Data + Perspectives: Clinical Investigators Discuss the Current and Future Clinical Care of Patients with HER2-Positive Gastrointestinal Cancers

Sunday, June 1, 2025
7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Haley Ellis, MD
Sara Lonardi, MD
Kanwal Raghav, MD, MBBS

Moderator

Christopher Lieu, MD

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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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Dr Lonardi — Disclosures
Faculty

No relevant conflicts of interest to disclose.

Dr Raghav — Disclosures
Faculty

Advisory Committees and Contracted Research	AbbVie Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Guardant Health, Janssen Biotech Inc, Merck, Pfizer Inc
Data and Safety Monitoring Boards/Committees	AbbVie Inc, Pfizer Inc

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Dr Lieu — Disclosures
Moderator

Consulting Agreements (to Institution)	Pfizer Inc
Contracted Research (All to Institution)	Genentech, a member of the Roche Group, Janssen Biotech Inc, Sanofi

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Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: Aadi Bioscience, AbbVie Inc, ADC Therapeutics, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Arvinas, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Black Diamond Therapeutics Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Clovis Oncology, Coherus BioSciences, CTI BioPharma, a Sobi Company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, Exact Sciences Corporation, Exelixis Inc, Genentech, a member of the Roche Group, Genmab US Inc, Geron Corporation, Gilead Sciences Inc, GSK, Hologic Inc, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Jazz Pharmaceuticals Inc, Johnson & Johnson, Karyopharm Therapeutics, Kite, A Gilead Company, Kura Oncology, Legend Biotech, Lilly, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Nuvalent, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Rigel Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Syndax Pharmaceuticals, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, and Tesaro, A GSK Company.

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, and Jazz Pharmaceuticals Inc.

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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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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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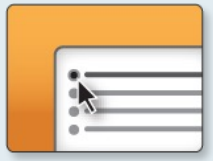
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



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

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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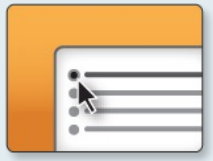
Clinicians Attending via Zoom

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 CME 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: Gastroesophageal Cancers — Dr Lonardi

MODULE 2: Biliary Tract Cancers — Dr Ellis

MODULE 3: Colorectal Cancer — Dr Raghav

Agenda

MODULE 1: Gastroesophageal Cancers — Dr Lonardi

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ISTITUTO ONCOLOGICO VENETO

OECI COMPREHENSIVE Cancer Centre

ESMO Designated Centers of Integrated Oncology and Palliative Care

Regione del Veneto

ASCO Gastrointestinal Cancers Symposium
Sunday, June 1, 2025

HER2+ Gastric/GEJ Cancer

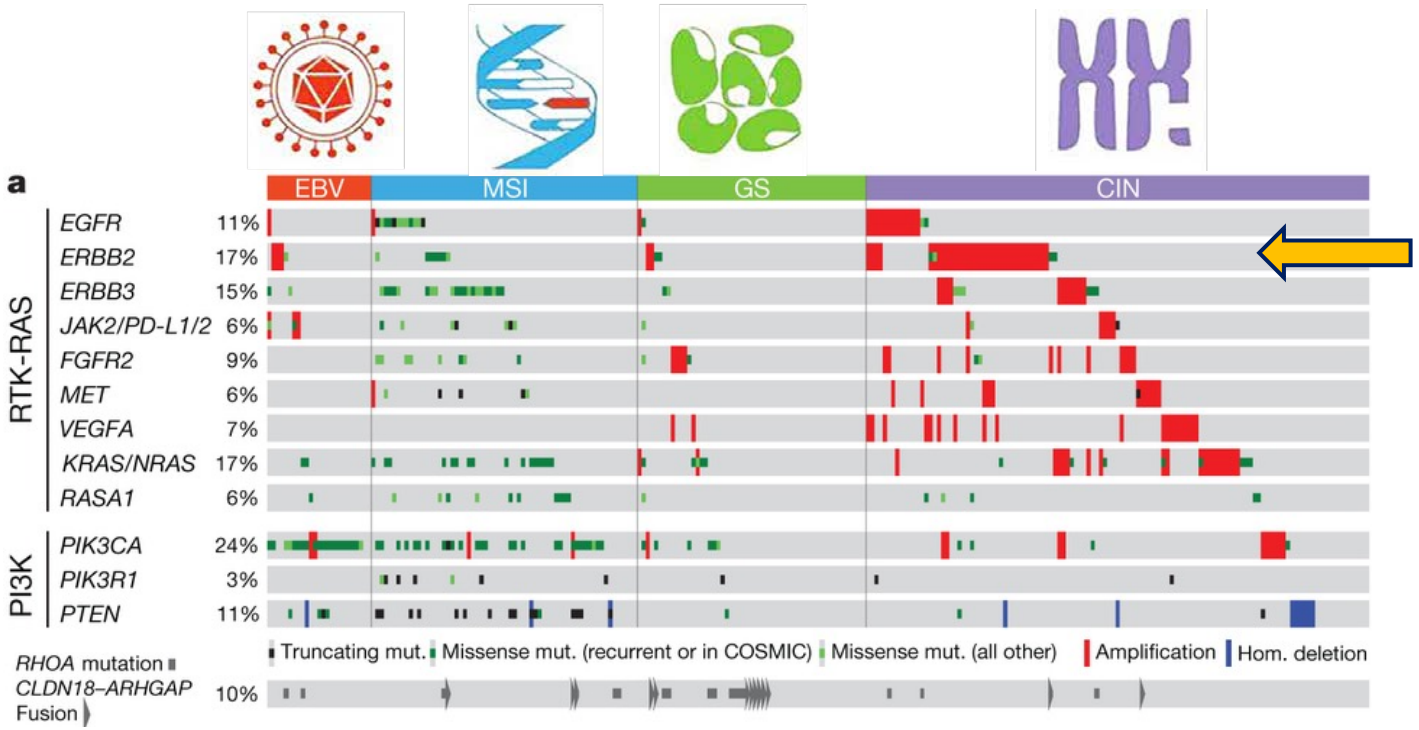
Sara Lonardi

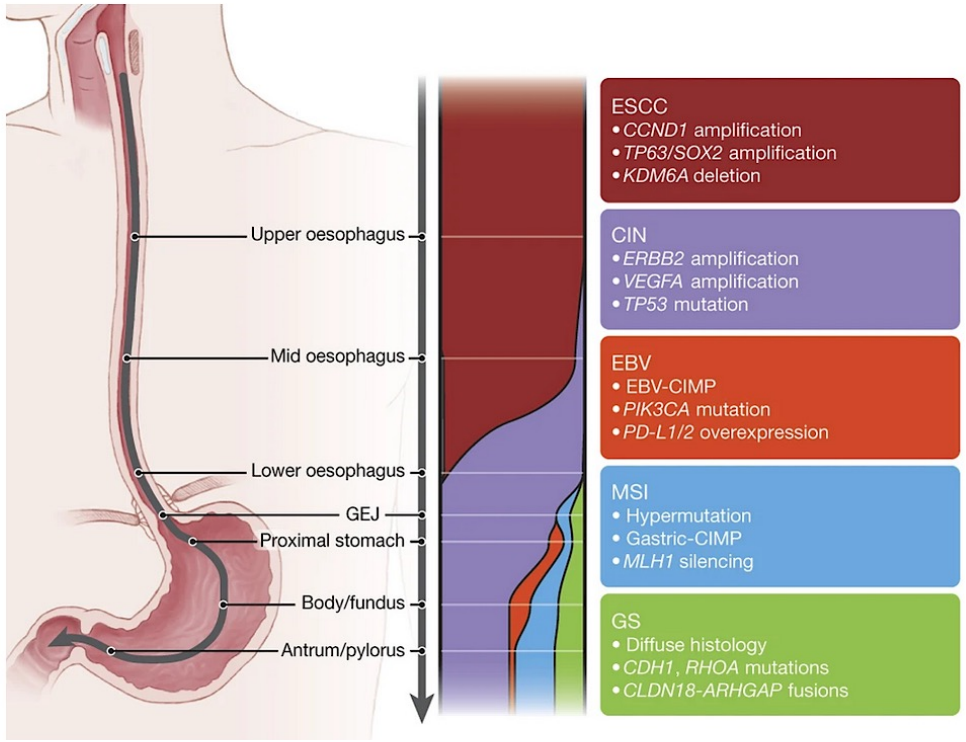
Medical Oncology 1

Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

The molecular landscape

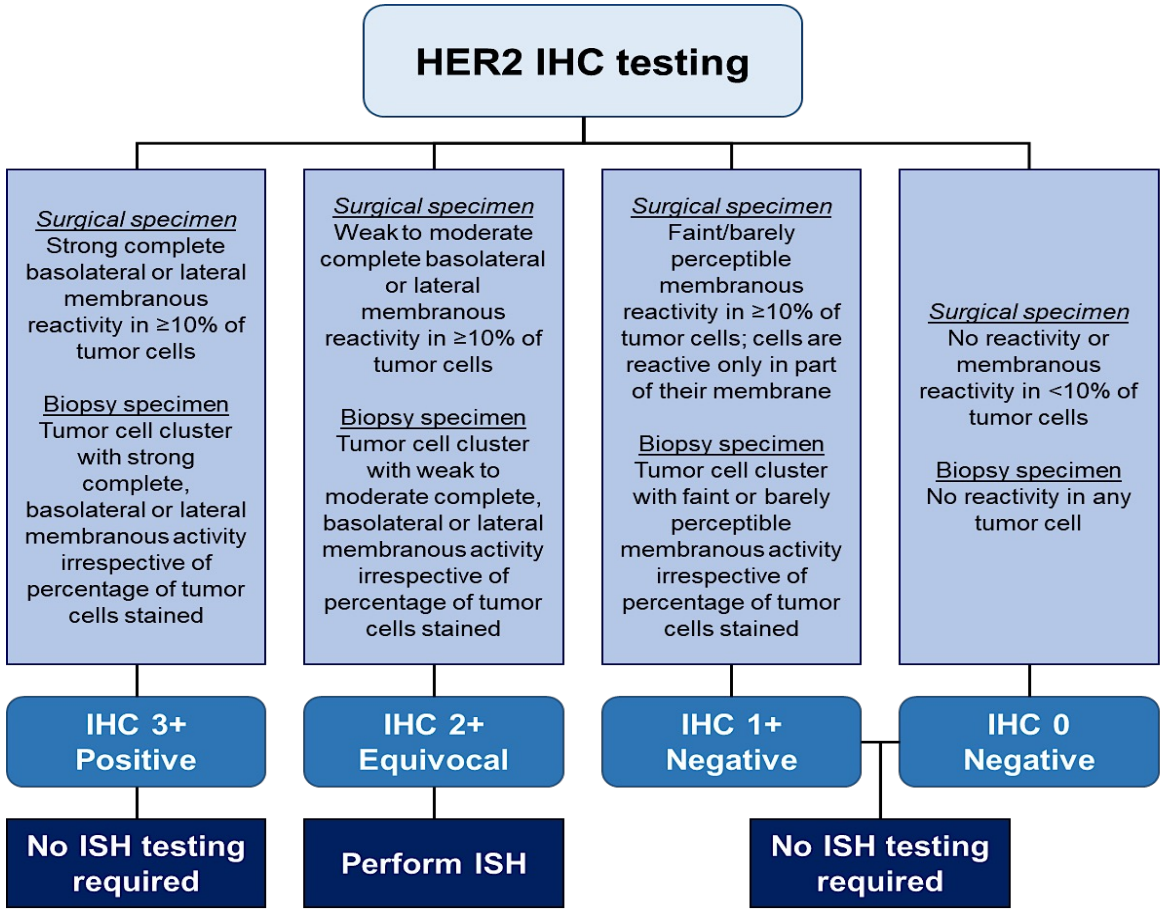
HER2 (ERBB2) is the most frequently amplified gene in GC

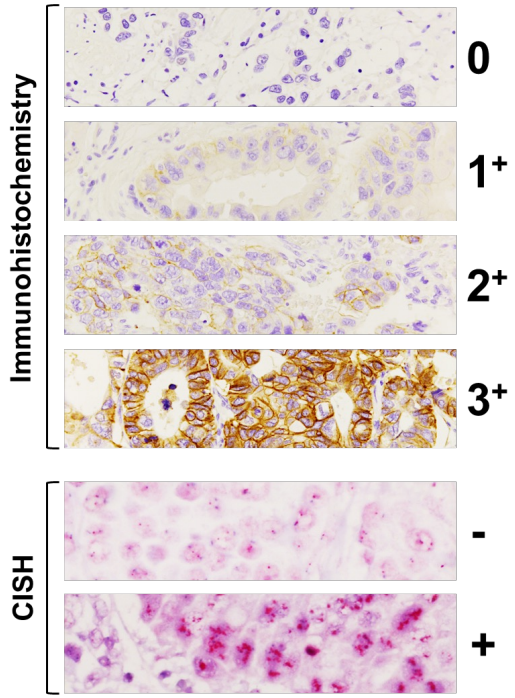




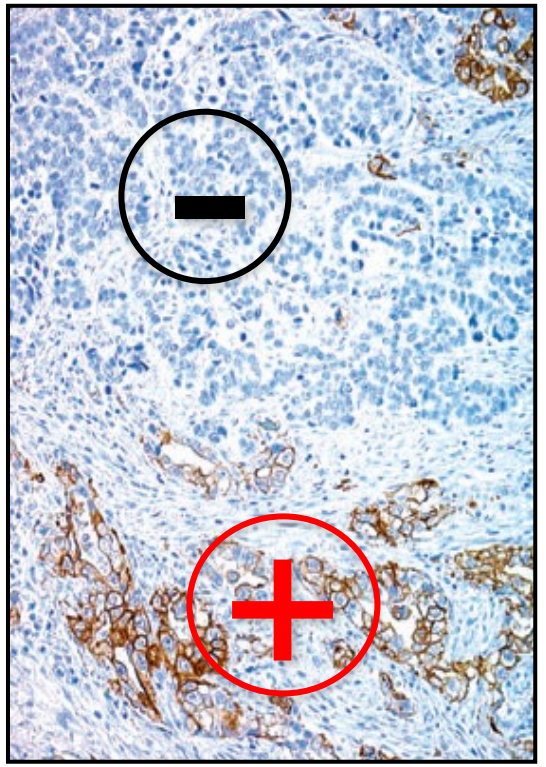
Cancer Genome Atlas Network – *Nature* 2017; 169–175

HER2 testing in gastroesophageal cancer





TUMOR HETEROGENEITY



At least 6 biopsy samples to have a reliable result!

Fassan M et al, Pathologica 2020

HER2 expression as a driver of treatment choice in the last 15 years

HER2 positive (3+/2+ ISH+)

Trastuzumab + platin based doublet

HER2 negative

Platin based doublet

HER2 expression as a driver of treatment choice.. But not alone!

HER2 positive (3+/2+ ISH+)

Trastuzumab + platin based doublet

HER2 negative

Platin based doublet+CPI (according to PD-L1)

TOGA Trial set the Standard treatment in EGJ

Trastuzumab + Cis/Oxa + 5FU/Cape

mOS: 16.0 months

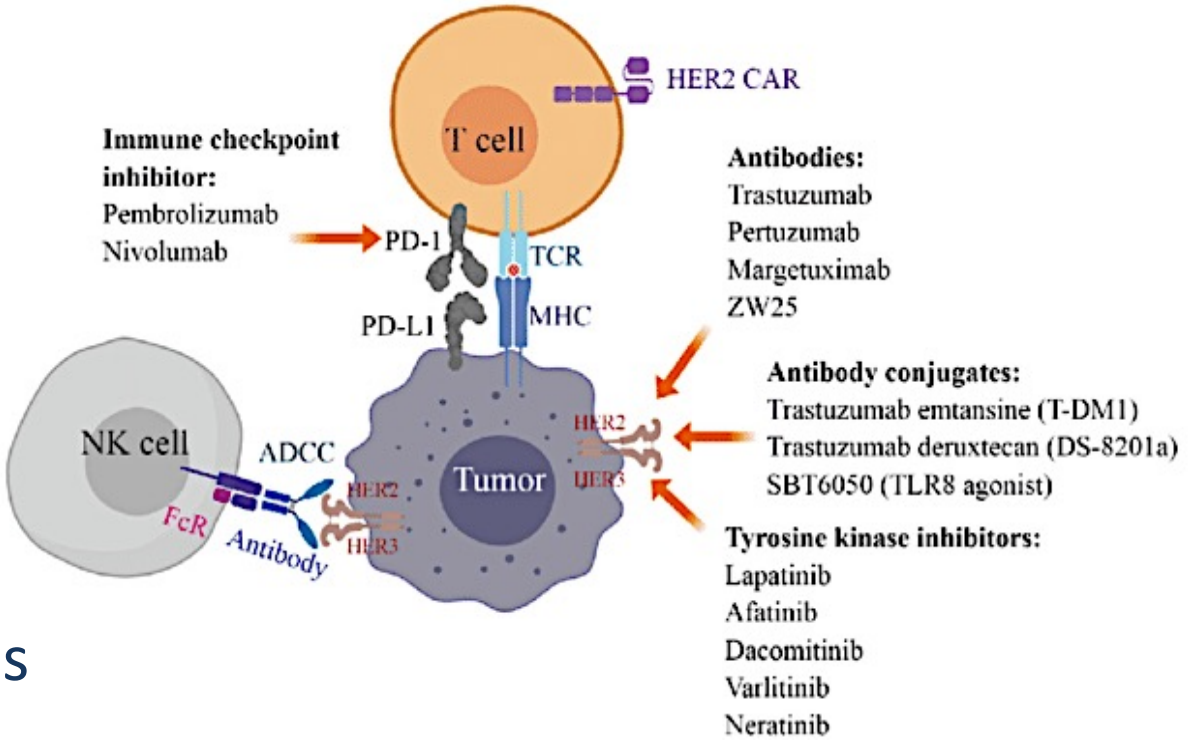
Synergy between HER2 and PD-1 inhibitors

Co-administration of CPI and trastuzumab has been shown to:

- enhance HER2-specific T-cell responses

- promote immune cell trafficking

- induce expansion of peripheral memory T cells



Janjigian Y et al, Nature 2021

Zhao P et al, J Hematol Oncol 2019

The KeyNote 811 trial

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

Stratification Factors

- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Endpoints

- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

https://clinicaltrials.gov/study/NCT03615326. Accessed Feb 2024

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer

https://doi.org/10.1038/s41586-021-04161-3
Received: 25 May 2021
Accepted: 30 September 2021
Published online: 15 December 2021

Yelena Y. Janjigian[1]✉, Akihito Kawazoe[2], Patricio Yañez[3], Ning Li[4], Sara Lonardi[5], Oleksii Kolesnik[6], Olga Barajas[7], Yuxian Bai[8], Lin Shen[9], Yong Tang[10], Lucjan S. Wyrwicz[11], Jianming Xu[12], Kohei Shitara[2], Shukui Qin[13], Eric Van Cutsem[14], Josep Tabernero[15], Lie Li[16], Sukrut Shah[16], Pooja Bhagia[16] & Hyun Cheol Chung[17]

MADRID 2023 ESMO congress

Pembrolizumab plus Trastuzumab and Chemotherapy for HER2+ Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma: Survival Results from the Phase 3, Randomized, Double-blind, Placebo-Controlled KEYNOTE-811 Study

Yelena Y. Janjigian,[1] Akihito Kawazoe,[2] Yuxian Bai,[3] Jianming Xu,[4] Sara Lonardi,[5] Jean Phillipe Metges,[6] Patricio Yañez,[7] Lucjan S. Wyrwicz,[8] Lin Shen,[9] Yuriy Ostapenko,[10] Mehmet Bilici,[11] Hyun Cheol Chung,[12] Kohei Shitara,[2] Shu-Kui Qin,[13] Eric Van Cutsem,[14] Josep Tabernero,[15] Kan Li,[16] Chie-Schin Shih,[16] Pooja Bhagia,[16] Sun Young Rha[12]

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial

*Yelena Y Janjigian, Akihito Kawazoe, Yuxian Bai, Jianming Xu, Sara Lonardi, Jean Phillipe Metges, Patricio Yanez, Lucjan S Wyrwicz, Lin Shen, Yuriy Ostapenko, Mehmet Bilici, Hyun Cheol Chung, Kohei Shitara, Shu-Kui Qin, Eric Van Cutsem, Josep Tabernero, Kan Li, Chie-Schin Shih, Pooja Bhagia, Sun Young Rha, on behalf of the KEYNOTE-811 Investigators**

Published Online
October 20, 2023
https://doi.org/10.1016/S0140-6736(23)02033-0

Overall Survival From Final Analysis of the Phase 3 KEYNOTE-811 Study Evaluating Pembrolizumab Plus Trastuzumab and Chemotherapy in Unresectable or Metastatic HER2+ Gastric/GEJ Adenocarcinoma

Yelena Y. Janjigian,[1] Akihito Kawazoe,[2] Yuxian Bai,[3] Jianming Xu,[4] Sara Lonardi,[5*] Jean Phillipe Metges,[6] Patricio Yanez,[7] Lucjan S. Wyrwicz,[8] Lin Shen,[9] Yuriy Ostapenko,[10] Mehmet Bilici,[11] Hyun Cheol Chung,[12] Kohei Shitara,[2] Mauricio Mahave,[13] Eric Van Cutsem,[14] Josep Tabernero,[15] Linzhi Xu,[16] Kanu P. Sharan,[16] Pooja Bhagia,[16] Sun Young Rha[12]

BARCELONA 2024 ESMO congress

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Pembrolizumab in HER2-Positive Gastric Cancer

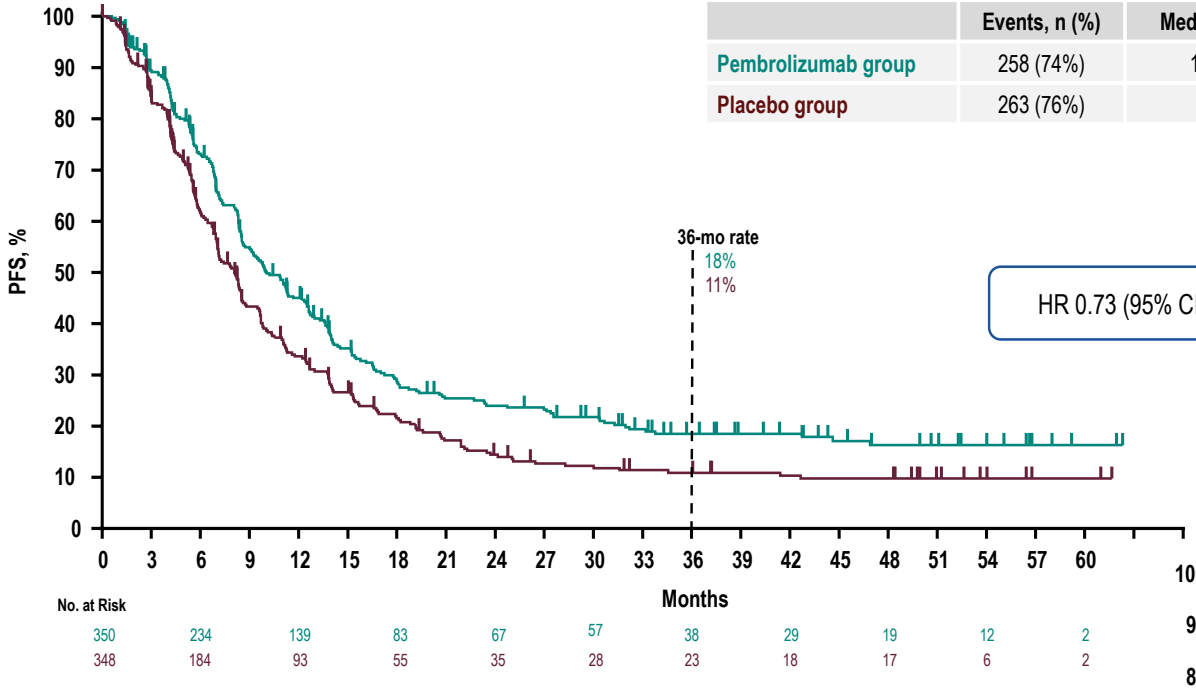
TO THE EDITOR: The phase 3, international, double-blind, randomized, placebo-controlled KEYNOTE-811 trial assessed whether adding pembrolizumab to trastuzumab and chemotherapy would lead to improved efficacy as compared with trastuzumab and chemotherapy alone as first-line therapy for unresectable, metastatic, human epidermal growth factor receptor 2 (HER2)–positive gastric or gastroesophageal junction adenocarcinoma (ClinicalTrials.gov number, NCT03615326). The protocol is available with the full text of this letter at NEJM.org.[1] Data from

At the final analysis, overall survival was significantly longer with pembrolizumab than with placebo. The median overall survival was 20.0 months with pembrolizumab, as compared with 16.8 months with placebo (hazard ratio, 0.80; 95% confidence interval [CI], 0.67 to 0.94; P=0.004). In participants with a PD-L1 combined positive score of 1 or more, the median overall survival was 20.1 months with pembrolizumab, as compared with 15.7 months with placebo (hazard ratio for death, 0.79; 95% CI, 0.66 to 0.95; P=0.006) (Fig. 1 and Table S4). The effect in prespecified

This letter was published on September 14, 2024, at NEJM.org.

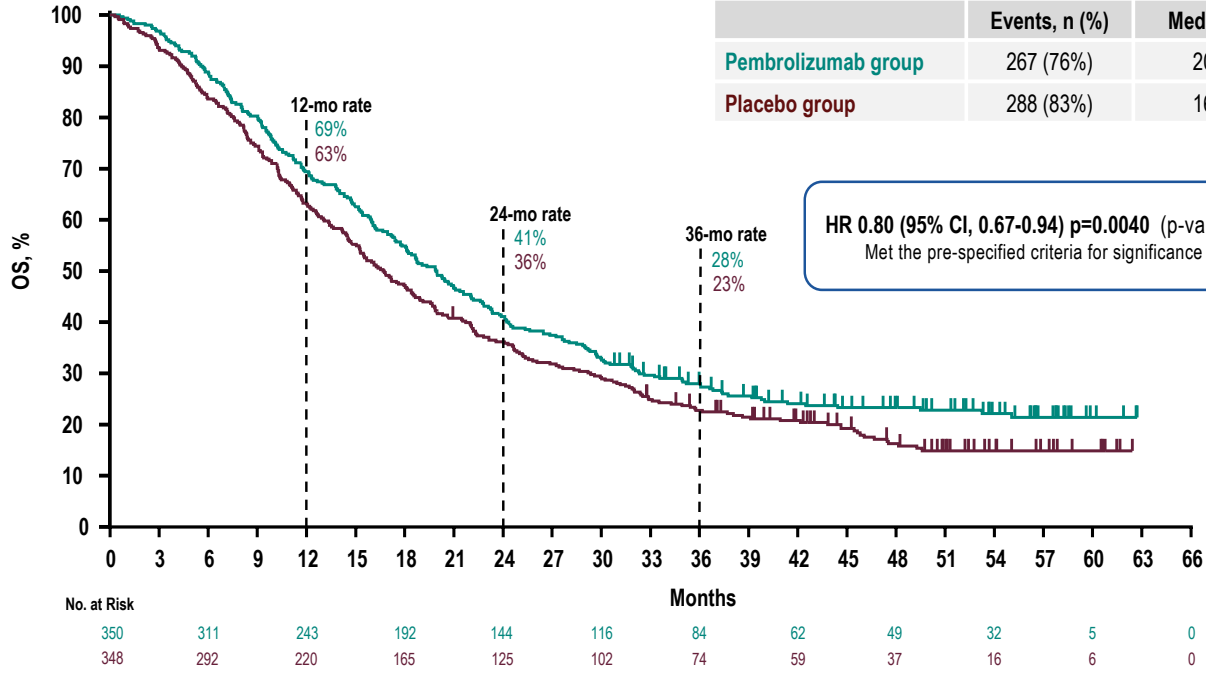
Progression-free and Overall Survival at Final Analysis (ITT)

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	258 (74%)	10.0 (8.6-12.2)
Placebo group	263 (76%)	8.1 (7.0-8.5)



HR 0.73 (95% CI, 0.61-0.87)

	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)



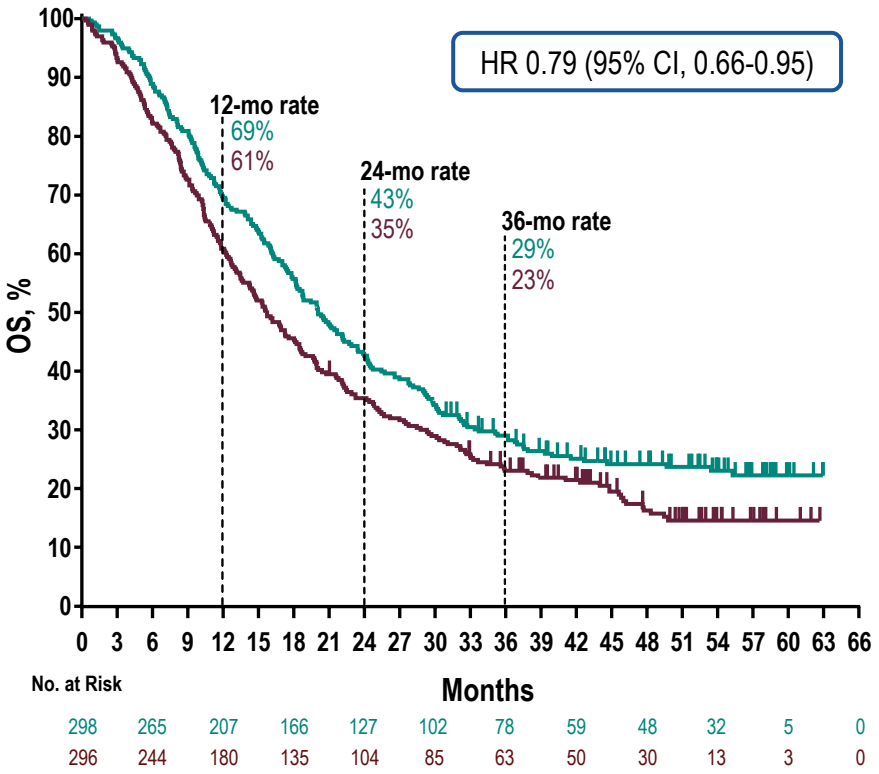
HR 0.80 (95% CI, 0.67-0.94) p=0.0040 (p-value bound 0.0201)
Met the pre-specified criteria for significance at final analysis

Data Cut-off 20 March 2024

Antitumor Activity in PD-L1 CPS ≥1 Subgroup at Final Analysis

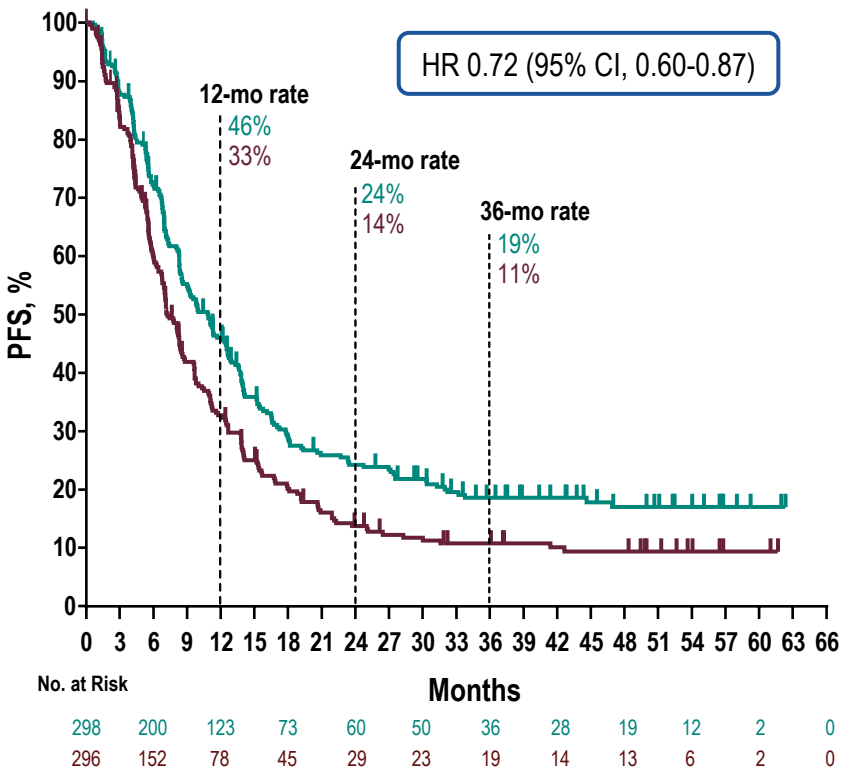
OS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	226 (76%)	20.1 (17.9-22.9)
Placebo group	244 (82%)	15.7 (13.5-18.5)



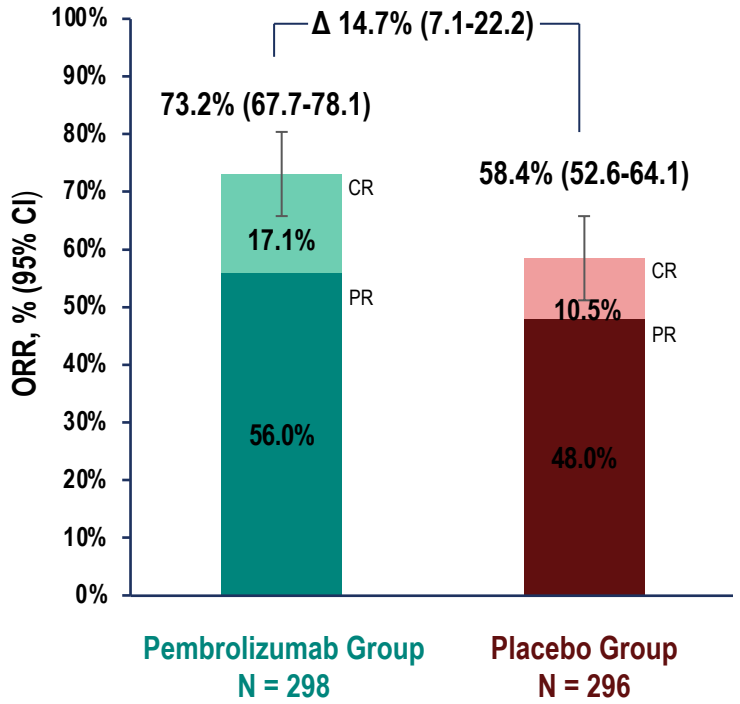
PFS

	Events, n (%)	Median (95% CI), mo
Pembrolizumab group	221 (74%)	10.9 (8.5-12.5)
Placebo group	226 (76%)	7.3 (6.8-8.4)



ORR and DOR

	Responders, n	Median DOR (range), mo
Pembrolizumab group	218	11.3 (1.1+ -to 60.8+)
Placebo group	173	9.5 (1.4+ to 60.5+)



Data cutoff date: 20 Mar 2024. DOR, duration of response.


PD-L1
MATTERS
!

Regulatory agencies approval

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

August 29, 2023

European Commission Approves (pembrolizumab) Plus Trastuzumab and Chemotherapy as First-Line Treatment for HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Expressing PD-L1 (CPS ≥1)

FDA U.S. FOOD & DRUG ADMINISTRATION

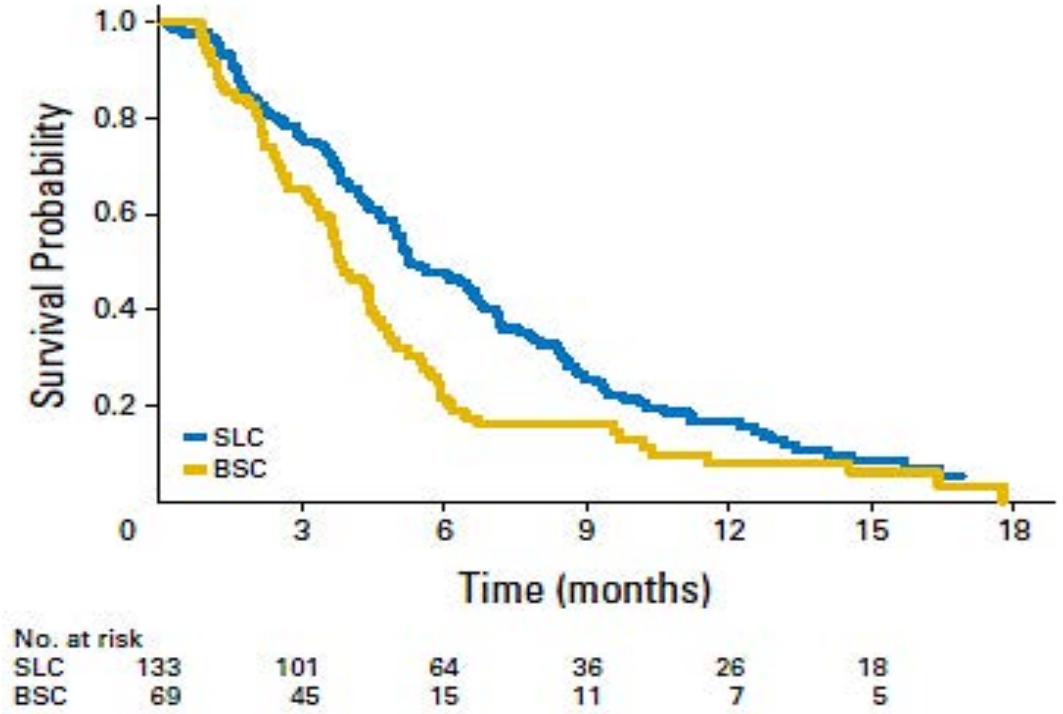
FDA amends pembrolizumab's gastric cancer indication

On November 7, 2023, the Food and Drug Administration revised the existing indication of pembrolizumab with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. **This updated indication, which remains approved under accelerated approval regulations, restricts its use to patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.**

Second-line CT is effective in aGC

VOLUME 30 · NUMBER 13 · MAY 1 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

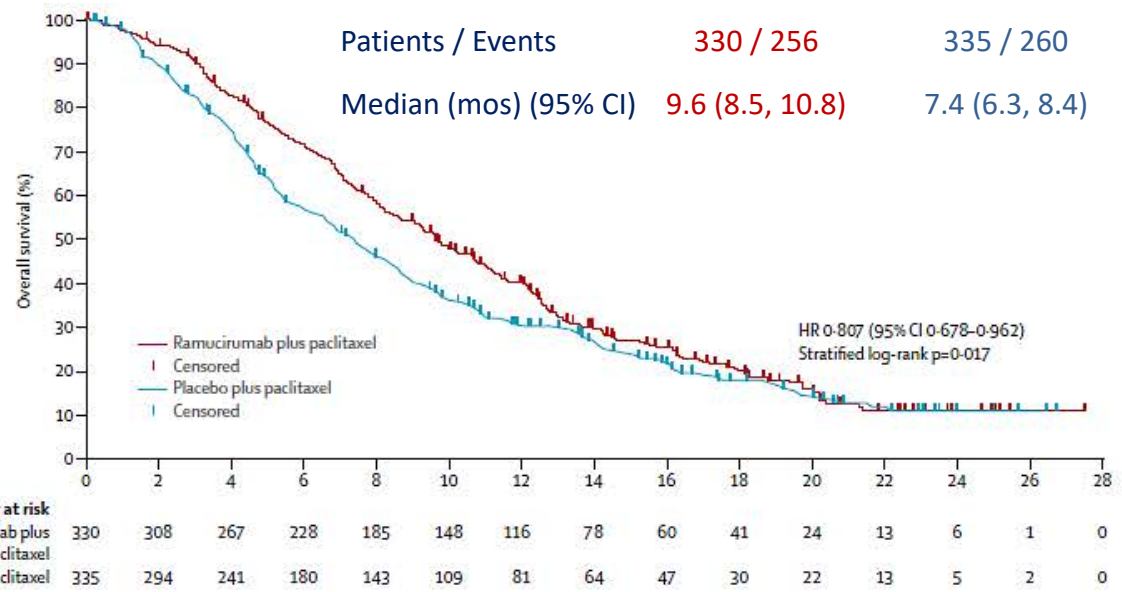
Salvage Chemotherapy for Pretreated Gastric Cancer: A Randomized Phase III Trial Comparing Chemotherapy Plus Best Supportive Care With Best Supportive Care Alone



Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial

Hansjochen Wilke, Kei Muro, Eric Van Cutsem, Sang-Cheul Oh, György Bodoky, Yasuhiro Shimada, Shuichi Hironaka, Naotoshi Sugimoto, Oleg Lipatov, Tae-You Kim, David Cunningham, Philippe Rougier, Yoshito Komatsu, Jaffer Ajani, Michael Emig, Roberto Carlesi, David Ferry†, Kumari Chandrawansa, Jonathan D Schwartz, Atsushi Ohtsu, for the RAINBOW Study Group*

	RAM+PTX	PBO+PTX
Patients / Events	330 / 256	335 / 260
Median (mos) (95% CI)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)



Wilke et al. Lancet Oncology 2014

Landmark clinical trials of HER2-positive gastric cancer

Trials	Patients	Line of therapy	Region	Phase	Study arms	Results	
ToGA [17]	HER2-positive, locally advanced, recurrent or metastatic gastric and GEJ adenocarcinoma	1st	Global	3	Trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) vs chemotherapy alone	Improvement of median OS with trastuzumab plus chemotherapy (13.8 vs 11 months, $P = 0.0046$)	✓
HELOISE [18]	HER2-positive metastatic gastric cancer and GEJ cancer	1st	Global	3	Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg VS 10 mg/kg every 3 weeks) plus cisplatin (80 mg/m^2 on day 1) and capecitabine (800 mg/m^2 twice daily on days 1–14)	No difference in median OS 12.5 vs 10.6 months (stratified HR, 1.24; 95% CI 0.86–1.78; $P = 0.2401$)	✗
TyTAN [32]	HER2 FISH-positive IHC 3+ advanced gastric cancer	2nd	Asia	3	Lapatinib plus weekly paclitaxel vs paclitaxel alone	No difference in median OS (11.0 vs 8.9 months, $P = 0.1044$) nor median PFS (5.4 vs 4.4 months)	✗
LOGIC [19]	HER2-positive advanced or metastatic esophageal, gastric or GEJ adenocarcinoma	1st	Asia	3	Lapatinib with capecitabine plus oxaliplatin vs capecitabine plus oxaliplatin	No difference in median OS (12.2 vs 10.5 months, HR, 0.91; 95% CI 0.73–1.12, $P = 0.3492$) and median PFS (6.0 vs 5.4 months, $P = 0.0381$).	✗
JACOB [23]	HER2-positive metastatic gastric cancer or GEJ cancer	1st	Global	3	Pertuzumab, trastuzumab, and chemotherapy vs trastuzumab and chemotherapy	No difference in median OS (17.5 vs 14.2 months, $P = 0.057$)	✗
GATSBY [30]	HER2-positive gastric cancer	2nd	Global	2/3	IV TD-M1(2.4 mg/kg weekly) vs taxane (docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly)	No difference in median OS (7.9 vs 8.6 months, $P = 0.86$).	✗
T-ACT [33]	HER2-positive advanced gastric or GEJ adenocarcinoma	2nd	Japan	2	Paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 4 weeks vs paclitaxel plus trastuzumab	No difference in median PFS (3.19 vs 3.68 months, $P = 0.334$) and median OS (9.95 vs 10.20 months, $P = 0.199$)	✗

Zhao P et al, *J Hematol Oncol.* 2019;12(1):50

Can we further improve? Issues impacting on outcome

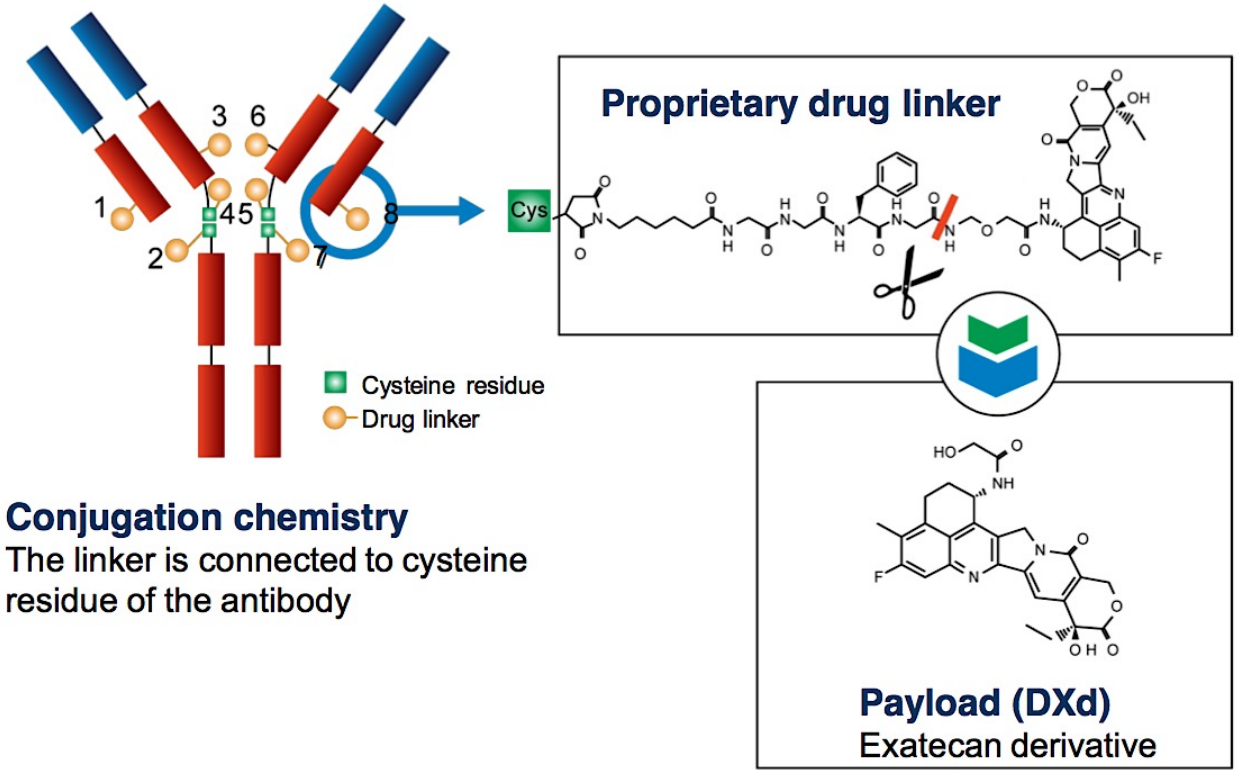
- Tumor heterogeneity

- Acquired resistance

- Low expression

Trastuzumab Deruxtecan characteristics

Novel, next-generation, HER2-directed antibody-drug conjugate composed of
- humanized monoclonal antibody targeting HER2
- cleavable tetrapeptide-based linker
- potent topoisomerase I inhibitor payload (DXd)



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

- **Payload with a different MOA**
- **High potency of payload**
- **Payload with short systemic half-life**
- **Bystander effect**
- **Stable linker-payload**
- **Tumor-selective cleavable linker**
- **High drug-to-antibody ratio**

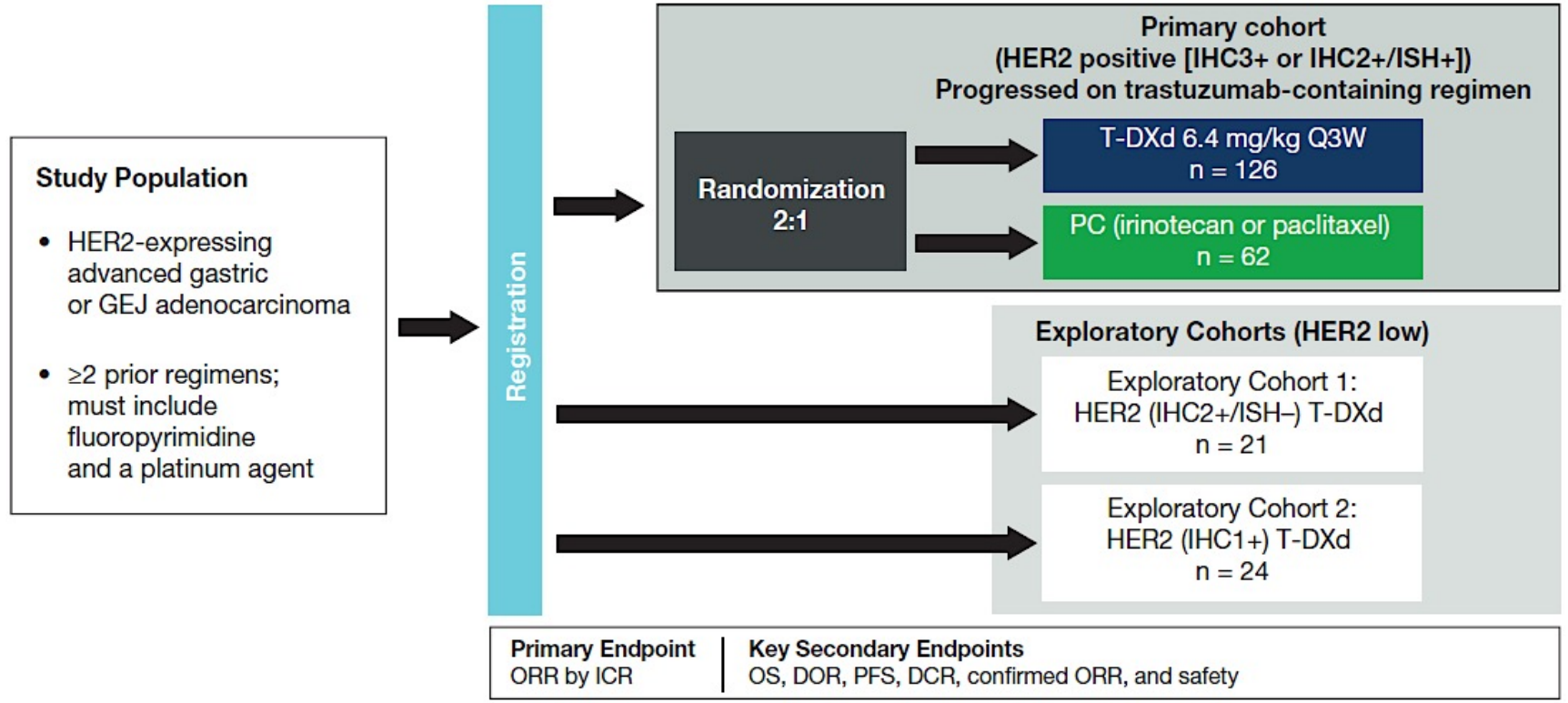
Trastuzumab deruxtecan designed with goal of improving critical attributes of an ADC

Phase 2 DESTINY-Gastric 01 trial

ORIGINAL ARTICLE

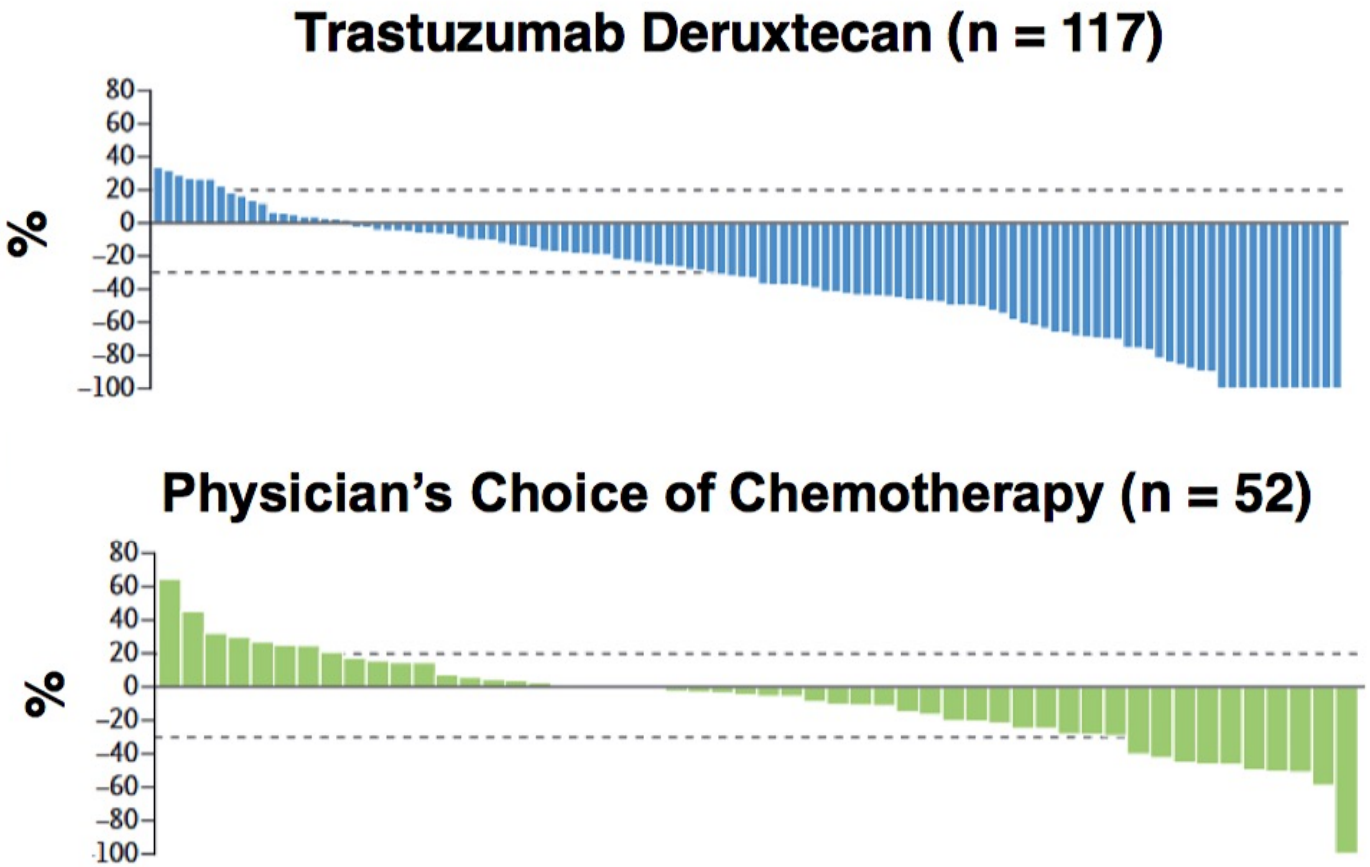
Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*



Shitara et al, New Engl J Med 2020

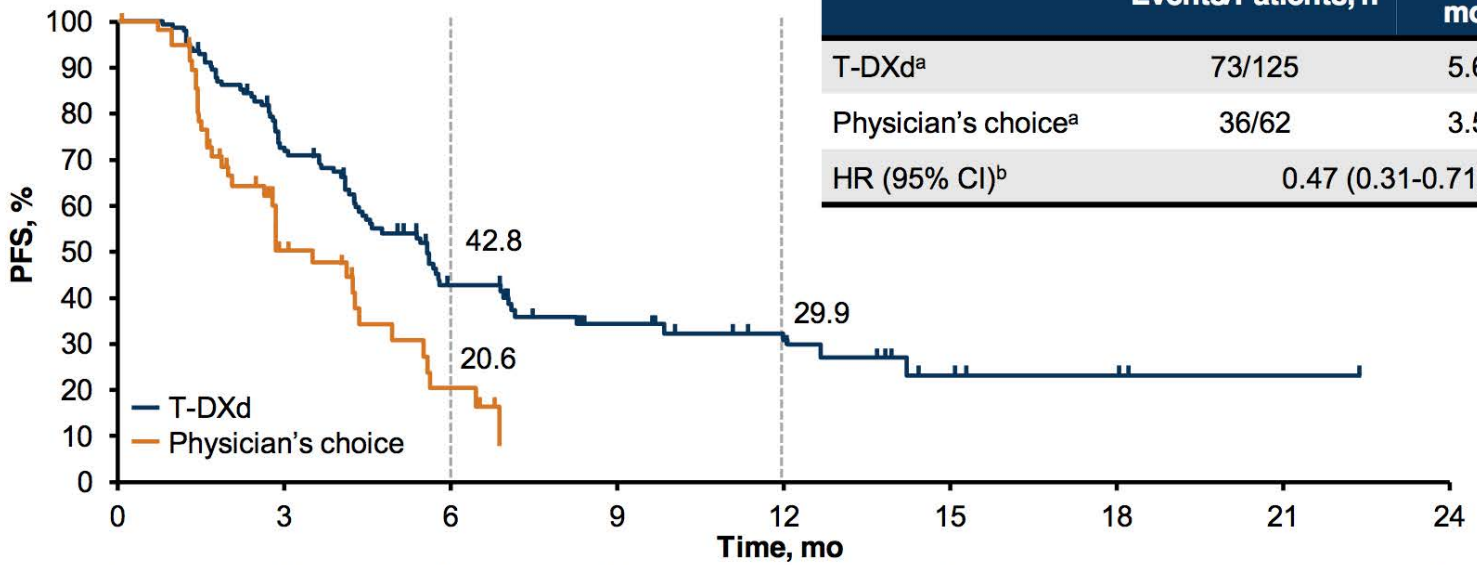
Phase 2 DESTINY-Gastric 01 trial



Endpoint/Outcome	T-DXd (n = 119)	PC Overall (n = 56)
ORR (CR + PR) by ICR, n (%)[a]	51.3% (n = 61) 95% CI, 41.9-60.5; *P* < .0001	14.3% (n = 8) 95% CI, 6.4-26.2
Confirmed ORR[a]	42.9% (n = 51) 95% CI, 33.8-52.3	12.5% (n = 7) 95% CI, 5.2-24.1
Confirmed DCR (CR + PR + SD), n (%)[a]	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1
Confirmed DOR, median, mo	11.3 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
TTR, median, mo	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

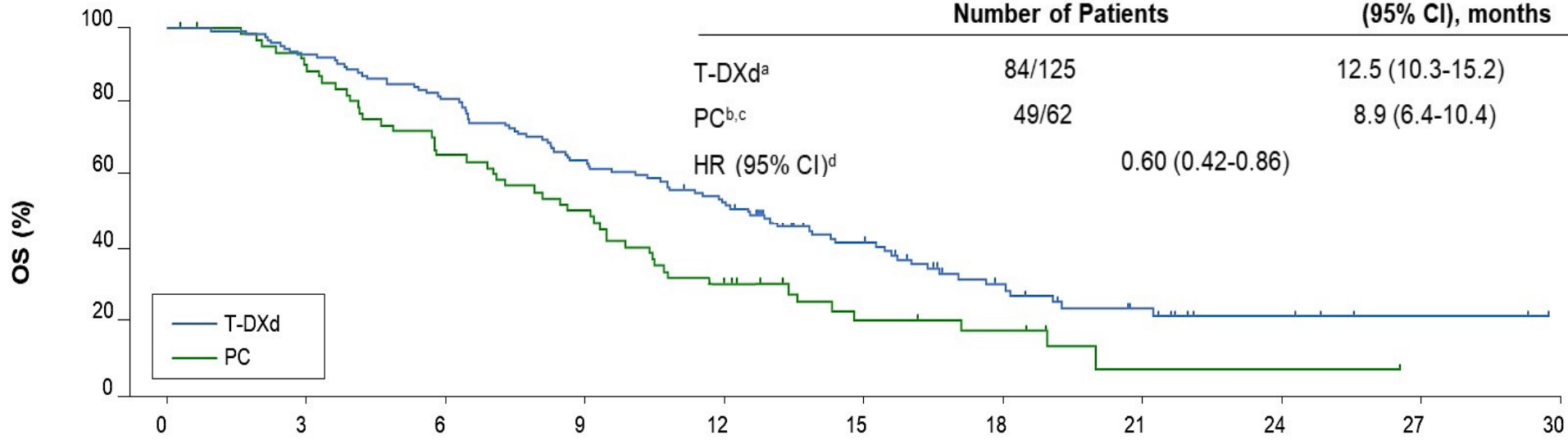
Shitara et al, New Engl J Med 2020

DESTINY-Gastric01 trial: PFS and OS



	Events/Patients, n	Median Duration, mo (95% CI)
T-DXd[a]	73/125	5.6 (4.3-6.9)
Physician's choice[a]	36/62	3.5 (2.0-4.3)
HR (95% CI)[b]	0.47 (0.31-0.71)	

Shitara et al, New Engl J Med 2020



	Number of Deaths/ Number of Patients	Median Duration (95% CI), months
T-DXd[a]	84/125	12.5 (10.3-15.2)
PC[b,c]	49/62	8.9 (6.4-10.4)
HR (95% CI)[d]	0.60 (0.42-0.86)	

Yamaguchi et al, ASCO GI 2022

DESTINY-Gastric 01 trial: analysis by prior ICI

Full analysis set	T-DXd (n = 125)	PC Chemotherapy (n = 62)
Prior ICI, n (%)	44 (35.2)	17 (27.4)
Nivolumab	33 (26.4)	15 (24.2)
Pembrolizumab	10 (8.0)	2 (3.2)
Avelumab	1 (0.8)	0

	Prior ICI		No Prior ICI	
	T-DXd (n = 44)	PC Chemotherapy (n = 17)	T-DXd (n = 81)	PC Chemotherapy (n = 45)
ORR,[a] %	65.9 (29/44)	25.0 (4/16)	42.7 (32/75)	10.0 (4/40)
95% CI	50.1-79.5	7.3-52.4	31.3-54.6	2.8-23.7
Confirmed ORR,[a,b] %	56.8 (25/44)	18.5 (3/16)	34.7 (26/75)	10.0 (4/40)
95% CI	41.0-71.7	4.0-45.6	24.0-46.5	2.8-23.7
Median OS,[a] months	16.6	8.6	10.3	8.4
95% CI	12.1-21.2	3.6-10.7	8.1-13.0	6.9-13.6
	HR, 0.31 (95% CI, 0.15-0.63)		HR, 0.83 (95% CI, 0.50-1.35)	

Shitara et al, ASCO GI 2022

Phase 2 DESTINY-Gastric 02 trial

Trastuzumab deruxtecan in patients in the USA and Europe with HER2-positive advanced gastric or gastroesophageal junction cancer with disease progression on or after a trastuzumab-containing regimen (DESTINY-Gastric02): primary and updated analyses from a single-arm, phase 2 study

Eric Van Cutsem, Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A Wainberg, Jaffer Ajani, Joseph Chao, Yelena Janjigian, Amy Qin, Jasmeet Singh, Ferdous Barlaskar, Yashinori Kawaguchi, Geoffrey Ku

Key eligibility criteria

- Pathologically documented, unresectable or metastatic gastric or GEJ cancer
- Centrally confirmed HER2 positive disease (defined as IHC 3+ or IHC 2+/ISH+) on biopsy after progression on first-line trastuzumab-containing regimen
- ECOG PS 0 or 1

→ **T-DXd**
6.4 mg/kg Q3W
N = 80[a]

Primary endpoint

- Confirmed ORR by ICR

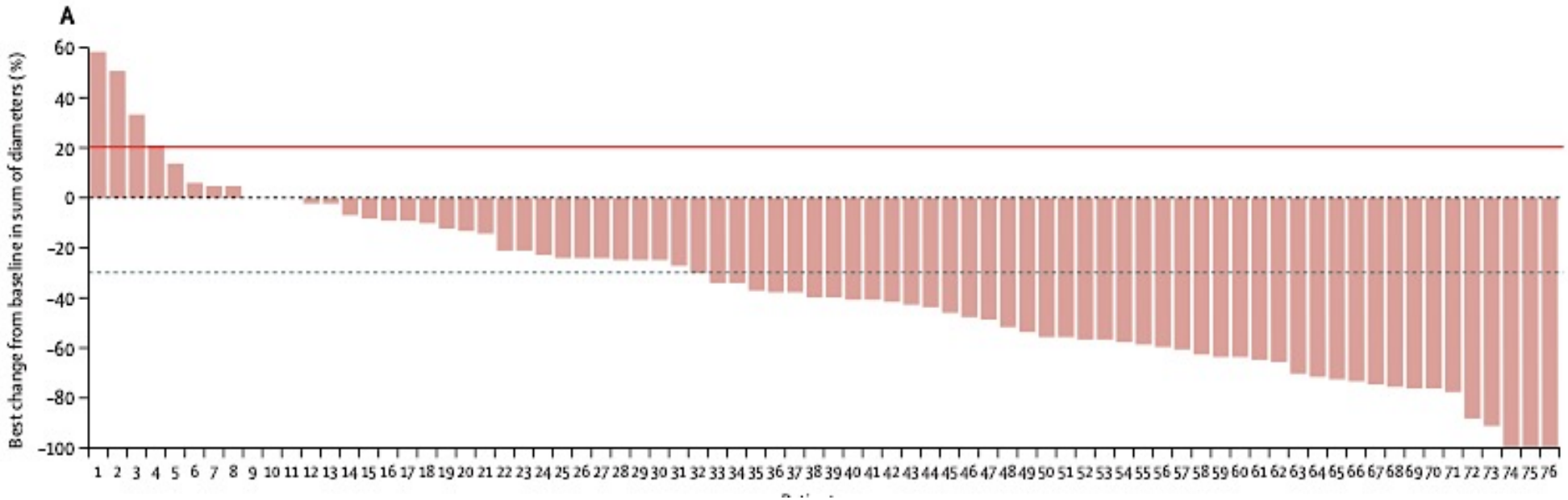
Secondary endpoints[b]

- PFS by ICR
- OS
- DoR by ICR
- Safety and tolerability

→ **Primary analysis**

Van Cutsem et al , Lancet Oncol 2023

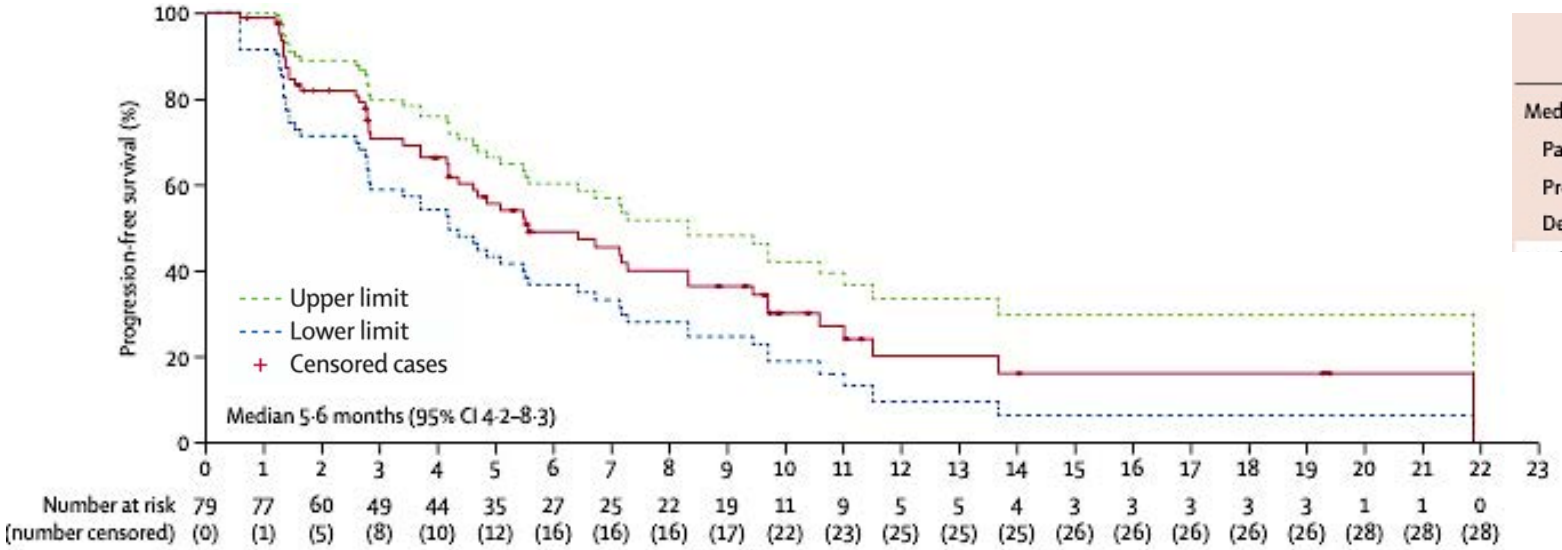
Phase 2 DESTINY-Gastric 02 trial



	April 9, 2021, data cutoff; patients (N=79)	Nov 8, 2021, data cutoff; patients (N=79)
Confirmed objective response	30 (38%; 27·3–49·6)	33 (42%; 30·8–53·4)
Confirmed best overall response		
Complete response	3 (4%)	4 (5%)
Partial response	27 (34%)	29 (37%)
Stable disease	34 (43%)	31 (39%)
Progressive disease	13 (16%)	13 (16%)
Not evaluable	2 (3%)	2 (3%)
Confirmed disease control	64 (81%; 70·6–89·0)	64 (81%; 70·6–89·0)

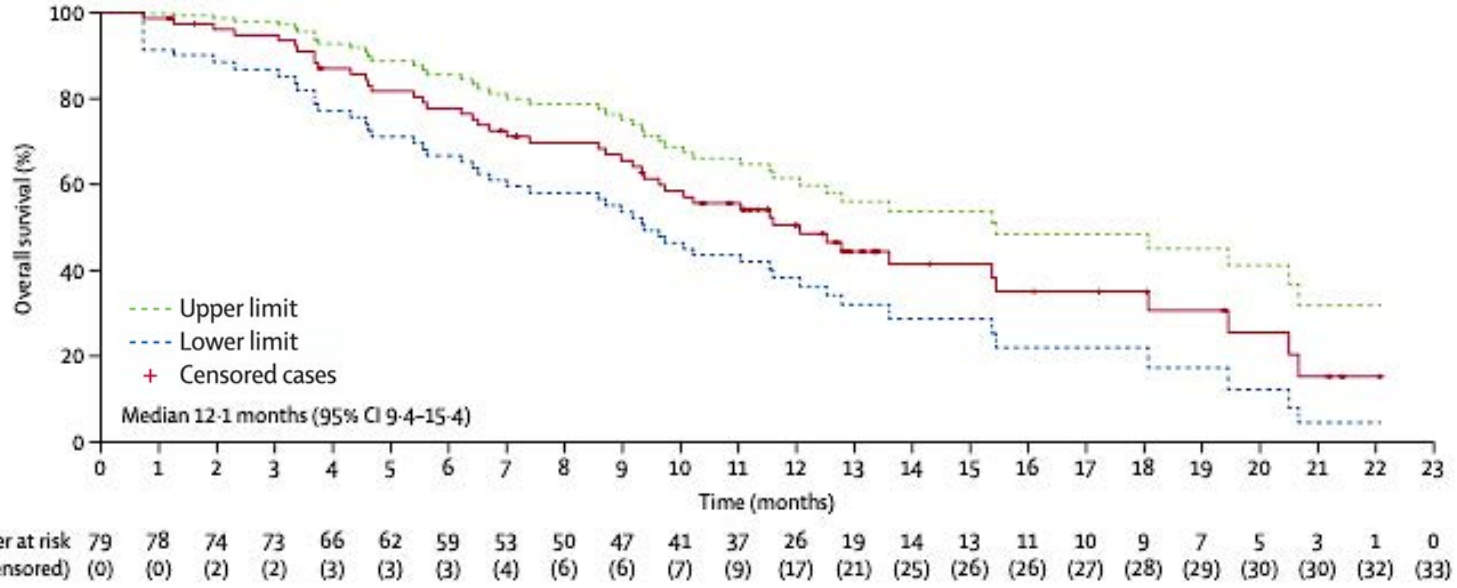
Van Cutsem et al , Lancet Oncol 2023

Phase 2 DESTINY-Gastric 02 trial



	April 9, 2021, data cutoff; patients (N=79)	Nov 8, 2021, data cutoff; patients (N=79)
Median progression-free survival, months	5·5 (4·2–7·2)*	5·6 (4·2–8·3)†
Patients with events	44 (56%)	51 (65%)
Progressive disease	37 (47%)	44 (56%)
Death	7 (9%)	7 (9%)

	April 9, 2021, data cutoff; patients (N=79)	Nov 8, 2021, data cutoff; patients (N=79)
Median overall survival, months	12·1 (8·6–NE)‡	12·1 (9·4–15·4)§
Patients with events	26 (33%)	46 (58%)
Patients without events (censored)	53 (67%)	33 (42%)
Alive	46 (58%)	26 (33%)
Lost to follow-up	7 (9%)	7 (9%)



Van Cutsem et al , Lancet Oncol 2023

What do the guidelines say?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Gastric Cancer

PRINCIPLES OF SYSTEMIC THERAPY

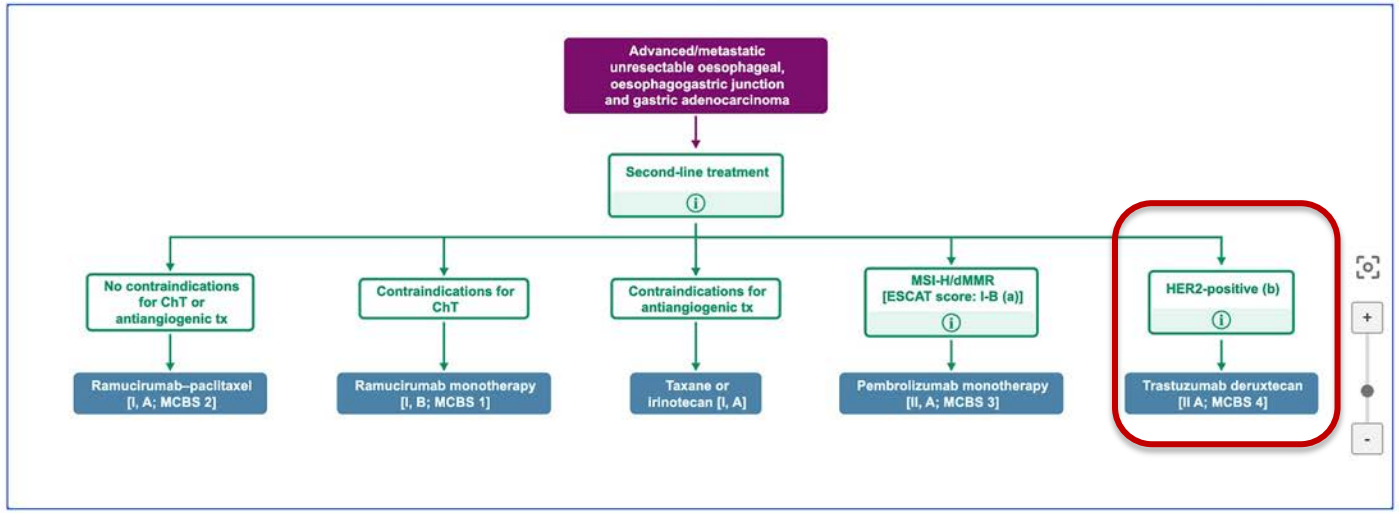
Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy • Dependent on prior therapy and PS
Preferred Regimens • Ramucirumab and paclitaxel (category 1)[50] • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression-positive adenocarcinoma[51] • Docetaxel (category 1)[41,42] • Paclitaxel (category 1)[37,38,52] • Irinotecan (category 1)[52-55] • Fluorouracil[a,g] and irinotecan[53,56,57] • Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[58]
Other Recommended Regimens • Ramucirumab (category 1)[59] • Irinotecan and cisplatin[24,60] • Fluorouracil and irinotecan + ramucirumab[a,g,61] • Irinotecan and ramucirumab[62] • Docetaxel and irinotecan (category 2B)[63]
Useful in Certain Circumstances • Entrectinib, larotrectinib, or repotrectinib[i] for *NTRK* gene fusion-positive tumors[47-49] • Pembrolizumab[e,f] for MSI-H/dMMR tumors[64-66] • Nivolumab and ipilimumab[e,f] for MSI-H/dMMR tumors[18] • Pembrolizumab[e,f] for TMB-high (TMB-H) (≥10 mutations/megabase) tumors[67] • Dostarlimab-gxly[e,f,j] for MSI-H/dMMR tumors[32] • Dabrafenib and trametinib for *BRAF* V600E-mutated tumors[68] • Selpercatinib for *RET* gene fusion-positive tumors[69]

ESMO Gastric Cancer Living Guideline

Second-line Therapy

v1.4 - September 2024



DESTINY Gastric-04: phase 3 Study of 2L T-DXd vs Ram-PTX

2025 ASCO ANNUAL MEETING

Trastuzumab deruxtecan vs ramucirumab plus paclitaxel in second-line treatment of patients with human epidermal growth factor receptor 2–positive (HER2+) unresectable and/or metastatic gastric cancer or gastroesophageal junction adenocarcinoma: Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study.

Kohei Shitara
National Cancer Center Hospital East, Kashiwa, Japan

Additional authors: Mahmut Gümüş, Filippo Pietrantonio, Sara Lonardi, Christelle de la Fouchardière, Clélia Coutzac, Jeroen Dekervel, Daniel Hochhauser, Lin Shen, Wasat Mansoor, Bo Liu, Lorenzo Fornaro, Min-Hee Ryu, Jeeyun Lee, Fabricio Souza, Lori Jukofsky, Yumin Zhao, Takahiro Kamio, Meredith Venerus, Aziz Zaanan, Eric Van Cutsem

Patient Population

- HER2+ (IHC 3+ or IHC 2+/ISH+)[a] GC/GEJA
- HER2-status confirmed locally or centrally[b] on a recent biopsy obtained after progression on trastuzumab
- ECOG PS 0 or 1
- No clinically active CNS metastases[c]

R 1:1

- T-DXd 6.4 mg/kg Q3W (n = 246)
- RAM + PTX[d] (n = 248)

Primary Endpoint
- OS

Secondary Endpoints
- PFS (INV)[e]
- Confirmed ORR (INV)[e]
- DCR (INV)[e]
- DOR (INV)[e]
- Safety

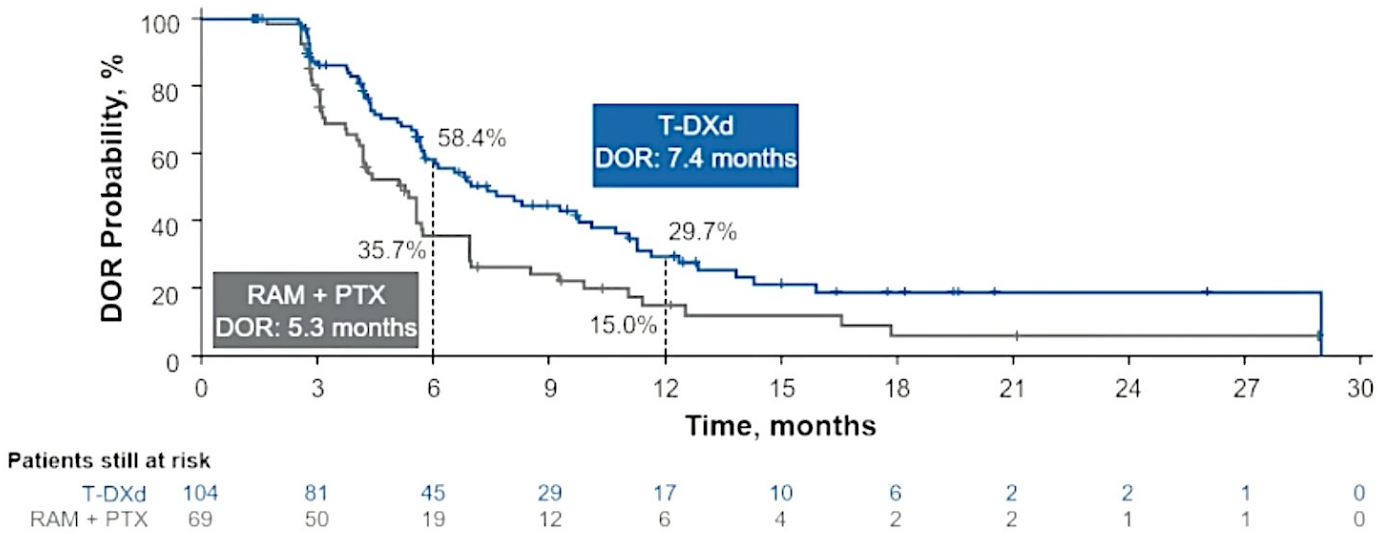
Exploratory Endpoints
- PRO[f]

Stratification factors
- HER2 status (IHC 3+ vs IHC 2+/ISH+)
- Geography (Asia [excl. mainland China], vs Western Europe vs mainland China/rest of the world)
- Time to progression on 1L therapy (<6 months vs ≥6 months)

DESTINY-Gastric04: Phase 3 Study of T-DXd in Patients in the 2L Setting

Confirmed ORR and DOR[a,b]

	T-DXd n = 246	RAM + PTX n = 248
Confirmed ORR (95% CI),[c] %	**44.3 (37.8-50.9)**	**29.1 (23.4-35.3)**
P value[d]	0.0006	
Difference (95% CI),[e] %	15.1 (6.1-24.2)	
DOR, median (95% CI), mo	**7.4 (5.7-10.1)**	**5.3 (4.1-5.7)**
DCR (95% CI), %	**91.9 (87.7-95.1)**	**75.9 (70.0-81.2)**
Confirmed BOR, n (%)		
CR[f]	7 (3.0)	3 (1.3)
PR	97 (41.3)	66 (27.8)
SD[g]	112 (47.7)	111 (46.8)
PD	13 (5.5)	22 (9.3)
NE	6 (2.6)	35 (14.8)

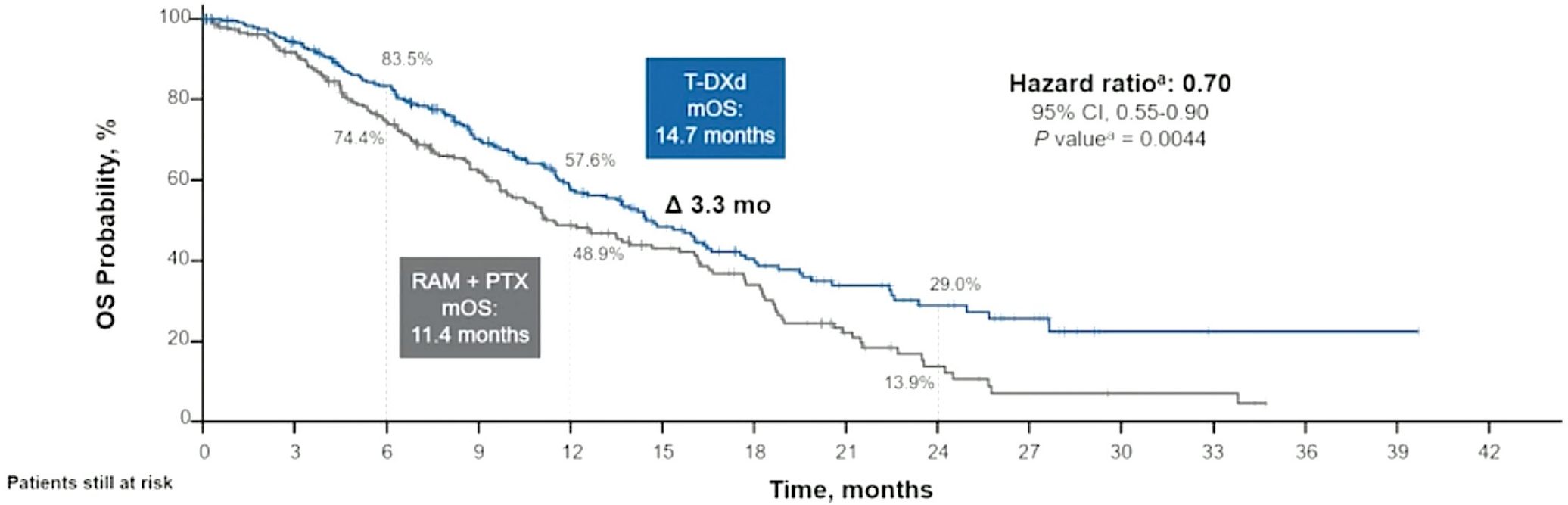


The confirmed ORR was 15.1% greater with T-DXd compared with RAM + PTX (*P* = 0.0006), with longer DOR

Shitara K et al. ASCO 2025;Abstract LBA4002.

DESTINY-Gastric04: Phase 3 Study of T-DXd in Patients in the 2L Setting

OS: Primary Endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in OS compared with RAM + PTX in HER2+ GC/GEJA, showing a 30% reduction in risk of death

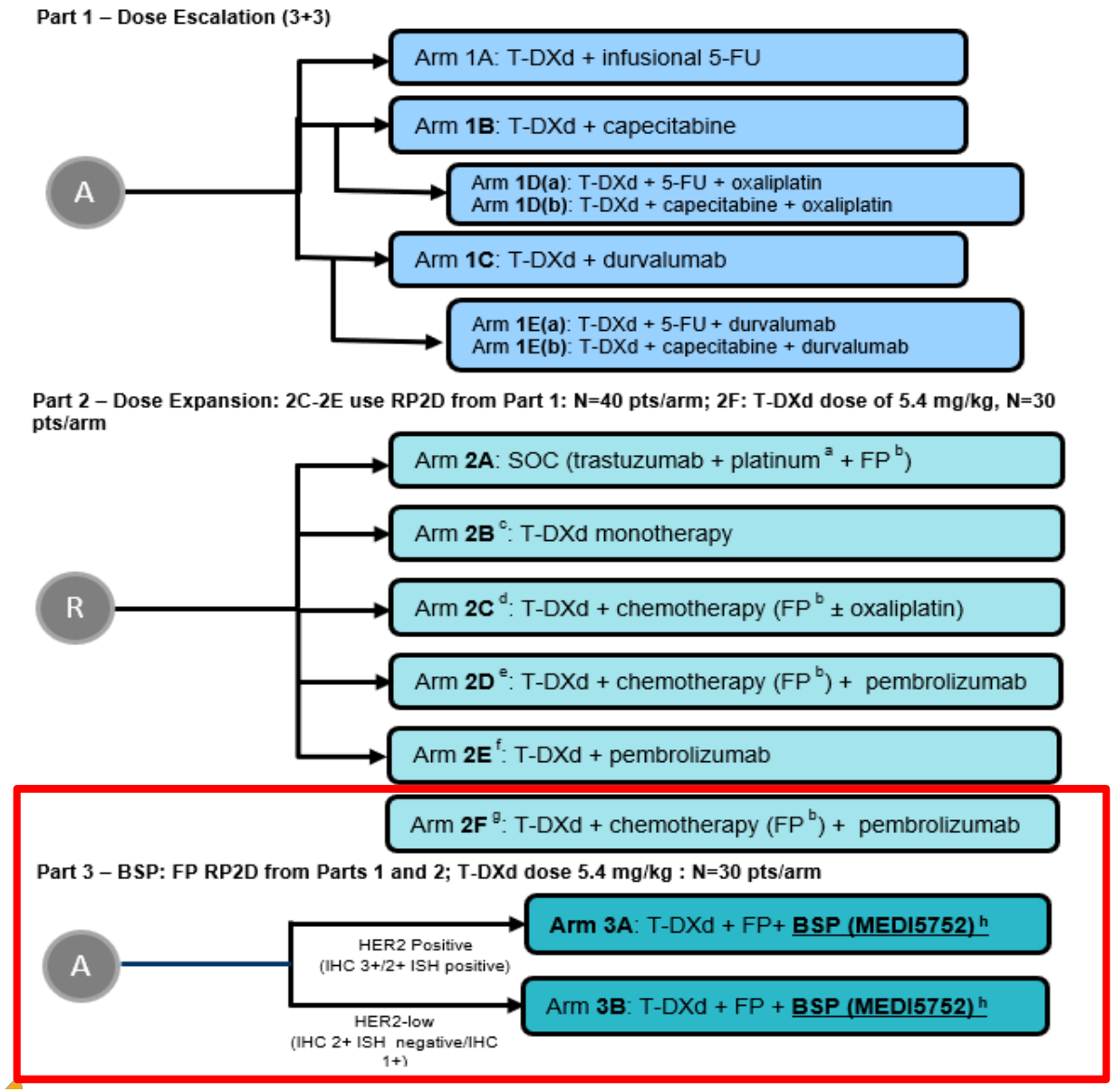
Shitara K et al. ASCO 2025;Abstract LBA4002.

DESTINY-Gastric03 Platform: study update

Patient population

- Metastatic or unresectable HER2+ GC, GEJ, & esophageal adenocarcinoma
- **Part 1:** ≥ 2L following trastuzumab containing therapy
- **Part 1 and 2**: IHC 3+ or 2+/ISH+ by local assessment
- **Part 2 and 3:** Previously untreated metastatic or unresectable GC
- **Part 3**: HER2 expressing (IHC 3+,2+,1+) by local assessment
- ECOG PS 0 or 1
- RECIST 1.1 evaluable

*FP: fluoropyrimidine; investigators choice of 5-FU or capecitabine from Arm 1A or 1B. **Chemo: FP +/- platinum from part 1.



Endpoints

Primary:
- Part 1: Safety, RP2D
- Part 2: ORR[h]
- Part 3: ORR[h]

Secondary:
- Part 1: ORR[h]
- Part 2 and 3: Safety
- PK and ADA (T-DXd, Durva, MEDI5752)
- ORR (central vs local HER2)

Exploratory:
- PK and ADA (pembrolizumab)
- Monitoring determinants of response/resistance through liquid and tissue samples.

Novel HER-2 directed therapies

Antibody-drug conjugate

- Trastuzumab deruxtecan (T-Dxd) (DS-8201a)
- RC48-ADC: ongoing phase 2 trial (NCT03556345)

Monoclonal antibodies

- Margetuximab (+ PD-1 inhibitor)

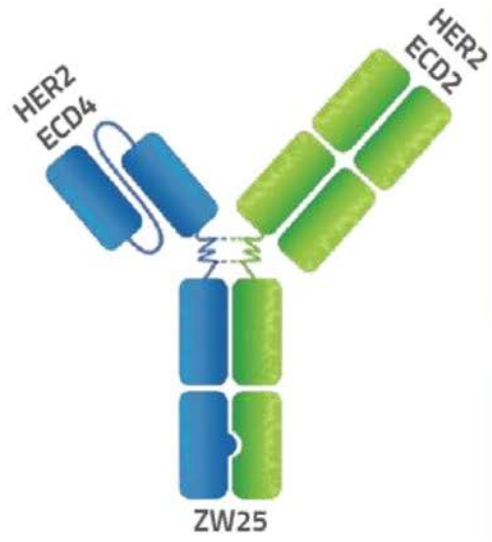
Bispecific antibodies

- ZW25; targets two areas on HER2 (phase 2 in combination with SOC chemo [NCT03929666], and phase 1/2 with chemo and PD-1 inhibitor [NCT04276493])

Combination with immunotherapy

- With durvalumab, nivolumab, and pembrolizumab (phase 3 KEYNOTE-811)

Zanidatamab: a HER2 targeted bispecific antibody



Biparatopic Binding Drives Unique Mechanisms of Action

Biparatopic binding targets two distinct HER2 epitopes

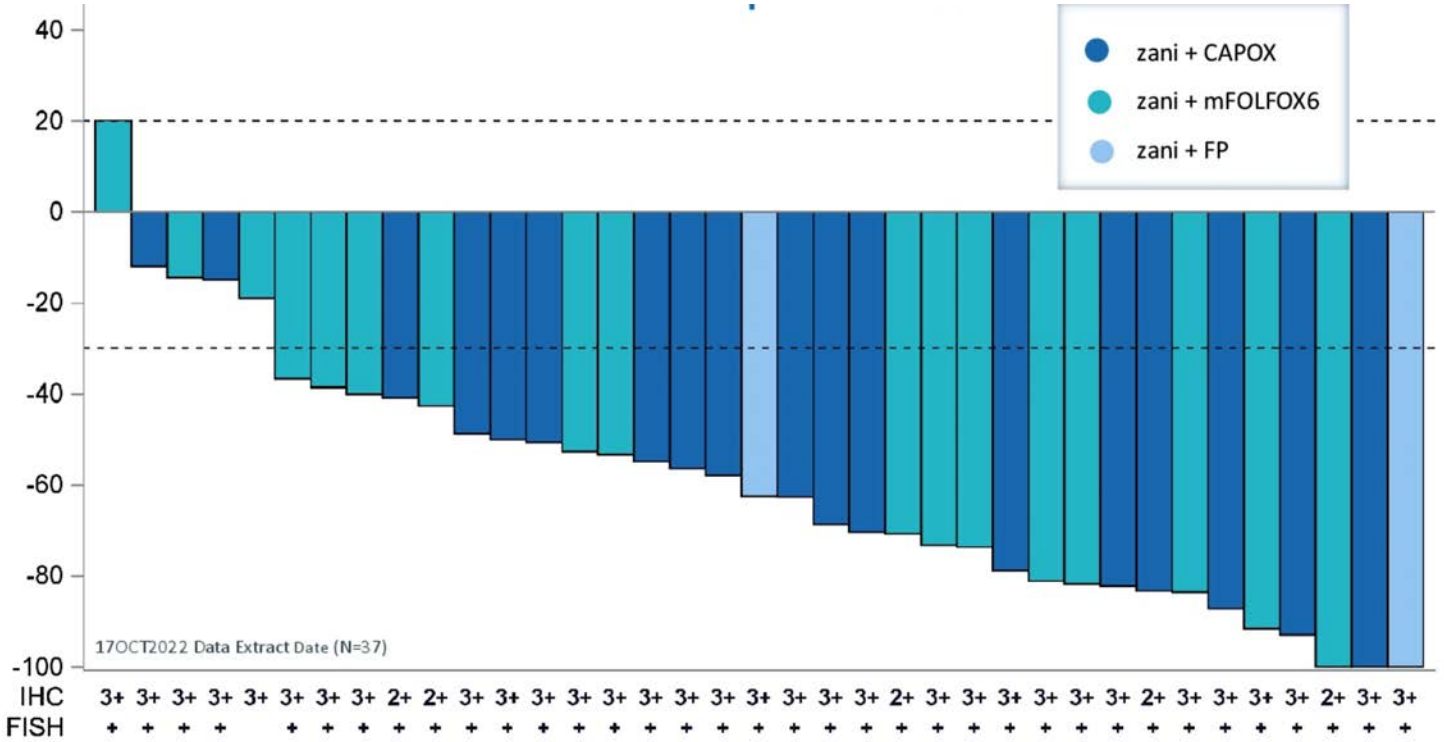
- Same domains as trastuzumab (ECD4) and pertuzumab (ECD2)

Unique mechanisms of action designed to expand activity

- Extended chain formation and dense HER2 receptor clustering
- Enhanced HER2 internalization and downregulation
- Increased tumor cell binding density and potent effector-mediated cytotoxicity
- Enhanced blockade of ligand-dependent and ligand-independent tumor growth

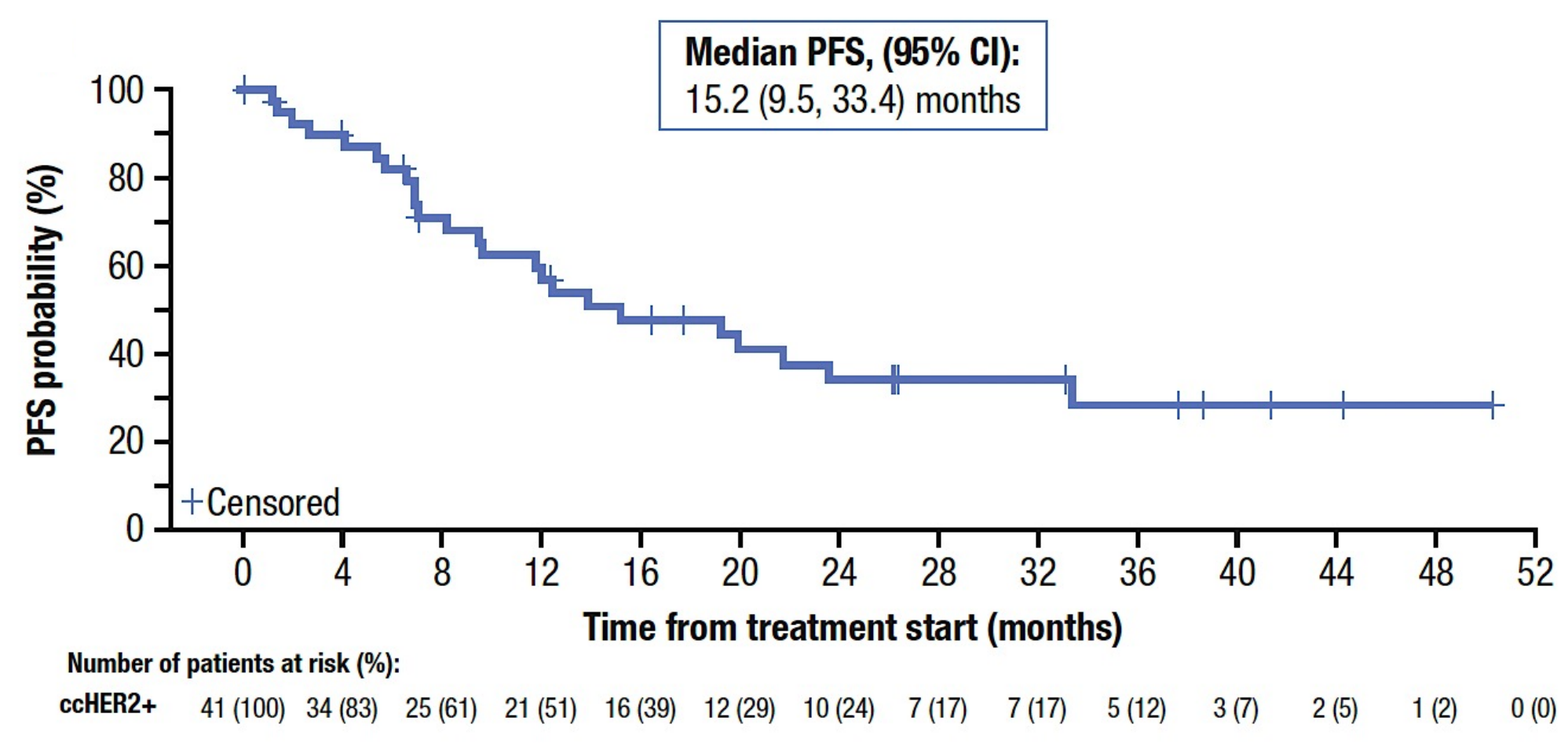
Active and Well-Tolerated in Preclinical Studies

- Active in low-to-high HER2-expressing cancer cell lines and breast, gastric, and ovarian CDX and PDX models
- Well-tolerated at doses up to 150 mg/kg in GLP toxicology studies in non-human primates (human equivalent dose equals 50 mg/kg)



Elimova et al, ASCO GI 2023

Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – PFS

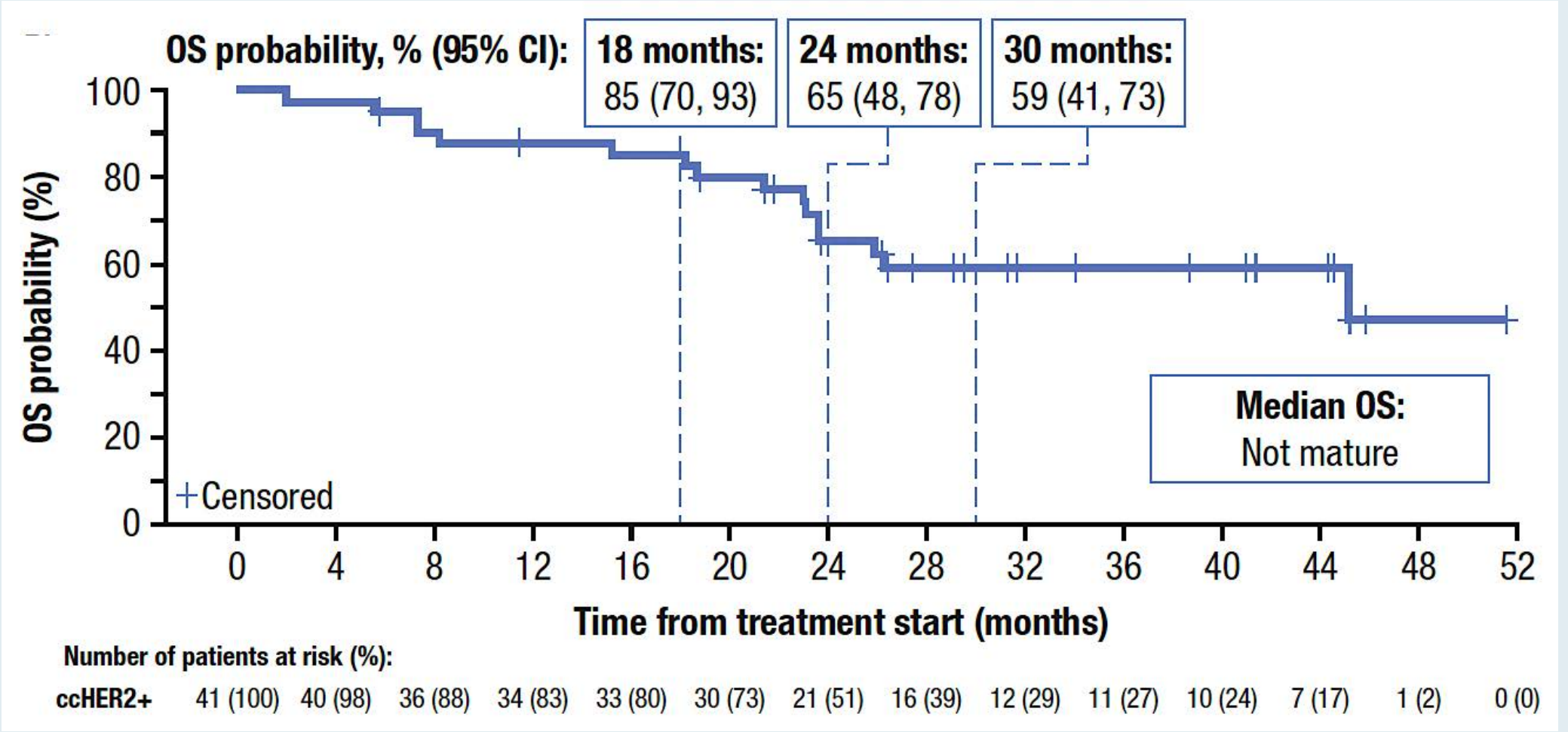


ccHER2+ = centrally confirmed HER2-positive

Elimova E et al. ESMO 2024;Abstract 3212.

RTP RESEARCH TO PRACTICE

Phase II Study of First-Line Zanidatamab and Chemotherapy for HER2-Positive Advanced GEJ Cancers – OS



Elimova E et al. ESMO 2024;Abstract 3212.

Phase II Study of First-Line Zanidatamab and Chemotherapy – Safety

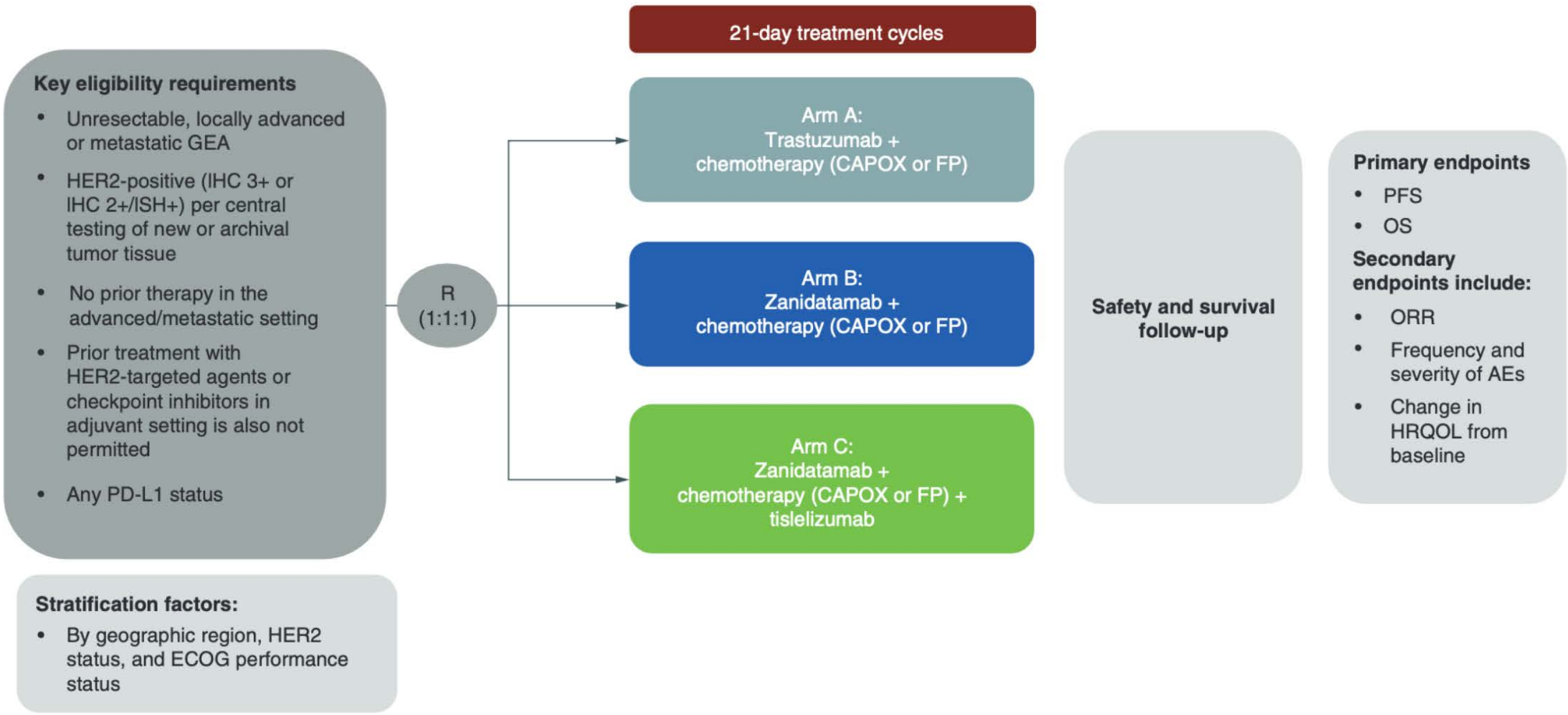
	Total (N=46)	
Any-grade TRAE,[a] n (%)	46 (100)	
Grades 1-2	17 (37)	
Grades 3-4	29 (63)	
Grade 5	0 (0)	
Serious TRAE,[a] n (%)	8 (17)	
TRAEs leading to zanidatamab discontinuation, n (%)	2 (4)[c]	
	All grades	**Grade ⩾3**
Most common TRAEs,[a,b] n (%)		
Diarrhoea[d]	43 (93)	16 (35)[d]
Nausea	37 (80)	3 (7)
Peripheral neuropathy	30 (65)	0 (0)
Fatigue	23 (50)	2 (4)
Decreased appetite	21 (46)	0 (0)
Vomiting	16 (35)	3 (7)
Hypokalaemia	14 (30)	10 (22)
Stomatitis	13 (28)	0 (0)
Anaemia	10 (22)	0 (0)
Dysgeusia	10 (22)	0 (0)
IRR	10 (22)	0 (0)
Decreased neutrophil count	10 (22)	2 (4)
PPE	10 (22)	1 (2)
Hypomagnesaemia	9 (20)	1 (2)
Decreased white blood cell count	7 (15)	2 (4)
Acute kidney injury	3 (7)	2 (4)
Treatment-related AESI occurring		
IRR	10 (22)	0 (0)
Ejection fraction decreased	2 (4)	0 (0)
Pneumonitis	0 (0)	0 (0)

TRAE = treatment-related adverse event;
IRR = infusion-related reaction;
AESI = adverse event of special interest

Elimova E et al. ESMO 2024;Abstract 3212.

RTP RESEARCH TO PRACTICE

Zanidatamab in mGC first line treatment: the Herizon GEA-01 Trial



Tabernero et al. Future Oncology 2022

Conclusions

- **Platin-based doublet** chemotherapy plus **trastuzumab** and **pembrolizumab** is the new standard first line treatment for HER2 positive, PD-L1 ≥1 advanced gastric cancer

- HER2-targeted therapy may lead to reduction in HER2 expression and emergence of other genetic alterations, therefore rebiopsy should be considered (but is not mandatory) after disease progression on trastuzumab

- **Trastuzumab deruxtecan** is the standard second line treatment for HER2 positive advanced gastric cancer

- Other HER2 inhibitors are under investigation

Faculty Case Presentations

Patient Characteristics and Diagnosis

2019

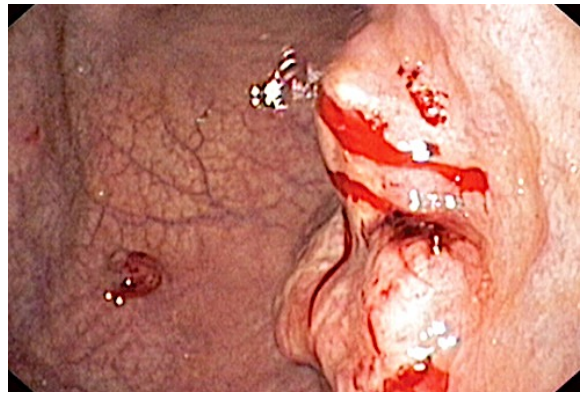
PS (ECOG) 0

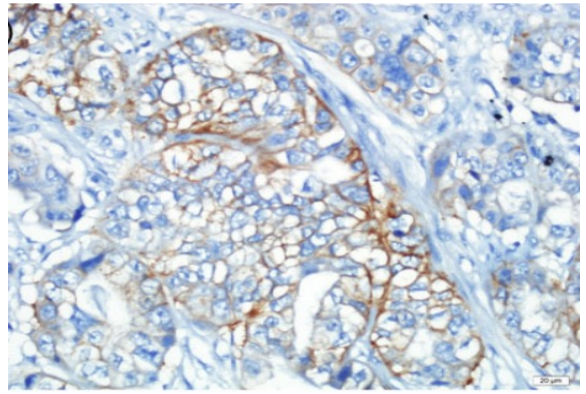
AGE: 51 y.o.
GENDER: Female
ALLERGIES: None
LOCATION: Italy
COMORBIDITIES: None

Symptoms:
weight loss & dyspepsia

Gastroscopy:
Sub-cardial lesion
H.E.:
Gastric adenocarcinoma, G3
MSS (IHC), HER2 3+ (IHC)

CT scan:
Stomach wall thickness and multiple abdominal lymphadenopathies



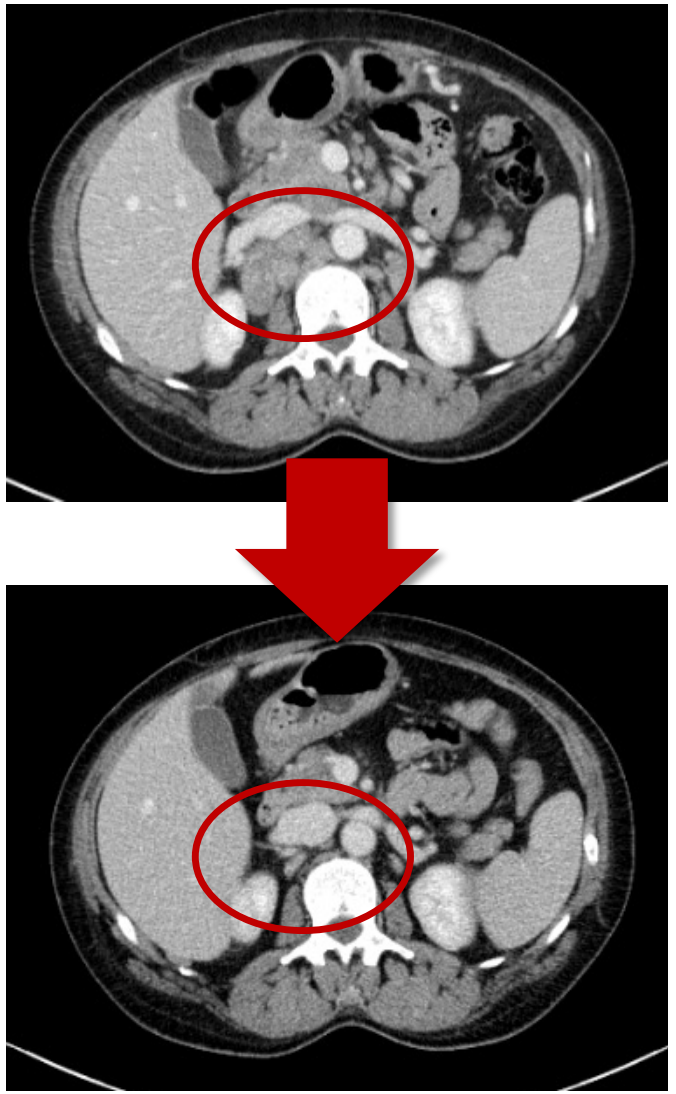


Treatment

November 2019 – March 2020
Keynote 811: Pembrolizumab/Placebo + Trastuzumab + cisplatin-FU
q3w, for 6 cycles

March 2020 – May 2020
Keynote 811: Pembrolizumab/Placebo + Trastuzumab + FU
q3w, for 3 cycles

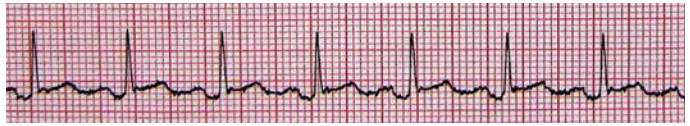
May 2020
Fever, hypotension -> Hospitalization in Oncology

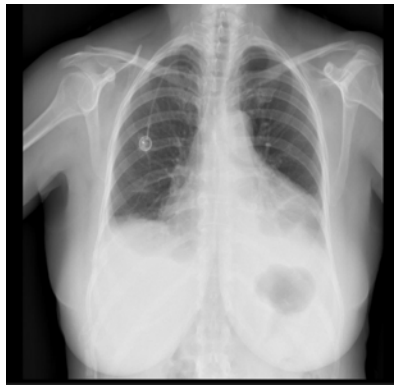


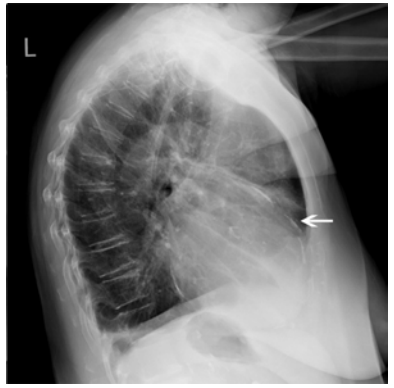
BR: RP

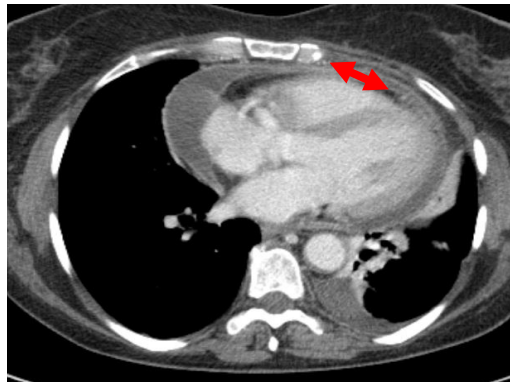
Immune-related toxicity

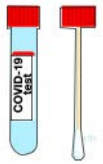
fever
hypotension
tachycardia (120-130 bpm, RS)
desaturation (SpO2 87%)









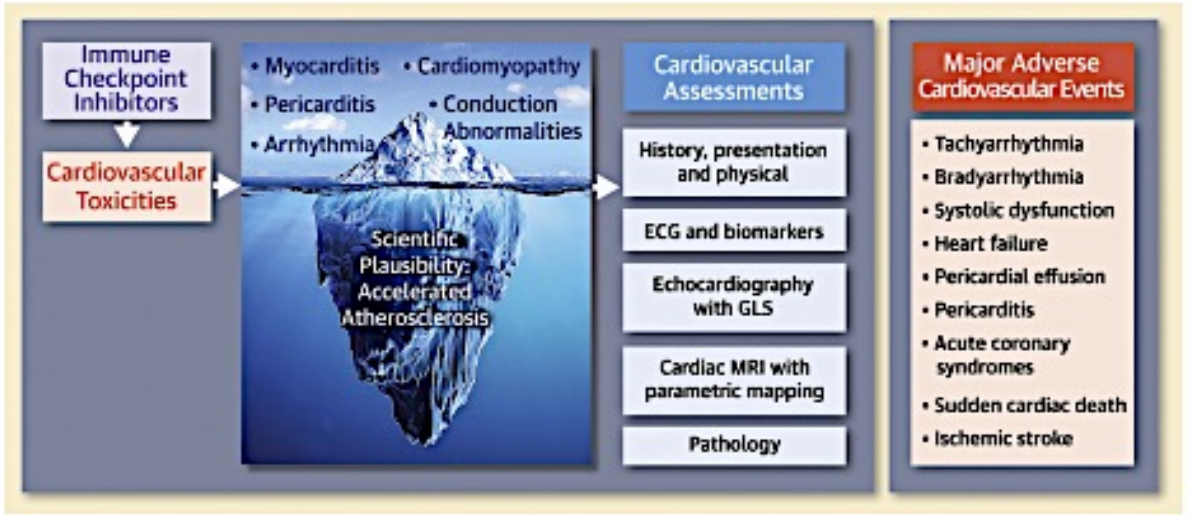


NEGATIVE

Immune-related Pericarditis

Colchicine
Prednisolone 1 mg/kg die
Ibuprofen

CENTRAL ILLUSTRATION Immune Checkpoint Inhibitors Leading to Cardiotoxicities and Major Adverse Cardiovascular Events



Zhang, L. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):35-47.

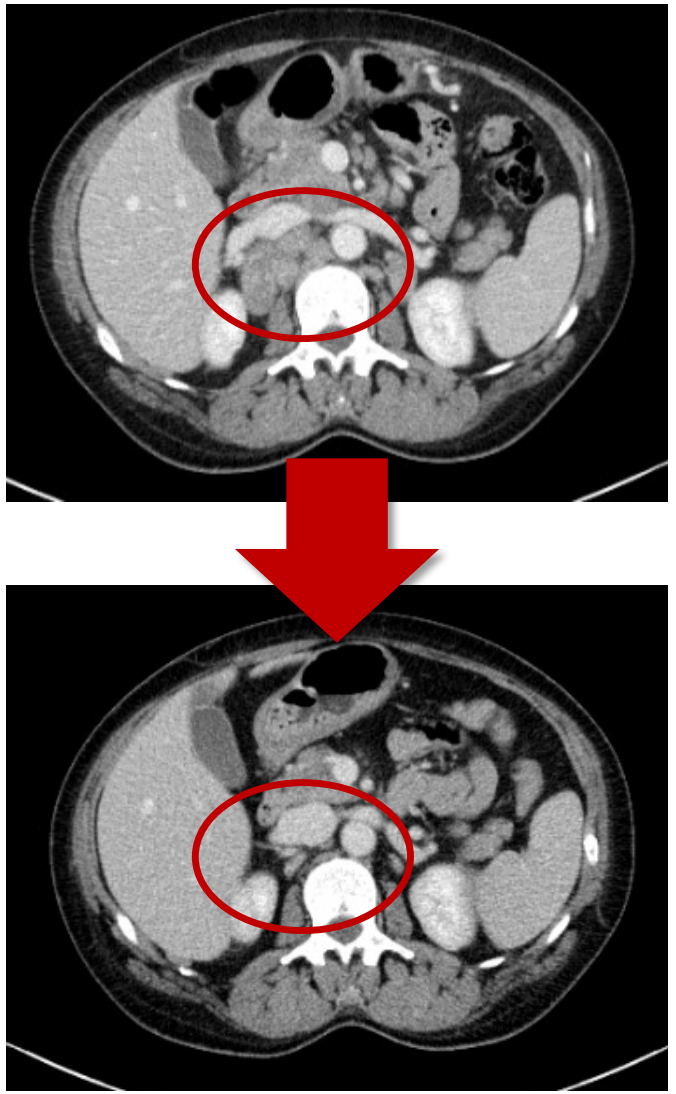
Treatment

November 2019 – March 2020
Keynote 811: Pembrolizumab/Placebo + Trastuzumab + cisplatin-FU
q3w, for 6 cycles

March 2020 – May 2020
Keynote 811: Pembrolizumab/Placebo + Trastuzumab + FU
q3w, for 3 cycles

May 2020
Fever, hypotension -> Hospitalization in Oncology
Immune-related pericarditis diagnosis

June 2020
Mild Disease Progression: increased **T and lymph-nodes, no new lesions**
First line treatment interruption



BR: RP

QUESTIONS FOR THE FACULTY

Given the revised indication, do you currently employ pembrolizumab as a component of up-front treatment in HER2-positive advanced gastroesophageal cancer only for patients with PD-L1-positive (CPS ≥1) disease? Are there any clinical situations in which you would be tempted to offer pembrolizumab in the first-line setting for a patient with a PD-L1 CPS <1?

Do you typically reassess HER2 status for patients with HER2-positive advanced gastroesophageal cancers, biliary tract cancers and metastatic CRC after disease progression on first-line therapy? How does it affect your approach to subsequent therapy in patients who lose HER2 positivity in each of these diseases?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

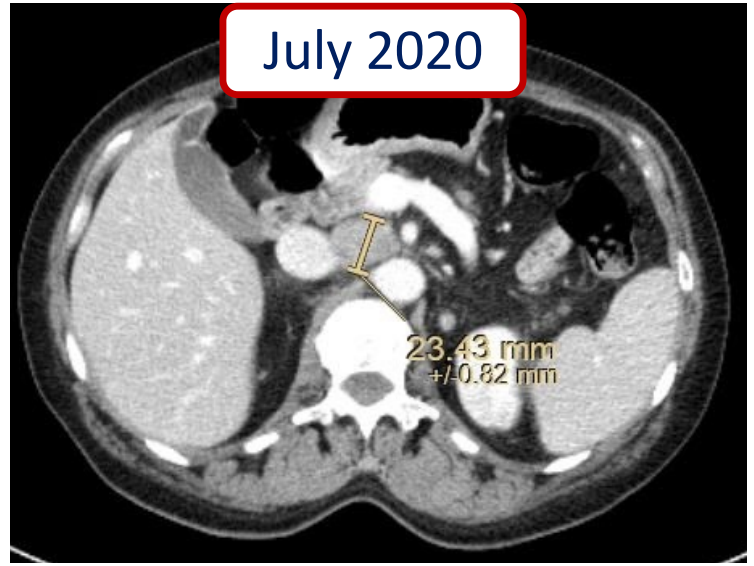
K. Shitara, Y.-J. Bang, S. Iwasa, N. Sugimoto, M.-H. Ryu, D. Sakai, H.-C. Chung, H. Kawakami, H. Yabusaki, J. Lee, K. Saito, Y. Kawaguchi, T. Kamio, A. Kojima, M. Sugihara, and K. Yamaguchi, for the DESTINY-Gastric01 Investigators*

ABSTRACT

Treatments

June 2020
First line treatment interruption

July 2020 – February 2021
DESTINY-Gastric02: Trastuzumab-Deruxtecan, q3w, for 11 cycles



- nausea G2
- vomiting G2
- neutropenia G3

Premedication: Aprepitant & Palonosetron

Adverse Reactions Across T-DXd Trials: Nausea and vomiting

5.4 mg/kg

- The pooled safety population for **5.4 mg/kg** T-DXd describes 1449 patients in clinical studies across multiple tumor types who received at least 1 dose of 5.4 mg/kg T-DXd IV every 3 weeks
  - The median duration of exposure to T-DXd was 9.6 months (range 0.2 to 45.1 months)

6.4 mg/kg

- The pooled safety population for **6.4 mg/kg** T-DXd describes 619 patients in clinical studies across multiple tumor types who received at least 1 dose of 6.4 mg/kg T-DXd IV every 3 weeks
  - The median duration of exposure to T-DXd was 5.6 months (range 0.7 to 41 months)

Locally Advanced or Metastatic Cancer (all tumor types) [a] (N=619)		
Dose	**Overall Incidence**	**Grade 3-4**
6.4 mg/kg	**71,1%**	**5.8%**

Locally Advanced or Metastatic Cancer (all tumor types) [a] (N=619)		
Dose	**Overall Incidence**	**Grade 3-4**
6.4 mg/kg	**39.1%**	**2.4%**

NCCN Guidelines®: Acute and Delayed Nausea and Vomiting

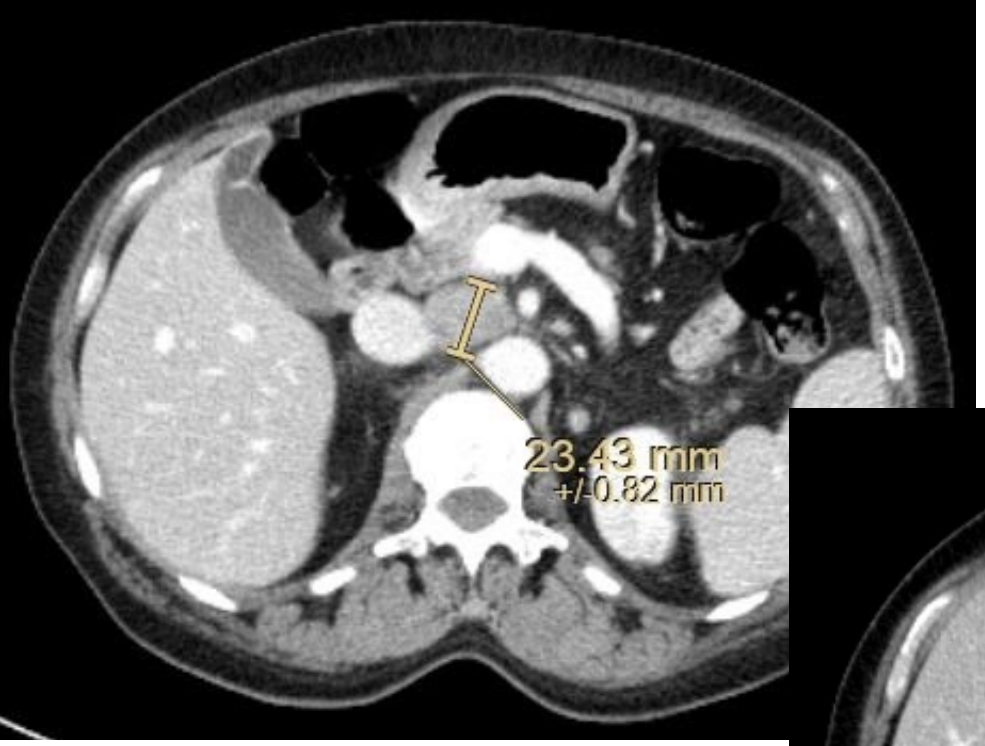
National Comprehensive Cancer Network® (NCCN®) Recommended

NCCN Guidelines® for Antiemesis lists fam-trastuzumab deruxtecan-nxki (ENHERTU) as a parenteral anticancer agent with *high emetic risk* (>90% frequency of emesis)[a] and recommends several prophylactic antiemetic regimens to decrease potential vomiting

High Emetic Risk Parenteral Anticancer Agents—
Acute and Delayed Emesis Prevention [b, c]

DAY 1:	Select treatment option A, B, or C	DAYS 2, 3, 4
	All treatment options are category 1 and should be started before anticancer therapy	
	Treatment option A (preferred), use the following combination: • Olanzapine[h] • NK1 RA • 5-HT_3 RA[i, j] • Dexamethasone[f, g]	Treatment option A: • Olanzapine on days 2,3,4[h] • Aprepitant on days 2,3 – *If aprepitant PO is used on day 1* • Dexamethasone[f, g] on days 2, 3, 4
	Treatment option B, use the following combination: • Olanzapine[h] • Palonosetron • Dexamethasone[f, g]	Treatment option B: • Olanzapine on days 2, 3, 4[h]
	Treatment option C, use the following combination: • NK1 RA • 5-HT_3 RA[i, j] • Dexamethasone[f, g]	Treatment option C: • Aprepitant on days 2,3 – *If aprepitant PO is used on day 1* • Dexamethasone on days 2, 3, 4[f, g]

[a] Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis. [b] Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors. [c] Especially for patients with anticipatory, anxiety-related, or breakthrough nausea, may consider adding lorazepam 0.5–1 mg PO or IV or sublingual (SL) every 6 hours as needed on days 1–4. Use the lowest effective dose and dosage interval possible. May be administered with or without H_2 blocker or proton pump inhibitor (PPI) if patient exhibits reflux symptoms. [f] Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (e.g., olanzapine).[g] Use of corticosteroid premedications should be avoided with cellular therapies. [h] Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for patients who are older or who are over sedated. [i] If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product used, no further 5-HT_3 RA is required. [j] When used in combination with an NK1 RA, there is no preferred 5-HT_3 RA.

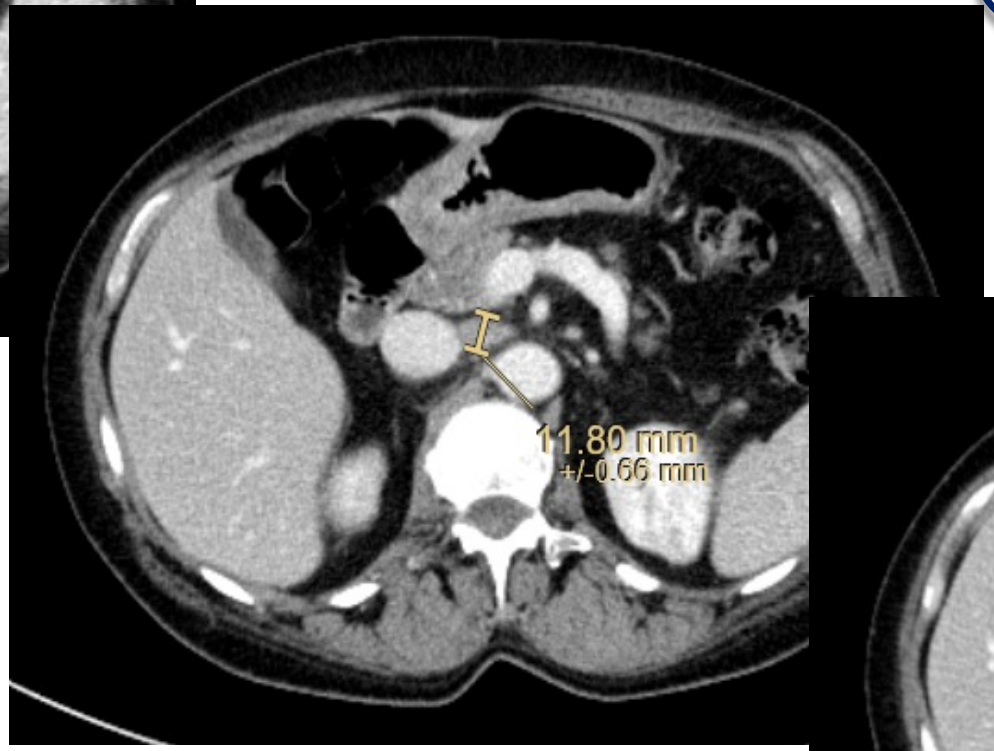


Baseline
July 20

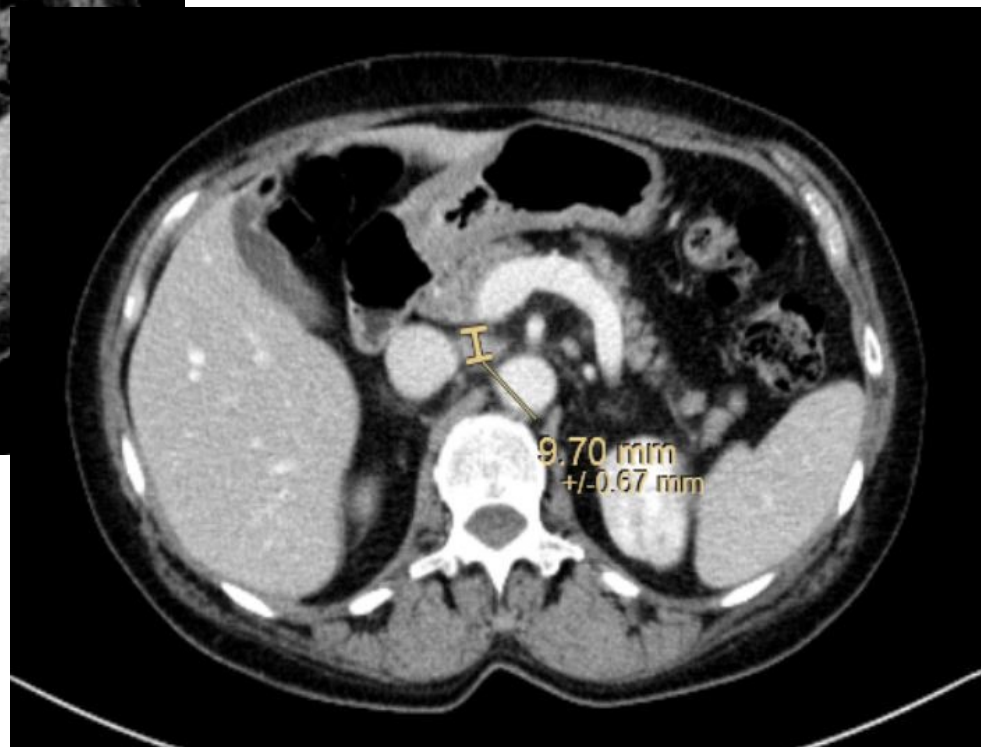
From baseline after 12 weeks of T-DXd

Reduction in the LSD of target lesion:

41 %



1st Restaging
September 20



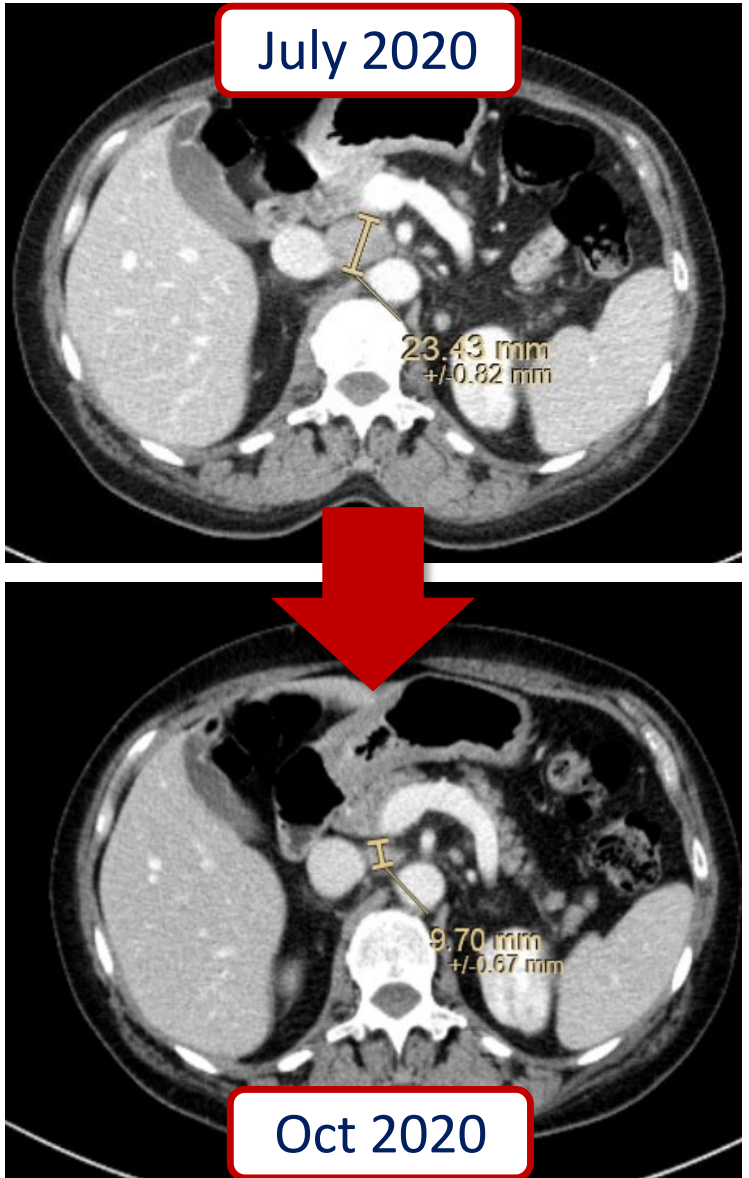
2nd Restaging
October 20

Treatments

June 2020
Fever, hypotension -> Hospitalization in Oncology

July 2020 – February 2021
DESTINY-Gastric02: ***Trastuzumab-Deruxtecan,*** q3w, for 11 cycles

March 2021
Disease Progression: ↑ **T and lymphnodes**



Comprehensive Genome Profiling

PATIENT
Subject ID **IOV-0997 Prescreening**
Site ID **09011**
Sex **Female**
Date of Birth **26NOV1967**
Diagnosis **Stomach carcinoma (NOS)**

SPECIMEN
Specimen ID **10034421**
Sample Type **Block**
Site **Stomach**
Collection Date **07DEC2020**
Received Date **19JAN2021**
Visit Type **Archival/Pre-Treatment**

GENE	ALTERATION
ERBB2	amplification
TP53	C135Y

NO TARGET

GENOMIC SIGNATURES

NOTE: This section includes information for genomic signatures reported in this test.

Biomarker	Result
Tumor Mutational Burden	1.26 mutations-per-megabase
Microsatellite Instability	MS-Stable

Treatments

***1st Line**: November 2019 – May 2020*
MK-3475-811: ***Pembrolizumab/Placebo + Trastuzumab + FP*** q3w, for 6 cycles, BR:PR

***2nd Line:** July 2020 – February 2021*
DESTINY-Gastric02: ***Trastuzumab-Deruxtecan,*** q3w, for 11 cycles, BR:PR

***3rd Line:** March 2021 – May 2021*
Paclitaxel-Ramucirumab, for 3 cycles, BR:PD

***4th Line:** June 2021 – September 2021*
FOLFIRI, for 8 cycles, BR:SD

2 years OS from 1st line

QUESTIONS FOR THE FACULTY

In which line of therapy are you typically recommending T-DXd for your patients with progressive HER2-positive gastroesophageal cancer? Given the results of the DESTINY-Gastric04 study, are you prioritizing T-DXd as second-line therapy in all cases?

What is your approach to the management of the acute nausea and vomiting associated with T-DXd? How do you manage breakthrough nausea and vomiting despite guideline-directed antiemetic prophylaxis?

QUESTIONS FOR THE FACULTY

How does the mechanism of action of zanidatamab differ from other currently available anti-HER2-targeted therapies?

Based on recent trial results evaluating zanidatamab/chemotherapy as first-line treatment for HER2-positive advanced GEJ cancers, if this regimen were to become available, for which patients would you prioritize its use?

Are you optimistic that the results of the HERIZON-GEA-01 trial will be positive? If so, how do you anticipate these results will impact clinical practice?

Agenda

MODULE 1: Gastroesophageal Cancers — Dr Lonardi

MODULE 2: Biliary Tract Cancers — Dr Ellis

MODULE 3: Colorectal Cancer — Dr Raghav

RTP RESEARCH TO PRACTICE

Research To Practice®

HER2-Positive Gastrointestinal Cancers
Sunday, June 1, 2025, 7:00 PM – 8:30 PM CT

HER2-Positive Biliary Tract Cancers (BTC)

Haley Ellis, MD

Hepatobiliary Oncologist | Clinical-Translational Investigator

Massachusetts General Hospital | Harvard Medical School

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

BROAD INSTITUTE

HARVARD MEDICAL SCHOOL

Mass General Brigham

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL

Overview of Presentation

- Therapeutic landscape and prevalence of HER2 in advanced BTC
- Clinical indications and methods for HER2 testing
- HER2-targeted therapies in BTC: efficacy and safety
  - Trastuzumab deruxtecan (DESTINY-PanTumor02 and HERB trials)
  - Zanidatamab (HERIZON-BTC-01 trial)
  - Ongoing phase 3 trials for treatment-naïve patients
- Clinical case discussions

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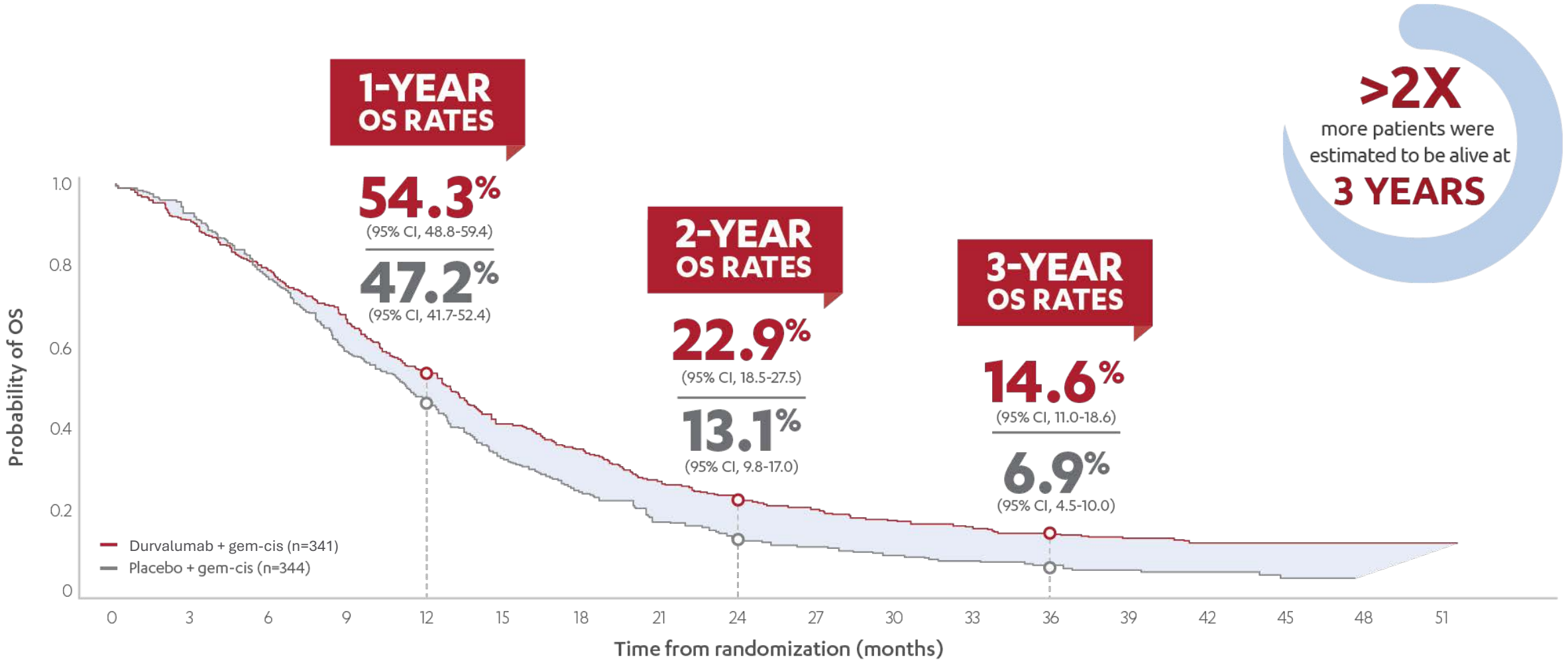
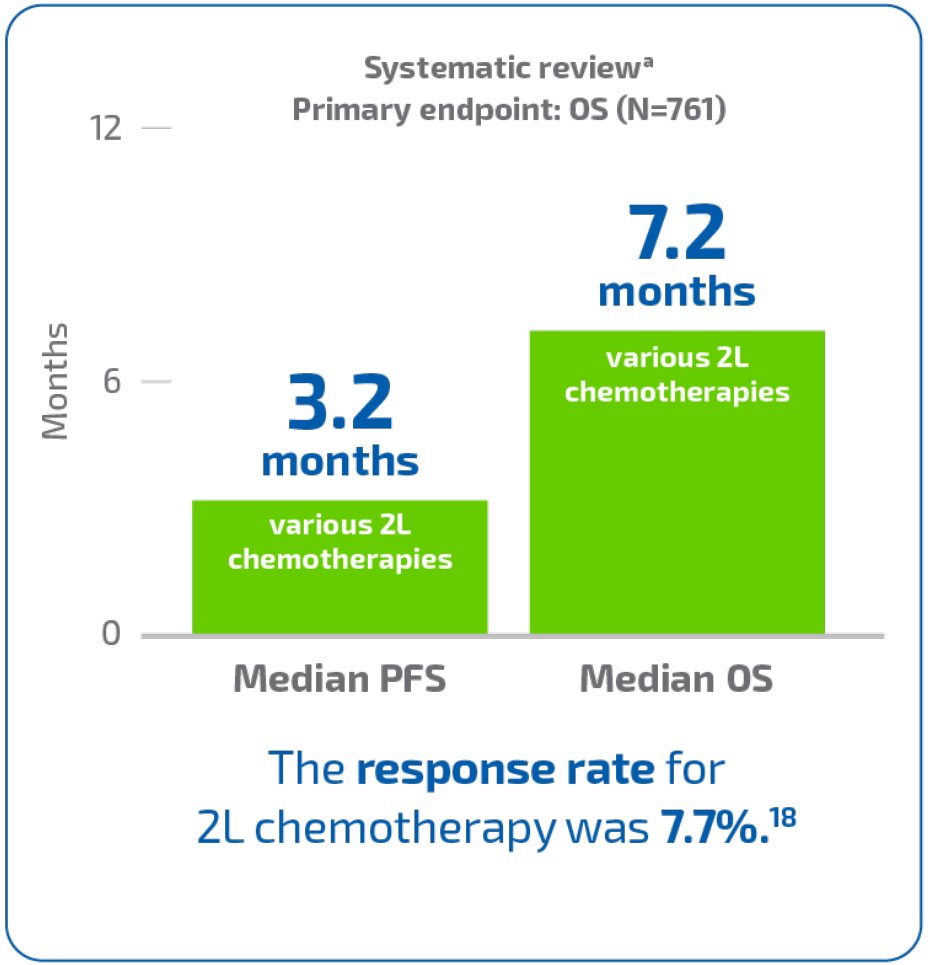
Chemotherapy + immunotherapy is now standard first-line treatment of advanced BTC

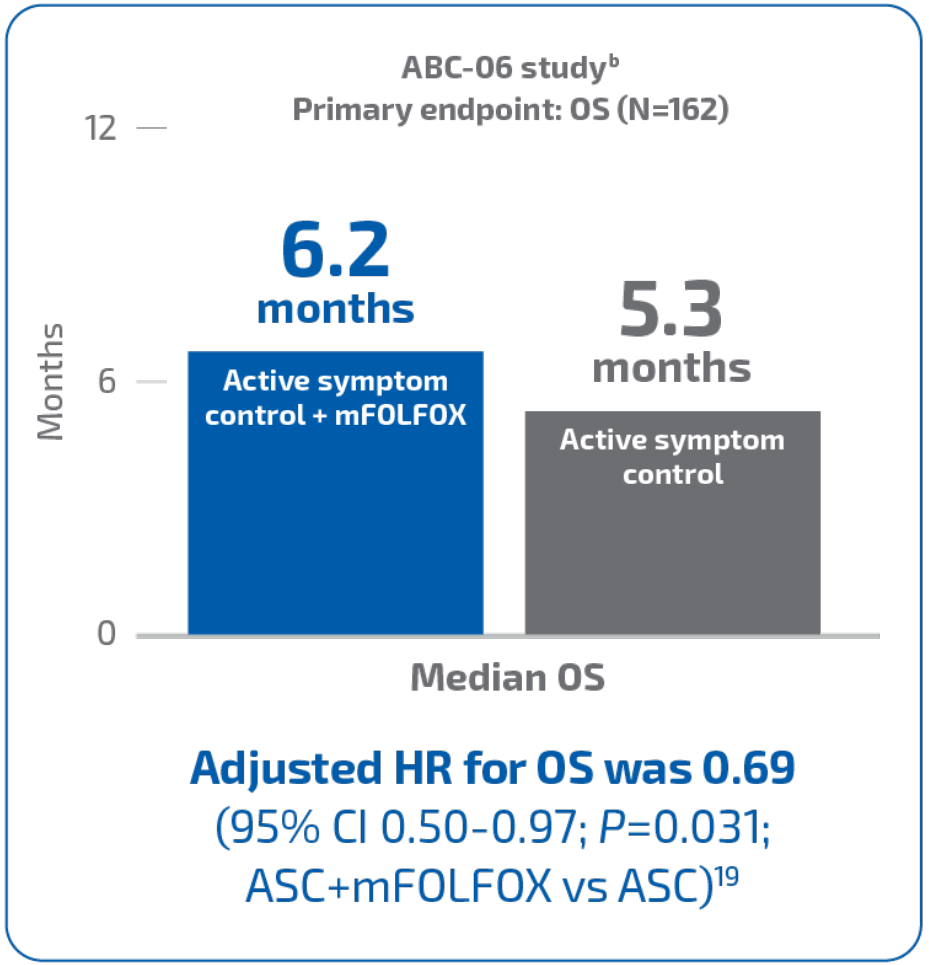


TOPAZ-1: Oh et al. NEJM Evid 2022 | Oh et al. J Hepatol 2025

Outcomes are poor with second-line chemotherapy



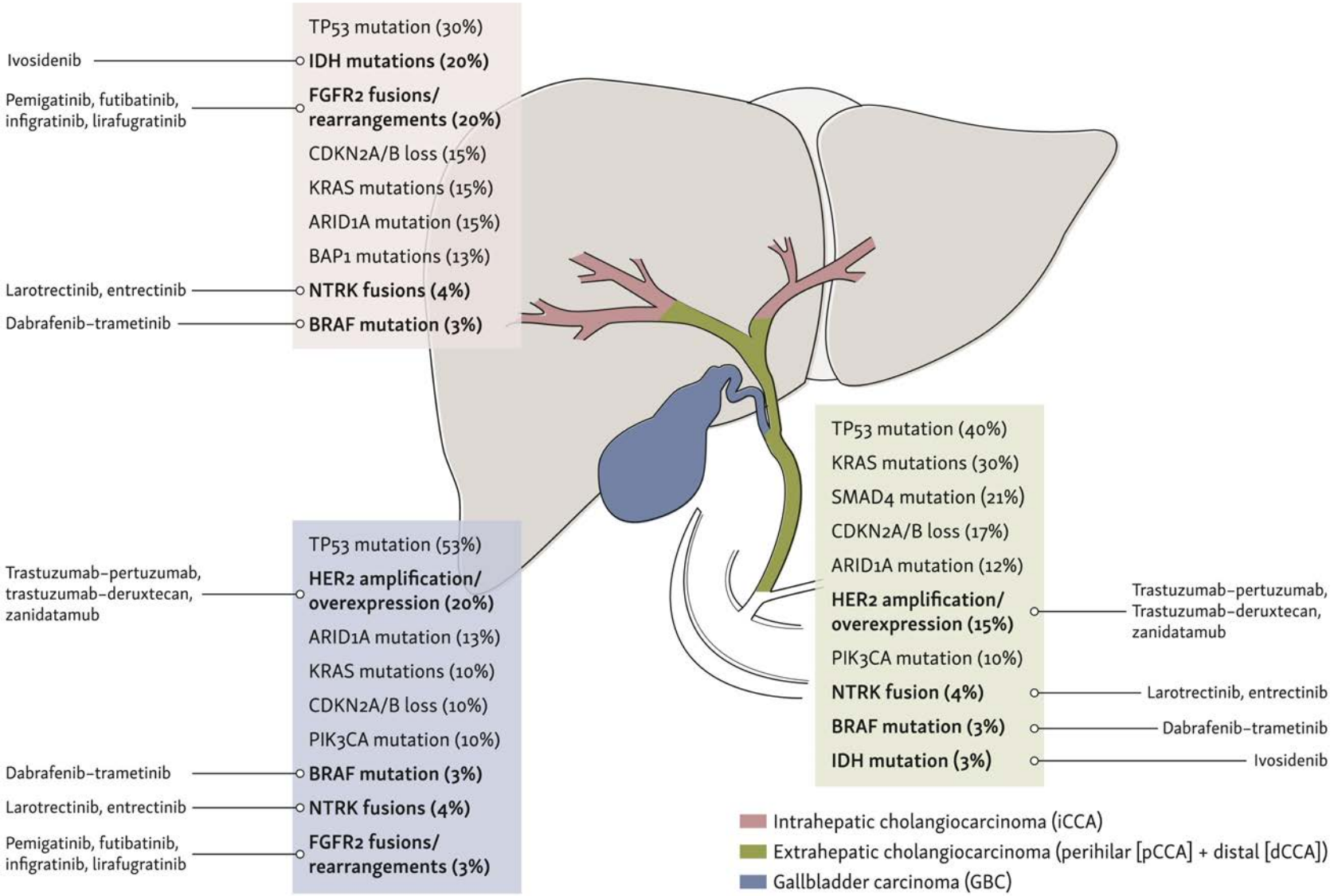
The **response rate** for 2L chemotherapy was **7.7%.**[18]



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

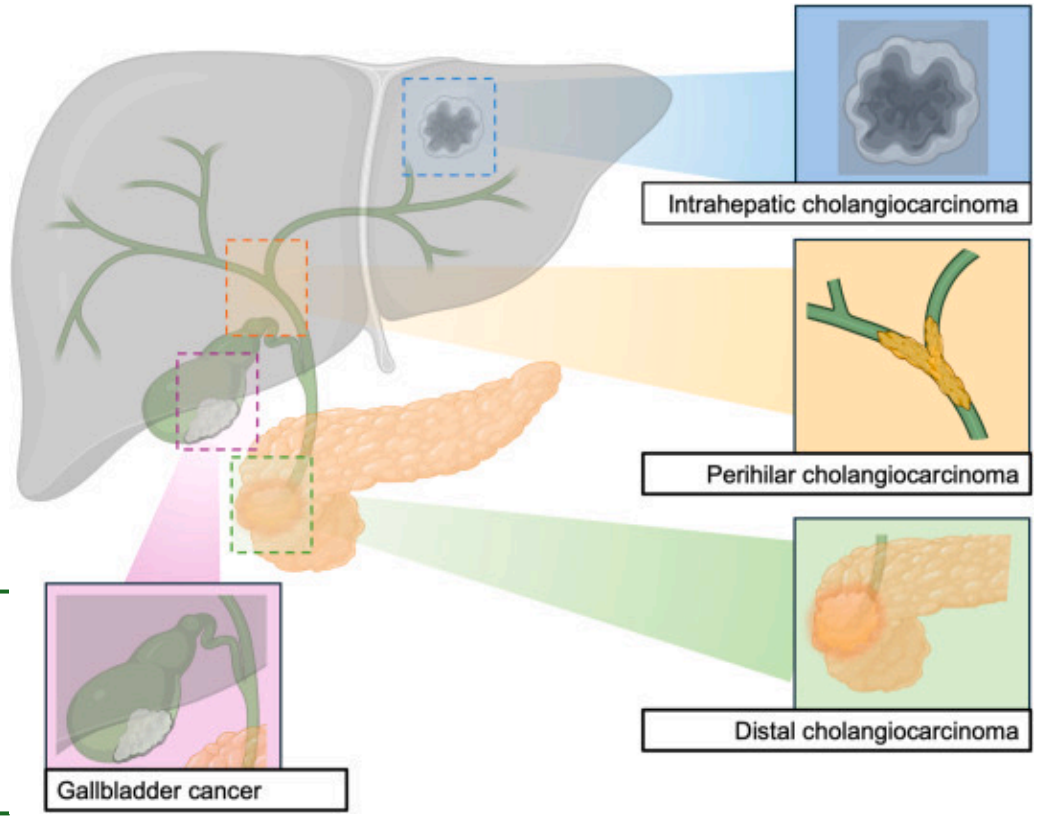
Lamarca et al. Ann Oncol 2014 | ABC-06: Lamarca et al. Lancet Oncol 2021 | Incyte 2023

BTC harbor targetable genomic alterations



Kehmann et al. ESMO Open 2024

HER2 amplification/overexpression spans all BTC subtypes



Intrahepatic cholangiocarcinoma (iCCA)
~3-5%

Extrahepatic cholangiocarcinoma (eCCA)
~10-20%

Gallbladder cancer (GBC)
~15-35%

HER2 positivity is associated with a **worse prognosis** in advanced BTC

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

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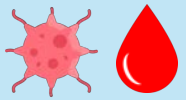
HER2 testing in BTC: who, when, and how

✅ **WHO:** All patients with locally advanced or metastatic BTC (GBC, eCCA, iCCA)

✅ **WHEN:** At diagnosis

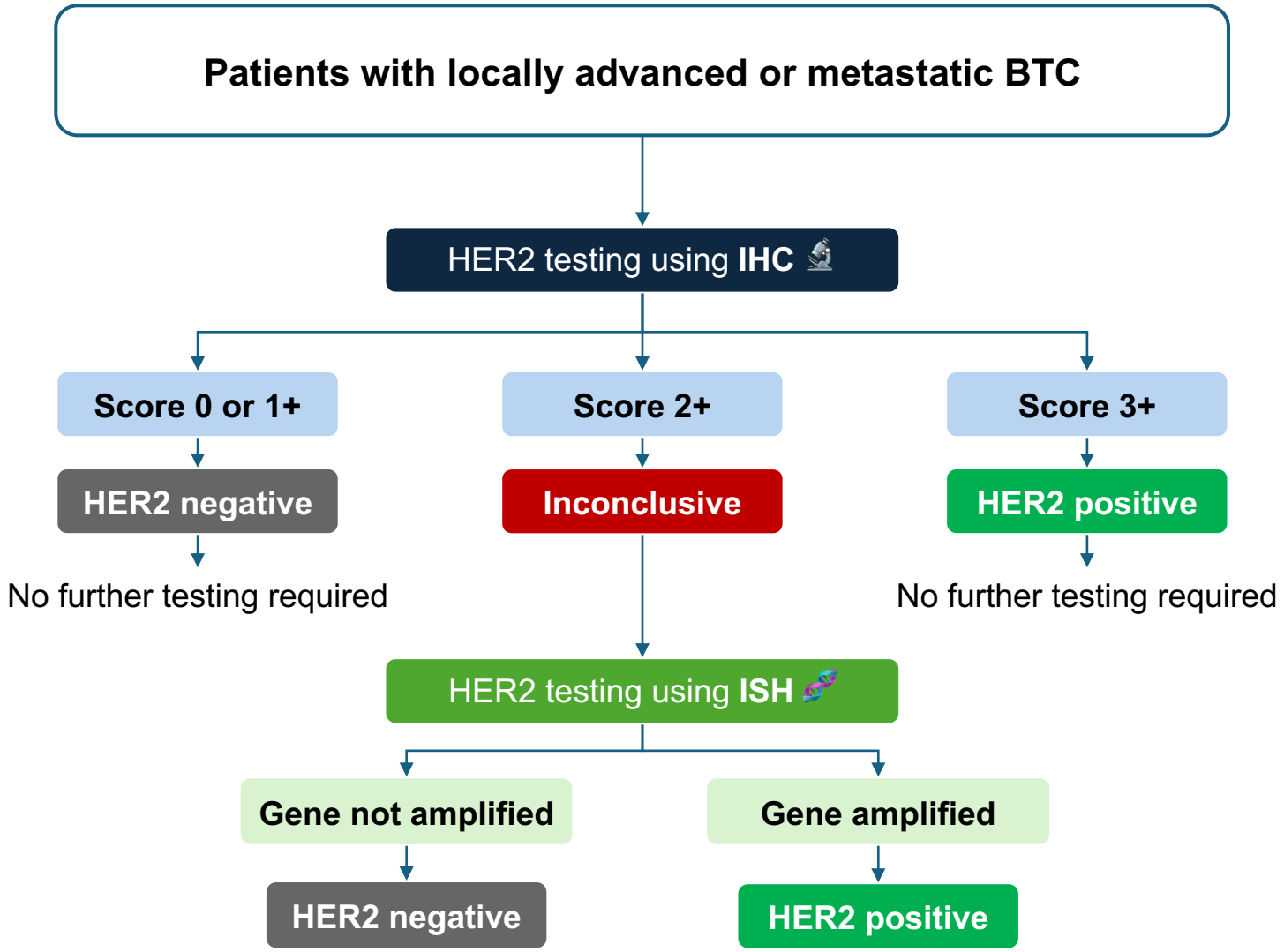
- 1st line trials!
- Future direction: consider earlier testing for neoadjuvant/perioperative strategies

✅ **HOW:**

	Immunohistochemistry (IHC) 🔬	*In situ* hybridization (ISH) 🧬	Next-generation sequencing (NGS) 🎯
What it detects	HER2 **protein**	*ERBB2* **DNA**	*ERBB2* **DNA**
What it indicates	HER2 **overexpression**	*ERBB2* **amplification**	*ERBB2* **amplification**
Tissue and/or blood-based			

Javle et al. Cancer 2016 | Jacobi et al. Oncol Res Treat 2021

HER2 testing in BTC follows gastroesophageal cancer guidelines



Comprehensive HER2 testing with NGS *and* IHC is important

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 HER2 assessment by NGS vs IHC in BTC

Lee et al. ASCO GI 2025

Overview of Presentation

- Therapeutic landscape and prevalence of HER2 in advanced BTC
- Clinical indications and methods for HER2 testing
- **HER2-targeted therapies in BTC: efficacy and safety**
  - **Trastuzumab deruxtecan (DESTINY-PanTumor02 and HERB trials)**
  - **Zanidatamab (HERIZON-BTC-01 trial)**
  - **Ongoing phase 3 trials for treatment-naïve patients**
- Clinical case discussions

Evolving treatment landscape in HER2+ BTC in second-line setting and beyond

	Treatment	Trial	# BTC pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
ABC-06[1] 2021	**FOLFOX**	Phase 3	162	--	--	5%	33%	--	4.0	6.2
MyPathway[2] 2021	**Trastuzumab + Pertuzumab**	Phase 2a	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	34	No	IHC 3+, IHC 2+/ISH+, or NGS Amp	29%	79%	4.9	5.1	10.7
HERIZON-BTC-01[4] 2023	**Zanidatamab**	Phase 2b	62 80	No	**IHC 3+** IHC 3+ or IHC 2+/Amp	**52%** 41%	**79%** 69%	**14.9** 12.9	**7.2** 5.5	**18.1** 15.5
SGNTUC-019[5] 2023	**Trastuzumab + Tucatinib**	Phase 2	30	No	IHC 3+, ISH+, or NGS Amp	47%	77%	6.0	5.5	15.5
DESTINY-PanTumor02[6] 2023	**Trastuzumab Deruxtecan**	Phase 2	16 41 14	**Yes (17%)**	**IHC 3+** IHC 3+ or 2+ IHC 2+	**56%** 22% 0%	**78%** -- --	**22.1** 8.6 --	**7.4** 4.6 4.2	**12.4** 7.0 6.0
HERB[7] 2024	**Trastuzumab Deruxtecan**	Phase 2	22 8	Yes (n=0)	**IHC 3+ or IHC 2+/ISH+** IHC 2+/ISH-, IHC 1+, or IHC 0/ISH+	**36%** 13%	**82%** 75%	**7.4** --	**5.1** 3.5	**7.1** 8.9

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

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

HER2-directed mAb[1]

- Provides targeted delivery of cytotoxic agent[1,2]
- Consists of the same amino acid sequence as trastuzumab[3]

Topoisomerase I inhibitor payload[1,2,a]

- Highly potent payload is an exatecan derivative, known as DXd, with a short systemic half-life[1,3]
- Upon release, membrane-permeable payload causes DNA damage and cell death, resulting in destruction of targeted tumor cells and neighboring cells present in the tumor microenvironment, known as the bystander antitumor effect[1,3,4]

Tumor-selective cleavable linker[1-3,a]

- Attaches payload to the antibody[1]
- Linker-payload is stable in plasma[2,3]
- Linker selectively cleaved by enzymes that are upregulated in tumor cells[1,3]

Enhertu HCP | Ogitani et al. Cancer Sci 2016 | Ogitani et al. Clin Cancer Res 2016 | Nakada et al. Chem Pharm Bull (Tokyo) 2019

DESTINY-PanTumor02 trial of T-DXd: baseline characteristics

Eligibility Criteria – BTC Cohort

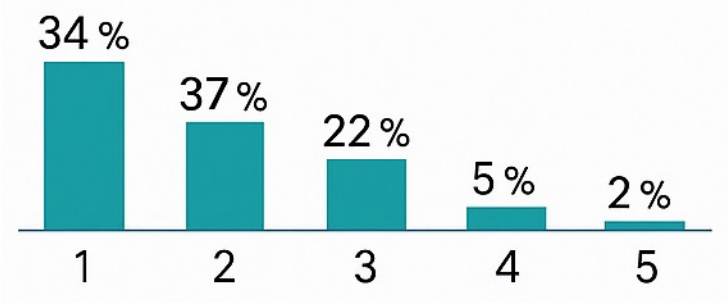
- Locally advanced, unresectable, or metastatic BTC
  - *Basket trial with 7 tumor cohorts*
- Progressed after ≥ 1 prior systemic therapy or without alternative treatment options

Demographics

- 51% Asian
- 49% White

Prior Lines of Therapy

- Median: 2



Prior HER2-Directed Therapy

- 17% (n=7)
  - Trastuzumab (n=6)
  - Pertuzumab (n=1)
  - Zanidatamab (n=1)

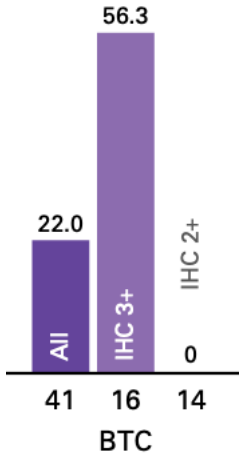
Meric-Bernstam et al. J Clin Oncol 2024

DESTINY-PanTumor02 trial of T-DXd: efficacy

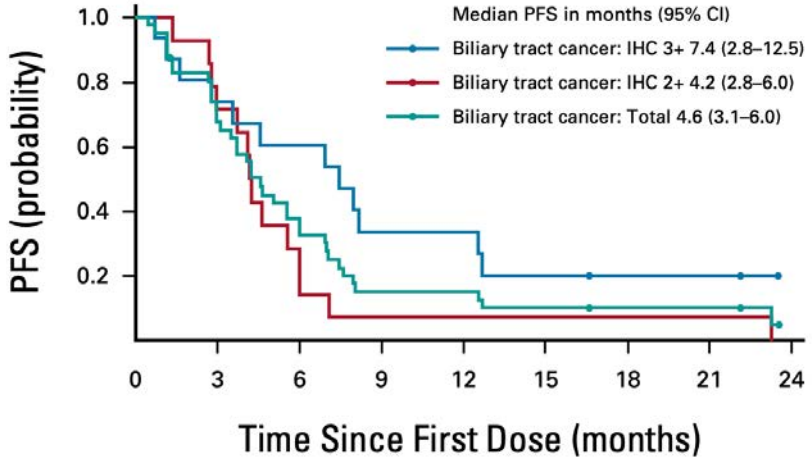
	Treatment	Trial	# BTC pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
DESTINY-PanTumor02 2023	**Trastuzumab Deruxtecan**	Phase 2 **(Global)**	16 41 14	**Yes (17%)***	**IHC 3+** IHC 3+ or 2+ IHC 2+	**56%** 22% 0%	**78%** -- --	**22.1** 8.6 --	**7.4** 4.6 4.2	**12.4** 7.0 6.0

***includes trastuzumab, pertuzumab, zanidatamab**

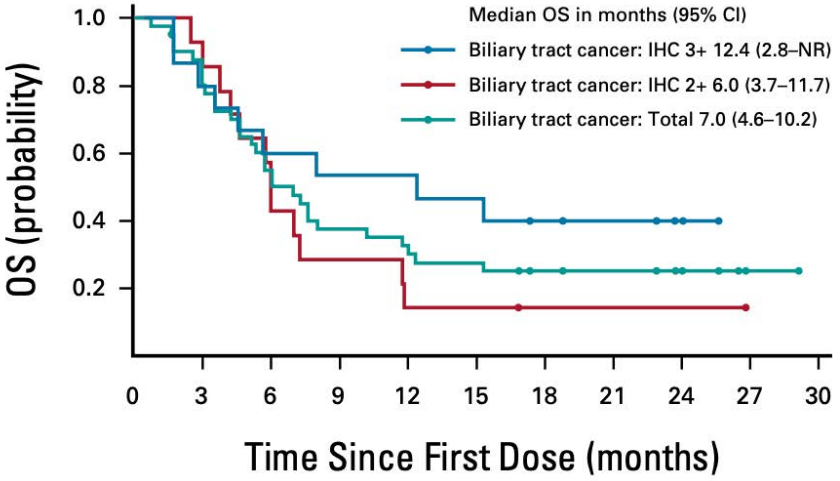
ORR in IHC 3+: 56%



mPFS in IHC 3+: 7.4 months



mOS in IHC 3+: 12.4 months



Meric-Bernstam et al. J Clin Oncol 2024; Oh D-Y et al. ASCO 2024;Abstract 4090

DESTINY-PanTumor02 trial of T-DXd: safety profile

- **Treatment-related adverse events (TRAEs)**
  - **12%** discontinued treatment
  - **32%** required dose modification

- **Most common TRAEs**
  - **Nausea** (46%), **diarrhea** (20%), **vomiting** (22%)
  - **Anemia** (24%), **fatigue** (22%), **neutropenia** (22%)

- **ILD/pneumonitis** (11%) – *across 267 patients in 7 cancer cohorts*
  - 🫁 Grade 1-2: **9%**
  - 🫁 Grade 3: **0.4%**
  - ❗ Grade 5: **1%** (including 1 BTC)

Meric-Bernstam et al. J Clin Oncol 2023

HERB trial of T-DXd: baseline characteristics

HER2-positive

IHC 3+ or IHC 2+/ISH+

- **50%** GBC, **27%** eCCA, **14%** iCCA
- **91%** Metastatic
- **45%** IHC 3+
- **73% had 2+ prior treatments**

HER2-low

IHC 2+/ISH-, IHC 1+, IHC 0/ISH+

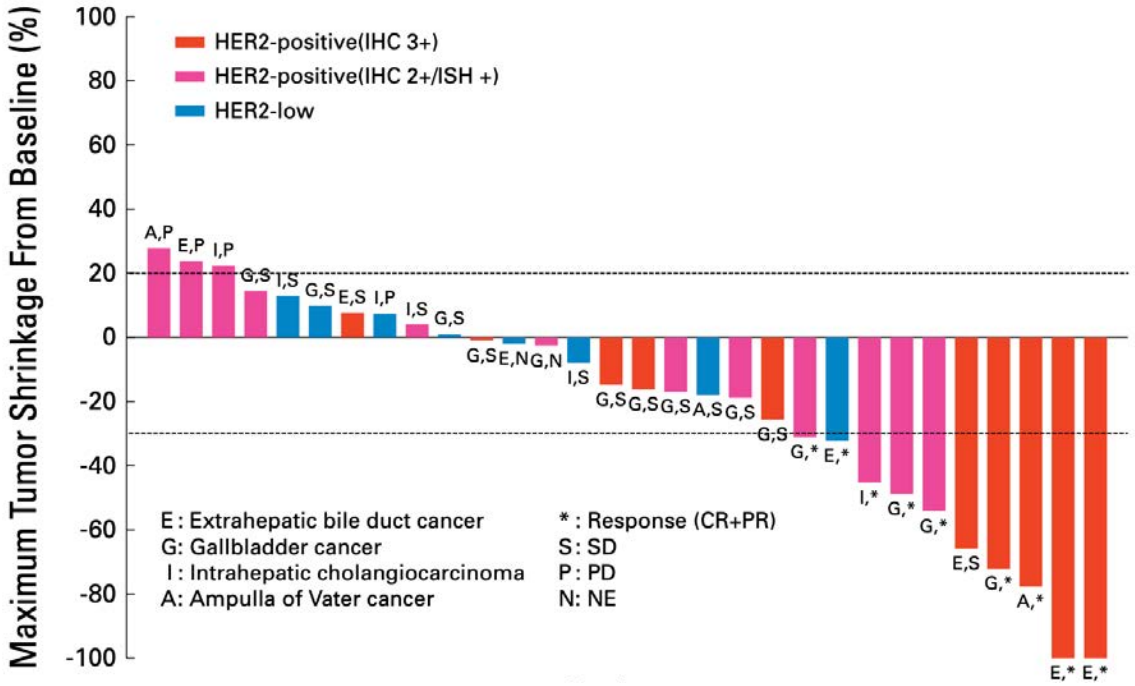
- Better ECOG PS
- More iCCA, less GBC
- Less pretreated

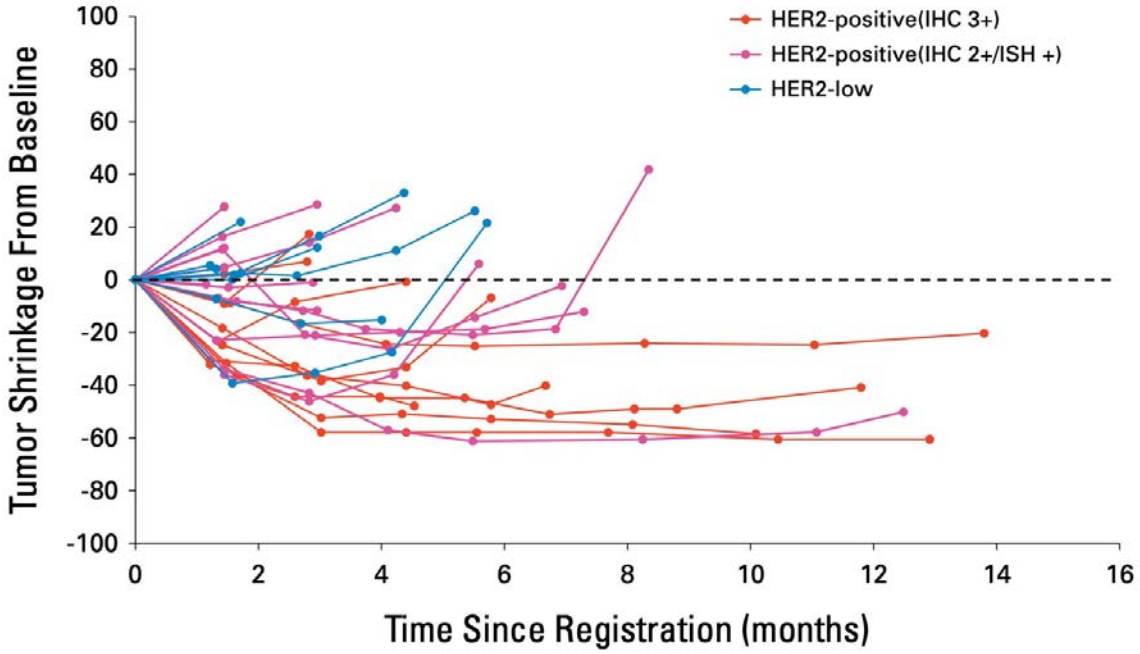
Characteristic	HER2-Positive (n = 22)	HER2-Low (n = 8)
Age, years, median (range)	67.5 (39-78)	68 (43-80)
Male, No. (%)	13 (59.1)	5 (62.5)
ECOG PS, No. (%)		
0	15 (68.2)	6 (75.0)
1	7 (31.8)	2 (25.0)
Primary tumor location, No. (%)		
Intrahepatic cholangiocarcinoma	3 (13.6)	3 (37.5)
Extrahepatic cholangiocarcinoma	6 (27.3)	2 (25.0)
Gallbladder cancer	11 (50.0)	2 (25.0)
Cancer of the ampulla of Vater	2 (9.1)	1 (12.5)
Disease status, No. (%)		
Unresectable	13 (59.1)	4 (50.0)
Recurrent	9 (40.9)	4 (50.0)
Disease extent, No. (%)		
Locally advanced	2 (9.1)	1 (12.5)
Metastatic	20 (90.9)	7 (87.5)
No. of previous regimens, No. (%)		
1	6 (27.3)	3 (37.5)
≥2	16 (72.7)	5 (62.5)

Ohba et al. J Clin Oncol 2024

HERB trial of T-DXd: efficacy

	Treatment	Trial	# BTC pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
HERB 2024	**Trastuzumab Deruxtecan**	Phase 2 **(Japan)**	22 8	Yes (n=0)	**IHC 3+ or IHC 2+/ISH+** IHC 2+/ISH-, 1+/+, 1+/-, 0/+	**36%** 13%	**82%** 75%	**7.4** --	**5.1** 3.5	**7.1** 8.9





Ohba et al. J Clin Oncol 2024

HERB trial of T-DXd: safety profile

- ***Consistent with known T-DXd toxicity, but interstitial lung disease (ILD) risk warrants close monitoring***

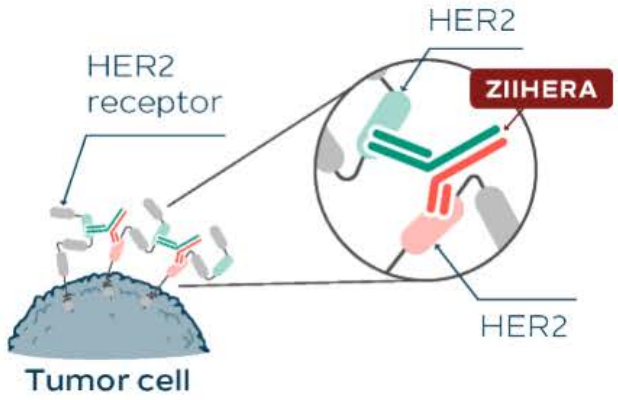
- **Treatment-related adverse events (TRAEs)**
  - **25%** discontinued treatment
  - **19%** required dose reductions

- **Most common ≥ Grade 3 TRAEs**
  - 🩸 **Anemia** (53%), **neutropenia** (31%), **leukopenia** (31%), **lymphopenia** (22%)

- **ILD/pneumonitis** (25%)
  - 🫁 ≥ Grade 3: **13%**
  - ❗ **2 fatal cases**

Ohba et al. J Clin Oncol 2024

Zanidatamab: HER2 biparatopic, bispecific antibody

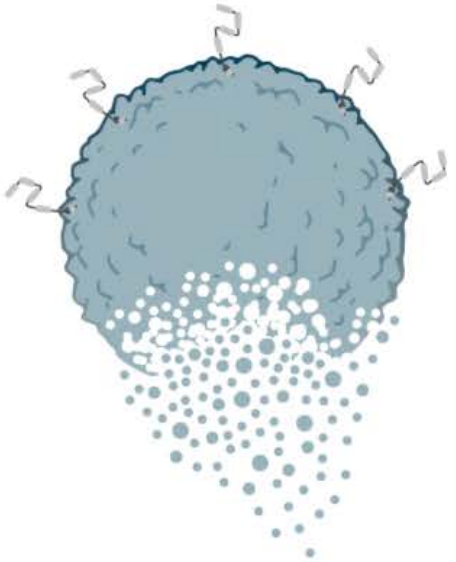


Zanidatamab is not a T-cell engager; instead, it binds to 2 distinct sites on HER2

Zanidatamab acts through multiple mechanisms of action:

- **HER2 internalization[1]**
- **Reduction of HER2 on cell surface[1]**
- **Induction of immune-mediated cytotoxicity (CDC, ADCC, and ADCP)[1]**

TUMOR CELL DEATH

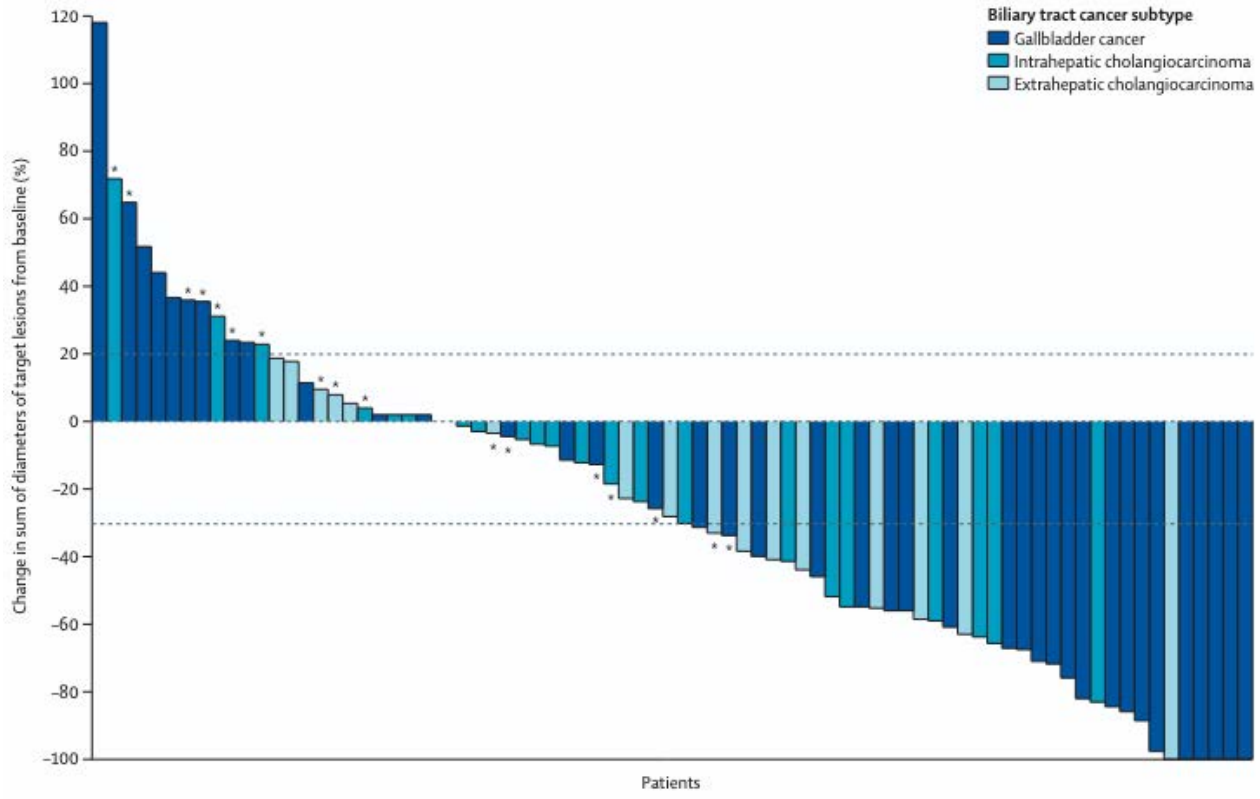


Mullard et al. Nat Rev Drug Discov 2024 | Ziihera HCP

HERIZON-BTC-01 trial of Zanidatamab: efficacy

	Treatment	Trial	# BTC pts	Prior HER2 Tx	HER2 Status	ORR	DCR	mDOR (mo)	mPFS (mo)	mOS (mo)
HERIZON-BTC-01 2023	**Zanidatamab**	Phase 2b **(Global)**	62 80	No	**IHC 3+** IHC 3+ or IHC 2+/Amp	**52%** 41%	**79%** 69%	**14.9** --	**7.2** 5.5	**18.1** 15.5

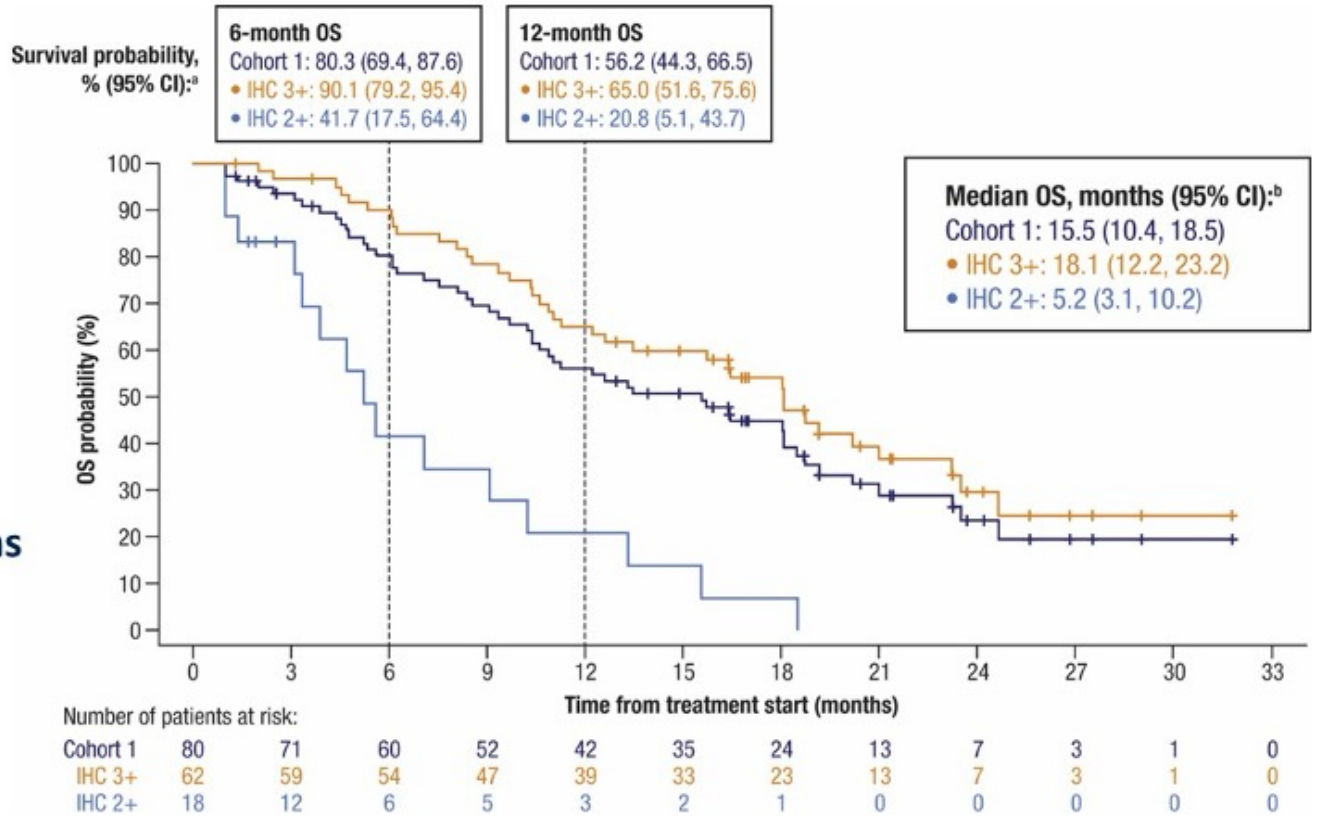
- Previously treated with median 1 LOT (1-2)
- IHC 3+/2+ with Amp
  - 65% Asian, 29% White
  - 51% GBC, 29% iCCA, 20% eCCA
  - 78% IHC 3+



Harding, Fan, et al. Lancet Oncol 2023

HERIZON-BTC-01 trial of Zanidatamab: Long-Term Follow-Up

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



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

Baseline characteristics were previously published.[1]

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

Pant S et al. ASCO 2024;Abstract 4091

HERIZON-BTC-01 trial of Zanidatamab: safety profile

Diarrhea (50%) – mostly grade 1-2

- Manage with fluids and antidiarrheals
- Hold dosing until grade ≤ 1
- Recurrent grade 3: withhold, then resume at 15 mg/kg after grade ≤ 1

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

- Premedicate 30-60 min before infusion with acetaminophen, antihistamine, steroid

LV dysfunction (4%) → resolved (70%); permanent discontinuation (0.9%)

***No cytokine release syndrome* (unlike many bispecifics)** – 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-positive 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-1/L1 inhibitor + Zanidatamab** vs **Gem/Cis +/- PD-1/L1 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

Overview of Presentation

- Therapeutic landscape and prevalence of HER2 in advanced BTC
- Clinical indications and methods for HER2 testing
- HER2-targeted therapies in BTC: efficacy and safety
  - Trastuzumab deruxtecan (DESTINY-PanTumor02 and HERB trials)
  - Zanidatamab (HERIZON-BTC-01 trial)
  - Ongoing phase 3 trials for treatment-naïve patients
- **Clinical case discussions**

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
- 1st-line trials should be considered in HER2 oncogene-driven BTC
- Therapy sequencing should be individualized, taking into account comorbidities, mechanism of action, prior treatments, side effect profile, etc.

Faculty Case Presentations

Dr Ellis: Clinical Case 1

Diagnosis

- 57M with no significant PMH presented with RUQ discomfort, weight loss, and jaundice
- CT with large mass centered in gallbladder fossa with invasion into adjacent liver and porta hepatis as well as multifocal liver metastases
- Liver biopsy confirmed poorly differentiated adenocarcinoma; IHC profile suggests pancreaticobiliary vs upper GI primary
- **Workup consistent with metastatic/unresectable gallbladder adenocarcinoma**

Tissue-based NGS

```
Single nucleotide variants:
TP53 ENSP00000269305.4:p.Arg273His
ARID1A ENSP00000320485.7:p.Arg1989Ter

Insertions/deletions:
SMAD4 ENSP00000341551.3:p.Thr453ProfsTer24

Copy number variants:
ERBB2 (HER2) amplification

HER2 IMMUNOHISTOCHEMISTRY:  Her2 score 3+/positive (cancer cell cluster with
strong complete basolateral or lateral membranous reactivity, irrespective of
percentage of cancer cells positive).
```

Plasma-based NGS

DETECTED ALTERATION(S) / BIOMARKER(S)	ASSOCIATED FDA-APPROVED THERAPIES	CLINICAL TRIALS (SEE PAGE 6)	% CFDNA OR COPY NUMBER
ERBB2 Amplification	✓ Trastuzumab deruxtecan ~ Ado-trastuzumab emtansine, Lapatinib, Neratinib, Trastuzumab, Trastuzumab+pertuzumab, Trastuzumab+tucatinib	Yes	High (+++)
ATM F2732L	~ Olaparib, Talazoparib	Yes	0.1%
ARID1A R1989*	None	Yes	2.2%
TP53 R273H	None	No	1.6%
SMAD4 T453fs	None	No	1.8%

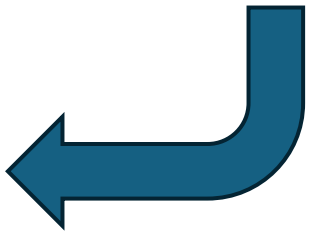
Dr Ellis: Clinical Case 1 (continued)

Diagnosis
- 57M with no significant PMH presented with RUQ discomfort, weight loss, and jaundice
- CT with large mass centered in gallbladder fossa with invasion into adjacent liver and porta hepatis as well as multifocal liver metastases
- Liver biopsy confirmed poorly differentiated adenocarcinoma; IHC profile suggests pancreaticobiliary vs upper GI primary
- **Workup consistent with metastatic/unresectable gallbladder adenocarcinoma**

Gem/Cis + Durva
- SD with eventual PD in liver after **6 months**
- Cytopenias, fatigue

Trastuzumab/Pertuzumab
- SD with eventual PD in GB and liver after **10 months**
- Diarrhea; counts recovered

Gastric outlet obstruction
- EGD with duodenal stent
- Biopsy confirmed persistence of **HER2 IHC 3+**



Trastuzumab deruxtecan
- PR with eventual PD in peritoneum after **11 months**
- Cytopenias, fatigue, nausea; no ILD/pneumonitis

QUESTIONS FOR THE FACULTY

Do you typically evaluate HER2 status in all patients with advanced BTCs? When in the treatment course do you generally test? What testing method do you use?

Is HER2 overexpression more common in specific tumor locations than others — eg, gallbladder versus extra- versus intrahepatic cholangiocarcinoma?

Have you been offering HER2-targeted treatment to patients with HER2-positive advanced BTCs at some point in their treatment course? Which agent(s) do typically use? What outcomes have you seen with these strategies?

QUESTIONS FOR THE FACULTY

Given that T-DXd has a tumor-agnostic indication in IHC3+ HER2-overexpressing solid tumors, in which line of therapy are you generally administering this agent for your patients with HER2-positive advanced BTCs? Are there clinical situations in which you would consider using T-DXd in patients with a lower level of HER2 expression?

What specific strategies are you using to monitor for interstitial lung disease (ILD) in your patients receiving T-DXd?

Do you continue T-DXd if a patients develops asymptomatic Grade 1 ILD? Symptomatic? At what level of ILD are you permanently discontinuing treatment even after resolution of symptoms?

RTP
RESEARCH
TO PRACTICE

Dr Ellis: Clinical Case 2

Diagnosis
- 45F with COPD presented with neck pain
- CT with C8 pathologic fracture, 2.5 cm hilar mass, numerous bone and lung metastases
- Fixation of C8 fracture with biopsy confirming poorly differentiated adenocarcinoma
- **Workup consistent with metastatic/unresectable perihilar cholangiocarcinoma**

Tissue-based NGS

Immunohistochemical analysis of the metastatic carcinoma for erbB-2 (Her2/neu) protein is POSITIVE (score 3+).

TP53 ENSP00000269305.4:p.Leu130Pro (ENST00000269305.4:c.389T>C)

Gem/Cis + Durva
- PR with eventual PD in lungs after **9 months**
- **ANC 950, Plt 70** with dose/schedule adjustments

Zanidatamab
- PR with DOR **10 months**
- Significant decline in CA19-9
- Low grade diarrhea

QUESTIONS FOR THE FACULTY

Based on the recent FDA approval of zanidatamab for patients with previously treated unresectable HER2-positive BTC, how do you integrate this agent into the treatment algorithm? How do you decide between T-DXd and zanidatamab? Have you or would you use these agents sequentially?

How would you indirectly compare the global efficacy of zanidatamab to that of T-DXd in patients with HER2-positive BTCs?

What are the most common toxicities you have observed with zanidatamab?

Agenda

MODULE 1: Gastroesophageal Cancers — Dr Lonardi

MODULE 2: Biliary Tract Cancers — Dr Ellis

MODULE 3: Colorectal Cancer — Dr Raghav

RTP RESEARCH TO PRACTICE

Advances in the Management of HER2-Positive Metastatic Colorectal Cancer

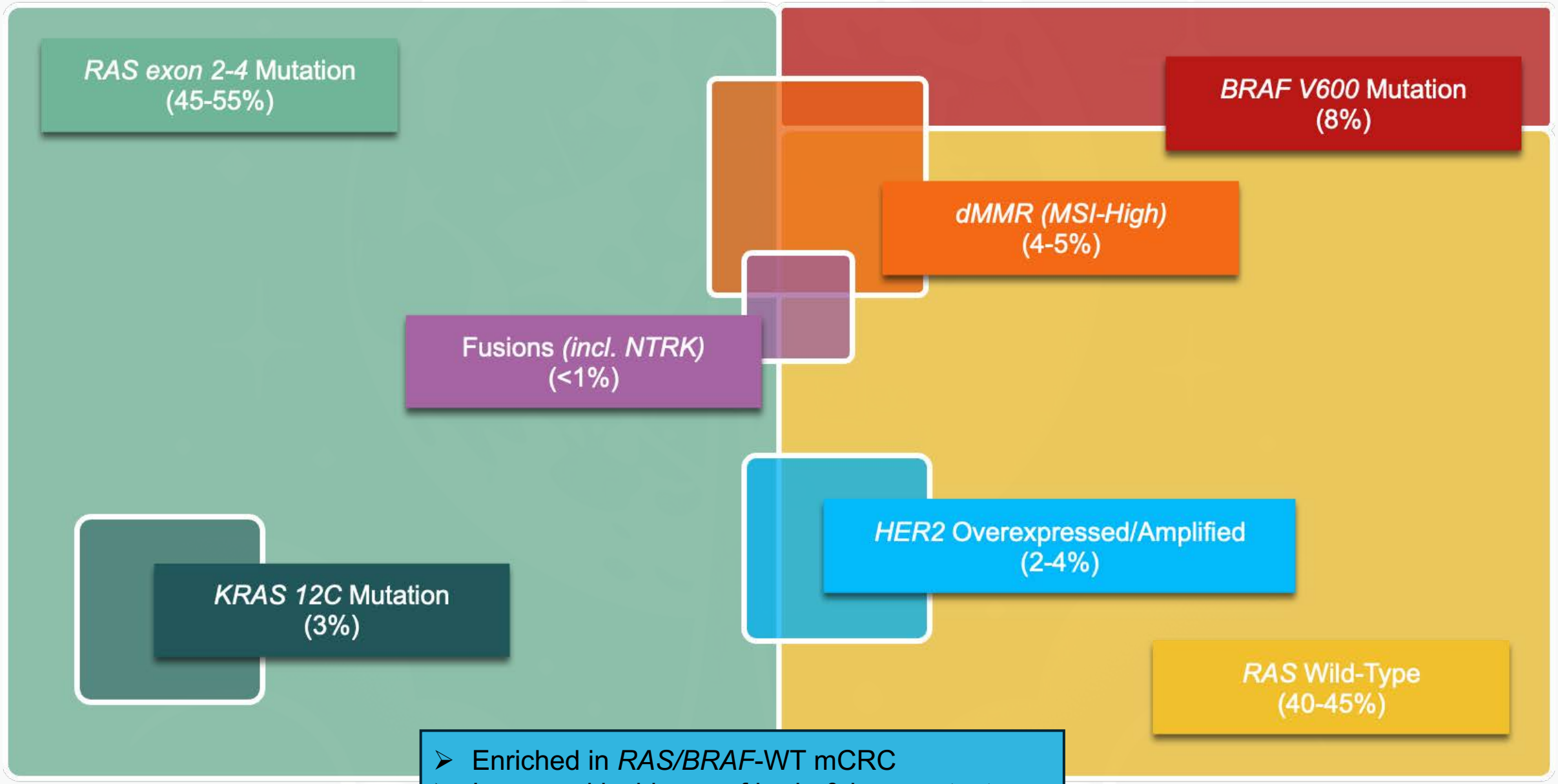
Kanwal Raghav, MD

Associate Professor, Dept. Gastrointestinal Medical Oncology

Associate Vice President (AVP), Ambulatory Medical Operations

The University of Texas MD Anderson Cancer Center, Houston, TX

HER2-Positive mCRC: Overview



- Enriched in *RAS/BRAF*-WT mCRC
- Increased incidence of brain & lung metastases

Raghav et. al. (unpublished) 2025; Singh et. al. CCR 2024; Chen et. al. EJC 2023; Prete et. al. BJC 2024; Sartore-Bianchi et. al. The Oncologist 2019

Trastuzumab + Tucatinib

MOUNTAINEER

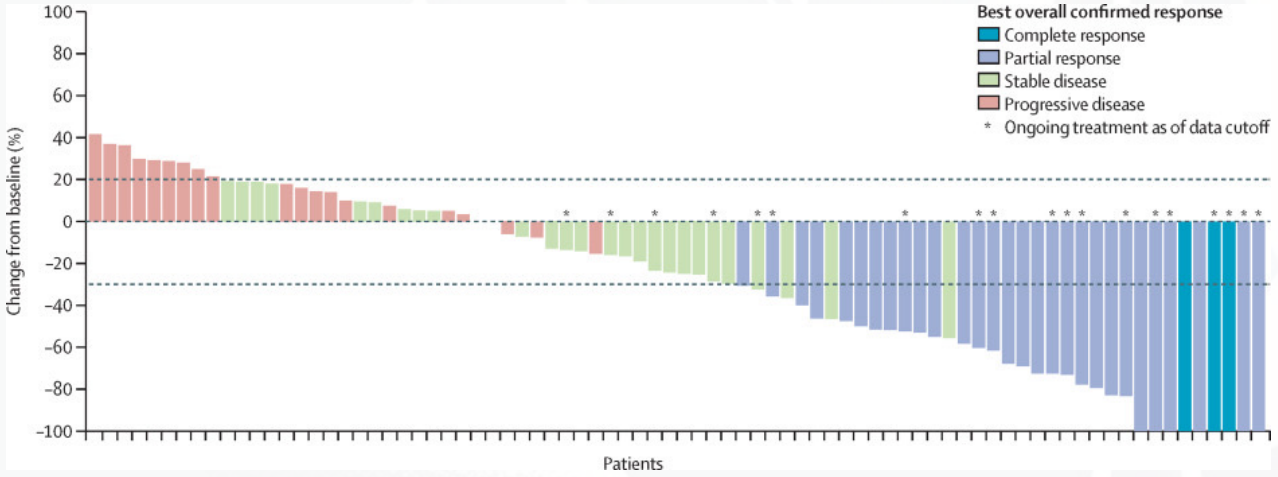
Eligibility Criteria (N = 117)

- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per local IHC/ISH/NGS testing
- *RAS*-WT
- Progression after receiving ≥2 lines of therapy

R 1:1

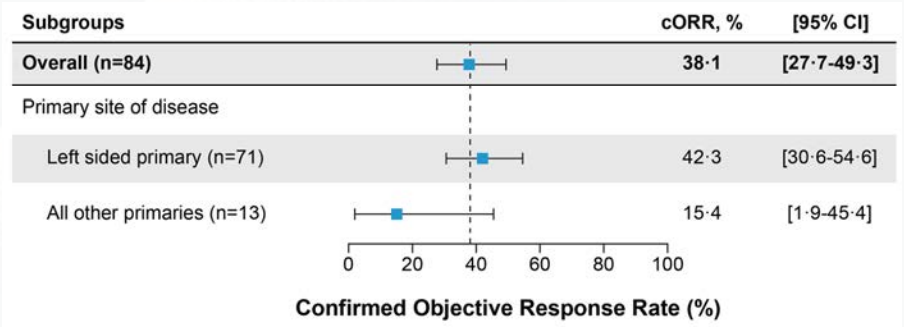
- Cohort A (N = 45) Trastuzumab + Tucatinib
- Cohort B (N = 41) Trastuzumab + Tucatinib
- Cohort C (N = 31) Tucatinib

Primary Endpoints
cORR (cohort A + B)
(Non-comparative randomization)



Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (3.6)	0	0
	PR	29 (34.5)	1 (3.3)	5 (17.9)
	SD[b]	28 (33.3)	23 (76.7)	18 (64.3)
	PD	22 (26.2)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2.4)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		**38.1 (27.7-49.3)[f]**	**3.3 (0.1-17.2)[g]**	**17.9 (6.1-36.9)[f]**
DCR[e] per BICR, n (%)		**60 (71.4)**	**24 (80.0)**	**23 (82.1)**

Responses	IHC 3+ (n=45)	IHC 2+/ISH+ (n=15)
Confirmed objective response rate†, % (95% CI)	46·7 (31·7–62·1)	20·0 (4·3–48·1)
Complete response, n (%)‡	3 (6·7)	0
Partial response, n (%)‡	18 (40·0)	3 (20·0)
Stable disease, n(%)‡,§	17 (37·8)	5 (33·3)
Progressive disease, n (%)‡	7 (15·6)	6 (40·0)
Not available, n (%)¶	0	1 (6·7)

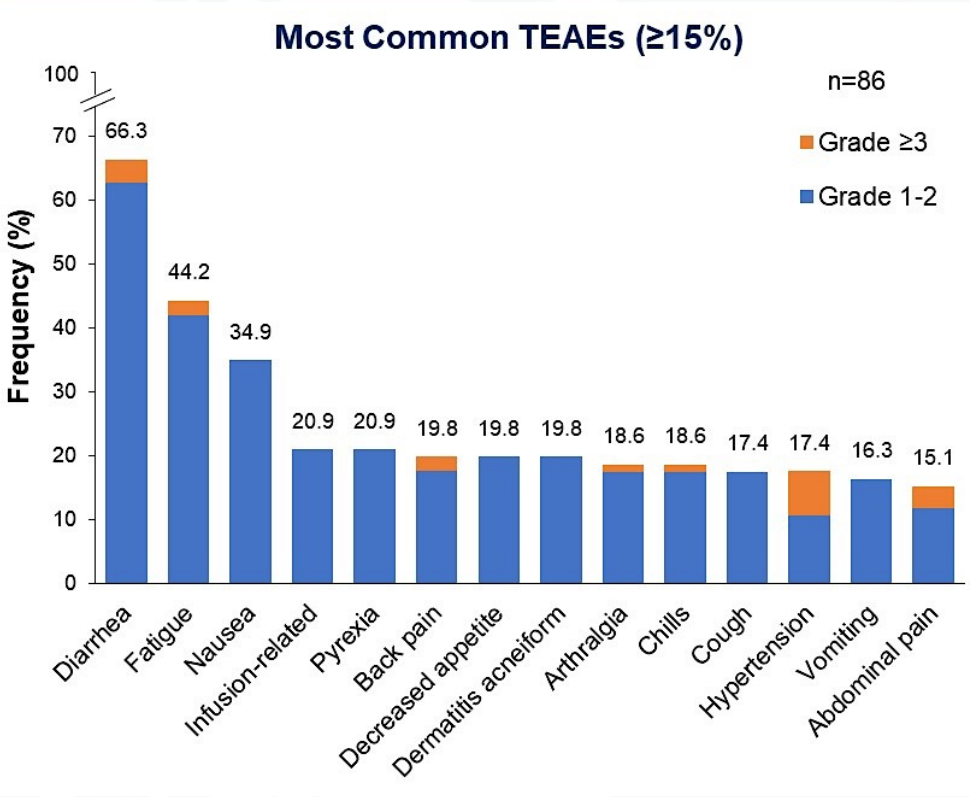


Strickler et. al. Lancet Oncology 2023; Strickler ASCO 2024

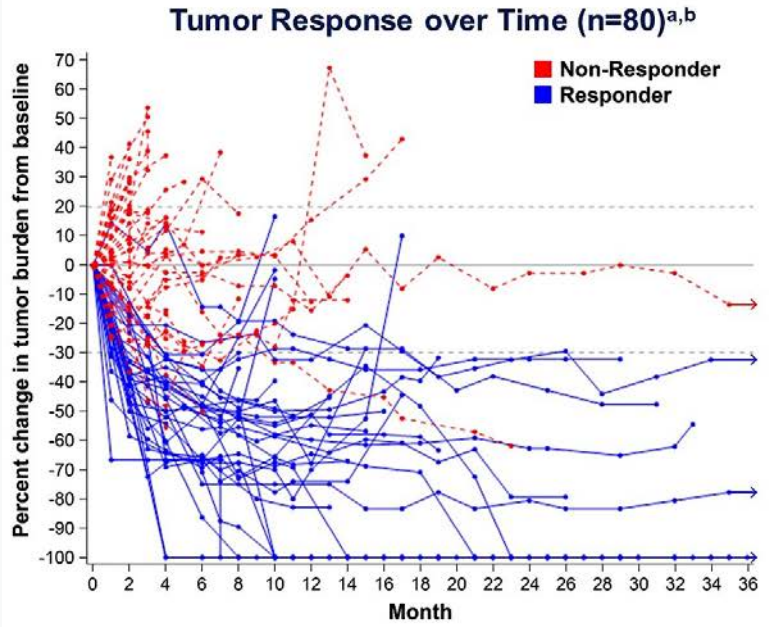
Trastuzumab + Tucatinib (Final Analyses)

	Cohorts A+B Final analysis (n=84)
cORR, % (95% CI)	**39.3** (28.8–50.5)
Median DOR, mo (95% CI)	**15.2** (8.9–20.5)
Median PFS, mo (95% CI)	**8.1** (4.2–10.2)
Median OS, mo (95% CI)	**23.9** (18.7–28.3)

- Median follow-up: 32.4 months



- TT appears to be a safe and effective therapy option for *RAS/BRAF*-WT, HER2-positive mCRC.
- Both tissue and blood and IHC/ISH and NGS for HER2 assessment seems reasonable.



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)

Trastuzumab + Pertuzumab

S1613

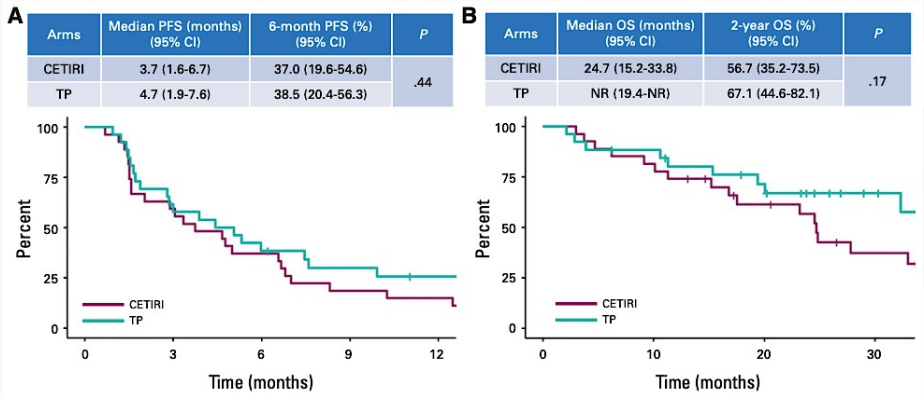
Eligibility Criteria (N = 54)

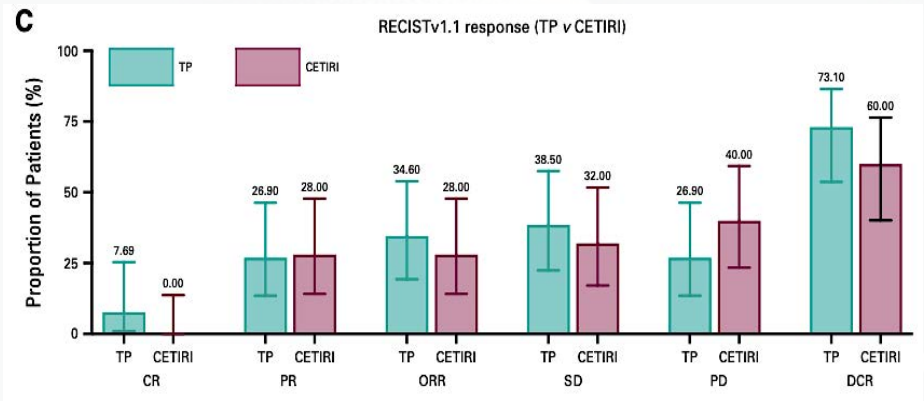
- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per central IHC/ISH testing
- *RAS/BRAF*-WT
- Progression after receiving 1 or 2 lines of therapy

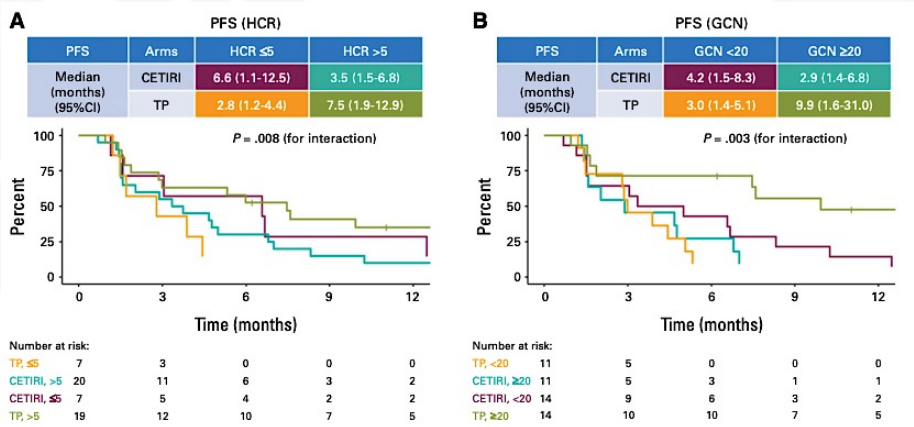
R 1:1

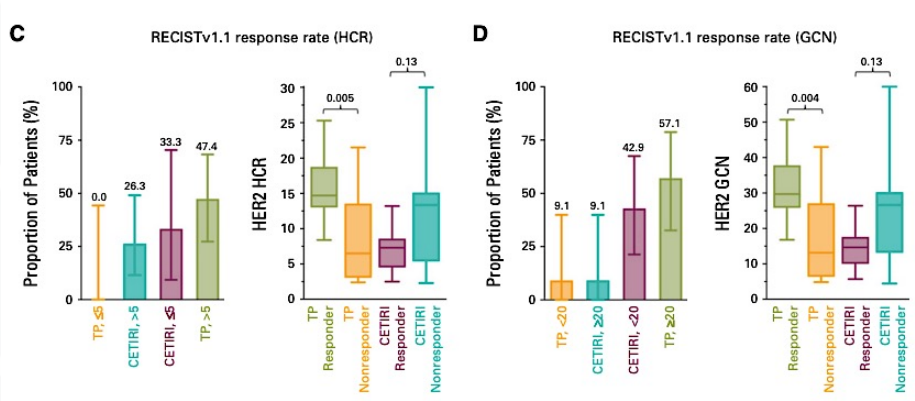
- Trastuzumab + Pertuzumab (N = 26)
- SOC (Cetux + Irinotecan) (N = 28)

Primary Endpoint
PFS









- TP appears to be a safe (Grade 3/4 TRAEs: 23% vs. 46%) and effective cytotoxic therapy free option for *RAS/BRAF*-WT, HER2-positive mCRC.
- Higher levels of *HER2* amplification ~ associated with greater benefit from TP vs. CETIRI

Raghav et.al. JCO 2025

Trastuzumab Deruxtecan

DESTINY-CRC01

Eligibility Criteria (N = 84)

- Confirmed metastatic colorectal adenocarcinoma
- HER2 per central IHC/ISH testing
- *RAS*-WT
- Progression after receiving >2 lines of therapy

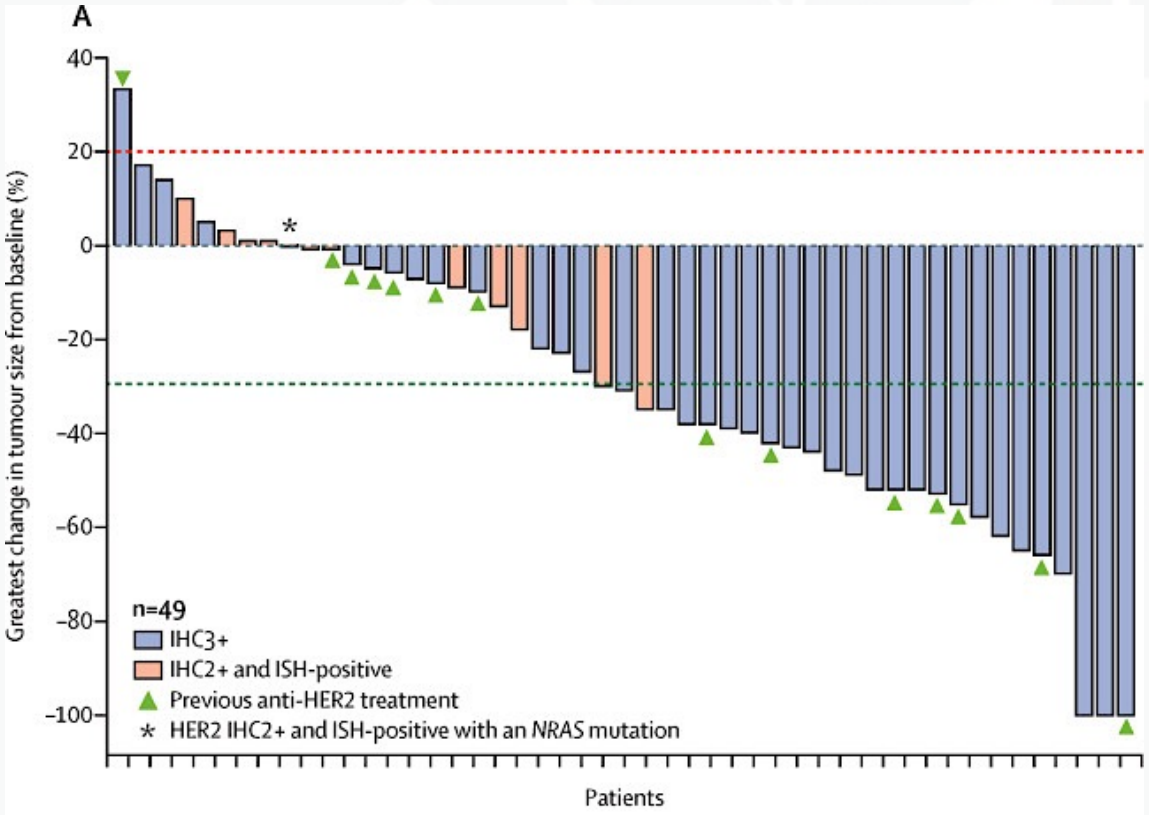
Cohort A (HER2-Positive) (N = 40)

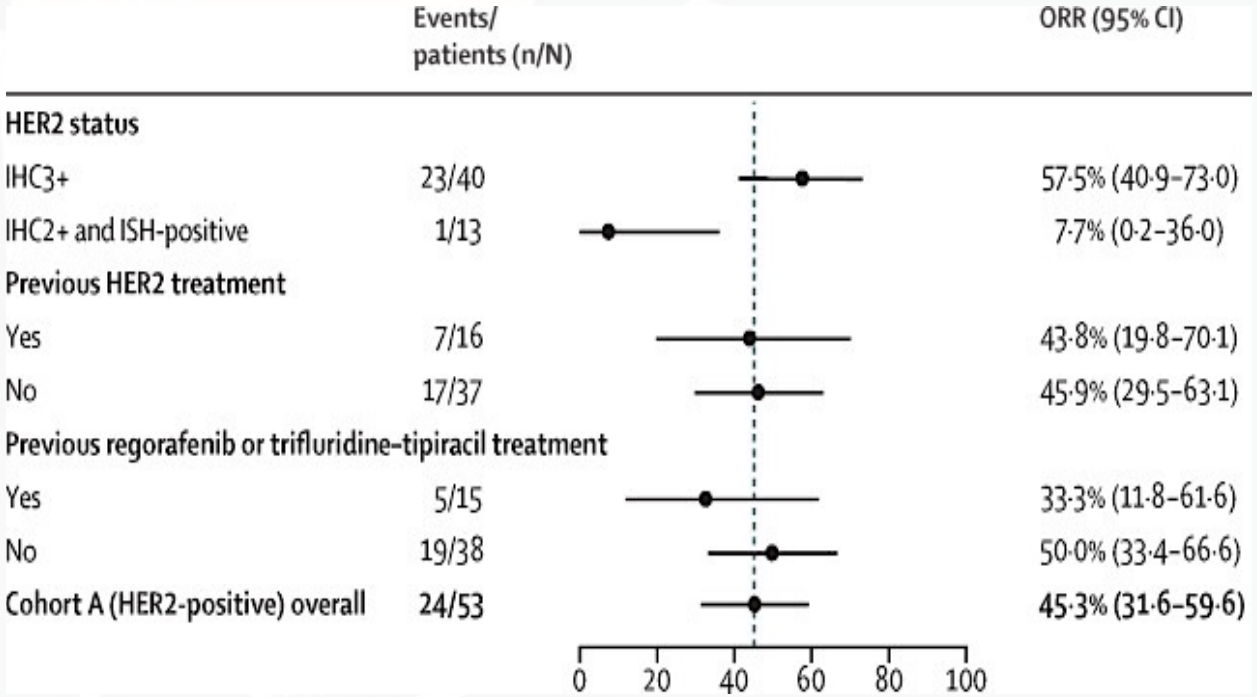
Cohort B (HER2 IHC 2+) (N = 15)

Cohort C (HER2 IHC 1+) (N = 18)

Primary Endpoint
cORR by BICR

	Cohort A (HER2-positive; n=53)
Confirmed ORR by ICR, % (95% CI)	45·3 (31·6–59·6)
Complete response	1 (2%)
Partial response	23 (43%)
Stable disease	20 (38%)
Progressive disease	5 (9%)
Non-evaluable*	4 (8%)
Confirmed ORR by investigator, % (95% CI)	45·3 (31·6–59·6)
Complete response	0
Partial response	24 (45%)
Stable disease	19 (36%)
Progressive disease	6 (11%)
Non-evaluable*	4 (8%)
Disease control rate, % (95% CI)	83·0 (70·2–91·9)
Median duration of response by ICR, months (95% CI)	NE (4·2–NE)





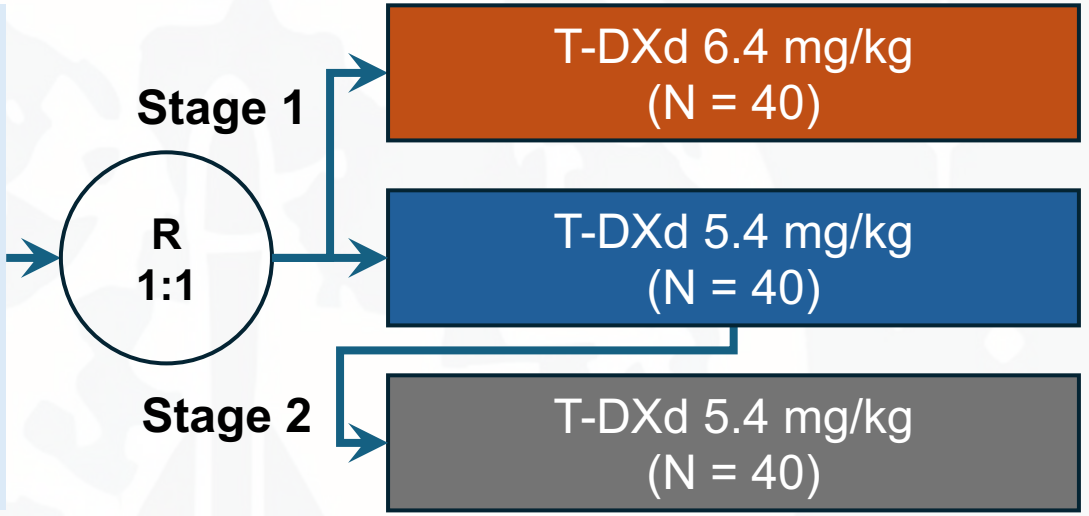
Siena et. al. Lancet Oncology 2021

Trastuzumab Deruxtecan

DESTINY-CRC02

Eligibility Criteria (N = 120)

- Confirmed metastatic colorectal adenocarcinoma
- HER2-positive per central IHC/ISH testing
- *RAS*-WT or *RAS*-MUT
- Progression after receiving >2 lines of therapy

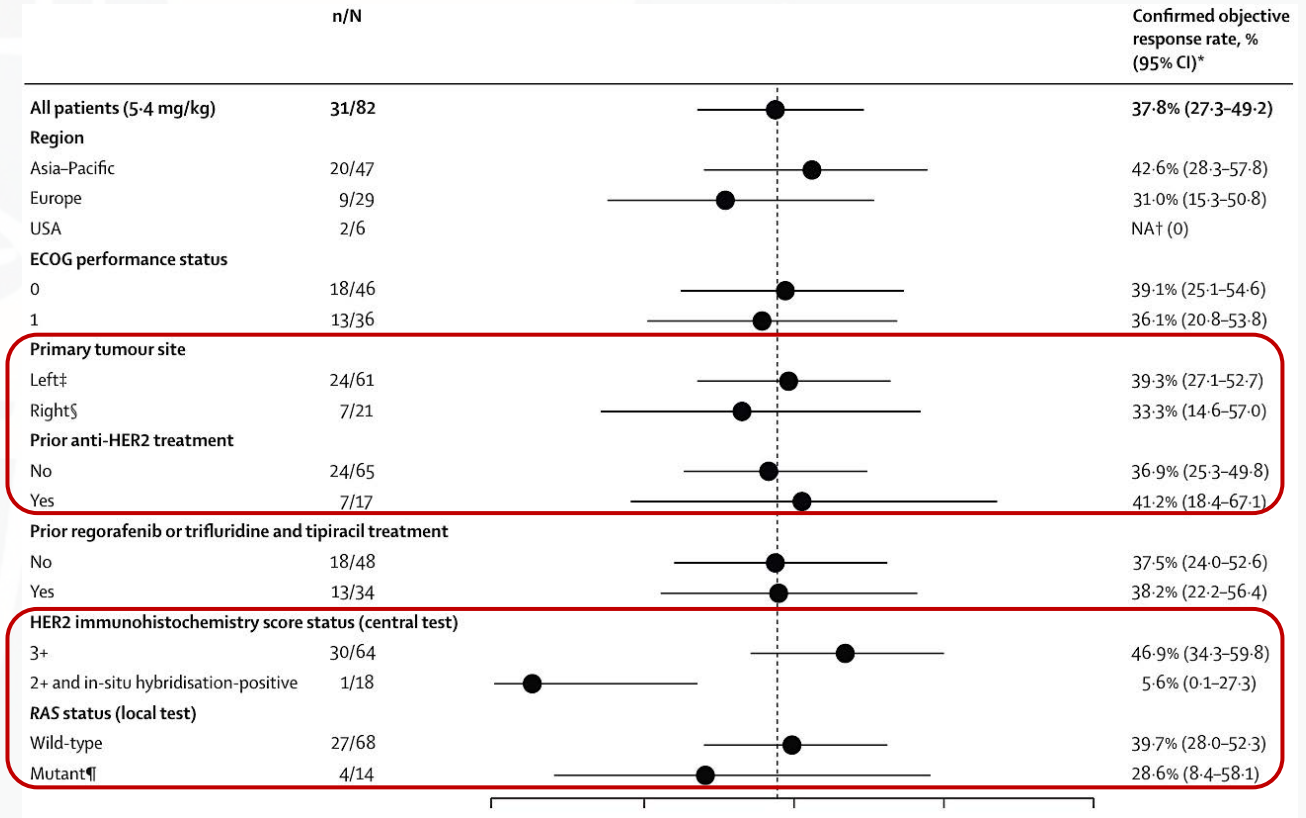


Dual Primary Endpoints
cORR by BICR

	Trastuzumab deruxtecan 5·4 mg/kg group (n=82)	Trastuzumab deruxtecan 6·4 mg/kg group (n=40)
Confirmed objective response rate* (% [95% CI)	31 (37·8% [27·3–49·2])	11 (27·5% [14·6–43·9])
Complete response	0	0
Partial response	31 (38%)	11 (28%)
Stable disease	40 (49%)	23 (58%)
Progressive disease	8 (10%)	4 (10%)
Not evaluable	3 (4%)	2 (5%)
Confirmed disease control rate* (% [95% CI])	71 (86·6% [77·3–93·1])	34 (85·0% [70·2–94·3])
Confirmed clinical benefit rate* (% [95% CI])	37 (45·1% [34·1–56·5])	13 (32·5% [18·6–49·1])
Median duration of response*, months (95% CI)	5·5 (4·2–8·1)	5·5 (3·7–NE)
Median progression-free survival*, months (95% CI)	5·8 (4·6–7·0)	5·5 (4·2–7·0)
Patients with events	54 (66%)	27 (68%)
Median overall survival, months (95% CI)	13·4 (12·5–16·8)	NE (9·9–NE)
Patients with events	26 (32%)	13 (33%)
Median follow-up, months (IQR)	8·9 (6·7–10·5)	10·3 (5·9–12·7)
Median treatment duration†, months (IQR)	5·5 (3·6–8·4)	4·9 (2·8–8·5)
Median total dose†, mg/kg (IQR)	37·8 (26·9–59·4)	40·8 (25·4–66·1)
Median cycles initiated† (IQR)	7·0 (5·0–11·0)	7·0 (4·0–11·0)

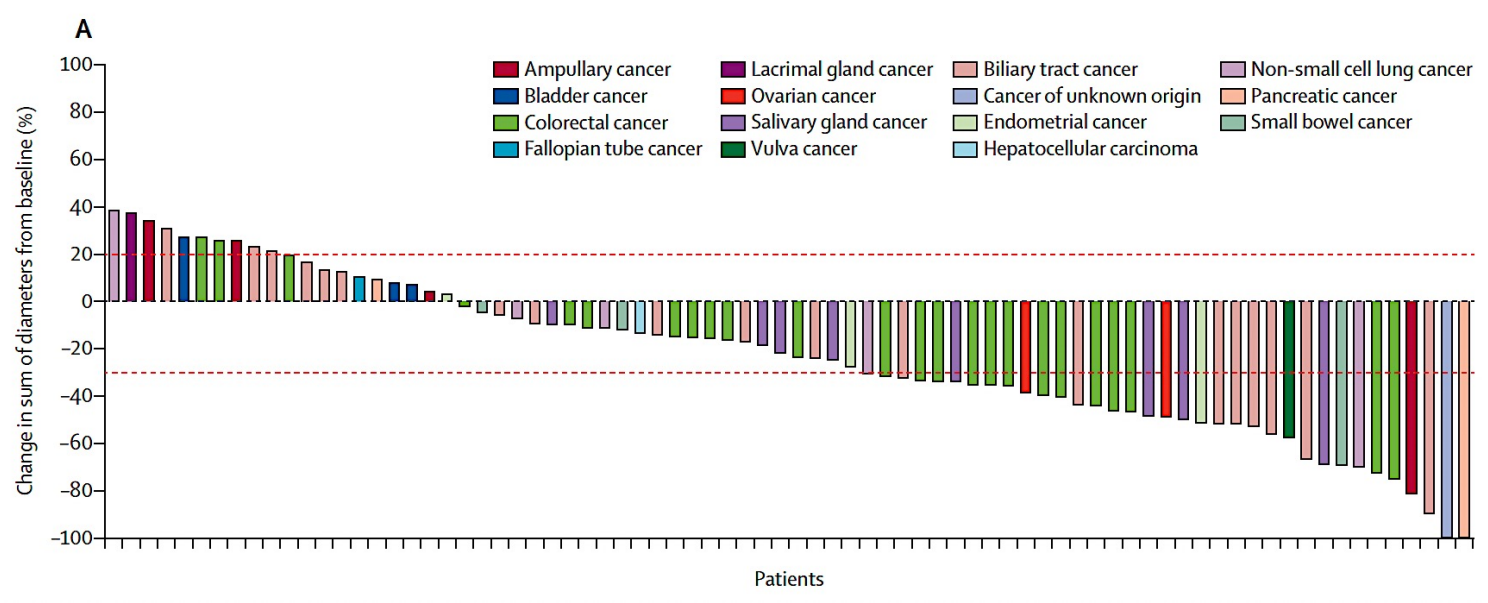
Data are n (%) except where otherwise stated. NE=not estimable. *Assessed by blinded independent central review. †Based on the total population treated with trastuzumab deruxtecan; 5·4 mg/kg, n=83; 6·4 mg/kg, n=39 (safety analysis set).

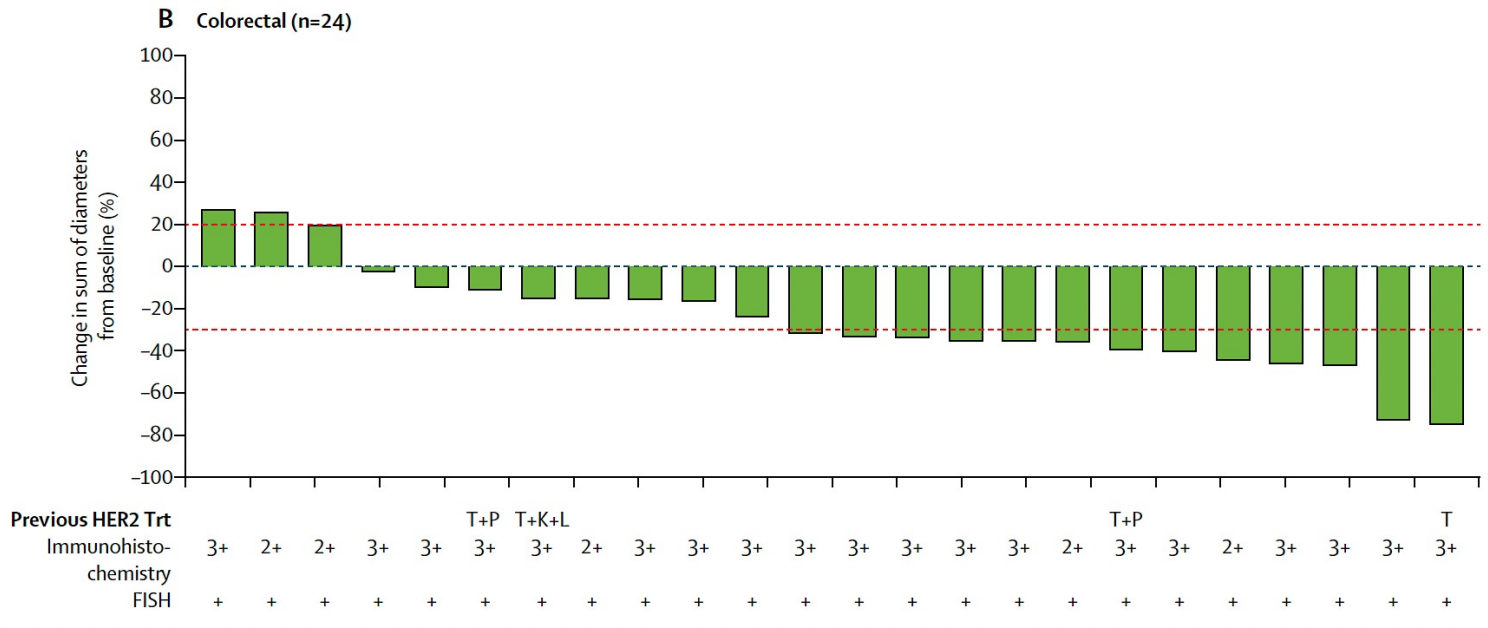
Table 2: **Antitumour activity endpoints**



Raghav et. al. Lancet Oncology 2024

Zanidatamab: Bispecific HER2 Antibody





	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%)

Data are % (95% CI) or median (95% CI), unless otherwise specified. *Clinical benefit rate was defined as stable disease for 24 weeks or longer or best overall response of complete response or partial response. †Disease control rate was defined as a best overall response of complete response, partial response, or stable disease. ‡Among patients with confirmed response. §Among all patients who received at least one dose.

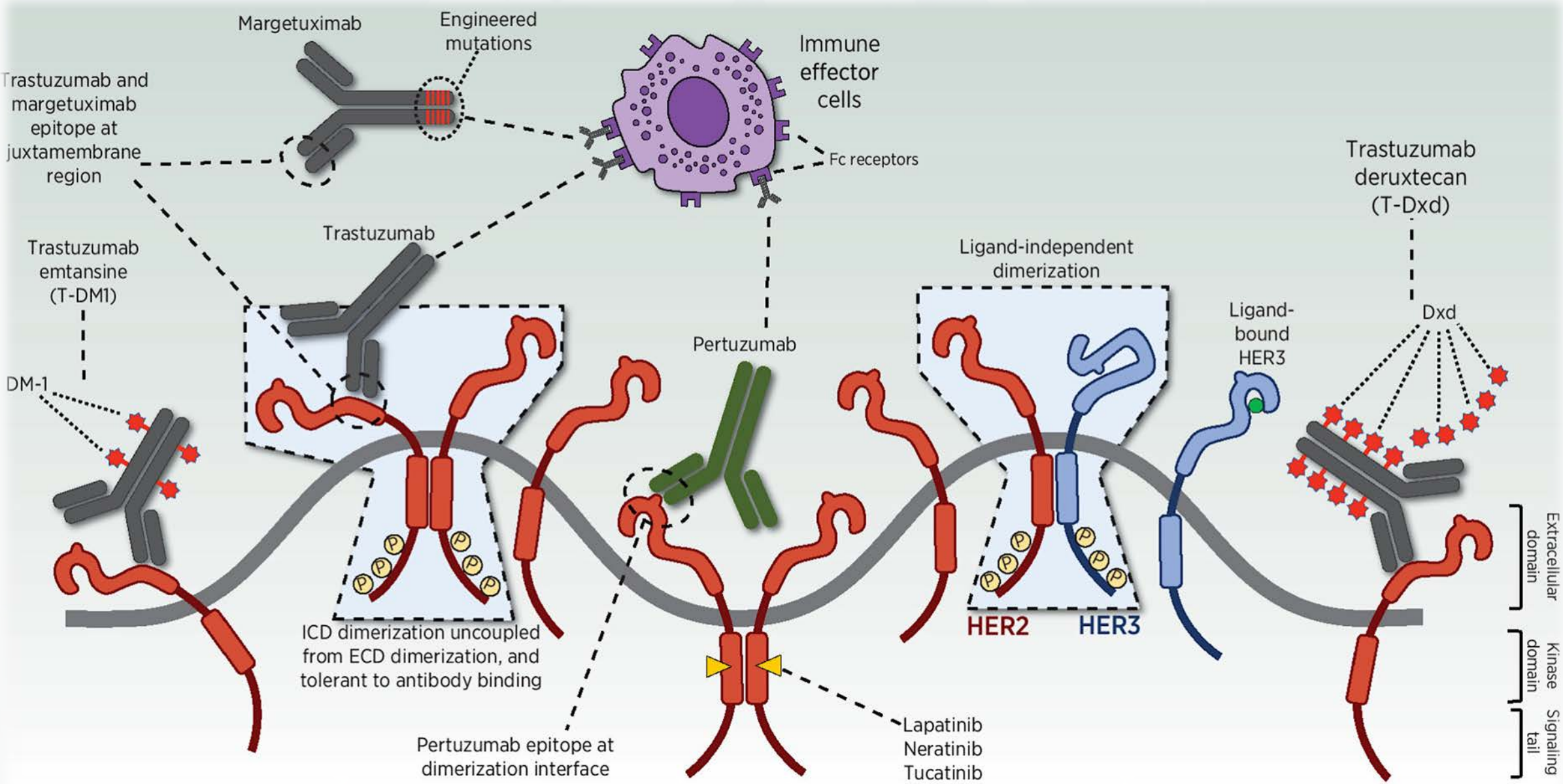
***Table 3*: Anti-tumour activity (in the part 2 response-evaluable population)**

Zanidatamab + mFOLFOX6-2 +/- bevacizumab: Phase 2 in the first-line HER2-positive mCRC:

- cORR: 83.3% (n = 6)
- cORR: 100% w Bev
- Median duration of response (DOR) for the overall population was not reached (NR; range, 2.9+ to 16.7+).

Meric-Bernstam et al. Lancet Onco. 2022; Rha et. al. ESMO (abstract) 2024

HER2 Targeting Strategies



Raghav and Moasser CCR 2023

Key Takeaways

- HER2 overexpression/amplification is seen in **2-3%** of CRC & enriched in ***RAS/BRAF* WT** tumors.
- Dual HER2 inhibition appears to be effective in this population.
- HER2 ADCs show promising activity along with activity in *RAS* mutant HER2+ mCRC.
- **HER2 testing should be performed early in CRC via either IHC/ISH or NGS**
- **Refer early for clinical trials.**

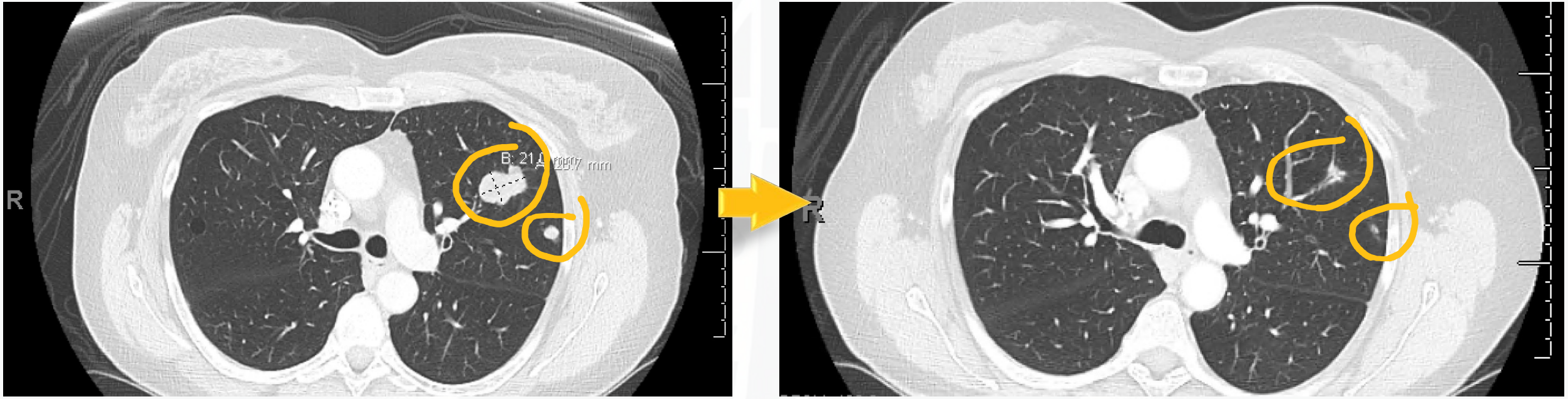
Faculty Case Presentations

Patient Case: 47-year-old male

- Presented with RUQ pain and intentional weight loss to ER.
- Scan showed a sigmoid colon mass with multiple multilobar liver and bilateral lung metastases. Biopsy showed moderately differentiated adenocarcinoma.
- Molecular profile: MSS (by IHC), APC mutation, *RAS/BRAF* wild-type and *ERBB2* amplification on NGS (HER2 IHC 3+ >90% cells and FISH + with HER2/CEP17: 12 [HER2 GCN: 24])
- Was treated with first-line cetuximab and FOLFIRI for 6 months with stable disease and then subsequent progression.
- Patient was treated with second-line therapy with bevacizumab and FOLFOX for 6 months with minor response and then progression.

Patient Case: 47-year-old male

- Third-line treatment: Trastuzumab plus pertuzumab for ~ 3 years with response (near complete CR).



QUESTIONS FOR THE FACULTY

Do you typically evaluate HER2 status in all patients with metastatic CRC? When in the treatment course do you generally test? How, if at all, does your approach to HER2 testing in patients with metastatic CRC differ from your approach to gastroesophageal cancers and BTCs?

In which line of therapy do you generally recommend HER2-targeted treatment for your patients with HER2-overexpressing metastatic CRC? What clinical and biologic factors influence your placement of HER2-targeted therapy in the treatment sequence for individual patients?

QUESTIONS FOR THE FACULTY

Do you believe that there is a greater incidence of brain metastases in patients with HER2-positive metastatic CRC? What about advanced gastroesphageal cancers? Advanced BTCs?

For patients with HER2 positive metastatic CRC and brain metastases, do you have a preferred HER2-targeted regimen? What about patients with advanced gastroesphageal cancers and brain metastases? BTCs and brain metastases?

Patient case: 71-year-old female

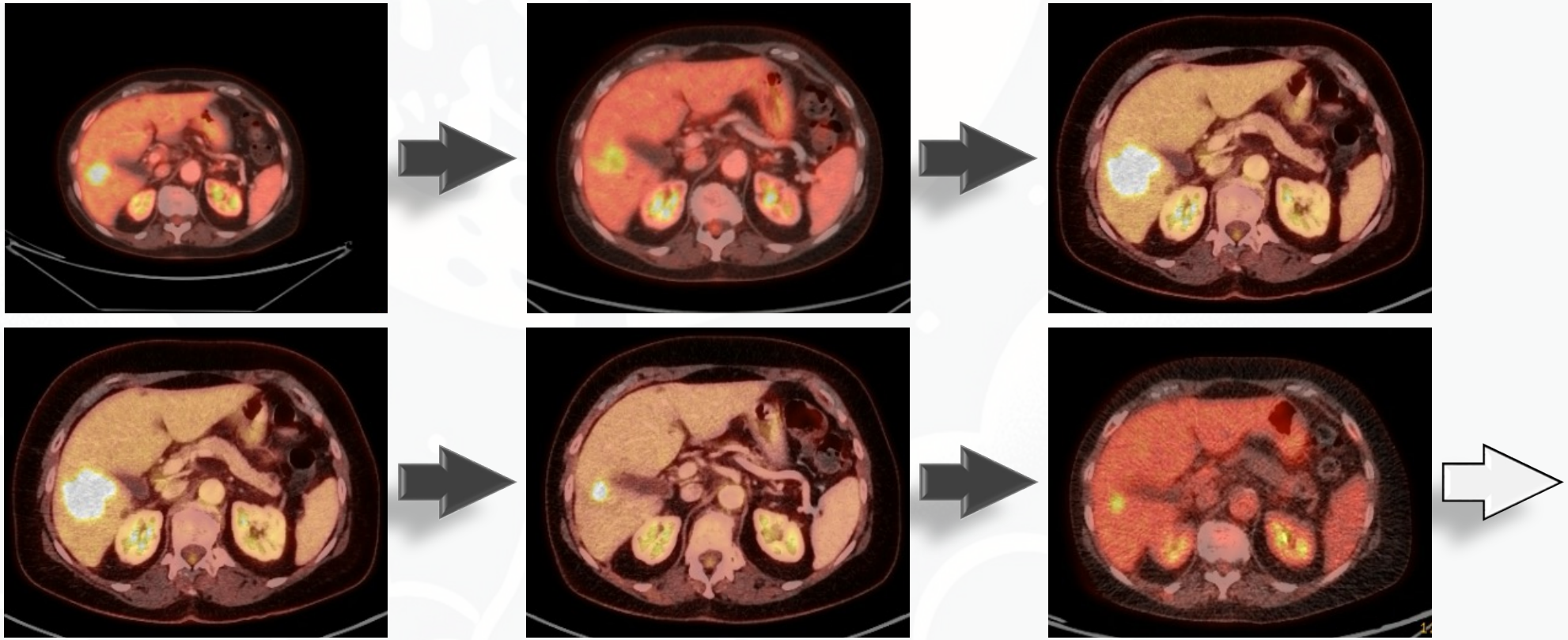
- Presented with BRBPR for past 6 months. No screening colonoscopy.
- Colonoscopy showed a circumferential proximal rectal mass and scans showed multiple liver and bilateral lung metastases. Biopsy showed poorly differentiated adenocarcinoma.
- Molecular profile: MSS, *RAS/BRAF* wild-type, APC, TP53 and PIK3CA mutation by NGS. HER2-positive with HER2 IHC: 3+ >90% cells (FISH: HER2/CEP17: 4.3 [HER2 GCN: 9.5])
- Was treated with first-line bevacizumab and FOLFOX for 7 months with response and then subsequent progression.
- Patient was treated with anti-HER2 therapy thereafter:

Patient case: 71-year-old female

- Second-line treatment: Trastuzumab plus tucatinib for 11 months with response. Progressed. LB showed HER2 amplification.
- Third-line treatment: Trastuzumab deruxtecan for 12 months with disease response and currently on treatment.

Trastuzumab + Tucatinib

Trastuzumab deruxtecan



QUESTIONS FOR THE FACULTY

How would you indirectly compare the global efficacy of tucatinib/trastuzumab to that of T-DXd? What about tolerability?

For patients to whom you have decided to administer HER2-targeted therapy, which of these regimens do you typically administer first? What clinical factors influence this decision?

Based on the recent data with zanidatamab plus mFOLFOX6-2 with or without bevacizumab as first-line therapy for patients with HER2-positive mCRC, would you like to have access to this regimen now? For which patients with HER2-positive mCRC would you prioritize its use?

RTP Live from Chicago: Investigator Perspectives on Available Research Findings and Challenging Questions in the Management of Renal Cell Carcinoma

Monday, June 2, 2025
7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Professor Laurence Albiges, MD, PhD
Tian Zhang, MD, MHS

Moderator

Neil Love, MD

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