OUR WEBINAR WILL BEGIN SHORTLY

UNDERSTANDING HER2: *WHAT PATIENTS NEED TO KNOW*

FIGHT COLORECTAL CANCER™

UNDESTANDING HER2: WHAT PATIENTS NEED TO KNOW

IN COLLABORATION WITH: Pfizer Oncology

TODAY'S WEBINAR

01 **QUESTIONS**

Ask a question in the panel on the right side of your screen.

02 **WEBINAR ARCHIVE**

Watch a recording of this webinar on the Fight CRC website. Visit FightCRC.org.

03 **TWEET ALONG!**

Follow along on Twitter. Use the hashtag: #CRCWebinar

RESOURCES

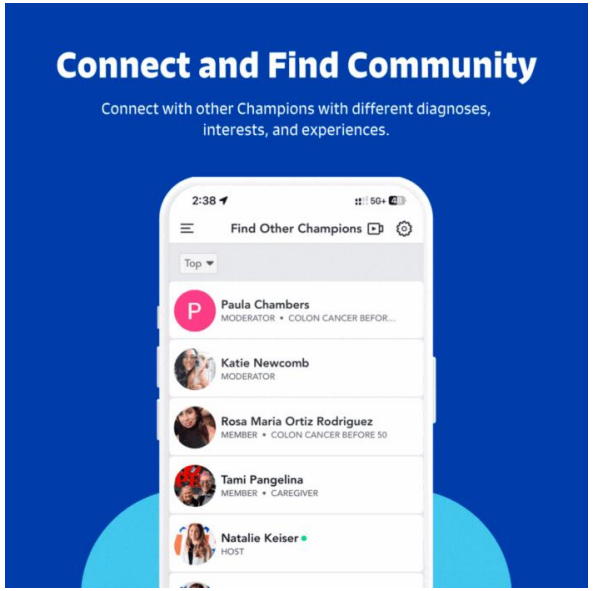
Fight CRC offers a wide variety of resources for those touched by colorectal cancer.

Visit **FightCRC.org** to view, download, and order the latest resources.

ONLINE TOOLS

CHATCRC

FREE RESOURCES



COMMUNITY OF CHAMPIONS APP

The information and services provided by Fight Colorectal Cancer are for general informational purposes only.

The information and services are not intended to be substitutes for professional medical advice, diagnoses or treatment.

If you are ill, or suspect that you are ill, see a doctor immediately. In an emergency, call 911 or go to the nearest emergency room.

Fight Colorectal Cancer never recommends or endorses any specific physicians, products or treatments for any condition.

TODAY'S PANELISTS

Al B. Benson III
MD, FACP, FACCC, FASCO
Professor of Medicine
Director for Cooperative Groups
Northwestern University

John Strickler
MD
Professor of Medicine
Principal Investigator of MOUNTAINEER
Duke University

Daad Abighanem
Stage IV Colorectal Cancer Survivor
Fight CRC Research Advocate

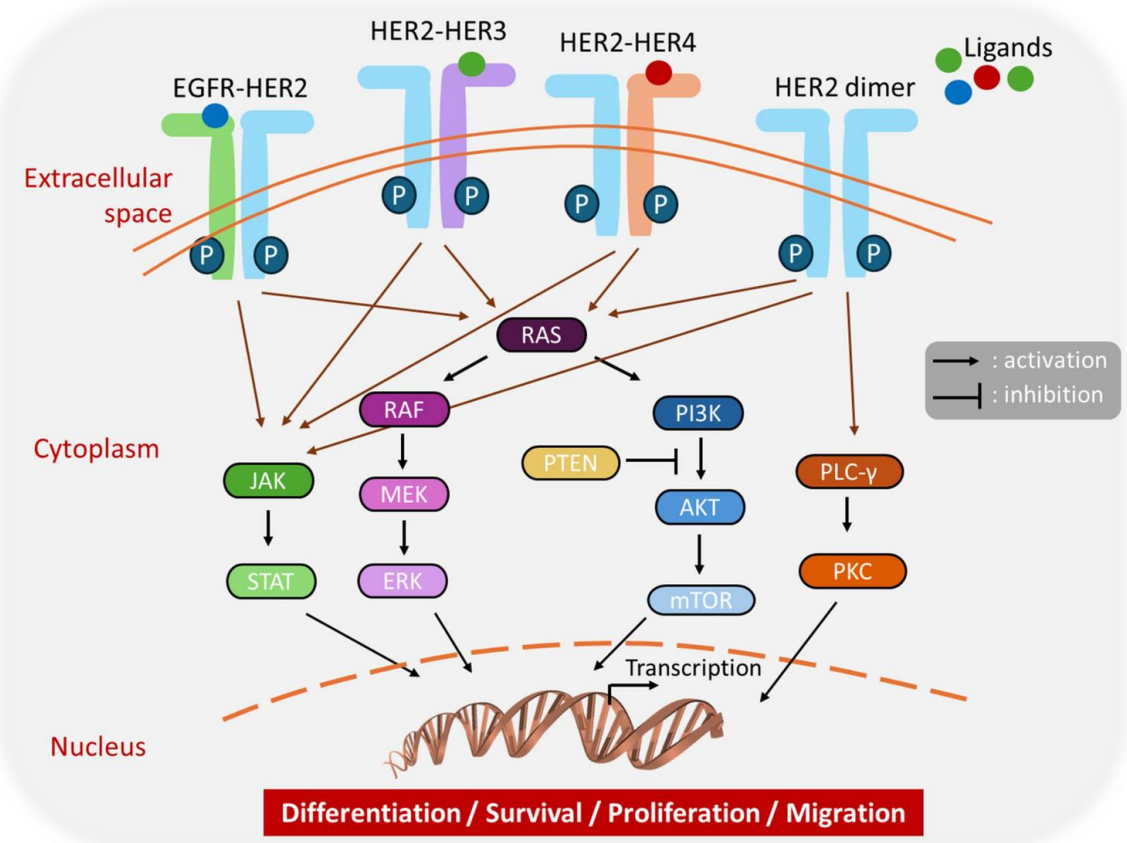
Dr. Al B. Benson III - Disclosures

Grants/Research/Scientific – COI 2024-2025

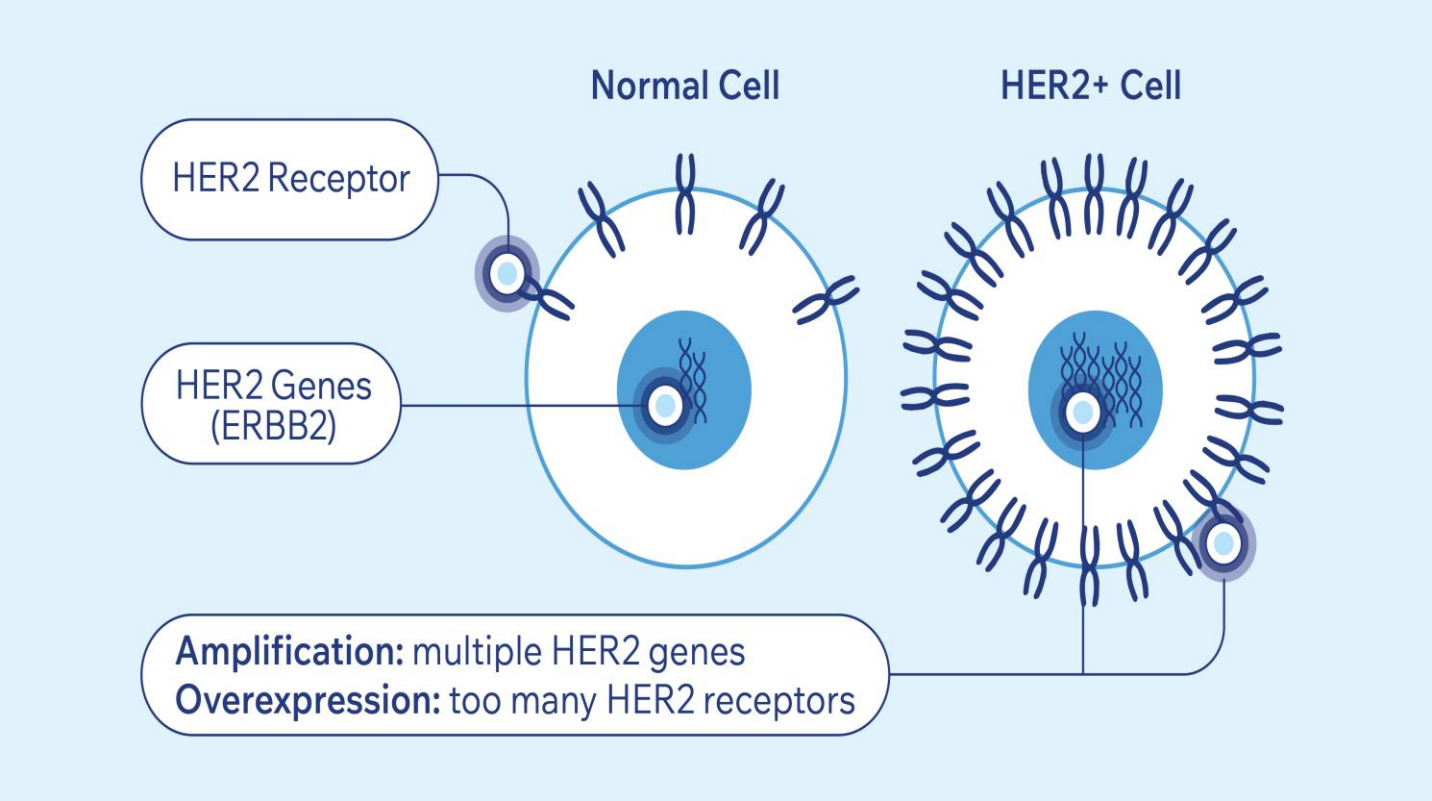
- GlaxosmithKline (GSK)
- WCG Clinical INC.
- Lewin Group
- American College of Radiology
- Inocras
- Merck Sharp & Dohme
- Taiho Pharmaceutical
- Bristol-Myers Squibb DMC
- Astellas Pharma DMC
- Amgen DMC
- Syncore DMC
- Tyme, Inc. DMC
- ITM Solucin GmbHm
- RM-110-Elevar Therapeutics, Inc.
- STP-ST-01 – St. Pharm Co., LTD
- Abbvie, Inc.
- Pfizer
- ITM Samsung Bioepsis
- Eikon Therapeutics
- Novartis DMC
- Boehringer Ingelheim Pharmaceuticals
- AIM Immunotech DMC

WHAT IS HER2?

- HER2 = Human Epidural Growth Factor Receptor 2
  - Part of the HER/EGFR receptor family (HER1/EGFR, HER2, HER3, HER4)
- Gene that provides instruction for making a protein that is involved in cell growth and division



UNDERSTANDING HER2 IN COLORECTAL CANCER

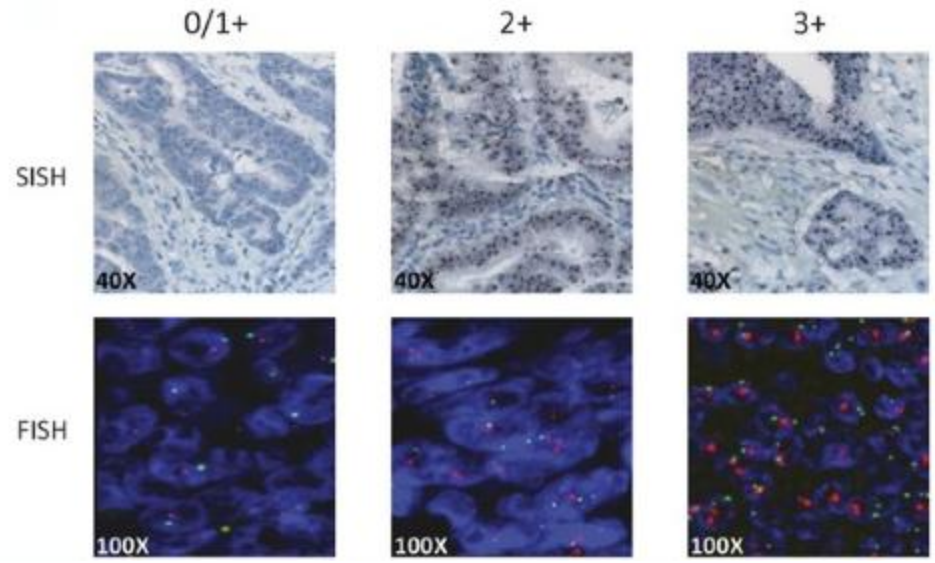


- HER2 is an important biomarker that can drive cancer growth in a subset of metastatic colorectal cancers (mCRC).
- HER2 amplification → continuous "growth signal" to the cell
- Occurs in ~3–5 % of metastatic CRC
- Leads to resistance to some targeted EGFR therapies

TESTING & GUIDELINES

- Testing for HER2 helps identify patients who may benefit from targeted therapies.
- HER2 testing recommended for all metastatic colorectal cancer patients (NCCN 2025)
  - Especially those with **RAS/BRAF wild-type, MSS tumors**.
- Common testing methods:
  - IHC (Immunohistochemistry) – protein overexpression
  - ISH/FISH (In Situ Hybridization) – gene amplification
  - NGS – detects HER2 status within broader panel
- HER2 positivity is defined as IHC 3+ or IHC 2+ with ISH amplification.

SCORE	0	1+	2+	3+
Intensity	No staining, or staining in less than 10% of cells	Faint, barely perceptible in more than 10% of the cells	Weak to moderate in more than 10% of the cells	Intense in more than 10% of the cells
Pattern	-	segmental or granular	circumferential, basolateral or lateral	circumferential, basolateral or lateral



WHY HER2 TESTING MATTERS

- Identifies who may benefit from targeted therapy
- Early identification can prevent exposure to ineffective EGFR inhibitors
- Supports access to HER2-focused clinical trials for targeted therapies.
- Helps inform treatment decisions and precision oncology planning.

CURRENT HER2 TARGETED THERAPIES IN MCRC

- Currently available after initial treatment:
  - Tucatinib + Trastuzumab (MOUNTAINEER study – FDA-approved 2023)
  - Trastuzumab combined with Pertuzumab, Lapatinib, or Tucatinib
  - Fam-Trastuzumab Deruxtecan-nxki (T-DXd – FDA-approved 2024 for HER2+ solid tumors)

These regimens are available options following initial therapy for patients with HER2-positive, RAS/BRAF wild-type mCRC.

ONGOING RESEARCH & EMERGING THERAPIES

- Emerging therapies and combinations:
  - Next generation TKIs (e.g., Poziotinib)
  - Novel antibody-drug conjugates (ADCs) and dual-targeting approaches
- Research Focus:
  - Optimizing sequencing and combinations with chemotherapy and immunotherapy
  - Using HER2 therapy earlier in treatment

FUTURE DIRECTIONS

- HER2-targeted therapy is moving earlier in the treatment line for mCRC.
- Research focuses on resistance mechanisms and novel combinations with immunotherapy.
- HER2 is an essential biomarker for precision treatment in colorectal cancer.
- Clinical trials and advocacy continue to drive progress in HER2+ mCRC.

Al B. Benson III Disclosures

Consultant/ Advisor	Research Funding	Stock	IDMC/DSMB
Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Beigene, BMS, Cytovation, Daiichi-Sankyo, Eli Lilly, GE Healthcare, GSK, Incyte, Ipsen, Johnson and Johnson, Jazz Pharmaceuticals, Leap, Merck, Natera, Pfizer, Quanta Therapeutics, Roche/Genentech, Regeneron, Sanofi, Taiho, Takeda, Xilio Therapeutics	Abbvie, Amgen, Apollo Therapeutics, AStar D3, Bayer, Beigene, Curegenix, Daiichi-Sankyo, Eli Lilly, Erasca, GSK, Leap Therapeutics, Novartis, Pfizer, Quanta Therapeutics, Revolution Medicines, Roche/ Genentech	Triumvira Immunologics (stock options)	Johnson and Johnson, Abbvie

QUESTION & ANSWER

Clinical Impact of the MOUNTAINEER Trial and What's Next in HER2-Targeted Research

John H. Strickler, MD
Professor of Medicine
Duke University Medical Center

November 5, 2025

Disclosures

Consultant/ Advisor	Research Funding	Stock	IDMC/DSMB
Abbvie, Amgen, Astellas, AstraZeneca, Bayer, Beigene, BMS, Cytovation, Daiichi-Sankyo, Eli Lilly, GE Healthcare, GSK, Incyte, Ipsen, Johnson and Johnson, Jazz Pharmaceuticals, Leap, Merck, Natera, Pfizer, Quanta Therapeutics, Roche/Genentech, Regeneron, Sanofi, Taiho, Takeda, Xilio Therapeutics	Abbvie, Amgen, Apollo Therapeutics, AStar D3, Bayer, Beigene, Curegenix, Daiichi-Sankyo, Eli Lilly, Erasca, GSK, Leap Therapeutics, Novartis, Pfizer, Quanta Therapeutics, Revolution Medicines, Roche/ Genentech	Triumvira Immunologics (stock options)	Johnson and Johnson, Abbvie

MOUNTAINEER: Clinical Impact

- MOUNTAINEER was a multi-center, open-label, phase 2 trial that evaluated tucatinib + trastuzumab and tucatinib monotherapy in adults with HER2+, *RAS* wild-type, metastatic colorectal cancer (CRC)
- Tucatinib + trastuzumab was well tolerated with sustained and clinically meaningful activity
- Tucatinib + trastuzumab is FDA-approved and should be included in a “HER2 directed” treatment algorithm for metastatic CRC

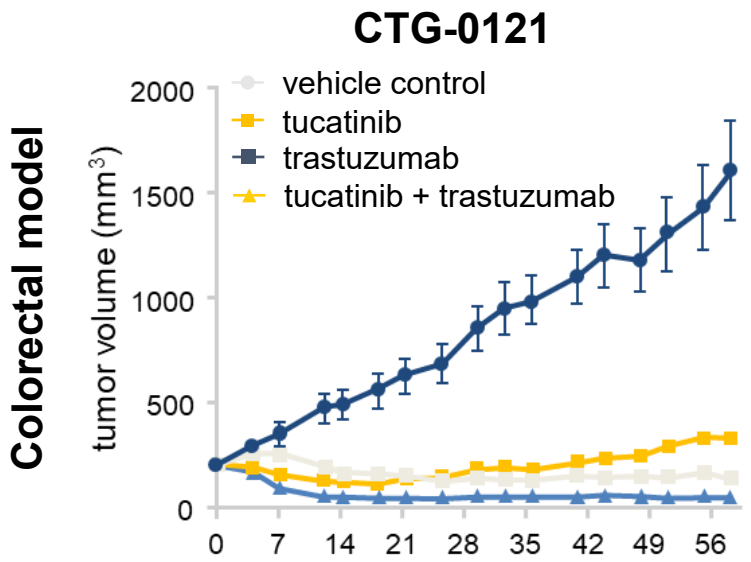

Image generated by MS Co-pilot AI

MOUNTAINEER: Background

- HER2 amplification/overexpression (HER2+) occurs in ~3-5% of patients with mCRC[1]
- Tucatinib is a highly selective TKI for HER2 with minimal inhibition of EGFR[2]
- In preclinical models of HER2+ mCRC, tucatinib + trastuzumab showed significantly greater antitumor activity compared with either agent alone
- The MOUNTAINEER trial evaluated the safety and efficacy of tucatinib + trastuzumab in patients with HER2+ and RAS wild-type mCRC[3]

	HER2 IC_{50}* (nmol/L)	EGFR IC_{50}* (nmol/L)
Tucatinib	6.9	449
Lapatinib	109	48
Neratinib	5.6	1.8

* Calculated IC_{50} values for tucatinib, lapatinib, and neratinib in a kinase assay using recombinant HER2 and EGFR.

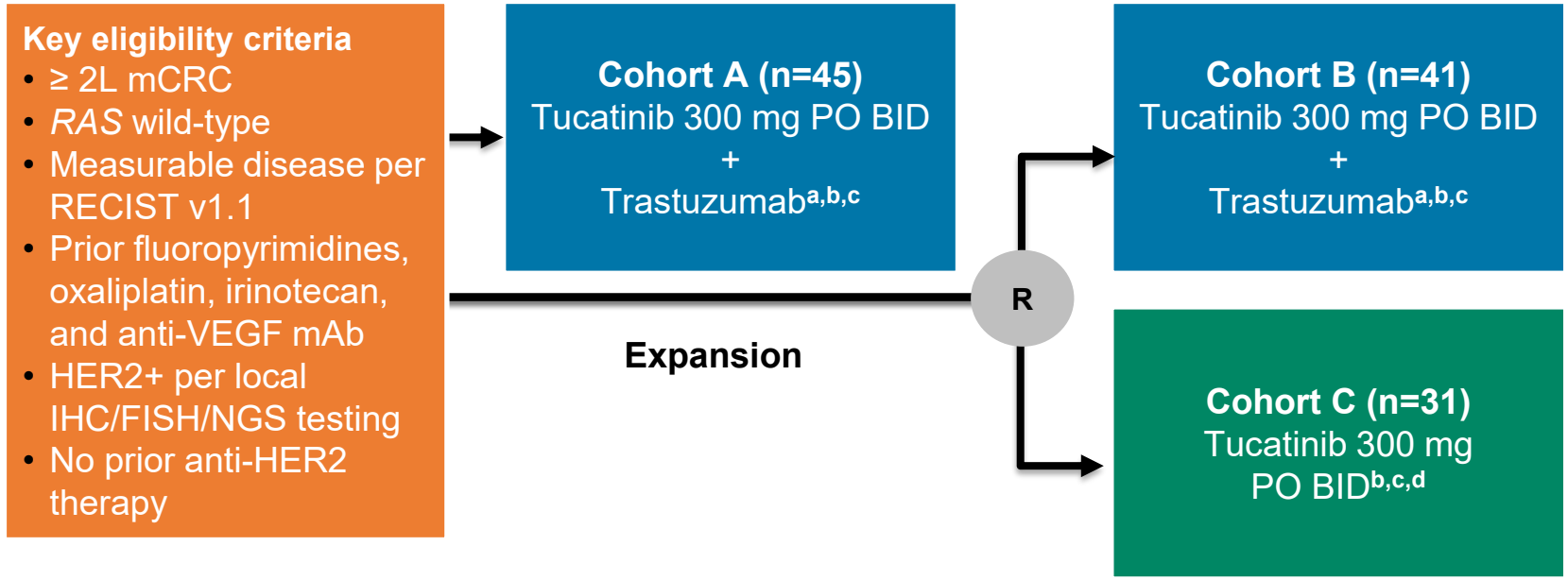


BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; RAS, rat sarcoma virus; TKI, tyrosine kinase inhibitor.

1. SIngh et al. JNCI Cancer Spectr. Jan 4 2024;8(1). 2.Kulukian et al. Mol Cancer Ther. 2020;19:976. 3. www.clinicaltrials.gov **NCT03043313**

MOUNTAINEER: Study Design

Phase 2, randomized, open-label, global multicenter study (NCT03043313)



Study Endpoints

Efficacy in Cohorts A+B

- *Primary:* cORR, RECIST v1.1 per BICR
- *Secondary:* DOR and PFS per BICR, and OS

Safety:

- TEAEs

Biomarker Analyses:

- Clinical outcomes by HER2 testing methods

Final data cutoff: November 2, 2023

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)

[a] 6 mg/kg Q3W (loading dose 8 mg/kg); [b] each treatment cycle is 21 days; [c] Patients remained on therapy until evidence of radiographic or clinical progression or death, unacceptable toxicity, withdrawal of consent, or study closure; [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 partial or complete response by week 12. For the final analysis (cutoff date of November 2, 2023), the efficacy and safety endpoints evaluated remained the same. Biomarker analyses, including a long-term responder analysis, were exploratory. ≥ 2L, second line and later; BICR, blinded independent central review; BID, twice a day; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; R, randomization; *RAS*: rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE; treatment-emergent adverse event; VEGF, vascular endothelial growth factor.

Key Baseline Characteristics

Characteristics		Tucatinib + trastuzumab Cohorts A + B N= 84[a]	Tucatinib monotherapy Cohort C N= 30[b]
Median age, years (range)		55.0 (24, 77)	59.5 (29, 75)
Sex, N (%)	Male Female	51 (61) 33 (39)	15 (50) 15 (50)
Geographical Region, N (%)	North America Europe	69 (82) 15 (18)	16 (53) 14 (47)
ECOG PS, N (%)	0 1 2	50 (60) 31 (37) 3 (4)	17 (57) 13 (43) 0
Site of primary tumor, N (%)	Left colon/ rectum Transverse colon Right colon Multiple/ overlapping	71 (85) 7 (8) 5 (6) 1 (1)	27 (90) 0 3 (10) 0
Liver metastases at study entry, N (%)		54 (64)	15 (50)
Lung metastases at study entry, N (%)		59 (70)	20 (67)

Summary of Prior Systemic Anticancer Therapies

Prior Systemic Therapies		Tucatinib + trastuzumab Cohorts A + B N= 84	Tucatinib monotherapy Cohort C N= 30
Prior lines of systemic therapy in any setting, median (range)[a]		3.0 (1-6)	2.0 (1-5)
Prior lines of systemic therapy in metastatic or recurrent setting, n (%)	1 2 ≥ 3	19 (23) 32 (38) 33 (39)	5 (17) 16 (53) 9 (30)
Prior systemic therapies in any setting, n (%)	5FU Oxaliplatin Irinotecan Anti-VEGF Ab EGFR Ab Trifluridine+tipiracil Other[b] Regorafenib	84 (100) 84 (100) 83 (99) 72 (86) 44 (52) 7 (8) 6 (7) 1 (1)	30 (100) 30 (100) 30 (100) 26 (87) 17 (57) 1 (3) 4 (13) 1 (3)

Tucatinib + Trastuzumab: Safety Summary

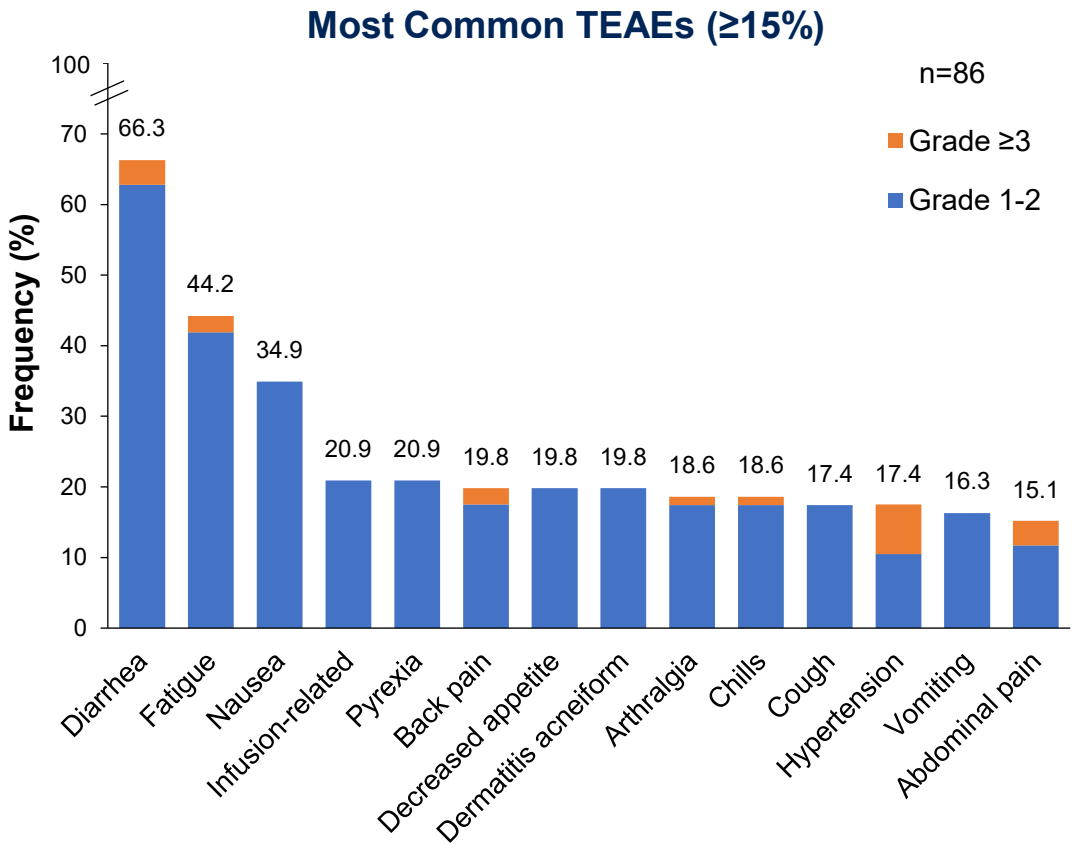
- Tucatinib + trastuzumab continued to have a good safety profile and be well-tolerated with long-term follow-up
- Rate of treatment discontinuation due to AEs was low
- No Grade 5 TEAEs

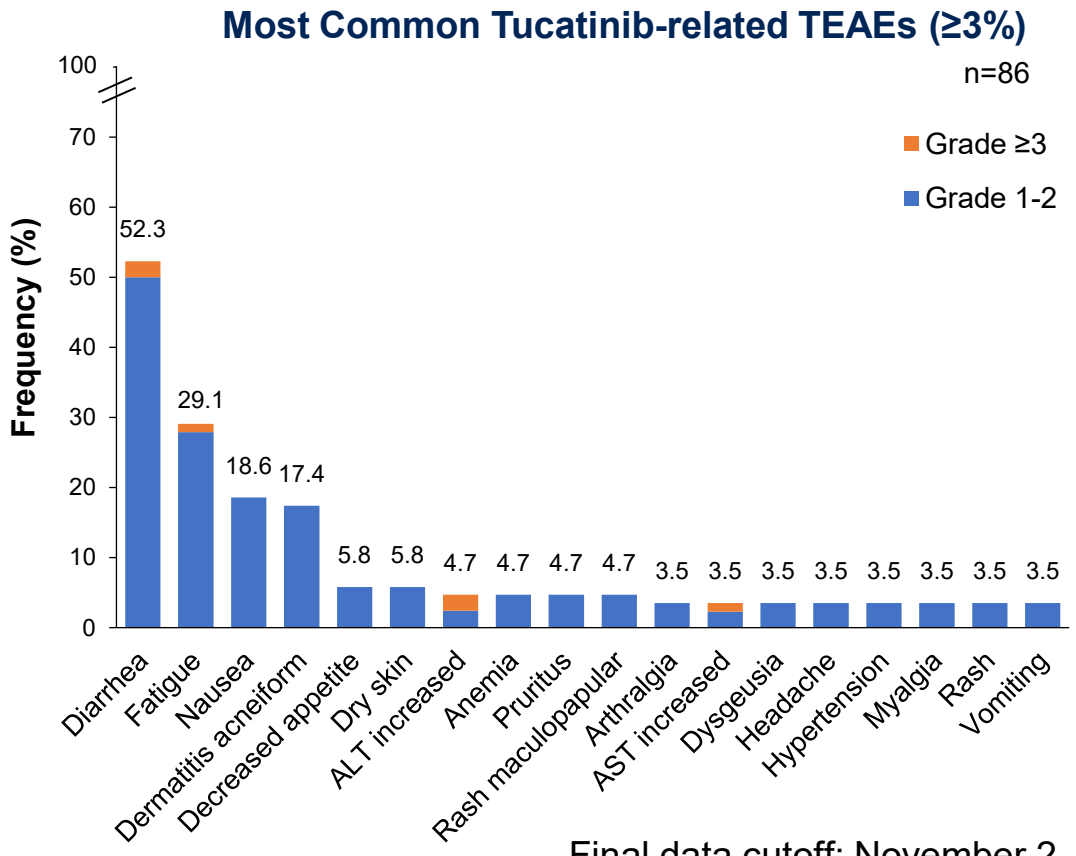
TEAE, n (%)	Cohorts A+B (n=86)
Any TEAE	82 (95.3)
≥ Grade 3 TEAE	35 (40.7)
Any serious TEAE	20 (23.3)
Grade 5 TEAE	0
Tucatinib-related TEAE	64 (74.4)
Trastuzumab-related TEAE	59 (68.6)
TEAE leading to discontinuation of any study treatment	5 (5.8)
Discontinued tucatinib	5 (5.8)
Discontinued trastuzumab	3 (3.5)
TEAE leading to tucatinib dose modification	25 (29.1)
Held	23 (26.7)
Reduced	9 (10.5)

AE, adverse event; TEAE, treatment-emergent adverse event.

Tucatinib + Trastuzumab: TEAS

- Majority of TEAEs were low grade, and rates were stable with longer follow-up
- Common TEAEs included diarrhea (66.3%), fatigue (44.2%) and nausea (34.9%)
- Most tucatinib-related TEAEs were of low grade





Final data cutoff: November 2, 2023

MOUNTAINEER: Efficacy Outcomes

Tucatinib + Trastuzumab

	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)

CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

Median follow-up: 32.4 months

Tucatinib Monotherapy

	Cohort C Final analysis (n= 30)
ORR per BICR, % (95% CI)[a-c]	3.3 (0.1-17.2)
ORR per investigator, % (95%CI)[c]	3.3 (0.1-17.2)
cORR post-crossover, % (N=28)	28.6
DCR[d] per BICR, (%)	80.0

a Best overall response assessed per RECIST 1.1 by 12 weeks of treatment or before start of cross-over if the patient crosses over earlier than 12 weeks. No confirmation needed; b Includes patients with no post-baseline response assessment and patients whose disease assessment are not evaluable; c Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); d Defined as sum of CR, PR, and SD

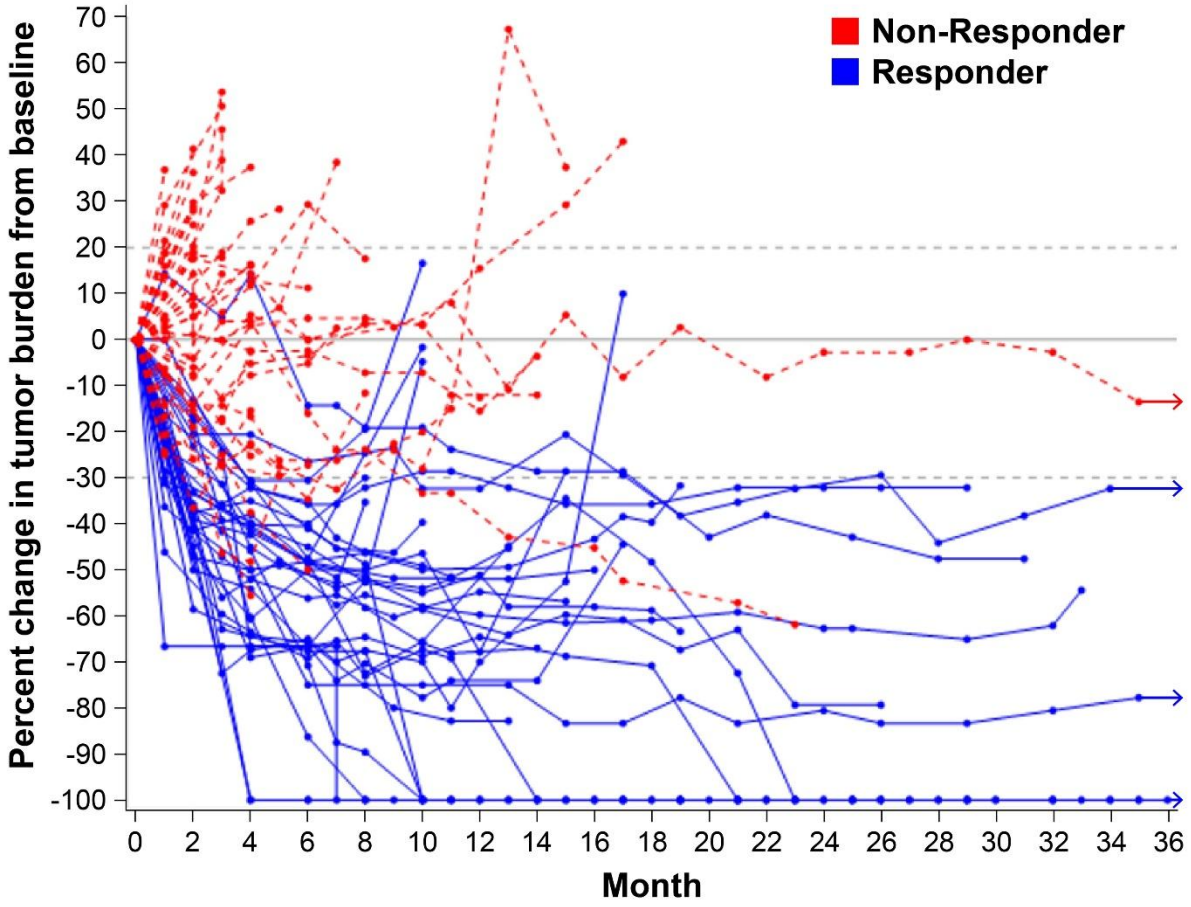
BICR, blinded independent central review; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Final data cutoff: November 2, 2023

Tucatinib + Trastuzumab: Deep and Durable Responses

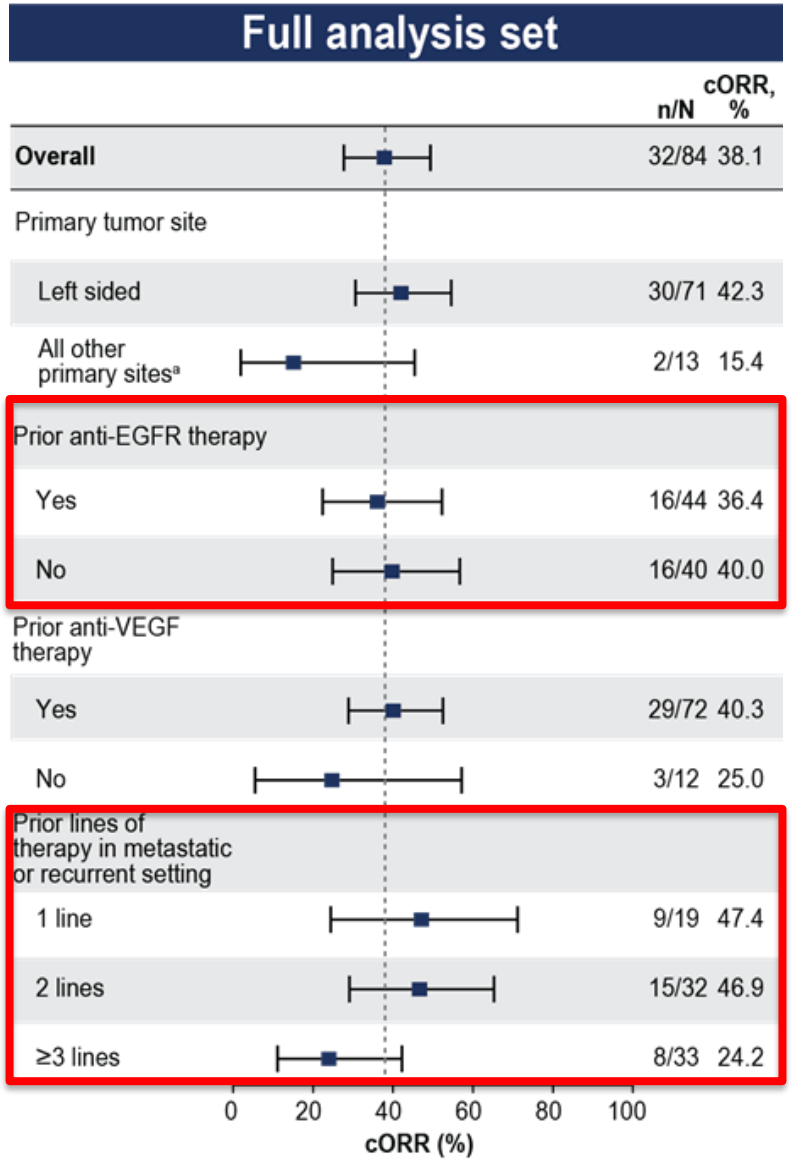
- 5/60 patients (8.3%) with HER2+ disease by IHC/FISH had a complete response
- Several patients experienced deep/ durable responses lasting more than 3 years

Tumor Response over Time (n=80)[a,b]



[a] Data up to 36 months are included; [b] Arrows denote treatment duration beyond 36 months.
CI, confidence interval; cORR, confirmed objective response rate; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival.

Tucatinib + trastuzumab: cORR in Key Subgroups



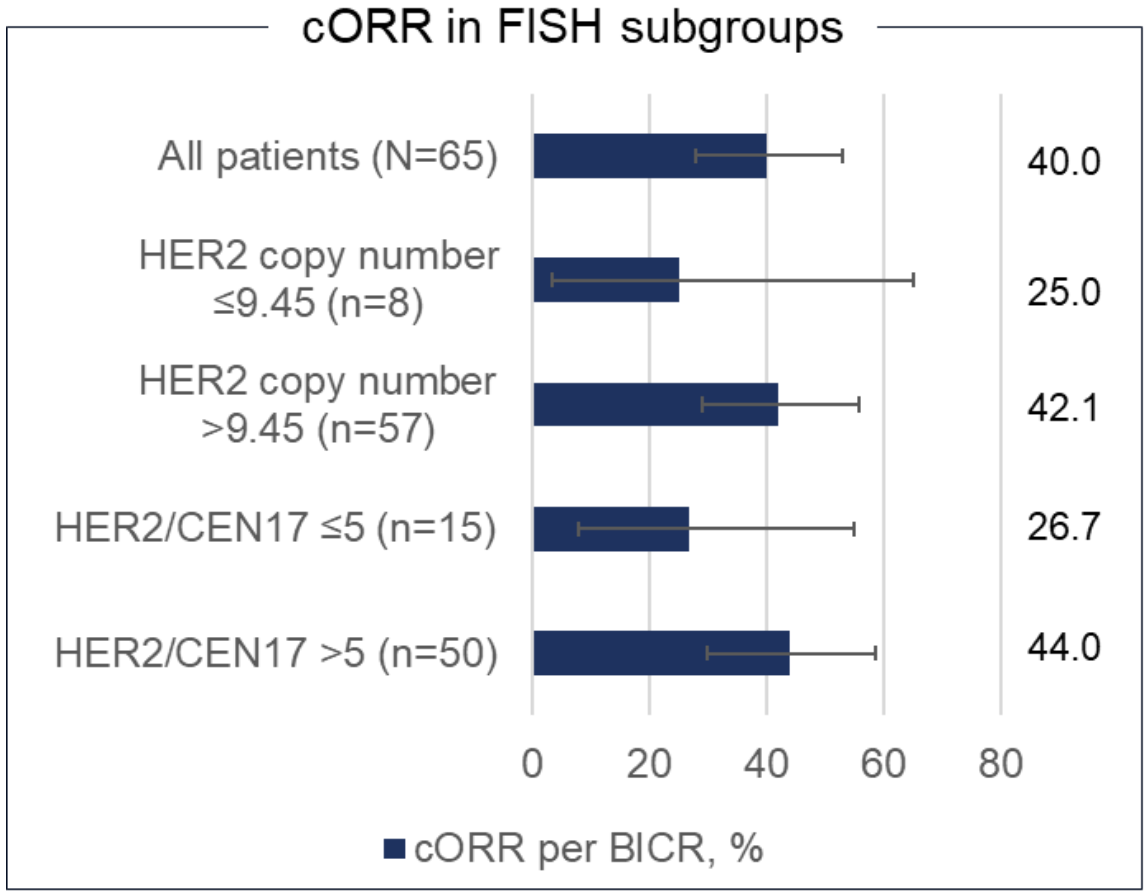
Response	Central IHC + FISH		
	Positive (IHC3+) (n=45)	Positive (IHC2+/ISH+) (n=15)	Negative (n=10)
CR	3	0	0
PR	18	3	1
SD[a]	17	5	4
PD	7	6	5
NA	0	1	0
cORR, n (%) (95% CI)	**21 (46.7%) (31.7-62.1)**	**3 (20.0%) (4.3-48.1)**	**1 (10.0%) (0.3-44.5)**

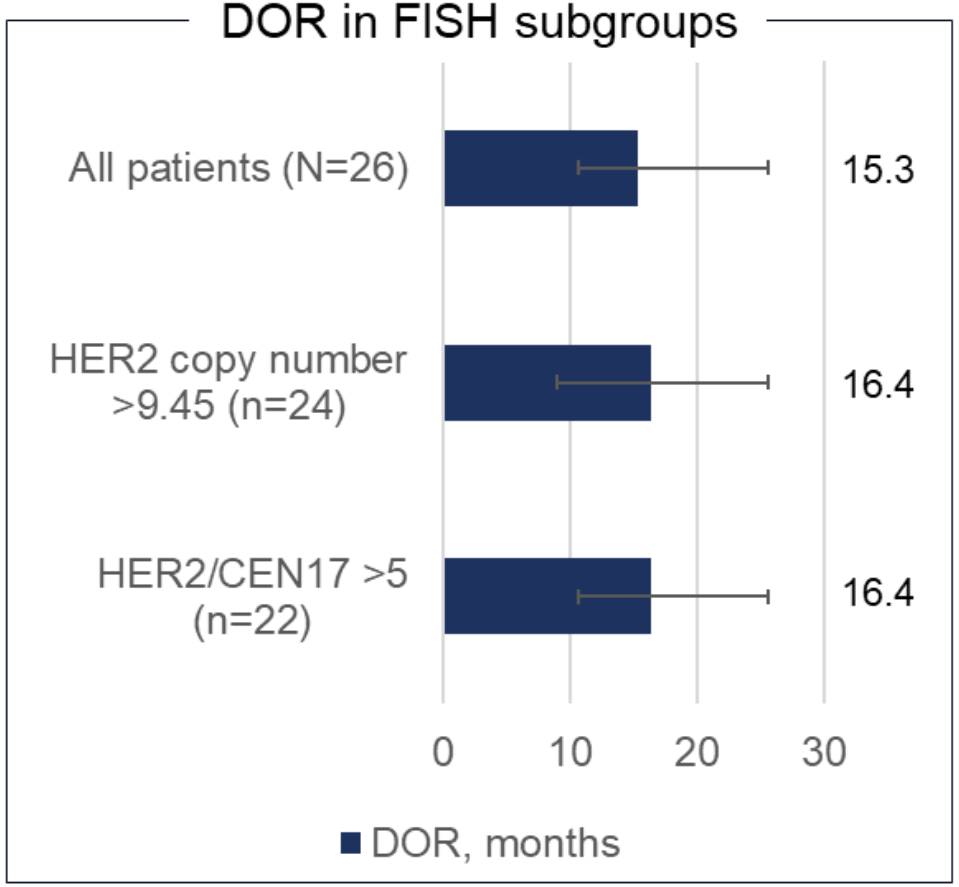
a includes non-CR/non-PD

CI: confidence interval **cORR:** confirmed objective response rate; **CR:** complete response; **HER2:** human epidermal growth factor receptor 2; **IHC**: immunohistochemistry; **ISH:** in situ hybridization; **mDOR:** median duration of response; **mPFS:** median progression-free survival; **NGS:** next-generation sequencing; **PD:** progressive disease; **PR:** partial response; **SD:** stable disease

Primary analysis data cutoff: 28 March 2022

Tucatinib + Trastuzumab: Impact of *ERBB2* Copy Number and *ERBB2*:CEN17 Ratio on Efficacy



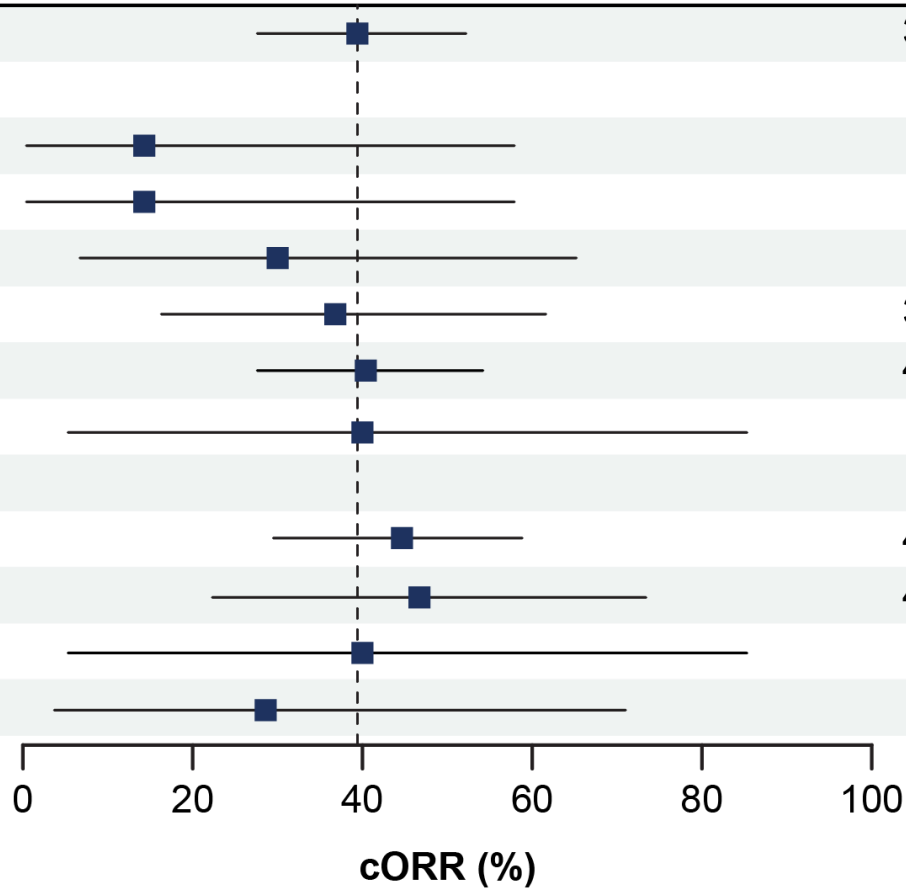


Primary analysis data cutoff: 28 March 2022

DOR subgroups not shown had < 5 responders and analyses were not performed. Error bars represent 95% confidence intervals.
BICR, blinded independent central review committee; CEN17, centromere of chromosome 17; cORR, confirmed objective response rate; DOR, duration of response; FISH, fluorescence in situ hybridization; NE, not estimable.

Tucatinib + Trastuzumab: Impact of Baseline Co-Amplifications and Co-Mutations Detected by Blood NGS

Category	Total	Responders	cORR (95% CI)	DOR, months (95% CI)
ctDNA NGS	66	26	39.4 (27.6-52.2)	12.4 (8.3-20.5)
Amplifications				
BRAF	7	1	14.3 (0.4-57.9)	–
CCND1	7	1	14.3 (0.4-57.9)	–
CDK6	10	3	30.0 (6.7-65.2)	–
EGFR	19	7	36.8 (16.3-61.6)	12.5 (4.2-NE)
ERBB2	57	23	40.4 (27.6-54.2)	12.4 (6.2-38.3)
PIK3CA	5	2	40.0 (5.3-85.3)	–
Selected Mutations*				
APC	42	18	42.9 (27.7-59.0)	15.3 (6.2-38.3)
ERBB2	17	8	47.1 (23.0-72.2)	11.4 (6.1-NE)
KRAS/NRAS	5	2	40.0 (5.3-85.3)	–
PIK3CA	7	2	28.6 (3.7-71.0)	–



Primary analysis data cutoff: 28 March 2022

Tucatinib + Trastuzumab: Efficacy by HER2 Testing Method

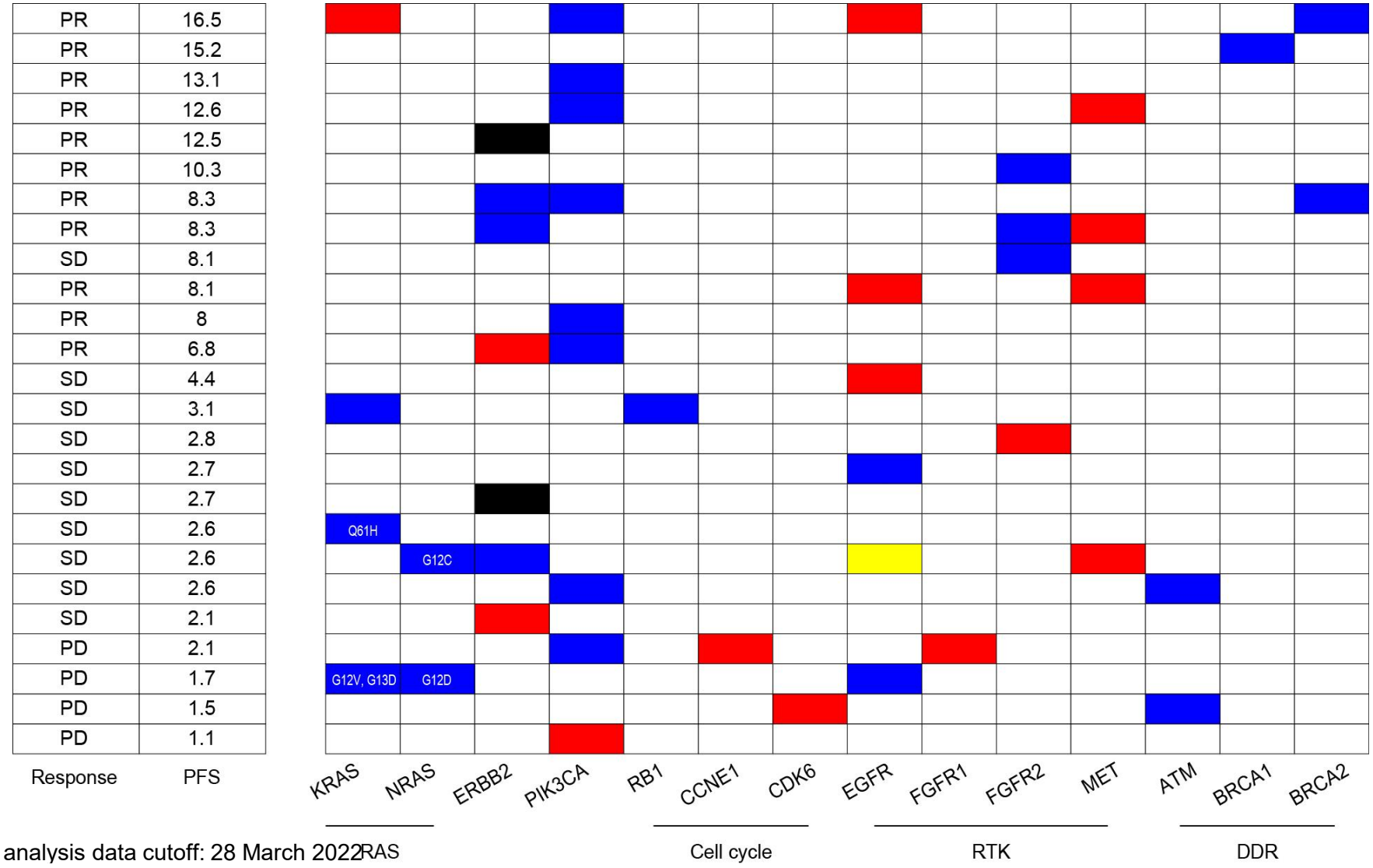
Clinical efficacy was similar across all 3 central HER2 testing methods

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.

Tucatinib + Trastuzumab: Genomic Landscape of Acquired Alterations at the Progression or EOT Timepoint*



n=31; 1 patient removed from analysis due to no detected alterations at baseline, leading to analysis set of 30; 23/30 showed alteration gains; 2/30 showed ERBB2 loss; 5/30 showed no alteration gains and no ERBB2 loss.

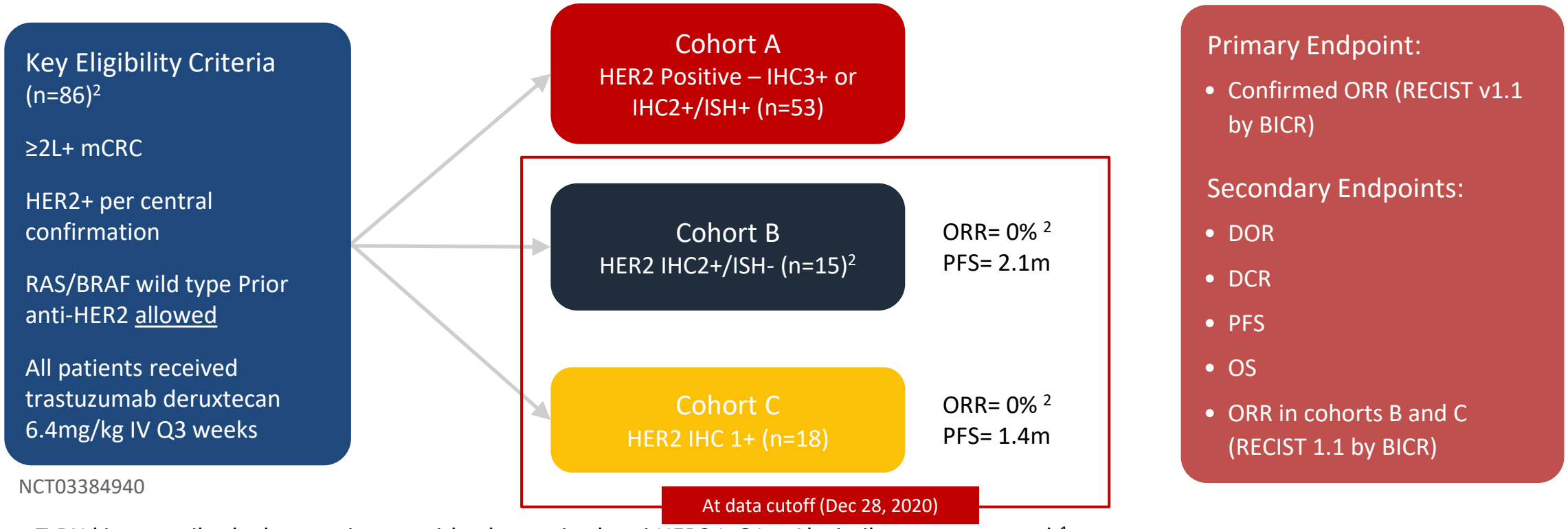
- SNV/INDEL
- Amplification
- SNV/INDEL and amplification
- Loss of amplification

Note: a single BLUE or YELLOW box can represent multiple SNV/INDEL detections in the same gene

DDR: DNA Damage Response; EOT, end of treatment; PFS, progression-free survival; RTK: Receptor Tyrosine Kinase; SNV, single nucleotide variation

* Primary analysis data cutoff: 28 March 2022

DESTINY-CRC-01: Trastuzumab deruxtecan (T-DXd; ds8201a) for HER2+ mCRC - Phase 2 Study Design



- T-DXd is an antibody drug conjugate with a humanized anti-HER2 IgG1 mAb similar to trastuzumab[1]
- Topoisomerase I inhibitor payload[1]
- High payload-to-antibody ratio (8:1)[3]

BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; HER2+ = HER2 gene amplification; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; mAb = monoclonal antibody; mCRC = metastatic colorectal cancer; ORR, objective response rate; OS = overall survival; PFS = progression-free survival; Q3 = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

Cohort A, N=53 (response assessed by BICR)[1-3]

Confirmed ORR, % (95% CI)	45.3% (31.6-59.6)
mDOR, months (95% CI)[2]	7.0 months (5.8-9.5)
Disease control rate, % (95% CI)	83.0% (70.2-91.9)
PFS, months (95% CI)[2]	6.9 months (4.1-8.7)
OS, months (95% CI)[2]	15.5 months (8.8-20.8)

Data cutoff (Dec 28, 2020)

BICR = blinded independent central review; CI = confidence interval; HER2+ = HER2 gene amplification;
mCRC = metastatic colorectal cancer; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

DESTINY-CRC01: Trastuzumab deruxtecan for HER2+ mCRC - Most Common TEAEs (≥ 10%)

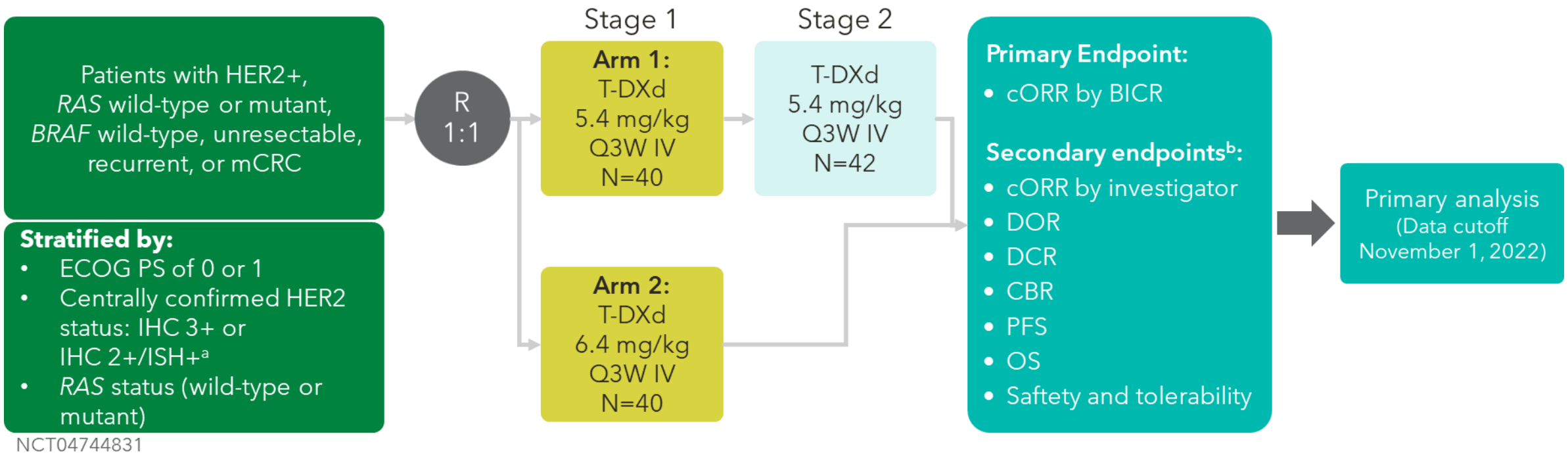
(All cohorts, N=86)

Preferred term	Any grade	Grade ≥3
Patients with any TEAE	86 (100)	56 (65.1)
Nausea	53 (61.6)	5 (5.8)
Anemia	31 (36.0)	12 (14.0)
Fatigue	31 (36.0)	1 (1.2)
Decreased appetite	30 (34.9)	0
Platelet count decreased	28 (32.6)	8 (9.3)
Vomiting	27 (31.4)	1 (1.2)
Neutrophil count decreased	26 (30.2)	19 (22.1)
Diarrhea	23 (26.7)	1 (1.2)

- Eight (9.3%) of 86 patients had interstitial lung disease or pneumonitis
  - Grade 2 = 4 patients
  - Grade 3 = 1 patient
  - Grade 5 = 3 patients
- Median time to onset date of interstitial lung disease or pneumonitis was 66.5 days
- 4 recovered, 1 did not recover and died of disease progression, and 3 died due to the AE

DESTINY-CRC02 - Study Design

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



NCT04744831

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

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

DESTINY-CRC02: Trastuzumab deruxtecan for HER2+ mCRC - Efficacy Outcomes

	5.4 mg/kg Q3W (n = 82)	6.4 mg/kg Q3W (n = 40)
Confirmed ORR, % (95% CI)	37.8% (27.3-49.2)	27.5% (14.6-43.9)
mDOR, months (95% CI)	5.5 months (4.2-8.1)	5.5 months (3.7-NE)
Disease control rate, % (95% CI)	86.6% (77.3-93.1)	85.0% (70.2-94.3)
PFS, months (95% CI)	5.8 months (4.6-7.0)	5.5 (4.2-7.0)
OS, months (95% CI)	13.4 months (12.5-16.8)	NE (9.9-NE)

DESTINY-CRC02: Adjudicated Drug-Related ILD/ Pneumonitis by Independent Adjudication Committee

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 41[a]	Stage 2 n = 42	Total N = 83	Stage 1 N = 39
Any grade	4 (9.8)	3 (7.1)	7 (8.4)	5 (12.8)
Grade 1	1 (2.4)	0	1 (1.2)	2 (5.1)
Grade 2	3 (7.3)	3 (7.1)	6 (7.2)	2 (5.1)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	1 (2.6)

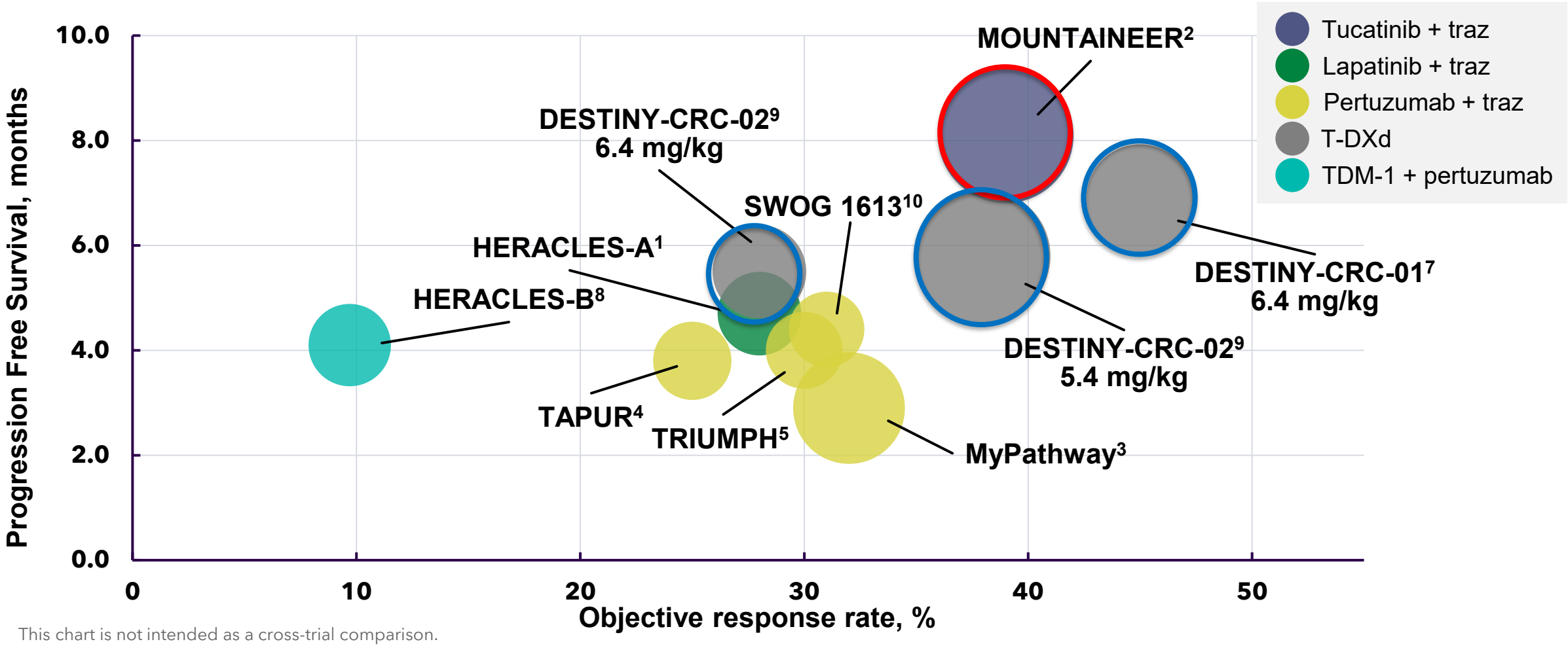
DESTINY-CRC-02: Trastuzumab deruxtecan for HER2+ mCRC - Best ORR (BICR) by T-DXd 5.4 mg/kg Subgroup

		ORR, % (n/N)	95% CI[a]
All patients (5.4 mg/kg)	**N = 82**	**37.8 (31/82)**	27.3-49.2
HER2 status	IHC 3+	**46.9 (30/64)**	34.3-59.8
	IHC 2+/ISH+	**5.6 (1/18)**	0.1-27.3
***RAS* status**	Wild-type	**39.7 (27/68)**	28.0-52.3
	Mutant[b]	**28.6 (4/14)**	8.4-58.1
ECOG PS	0	**39.1 (18/46)**	25.1-54.6
	1	**36.1 (13/36)**	20.8-53.8
Primary tumor site	Left colon[c]	**39.3 (24/61)**	27.1-52.7
	Right colon[d]	**33.3 (7/21)**	14.6-57.0
Prior anti-HER2 treatment	No	**36.9 (24/65)**	25.3-49.8
	Yes	**41.2 (7/17)**	18.4-67.1

[a]Based on the exact Clopper-Pearson method for binomial distribution. [b]All RASm responders were IHC 3+. [c]Includes rectum, sigmoid, and descending. [d]Includes cecum, ascending, and transverse.

Therapeutic landscape for HER2+ metastatic CRC

Size of data point adjusted for sample size

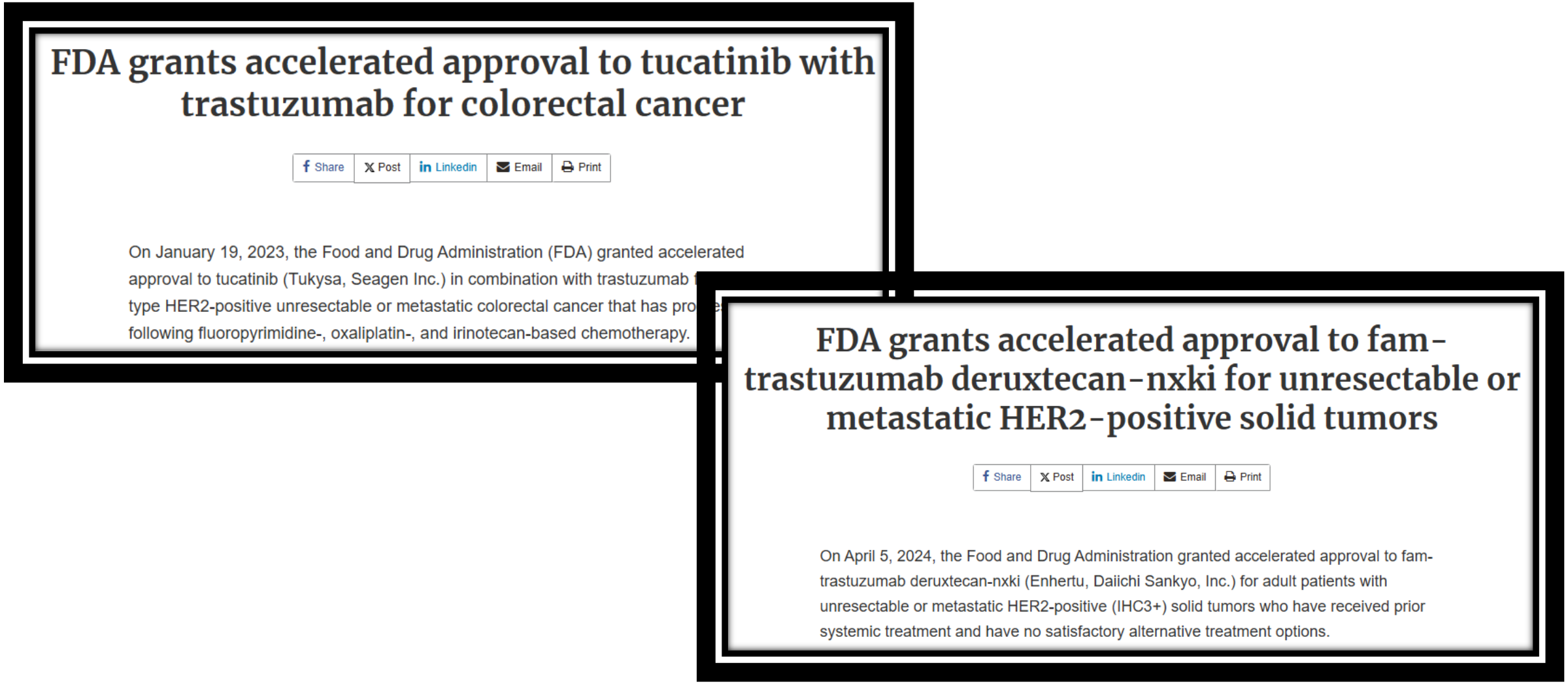


This chart is not intended as a cross-trial comparison.

CRC, colorectal cancer; HER2, human epidermal growth factor receptor 2; HER2+, HER2 gene amplification; T-DXd, trastuzumab-deruxtecan; TDM-1, trastuzumab emtansine; traz, trastuzumab.

1. Tosi F et al., Clin Colorectal Cancer 2020; 2. Strickler JH et al., Lancet Oncol. 2023; 3. Meric-Bernstam F et al., Lancet Oncol 2019; 4. Gupta et al., J Clinical Oncol. 2020; 5. Nakamura Y et al., Nature Medicine 2021; 6. Meric-Bernstam F et al., Ann Oncol. 2019; 7. Yoshino T et al., Nat. Commun. 2023. 8. Sartore-Bianchi A et al., ESMO Open 2020; 9. Raghav K et al., presented at ASCO Annual Meeting 2023, Chicago (USA), June 2-6. Oral Abstract 3501; 10. Raghav K et al., J Clin Oncol. 2023.

Anti-HER2 Therapies: FDA approved for HER2+ mCRC



FDA grants accelerated approval to tucatinib with trastuzumab for colorectal cancer

Share | Post | Linkedin | Email | Print

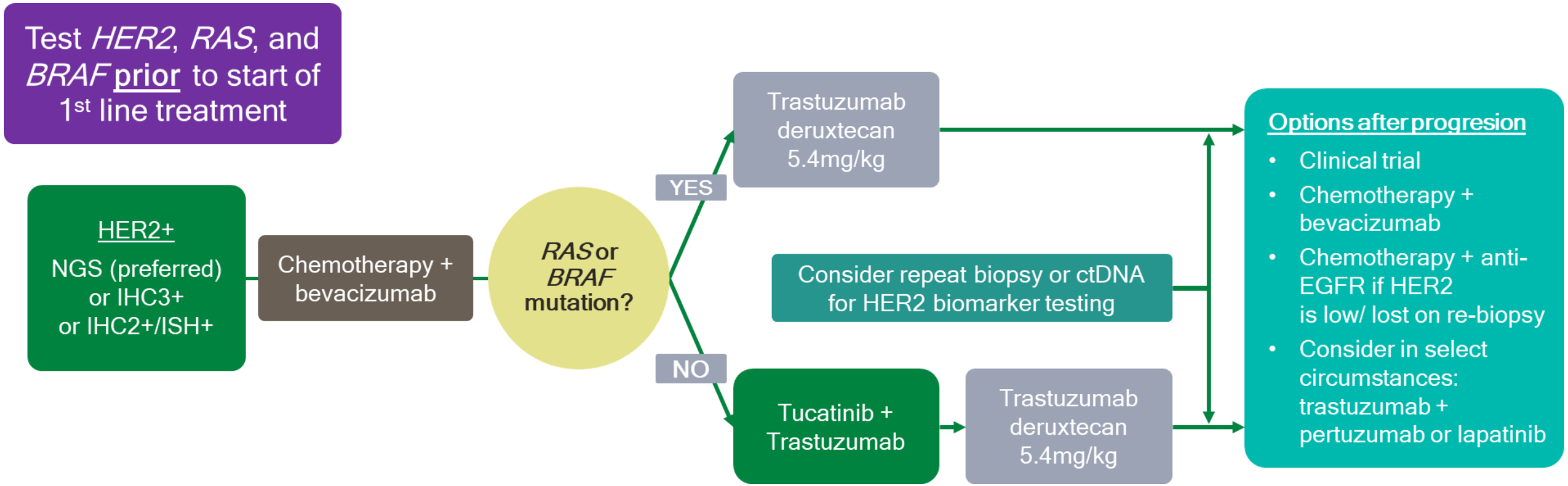
On January 19, 2023, the Food and Drug Administration (FDA) granted accelerated approval to tucatinib (Tukysa, Seagen Inc.) in combination with trastuzumab f type HER2-positive unresectable or metastatic colorectal cancer that has pro following fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

Share | Post | Linkedin | Email | Print

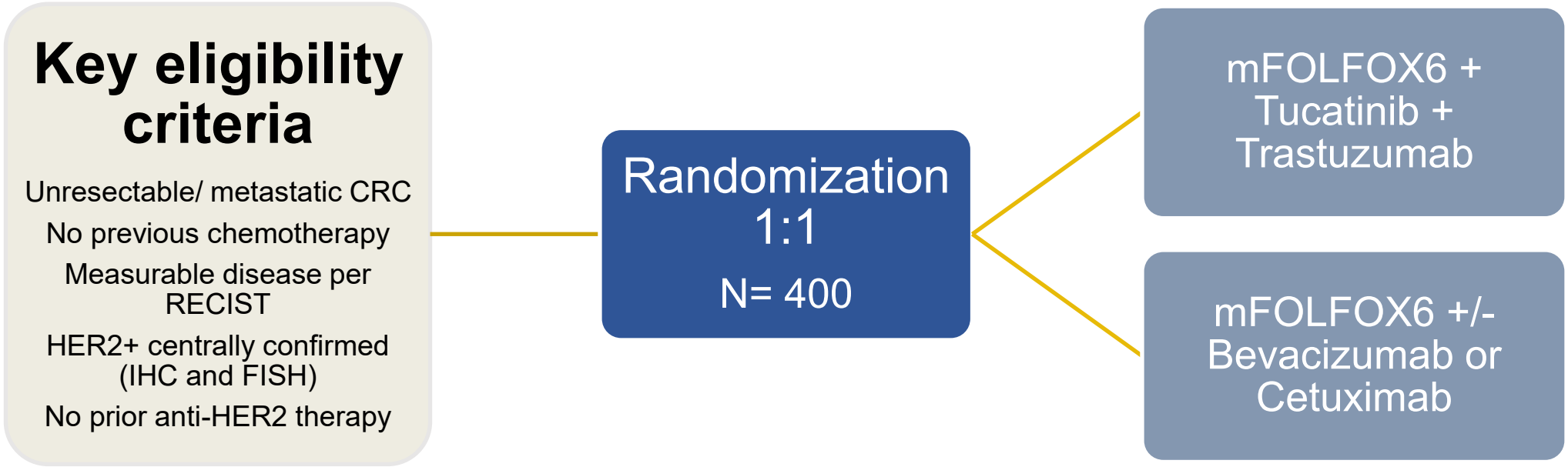
On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu, Daiichi Sankyo, Inc.) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

How I treat HER2+ metastatic CRC



MOUNTAINEER-03: Study Design

Phase 3, randomized, open-label, global multicenter study for 1L treatment of metastatic CRC (NCT05253651)

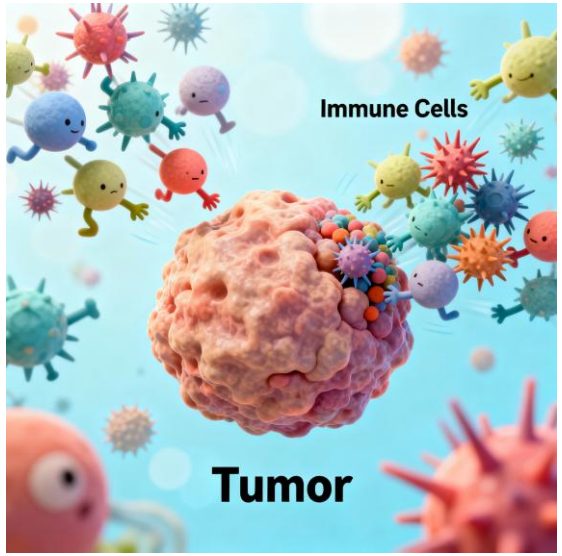


Stratification factors: Primary tumor sidedness (L vs other); liver metastases (Y/N)

Primary endpoint: PFS (RECIST 1.1 by BICR)
Secondary endpoints: OS, ORR, DOR, PFS2, safety

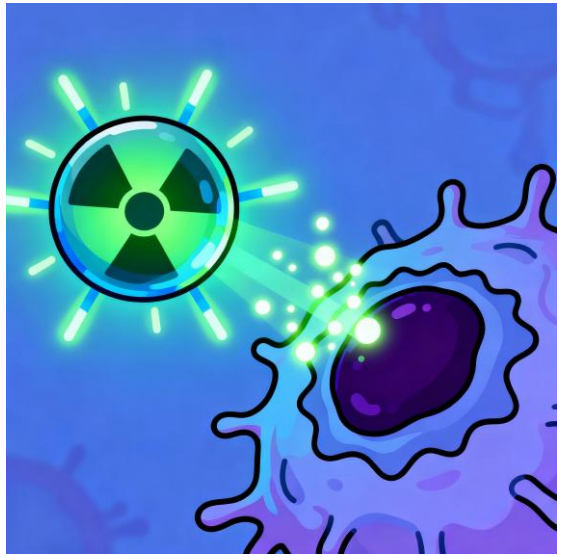
Potential therapeutic strategies to target HER2

Targeted therapeutics



Immunotherapies

Antibody drug conjugates



Radioligands

Future directions for targeting HER2

- Tucatinib + trastuzumab is safe and well tolerated with clinically meaningful anti-tumor activity for patients with *RAS* wild-type HER2+ mCRC

- However… acquired genomic alterations may drive resistance

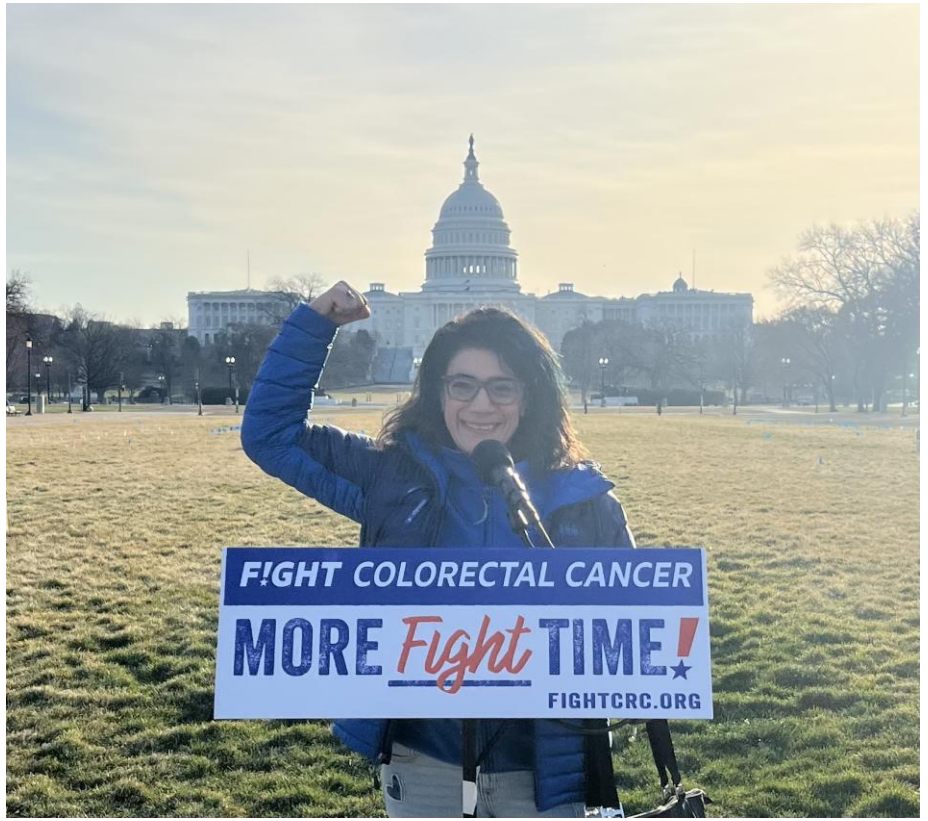
- Successful treatment approaches will either pair cytotoxic chemotherapy with tucatinib + trastuzumab or leverage an antibody drug conjugate

- New therapeutic strategies are needed to overcome acquired resistance

QUESTION & ANSWER

MY JOURNEY

- Diagnosed with Stage IV colorectal cancer at age 48 after routine colonoscopy.
- Underwent surgery, chemotherapy, and microwave ablations.
- Joined Fight CRC's Research Advocacy Training and Support (RATS) Program to:
  - raise awareness about biomarker testing, clinical trial participation, and surveillance options.
  - empower survivors to advocate for themselves.
  - give survivors a permanent seat at the decision-making table.



DISCOVER BIOMARKER TESTING

Helps patients understand their disease

[MMR, KRAS, BRAF, CEA, HER2, TMB, ctDNA]

Empowers patients to ask informed questions about treatment & surveillance options

Allows patients to actively participate in their care

Connects patients to research progress & gives them options for future treatments, if needed.

BARRIERS TO BIOMARKER TESTING

- Among patients & providers: Limited awareness of the importance of biomarker testing & its role in improved treatment options
- Cost and insurance coverage
- Access disparities related to geographical areas, age, socioeconomic status, and education level
- Evolving biomarker landscape

BARRIERS TO CLINICAL TRIAL PARTICIPATION

Patient-level barriers

- Mistrust of experimental procedures
- Health insurance coverage
- Logistical and financial burdens: Travel, lodging, time off work, childcare
- Language barriers
- Understanding consent forms and medical terminology
- Immigration status
- Support for care partners

BARRIERS TO CLINICAL TRIAL PARTICIPATION

Provider-level barriers	Clinical-level barriers
• Limited awareness of available trials • Time constraints • Non-cooperation from colleagues	• Restrictive eligibility criteria • Complex clinical design and implementation strategies

THE ROLE OF ADVOCACY

- Raising awareness and educating patients and providers about the clinical utility of biomarker testing and clinical trial participation
- Promoting equity and access to care across populations.
- Sharing personal stories and the impact of emerging technologies. Advocacy is strongest when it’s personal.

THE ROLE OF ADVOCACY – CLINICAL TRIAL PARTICIPATION

RATS
RESEARCH ADVOCACY TRAINING & SUPPORT
FIGHT CRC

- Fight CRC's RATS program ensures survivors have a seat at the research table.
- Together, patients and advocates shape the progress of equitable cancer care and cultivate public trust in science and medicine.

QUESTION & ANSWER

KEY TAKEAWAYS

Understand HER2 and ask about biomarker testing early.

Explore HER2-targeted therapies and clinical trials.

Join advocacy efforts – your voice drives progress.

QUESTION & ANSWER

HOW TO GET INVOLVED WITH FIGHTCRC

- Join our Resource Champions program
- Join us for in person events (Call on Congress, Climb for a Cure, others!)
- Apply to be a RATS Advocate
- Apply to our Ambassador Program
- Request resources to distribute for awareness, health fairs, or other events
- Reach out for volunteer opportunities

Special opportunity: Paid focus groups for survivors of mCRC

THANK YOU!

FIGHT COLORECTAL CANCER MISSION

We FIGHT to cure colorectal cancer and serve as relentless champions of hope for all affected by this disease through informed patient support, impactful policy change, and breakthrough research endeavors.

THANK YOU!

F!GHT COLORECTAL CANCER™