*)				Trastuzumab deruxtecan 6·4 mg/kg group (n=39)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any drug-related treatment-emergent adverse events	42 (51%)	29 (35%)	4 (5%)	1 (1%)	18 (46%)	13 (33%)	6 (15%)	0
Nausea	39 (47%)	6 (7%)	0	0	22 (56%)	0	0	0
Alopecia	18 (22%)	NA	NA	NA	11 (28%)	NA	NA	NA
Decreased appetite	16 (19%)	2 (2%)	0	0	6 (15%)	0	0	0
Diarrhoea	14 (17%)	2 (2%)	0	0	8 (21%)	0	0	0
Asthenia	14 (17%)	2 (2%)	0	0	3 (8%)	2 (5%)	0	0
Fatigue	12 (14%)	4 (5%)	0	0	7 (18%)	0	0	0
Platelet count decreased	11 (13%)	3 (4%)	1 (1%)	0	7 (18%)	2 (5%)	2 (5%)	0
Anaemia	11 (13%)	6 (7%)	0	0	6 (15%)	8 (21%)	0	0
Vomiting	11 (13%)	3 (4%)	0	0	3 (8%)	0	0	0
Stomatitis	9 (11%)	0	0	0	5 (13%)	1 (3%)	0	0
Constipation	9 (11%)	0	0	0	1 (3%)	0	0	0
Aspartate aminotransferase increased	7 (8%)	0	0	0	5 (13%)	0	0	0
Neutropenia	6 (7%)	1 (1%)	0	0	0	1 (3%)	0	0
Neutrophil count decreased	5 (6%)	11 (13%)	2 (2%)	0	6 (15%)	6 (15%)	4 (10%)	0
White blood cell count decreased	4 (5%)	5 (6%)	0	0	2 (5%)	4 (10%)	0	0
Pneumonitis	4 (5%)	0	0	0	4 (10%)	0	0	0
Malaise	3 (4%)	1 (1%)	0	0	4 (10%)	0	0	0
Epistaxis	3 (4%)	1 (1%)	0	0	2 (5%)	0	0	0
Lymphocyte count decreased	3 (4%)	0	0	0	1 (3%)	1 (3%)	1 (3%)	0
Thrombocytopenia	3 (4%)	0	0	0	1 (3%)	0	1 (3%)	0
Hypoalbuminaemia	1 (1%)	1 (1%)	0	0	0	0	0	0
Candida infection	0	1 (1%)	0	0	0	0	0	0
Pneumonia bacterial infection	0	1 (1%)	0	0	0	0	0	0
Dizziness	0	1 (1%)	0	0	0	0	0	0
Febrile neutropenia	0	1 (1%)	0	0	0	0	1 (3%)	0
Pancytopenia	0	0	1 (1%)	0	0	0	0	0
Sepsis	0	0	1 (1%)	0	0	0	0	0
Hepatic failure	0	0	0	1 (1%)	0	1 (3%)	0	0
Hypokalaemia	0	0	0	0	0	2 (5%)	0	0
Hepatic encephalopathy	0	0	0	0	0	0	1 (3%)	0

Data are n (%). Data are from the total population treated with trastuzumab deruxtecan (safety analysis set). For treatment-emergent adverse events of grade 1 or 2, any occurring in ≥10% of patients are reported here. All grade 3, 4, and 5 events are reported. NA=not applicable. *One patient randomly assigned to receive trastuzumab deruxtecan 6·4 mg/kg was mistakenly given trastuzumab deruxtecan 5·4 mg/kg and counted in the 5·4 mg/kg group safety analysis set.

Table 3: **Drug-related treatment-emergent adverse events**

Adjudicated drug-related interstitial lung disease or pneumonitis

- **Destiny CRC-02: n=7 (8%) in 5.4 mg/kg**
  n=5 (13%) in 6.4 mg/kg
  all grade 1 or 2
- **Destiny CRC-01:**

Table 6 | Drug-related adjudicated interstitial lung disease/ pneumonitis events

	HER2 IHC 3 + or IHC 2 + /ISH + Cohort A *n* = 53	HER2 IHC 2 + / ISH − Cohort B *n* = 15	HER2 IHC 1 + Cohort C *n* = 18	All Patients *N* = 86
Grade 1	0	0	0	0
Grade 2	2 (3.8)	2 (13.3)	0	4 (4.7)
Grade 3	0	0	1 (5.6)	1 (1.2)
Grade 4	0	0	0	0
Grade 5	2 (3.8)	1 (6.7)	0	3 (3.5)
Any grade/ total	4 (7.5)	3 (20.0)	1 (5.6)	8 (9.3)[a]

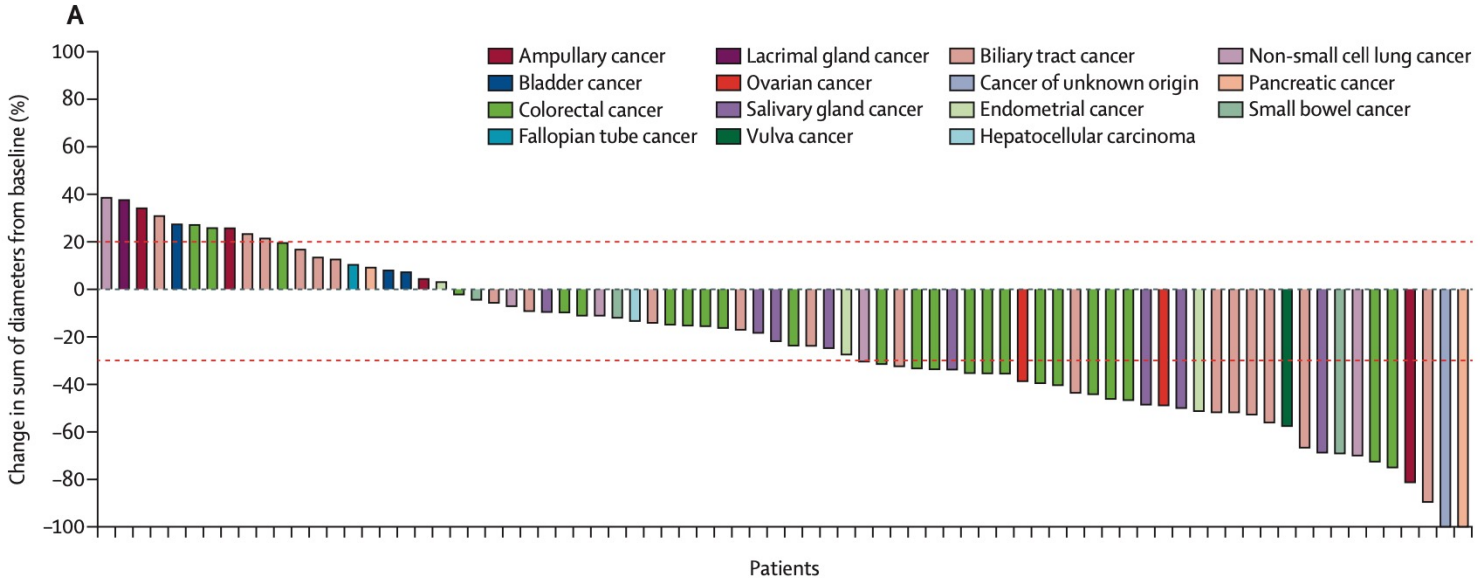
Data are presented as *n* (%).
HER2 human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *ILD* interstitial lung disease, *ISH* in situ hybridization.
[a]ILD grades are the highest/most severe grade recorded in a patient.

Yoshino T et al, Nat Comm 2023
Raghav K... Yoshino T. Lancet Oncol 2024.

Zanidatamab in HER2+ solid tumors

	Biliary tract cancer (n=21)	Colorectal cancer (n=26)	Other cancer types (n=36)	Total (n=83)
Confirmed objective response, n (% [95% CI])	8 (38% [18 to 62])	10 (38% [20 to 59])	13 (36% [21 to 54])	31 (37% [27 to 49])
Partial response, n (%)	8 (38%)	10 (38%)	13 (36%)	31 (37%)
Stable disease, n (%)	5 (24%)	10 (38%)	16 (44%)	31 (37%)
Progressive disease, n (%)	8 (38%)	6 (23%)	7 (19%)	21 (25%)
Clinical benefit rate*	38% (18 to 62)	58% (37 to 77)	53% (35 to 70)	51% (39 to 62)
Disease control rate†	62% (38 to 82)	77% (56 to 91)	81% (64 to 92)	75% (64 to 84)
Median duration of response, months‡	8·5 (3·2 to not estimable)	5·6 (2·8 to 16·7)	9·7 (3·7 to not estimable)	6·9 (5·6 to 16·7)
Had event, n/n (%)	6/8 (75%)	9/10 (90%)	7/13 (54%)	22/31 (71%)
Censored, n/n (%)	2/8 (25%)	1/10 (10%)	6/13 (46%)	9/31 (29%)
Progression-free survival, months§	3·5 (1·8 to 6·7)	6·8 (3·5 to 7·8)	5·5 (3·6 to 8·3)	5·4 (3·7 to 7·3)
Had event, n (%)	19/22 (86%)	24/28 (86%)	28/36 (78%)	71/86 (83%)
Censored, n (%)	3/22 (14%)	4/28 (14%)	8/36 (22%)	15/86 (17%)

	Part 1: dose escalation (n=46)		Part 2: dose expansion (n=86)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Diarrhoea	24 (52%)	0	36 (42%)	1 (1%)
Infusion reaction	20 (43%)	0	29 (34%)	0
Nausea	9 (20%)	0	8 (9%)	0
Fatigue	8 (17%)	1 (2%)	8 (9%)	0
Vomiting	5 (11%)	0	6 (7%)	0
Decreased appetite	2 (4%)	1 (2%)	2 (2%)	0
Arthralgia	1 (2%)	1 (2%)	0	0
Hypertension	0	1 (2%)	0	0
Hypophosphataemia	0	1 (2%)	0	0

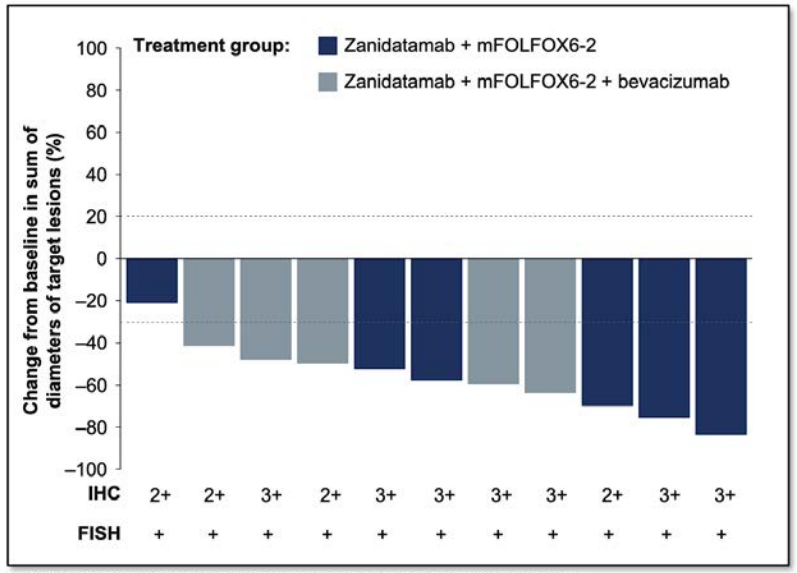


Meric-Bernstam F et al. Lancet Onc 2022

First-Line Zanidatamab + Chemotherapy for HER2-positive mCRC

	Zanidatamab + mFOLFOX6-2 (n=6)	Zanidatamab + mFOLFOX6-2 + bevacizumab (n=5)	Total (N=11)
cORR			
n (%)	5 (83.3)	5 (100)	10 (90.9)
95% CI	35.9, 99.6	47.8, 100	58.7, 99.8
cBOR, n (%)			
CR	0 (0)	0 (0)	0 (0)
PR	5 (83.3)	5 (100)	10 (90.9)
SD	1 (16.7)	0 (0)	1 (9.1)
PD	0 (0)	0 (0)	0 (0)
DCR[b]			
n (%)	6 (100)	5 (100)	11 (100)
95% CI	54.1, 100	47.8, 100	71.5, 100

Median (range) duration of response:
Not reached (2.9+-16.7+) months



Dotted lines indicate 20% increase or 30% decrease in sum of diameters of target tumours.

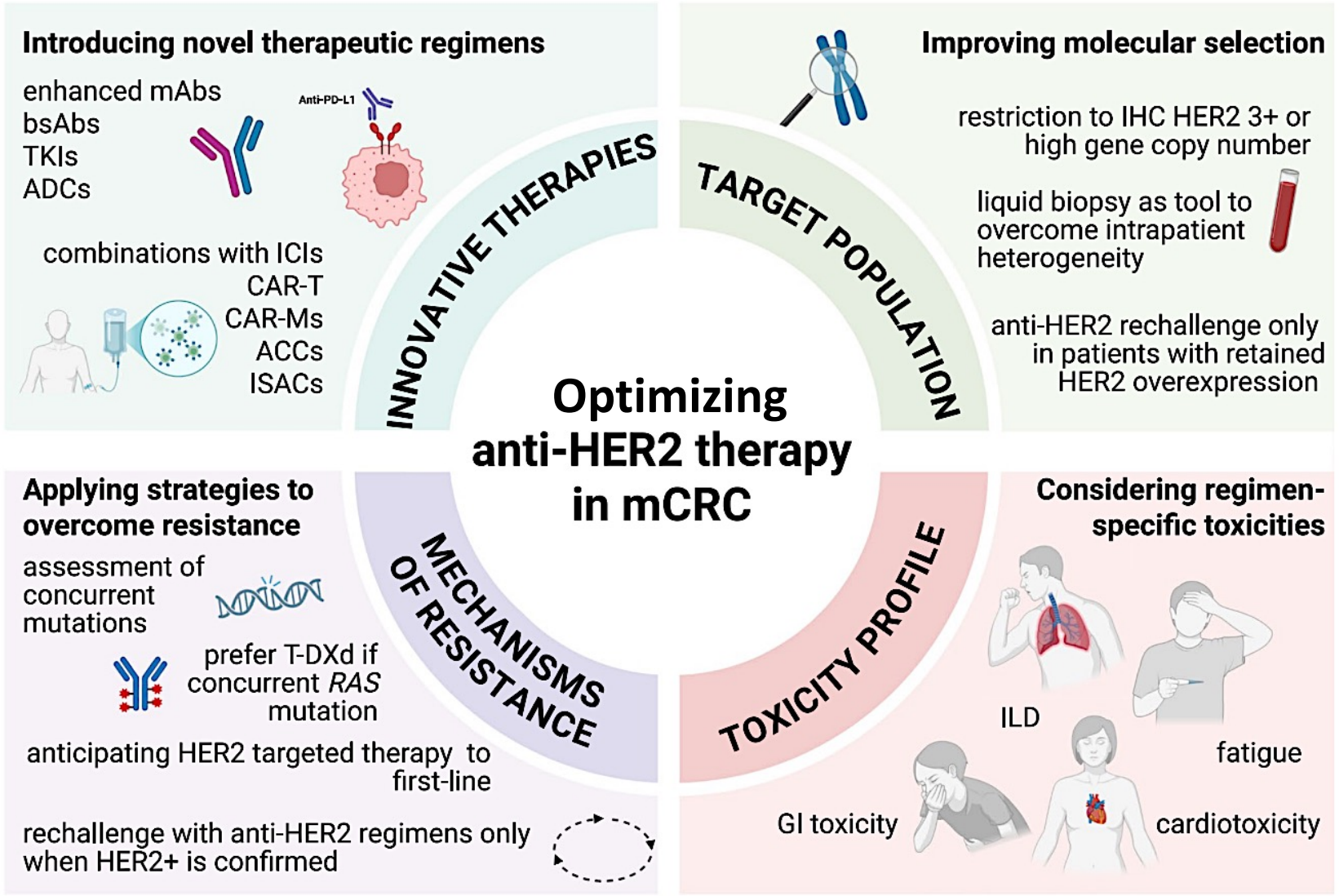
	Zanidatamab + mFOLFOX6-2 (n=6)		Zanidatamab + mFOLFOX6-2 + bevacizumab (n=7)[a]		Total (N=13)	
Any TEAE, n (%)	6 (100)		7 (100)		13 (100)	
Any TRAE,[b] n (%)	6 (100)		7 (100)		13 (100)	
Grade 1-2	4 (66.7)		4 (57.1)		8 (61.5)	
Grade 3-4	2 (33.3)		3 (42.9)		5 (38.5)	
Grade 5	0 (0)		0 (0)		0 (0)	
Serious TRAE,[b] n (%)	1 (16.7)		1 (14.3)		2 (15.4)	
TRAEs leading to zanidatamab discontinuation, n (%)	0 (0)		0 (0)		0 (0)	
Most common TRAEs,[b,c] n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Diarrhoea	4 (66.7)	1 (16.7)	7 (100)	2 (28.6)	11 (84.6)	3 (23.1)
Nausea	4 (66.7)	0 (0)	5 (71.4)	1 (14.3)	9 (69.2)	1 (7.7)
Peripheral sensory neuropathy	4 (66.7)	0 (0)	3 (42.9)	1 (14.3)	7 (53.8)	1 (7.7)
Fatigue	1 (16.7)	0 (0)	3 (42.9)	1 (14.3)	4 (30.8)	1 (7.7)
Infusion-related reaction	2 (33.3)	0 (0)	2 (28.6)	0 (0)	4 (30.8)	0 (0)
Stomatitis	3 (50.0)	0 (0)	1 (14.3)	0 (0)	4 (30.8)	0 (0)
Ejection fraction decreased	2 (33.3)	0 (0)	1 (14.3)	1 (14.3)	3 (23.1)	1 (7.7)
Vomiting	1 (16.7)	0 (0)	2 (28.6)	1 (14.3)	3 (23.1)	1 (7.7)

Two of 12 DLT-evaluable patients had DLTs (diarrhoea) – 1 in each regimen
- ✓ Diarrhoea resolved with concomitant medication

- Three serious TRAEs in 2 patients
  - ✓ One patient experienced dehydration
  - ✓ One patient experienced colitis and acute kidney injury
- No discontinuations of zanidatamab due to TRAEs and no treatment-related deaths

Rha SY et al. ESMO 2024; Abstract 516MO.

Strategies for optimizing anti-HER2 therapy in mCRC



Vaghi C et al, Drugs 2025, Nov 17. doi: 10.1007/s40265-025-02253-2

Anti-HER2 therapies under investigation

Table 3 Anti-HER2 therapies under investigation

Trial NCT identifier (name), phase	Treatment regimen	Patient eligibility criteria	Status
ADCs			
NCT05578287(DETECT) phase II	Disitamab vedotin–tislelizumab, low dose capecitabine, and celecoxib	HER2+ (HERACLES diagnostic criteria) pretreated mCRC	Recruiting
NCT05493683 phase II	Disitamab vedotin–tislelizumab	HER2+ (HERACLES diagnostic criteria) pretreated mCRC	Recruiting
NCT05350917 phase II	Disitamab vedotin–tislelizumab, pyrotinib	HER2+ (at least one tumor cell HER2 IHC 3+ or 2+/FISH+ or NGS confirmed amplification or mutation) progressed or intolerant to first-line therapy	Not yet recruiting
NCT05333809 phase II	Disitamab vedotin–pembrolizumab	HER2+ (HERACLES diagnostic criteria) pretreated mCRC	Unknown
NCT05785325 phase II	Disitamab vedotin–bevacizumab	HER2+ (IHC 3+ or 2+) pretreated mCRC	Unknown
NCT05661357 (HCCSC-C03) phase II	Disitamab vedotin–fruquintinib	HER2+ (IHC 1–3+ or amplification or mutation by NGS) pretreated mCRC	Active, not recruiting
NCT04704661 (DASH) phase I/Ib	T-DXd–ceralasertib	HER2+ (IHC 1–3+ or amplification by FISH or NGS) progressed to at least first-line therapy	Recruiting
NCT06500052 phase I	BL-M17D1	HER2 positive or low expressing pretreated advanced solid tumors	Recruiting
NCT06015048 phase I/IIb	Trastuzumab rezetecan–pyrotinib	HER2+ (overexpression or mutated) pretreated advanced solid tumors	Recruiting
bsAbs			
NCT06695845 (DiscovHER PAN-206) phase II	Zanidatamab	HER2 IHC 3+ pretreated advanced solid tumors	Recruiting
NCT03929666 phase II	Zanidatamab–mFOLFOX6, bevacizumab	HER2+ (IHC 3+ or amplification), *RAS/BRAF*WT, pretreated mCRC (CRC cohort)	Active, not recruiting
Combinations with ICI			
NCT05985707 phase II	KN026 (anti-HER2 bsAb)–chemotherapy +/- KN46 (anti–PD-L1/CTLA-4 bsAb)	HER2+ (IHC 3+ or 2+ and HER2/CEP17 > 2 or *HER* copy number > 6), *RAS/BRAF*-WT, untreated mCRC (cohort A and B)	Active, not yet recruiting
NCT05193292 phase II	Trastuzumab–camrelizumab, chemotherapy	HER2+ (HERACLES diagnostic criteria or NGS sequencing of tumor tissue/blood *HER2* amplification) untreated mCRC	Unknown
TKIs			
NCT05253651 (MOUNTAINEER-03) phase III	Tucatinib–trastuzumab, mFOLFOX6	HER2+, *RAS*-WT previously untreated mCRC	Recruiting
NCT04227041 phase I/II	Pyrotinib–capecitabine	HER2+ pretreated mCRC	Unknown
NCT06581432 (Beamion PANTUMOR-1) phase II	Zongertinib	*HER2*-mutated or amplified pretreated advanced solid tumors	Recruiting
NCT06328738 phase I/II	ELVN-002–trastuzumab, and mFOLFOX6	HER2+ (IHC3+ or 2+/ISH+ or amplification by NGS on tissue), *RAS/BRAF*-WT, pretreated mCRC (CRC cohort)	Recruiting
NCT03457896 phase II	Neratinib–trastuzumab or neratinib–cetuximab	*HER2*-amplified, *KRAS/NRAS/BRAF/PIK3CA*- WT, pretreated mCRC	Unknown
NCT06434597 phase II	SPH5030 (selective, potent, and irreversible anti-HER2 TKI)	HER2+ (overexpression or mutated) pretreated mCRC or advanced biliary tract carcinoma	Recruiting
NCT06253871 phase I/Ib	IAM1363 (selective and brain-penetrant anti-HER2 TKI)	HER2 altered, pretreated advanced solid tumors	Recruiting
Other drugs or combinations			
NCT05673512 phase II/III	IAH0968 (afucosylated anti-HER mAb)–CAPOX	HER2+ (3+ or 2+/ FISH +), *RAS/BRAF*-WT, previously untreated mCRC	Recruiting
NCT04831528 phase II	Trastuzumab–lapatinib or trastuzumab–pertuzumab (as second-line therapy in case of emergence of *HER2* amplification)	*HER2*-amplified mCRC at PD to first-line therapy	Not yet recruiting
NCT05786716 (DETERMINE-treatment arm 04) phase II	Trastuzumab–pertuzumab	*HER2*+ (amplified or mutated) pretreated advanced solid tumors	Recruiting
Adoptive cell therapies			
CAR-T			
NCT03740256 (VISTA) phase I	HER2-specific CAR T-cells, with intra-tumor injection of an oncolytic adenovirus CAdVEC	HER2+ (IHC ≥ 2+ in > 10% tumor cells) pretreated advanced solid tumors	Recruiting
CAR-Ms			
NCT04660929 phase I	Adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor	HER2+ pretreated advanced solid tumors	Not yet recruiting
ACCs			
NCT04319757 phase I	ACE1702 (anti-HER2 oNK cells)	HER2-expressing pretreated advanced solid tumors	Completed
ISACs			
NCT05514717 phase I	XMT-2056 (HT-19 conjugated to a STING agonist)	HER2 3+ or IHC 2+/ISH+ pretreated advanced solid tumors	Recruiting
NCT04278144 phase II	BDC-1001 (anti-HER2 mAb conjugated to a TLR 7/8 dual agonist) +/-nivolumab	HER2+ or amplified pretreated advanced solid tumors	Terminated
NCT05091528 phase I/II	pertuzumab zuvotolimod (pertuzumab conjugated to TLR8 agonist) +/ T-DXd or tucatinib–capecitabine	HER2+ or amplified pretreated advanced solid tumors	Terminated

ACCs antibody-cell conjugates, *ADCs* antibody-drug conjugates, *bsAbs* bispecific antibodies, *CAR-T* chimeric antigen receptor T-cells therapy, *CAR-Ms* chimeric antigen receptor macrophages, *FISH* fluorescent in situ hybridization, *ICIs* immune checkpoint inhibitors, *IHC* immunohistochemistry, *ISH* in situ hybridization, *ISACs* immune-stimulating antibody conjugates, *mAb* monoclonal antibody, *mCRC* metastatic colorectal cancer, *NCT* National Clinical Trial number (ClinicalTrials.org), *NGS* next-generation sequencing, *PD* progressive disease, *T-DXd* trastuzumab deruxtecan, *TLR* toll like receptor, *TKIs* tyrosine kinase inhibitors, *WT* wild-type

Vaghi C et al, Drugs 2025, Nov 17. doi: 10.1007/s40265-025-02253-2

Strategy in pretreated mCRC, HER2 pos

- **MOUNTAINEER study**
  Tucatinib and trastuzumab works well in *RAS* WT cases with IHC 3+, but also active in IHC2+/ISH+

- **DESTINY-CRC02 Study**
  Recommended dose of T-DXd for mCRC is 5.4 mg/kg
  T-DXd works well in IHC 3+ cases regardless of *RAS* status
  Regardless of prior anti-HER2 therapy

- Studies in earlier disease are ongoing (e.g. MOUNTAINEER-03)
- Studies with new agents are ongoing (e.g. zanidatamab)

Questions from General Medical Oncologists — Colorectal Cancer

74 yr old male initially diagnosed with Stage III colon cancer treated with 12 cycles of FOLFOX. 14 months later he developed multiple liver mets, HER2 IHC 3+, KRAS/BRAF WT. Would you skip FOLFIRI/bev and treat with the MOUNTAINEER regimen or T-DXd?

62 y/o male, advanced CRC that progressed on FOLFOX6 and bev. Liver lesion is HER2-amplified and RAS/BRAF WT. Choice between trastuzumab + tucatinib vs T-DXd?

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Questions from General Medical Oncologists — Colorectal Cancer

72-year-old man with metastatic colon cancer, HER2 mutation detected on NGS. Are HER2 mutations approached the same way as HER2 overexpression? What is the overall incidence of HER2 mutations in mCRC? Is the likelihood high enough to justify repeat tissue biopsy vs liquid biopsy at progression? What about lung TKIs — zongertinib and sevabertinib?

77 yr old male with metastatic colon cancer and multiple liver and peritoneal mets progressed on treatment with FOLFOX/bev and FOLFIRI/bev and now has brain mets. Tumor is KRAS/BRAF WT but HER2 IHC 3+. Is your preferred regimen tucatinib/trastuzumab or T-DXd?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Colorectal Cancer

62 yo F with HER2+ mCRC, also has KRAS mutation, progressed after 12 months of T-DXd. What is the impact of KRAS mutation on response to anti-HER2 therapy? What is the likelihood of response if changing therapy from T-DXd to tucatinib/trastuzumab?

54-year-old M with L-sided colon cancer with numerous hepatic mets, HER2 IHC 3+, RAS/BRAF WT, MSS. Treated 1L with FOLFOX + panitumumab. PD after 3 months with RP adenopathy and rising CEA, transitioned to tucatinib + trastuzumab. Has PR, then PD after 8 months with increasing hepatic mets. Biopsy shows persistent HER2 IHC 3+, newly acquired KRAS G12D mutation, new EGFR amplification. Would one consider T-DXd or target other pathways after patient has progressed through double HER2 blockade?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Colorectal Cancer

Patient with HER2+ mCRC, BRAF mutation-positive, KRAS wild-type, progressed after 18 months of T-DXd. What is the next line of therapy? Continue anti-HER2 agent and add a BRAF inhibitor? Or stop anti-HER2 therapy and change therapy to FOLFIRI/cetuximab/encorafenib?

I have a 60 yo man with no comorbidities with liver-only CRC, potentially resectable, KRAS G12D mutated, HER2 IHC 3+. As first-line therapy, would there be any role for HER2-targeted therapy in addition to FOLFOX/bev to shrink tumor for possible resection later?

45 yo with screening colonoscopy reveals sigmoid HER2+ colon cancer, T4 high-risk Stage II. What adjuvant tx do you offer?

RTP RESEARCH TO PRACTICE

Questions from General Medical Oncologists — Colorectal Cancer

72 yo w/ ASHD, HTN and DM, ejection fraction 39%. Progressed on FOLFOX6 and bev. Tumor is HER2-amplified. Is it safe to give T-DXd? What about tucatinib/trastuzumab? Is diarrhea a major problem with tucatinib? What is your recommended HER2 testing workflow in CRC (IHC/ISH vs NGS), and how do you handle equivocal or heterogeneous HER2 findings?

70 yr old female with colon cancer widely metastatic to the liver s/p treatment with FOLFOX + bev and FOLFIRI + bev and on regorafenib for the past 4 years. Now with progression. Patient has HER2-positive disease. Comorbidities: HTN, DM, diabetic neuropathy, CKD, chronic back issues with pain pump. I am thinking about T-DXd next as she is NRAS mutated, and I will obtain repeat NGS as her NGS testing was 10 year ago. Thoughts?

RTP RESEARCH TO PRACTICE

Expert Second Opinion: Current and Future Roles of Immunotherapy and Targeted Therapy in the Management of Advanced Gastroesophageal Cancers

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. Online/Zoom attendees: The CME credit link is posted in the chat room.

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