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How to Treat Colorectal Cancer in 2023

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VANDERBILT-INGRAM CANCER CENTER

Disclosures:

- Consultant:
  - Amgen
  - Elevation
  - General Electric
  - GSK
  - IGM
  - Merck
  - Natera
  - Pfizer
  - Seagen
  - Taiho

- Institutional Grants
  - Agenus
  - Gritstone
  - Hutchmed
  - Janssen
  - Merck
  - Pfizer
  - Sumitomo

Discussion Points

- Incidence
- Rectal Cancer Updates:
  - OPRA
  - RAPIDO
  - PRODIGE23
  - PROSPECT
  - MSI-H
- MCRC
  - PARADIGM: Left sided RAS WT
  - FRESCO-2
- Rare Subsets mCRC
  - BRAF V600 MT
  - HER-2+
- ctDNA

Incidence and Mortality of Colorectal CA in the US

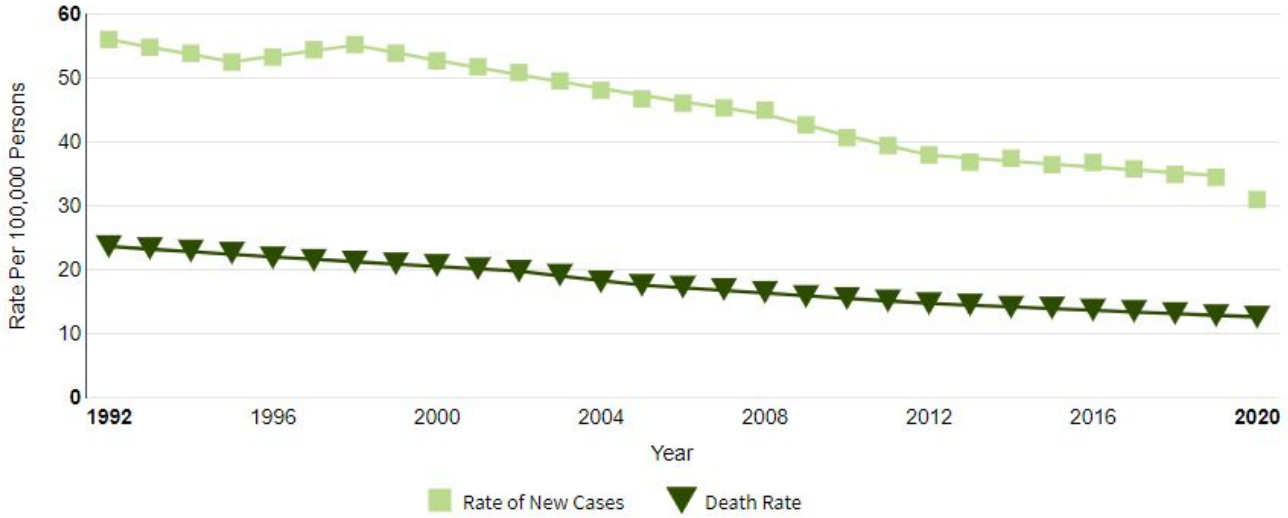
Estimated New Cases in 2023	153,020
% of All New Cancer Cases	7.8%

Estimated Deaths in 2023	52,550
% of All Cancer Deaths	8.6%

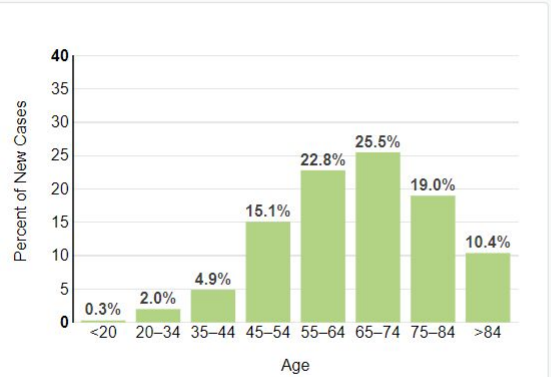
5-Year Relative Survival

65.0%

2013–2019



Percent of New Cases by Age Group: Colorectal Cancer



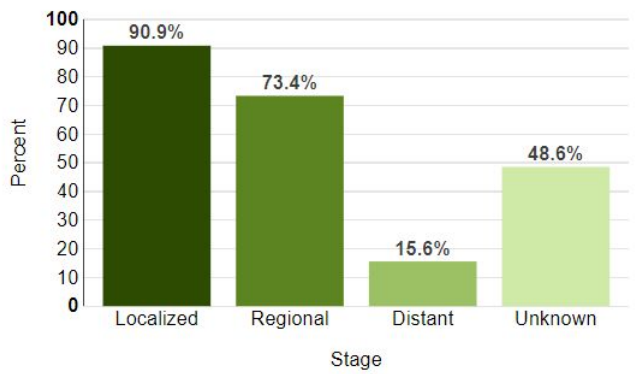
Colorectal cancer is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis

66

SEER 22 2016–2020, All Races, Both Sexes

5-Year Relative Survival



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Rectal Cancer

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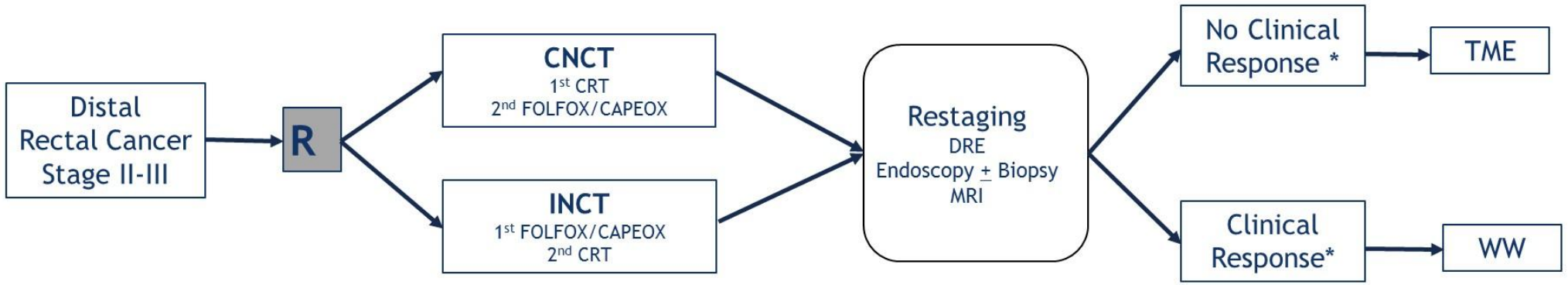
Organ Preservation in Rectal Cancer Trial (OPRA)

Investigational Arm



(*) Smith J et al, BMC Cancer 2015;15:767.

Sample Size Calculation

- Each group (CNCT and INCT) was designed as a single-stage study
- Primary Endpoint: DFS
  - Not powered for a formal comparison between groups
  - 3-year DFS rates of ***75% (historical)*** *vs* alternative of ***85% (investigational)***
  - Assume 85% power and two-sided type 1 error of 5%
  - Initial target accrual: 202 patients (101 in each groups)
  - 10% attrition/ 222 total accrual

Garcia-Aguilar et al: JCO 2022

Methods

Rectal Adenocarcinoma stage II-III

→ Randomized to total neoadjuvant therapy (TNT):

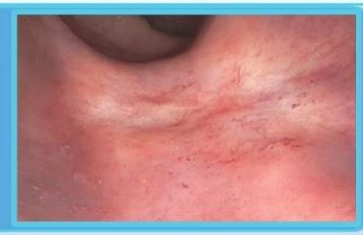
- **Consolidation (CNCT)**
  OR
- **Induction (INCT)**

→ 8 +/- 4 weeks

Three-Tier Clinical Response Assessment Schema

Clinical Complete Response (cCR)

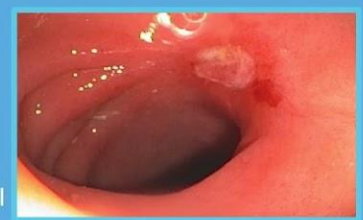
- Flat, white scar
- Telangiectasia
- No ulceration or nodularity
- Digital rectal exam (DRE): normal



→ Recommend WW

Near Complete Clinical Response (nCR)

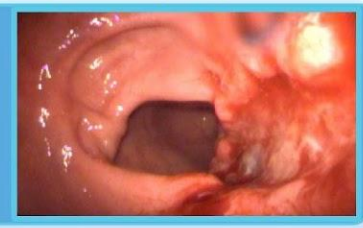
- Irregular mucosa
- Small nodules/minor mucosal abnormality
- Superficial ulceration
- Mild persisting erythema
- DRE: smooth induration/minor mucosal abnormality on DRE



→ or

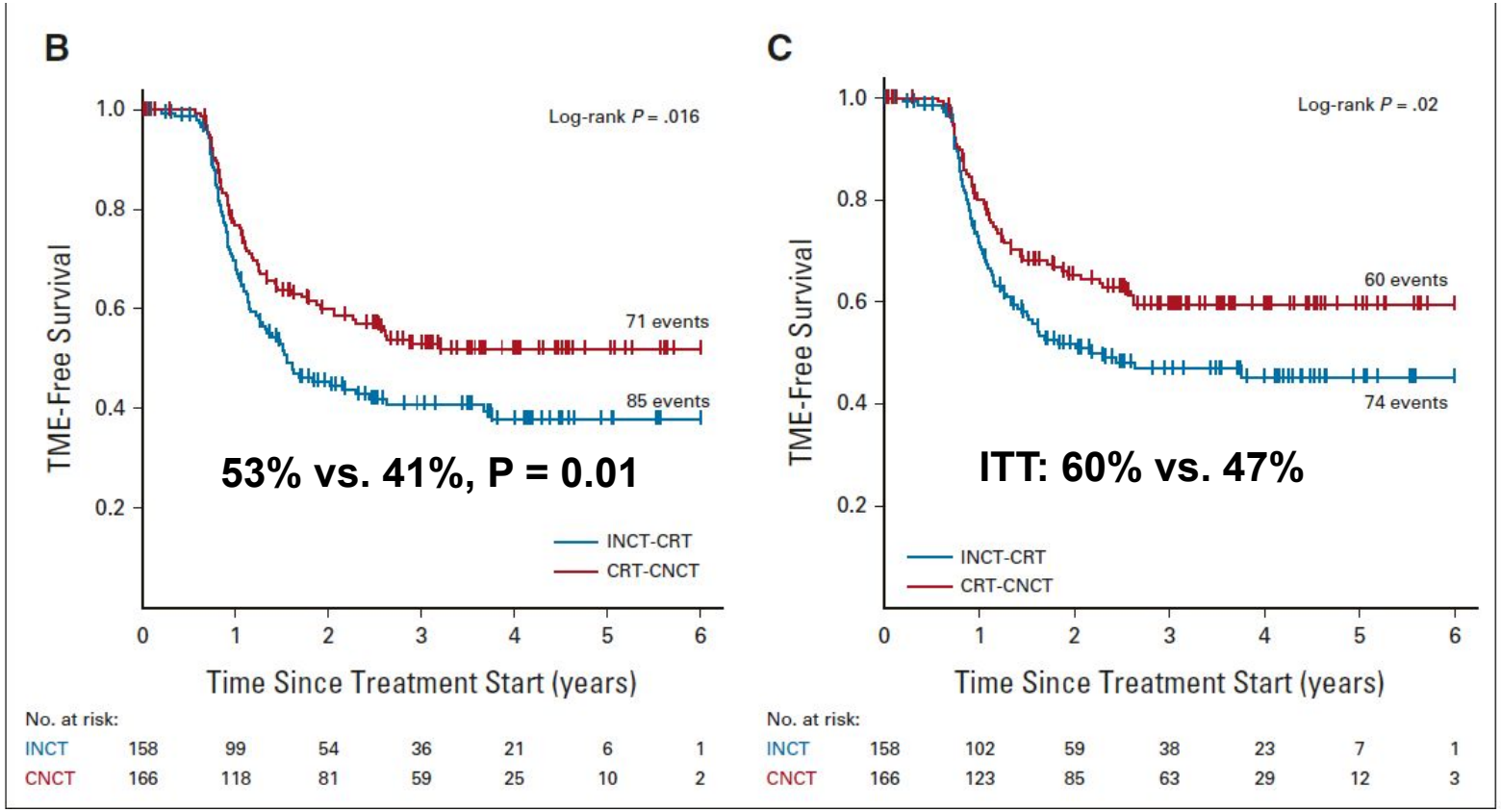
Incomplete Clinical Response (iCR)

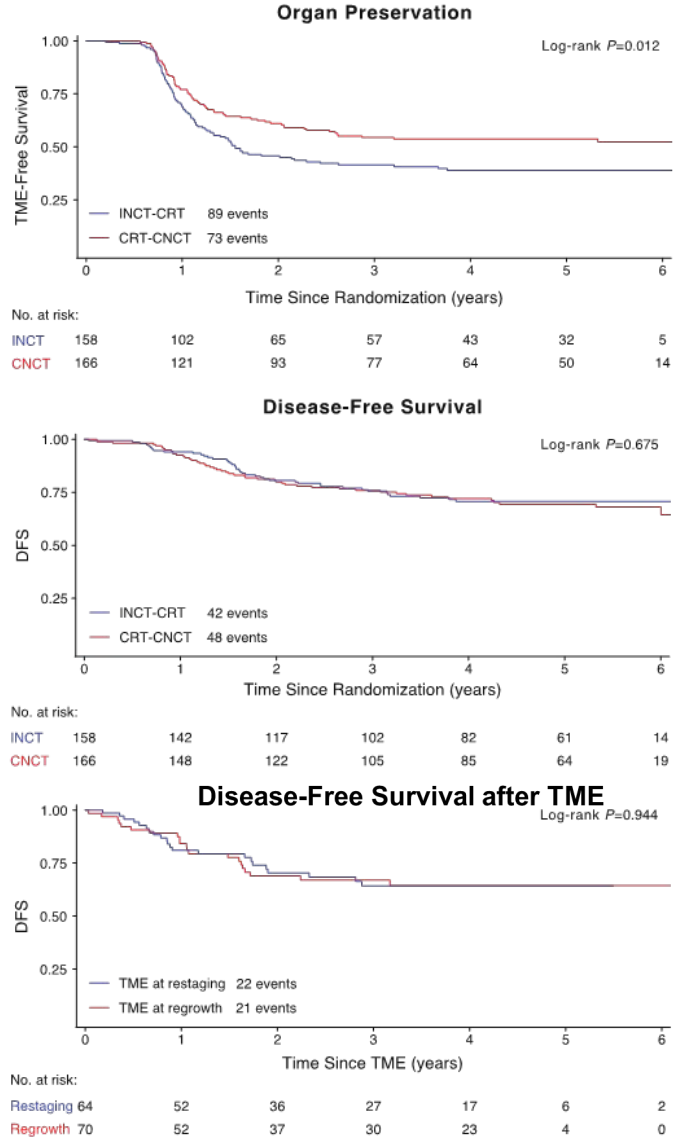
- Visible Tumor
- DRE: palpable tumor nodules



→ Recommend TME

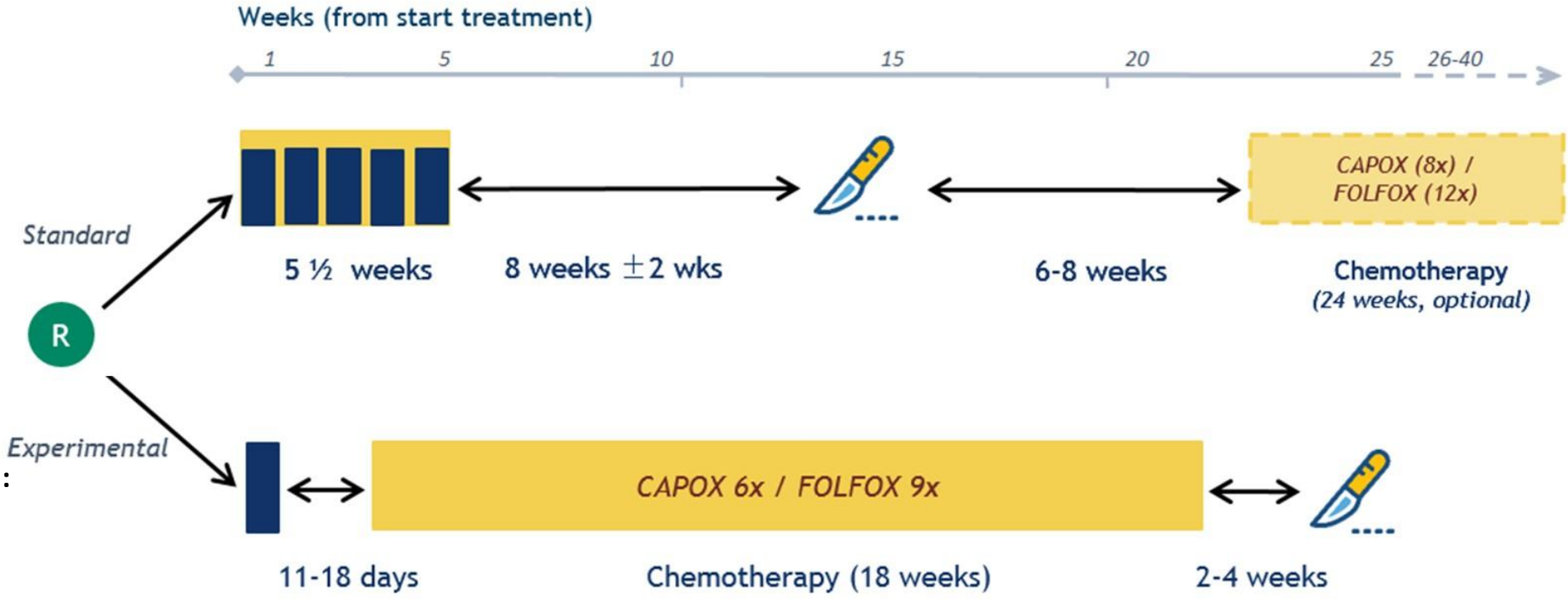
OPRA: 3-yr and 5-yr TME-Free Survival





Garcia-Aguilar et al: JCO, 2022; Verheij et al: ASCO 2023

Study design Rapido Study Design



Inclusion criteria:

- **T4a/b**
- **EMVI**
- **N2**
- **Mesorectal fascia (+)**
- **Enlarged lateral LN's**

Standard: week 1-6: 28x1.8 Gy or 25x2 Gy at working days combined with capecitabine b.i.d. 825 mg/m^2 (twice daily) day 1-33-38.
Experimental: week 1: 5x5 Gy, week 3-20: 6x CAPOX (capecitabine b.i.d.1000 mg/m^2 (twice daily) day 1-14 every 3 weeks orally, oxaliplatin 130 mg/m^2 day 1 every 3 weeks iv or alternatively 9x FOLFOX4 (folinic acid, fluorouracil and oxaliplatin all iv every 2 weeks)

Bahadoer et al: Lanc Onc, 2020

RAPIDO (Short Course) – 5-YR FOLLOW-UP

ANNALS OF SURGERY

	RAPIDO	Standard of Care	P-value
Local regional failure (LRF)	12%	8%	0.07
Local regional recurrence (LRR)	10%	6%	**0.027**
Disease-related treatment failure (DrTF)	28%	34%	0.048
Distant Mets	23%	30%	**0.011**
Overall survival (OS)	82%	80%	0.50

Dikjstra, et al: Annals of Surg, 2023

PRODIGE 23 trial: trial design

MRI staging
Randomisation: 1/1
Stratification:
- center
- cT3 vs cT4
- cN0 vs cN+
- T extramural extension (≥5 vs. <5 mm)
- tumor location (cm from anal verge)

461 patients included

RANDOMIZE

SoC arm

Radiotherapy 50.4 Gy /5wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → TME → mFOLFOX6, 12 cycles or capecitabine, 8 cycles*(6 months)

TNT arm

mFOLFIRINOX** 6 cycles, 3 months → Radiotherapy 50.4 Gy /5 wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → TME → mFOLFOX6, 6 cycles or capecitabine, 4 cycles* (3 months)

Primary endpoint: DFS

****mFOLFIRINOX:** At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)

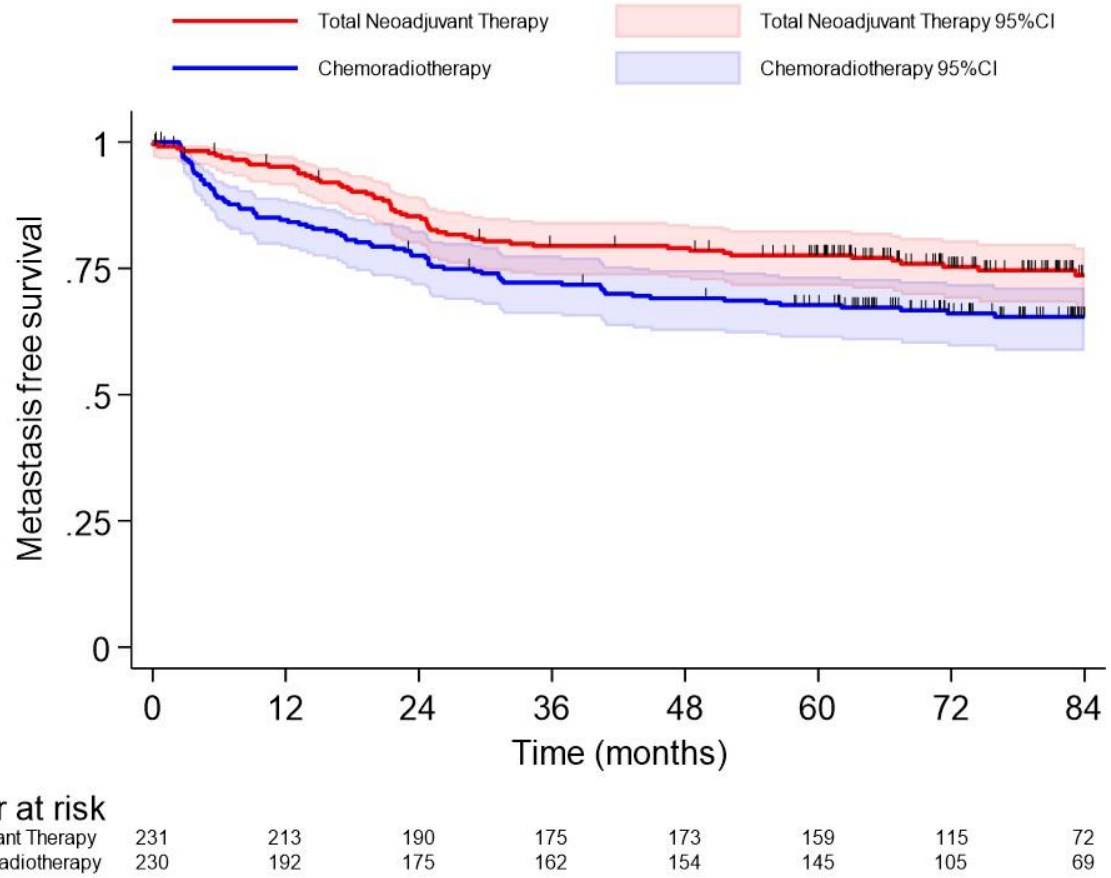
***according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.**

Tumor characteristics

Characteristics	TNT N=231	SoC N=230	p
Distance to anal verge			
≤5 cm	37.7%	36.1%	0.92
5.1-10 cm	49.3%	51.3%	
10.1-15 cm	13.0%	12.6%	
mrT stage			
T2/T3	1.3%/80.9%	0.9%/83.6%	0.70
T4	17.8%	15.6%	
cN stage			
N+	89.1%	90.0%	0.52
Predicted lateral margin			
≤1 mm	26.0%	27.7%	0.70

Metastasis-free Survival

At 5 years, the cumulative incidence of developing metastatic recurrences was 18.4% in the TNT arm vs 26.6% in the SoC arm.



138 events

7-yr MFS:

- 73.6% [95%CI: 67.0-79.2] TNT arm
- 65.4% [95%CI: 58.7-71.3] SoC arm

5-yr MFS:

- 77.6% [95%CI: 71.5-82.5] TNT arm
- 67.7% [95%CI: 61.2-73.4] SoC arm

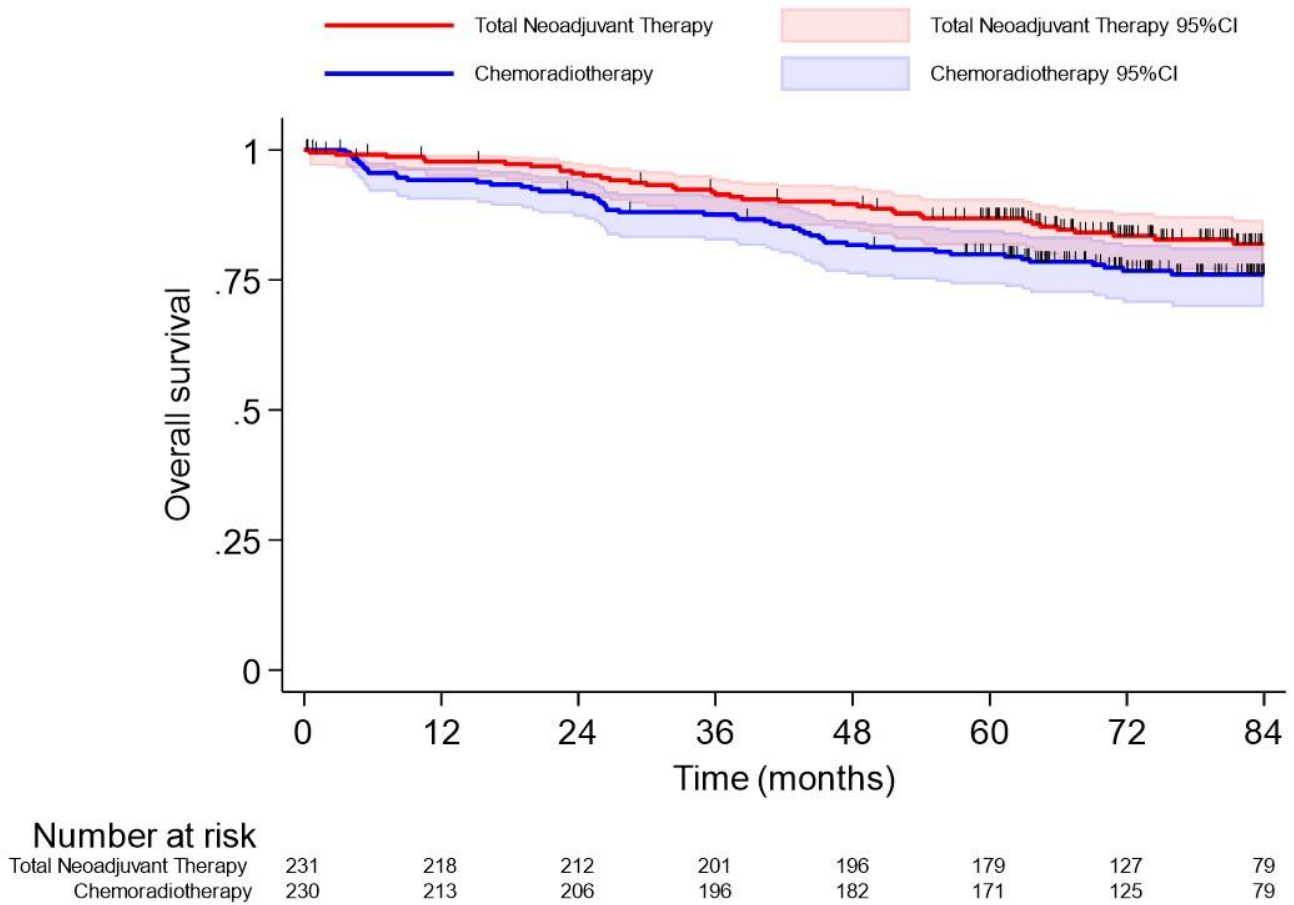
RMST (7-yr), months:

7.1 [1.65-12.63] MFS benefit for TNT arm

p=0.011

PRESENTED BY: T Conroy, MD

Overall Survival



98 events.

7-yr OS:

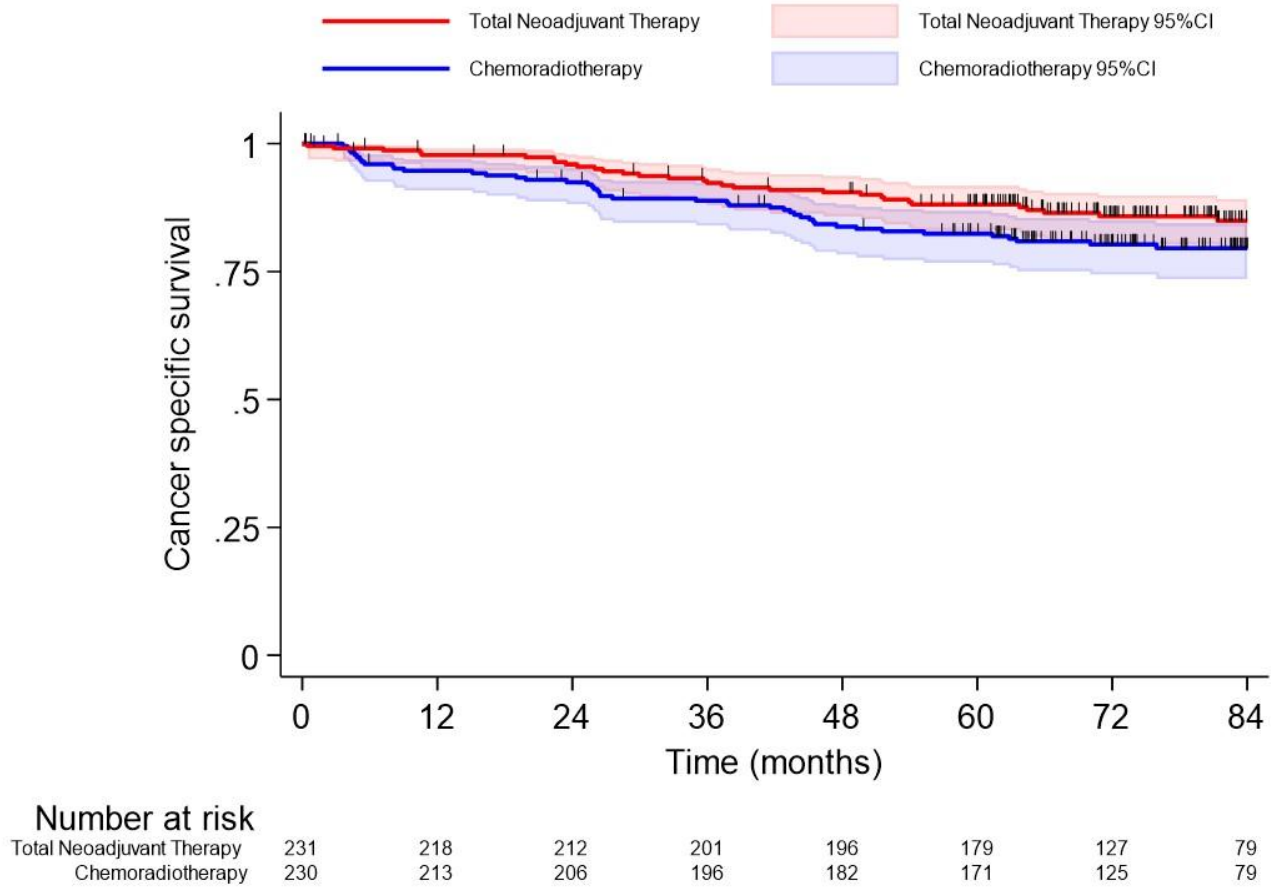
- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

5-yr OS:

- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

Cancer Specific Survival



80 events

7-yr CSS:

- 84.9% [95%CI: 79.1-89.2] TNT arm
- 79.6% [95%CI: 73.5-84.4] SoC arm

5-yr CSS:

- 88.1% [95%CI: 83.1-91.8] TNT arm
- 82.4% [95%CI: 76.7-86.8] SoC arm

RMST (7-yr), months: 3.84 [-0.02-7.71]
benefit for TNT arm
p = 0.051

PRESENTED BY: T Conroy, MD

PROSPECT Study Summary

Recruitment 2012-2018 from 264 practice sites in the USA, Canada and Switzerland

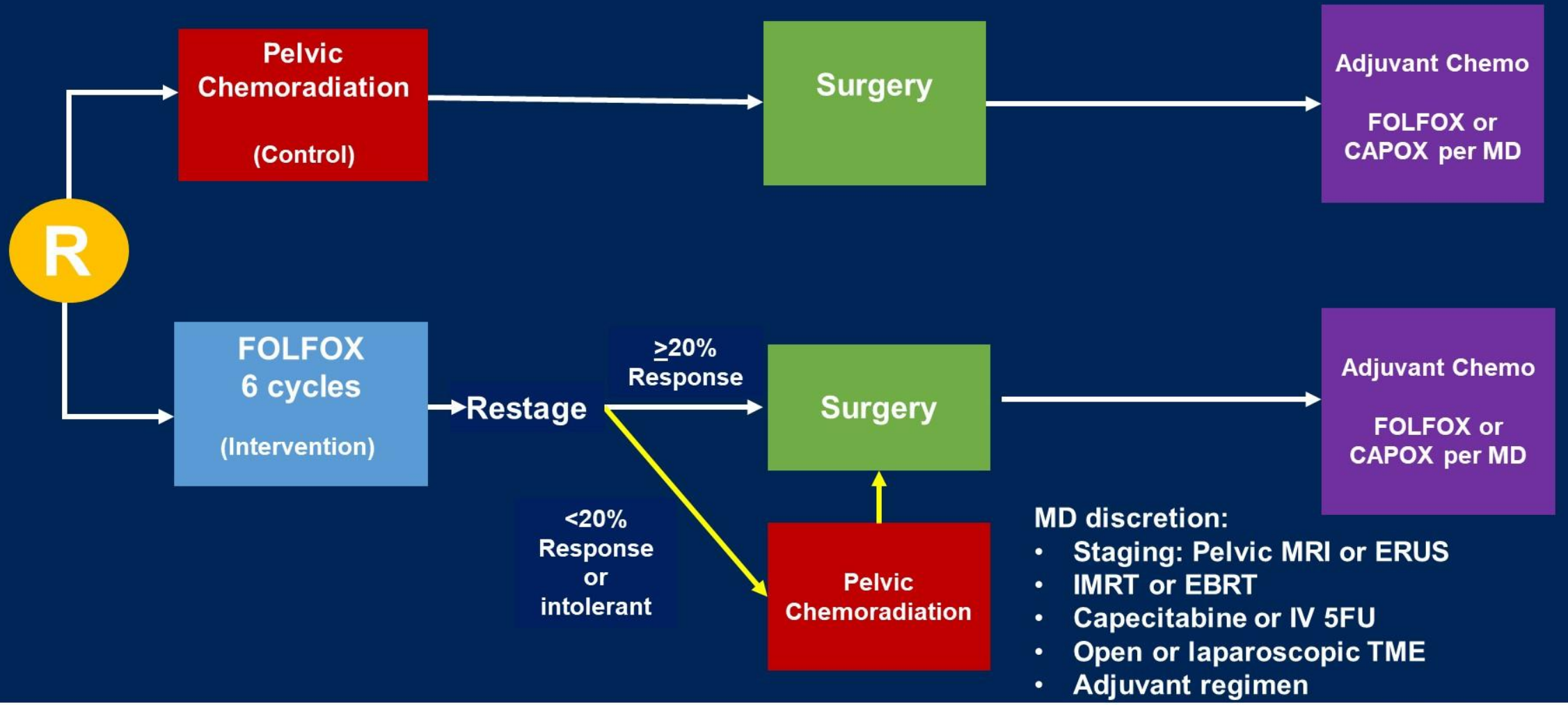
Neoadjuvant Treatment for cT2N+, cT3N-, cT3N+ Rectal Cancer

Primary endpoint: Non-inferior DFS

PRESENTED BY: Deb Schrag MD MPH FASCO

Schrag et al: NEJM, 2023

PROSPECT Study Full Schema



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Schrag et al: NEJM, 2023

Characteristics of PROSPECT Participants

Recruitment: 264 Centers	FOLFOX and Selective Chemoradiation	Chemoradiation
N	585	543
Age Mean (SD)	57 (11)	57(11)
Sex		
Female	37%	32%
Male	63%	68%
Tumor location from the anal verge in cm (SD)	8 (3)	8 (3)
Baseline Staging Performed with MRI	84%	84%
Clinical Stage at Baseline		
cT2N+	11%	7%
cT3N-	39%	37%
cT3N+	50%	56%

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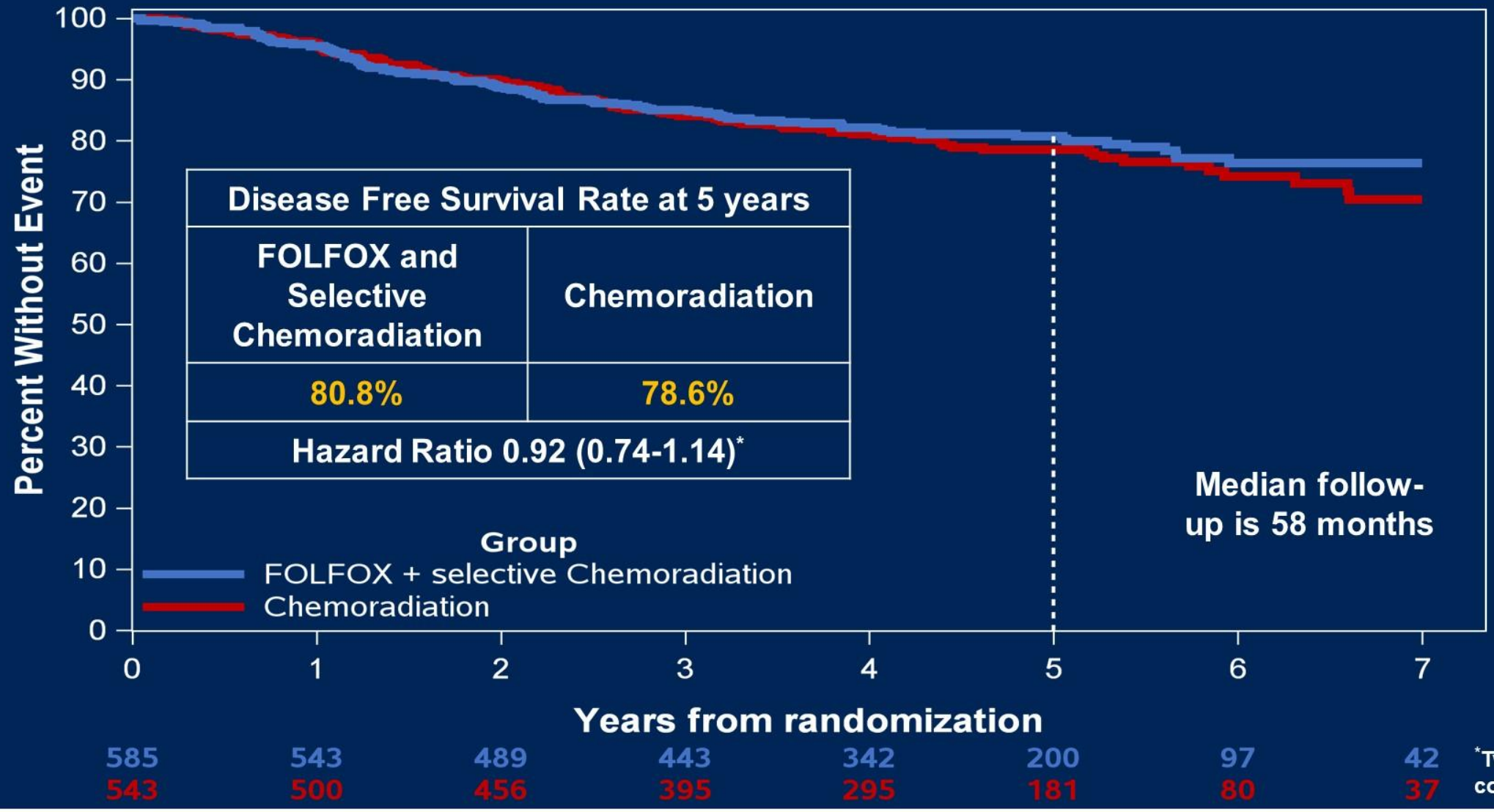
Schrag et al: NEJM, 2023

PROSPECT: Disease Free Survival



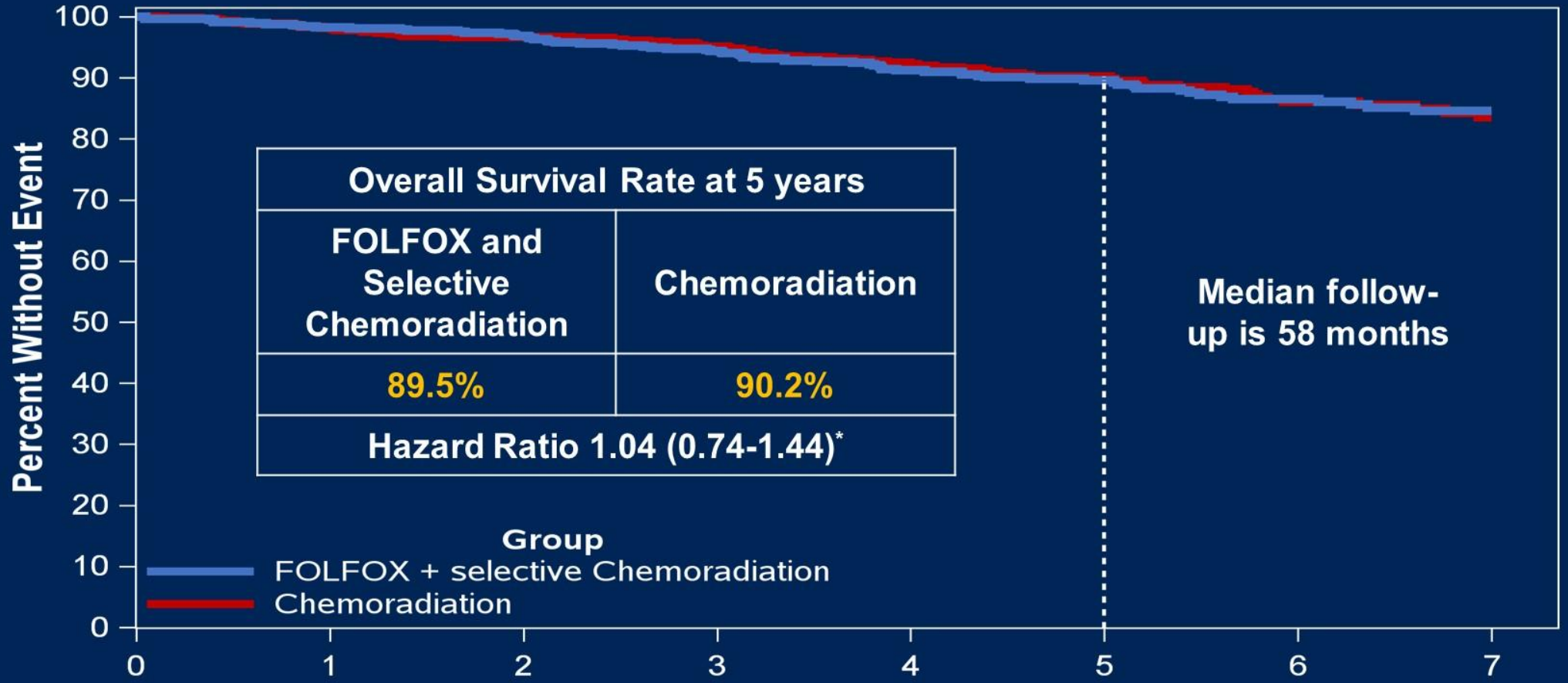
Disease Free Survival Rate at 5 years	
FOLFOX and Selective Chemoradiation	Chemoradiation
80.8%	78.6%
Hazard Ratio 0.92 (0.74-1.14)*	

*Two-sided 90.2% confidence interval

PRESENTED BY: Deb Schrag MD MPH FASCO

Schrag et al: NEJM, 2023

PROSPECT: Overall Survival



Overall Survival Rate at 5 years	
FOLFOX and Selective Chemoradiation	Chemoradiation
89.5%	90.2%
Hazard Ratio 1.04 (0.74-1.44)*	

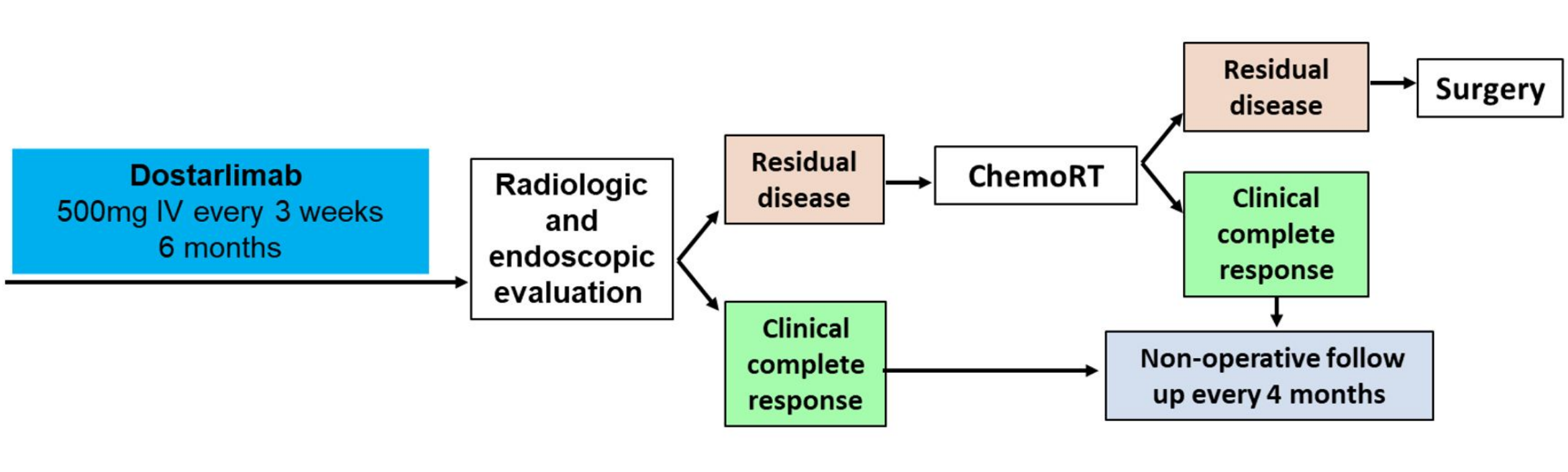
Median follow-up is 58 months

*Two-sided 95% confidence interval

PRESENTED BY: Deb Schrag MD MPH FASCO

Schrag et al: NEJM, 2023

PD-1 Blockade in Locally Advanced MSI-H Rectal Cancer



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

Cercek et al: NEJM, 2022

NCT04165772

Demographic and disease characteristics of the patients at baseline

		Value (%)
Sex		
	Male	6 (33)
	Female	12 (67)
Age, median (range)		54 (26-78)
Race/Ethnicity		
	White non-Hispanic	11 (61)
	Hispanic	1 (6)
	Black or African American	3 (17)
	Asian-Far East/Indian Subcontinent	3 (17)
Tumor Staging		
	T1/2	4 (22)
	T3, T4	14 (78)
Nodal Staging		
	Node-positive	17 (94)
	Node-negative	1 (6)
Germline Mutation Status n=17		
	MSH2, MLH1, MSH6, or PMS2	10 (59)
	Negative	7 (41)
BRAF V600E wild type		18 (100)
Tumor Mutational Burden (mut/Mb), mean (range)		67 (36 -106)

Cercek et al: NEJM, 2022

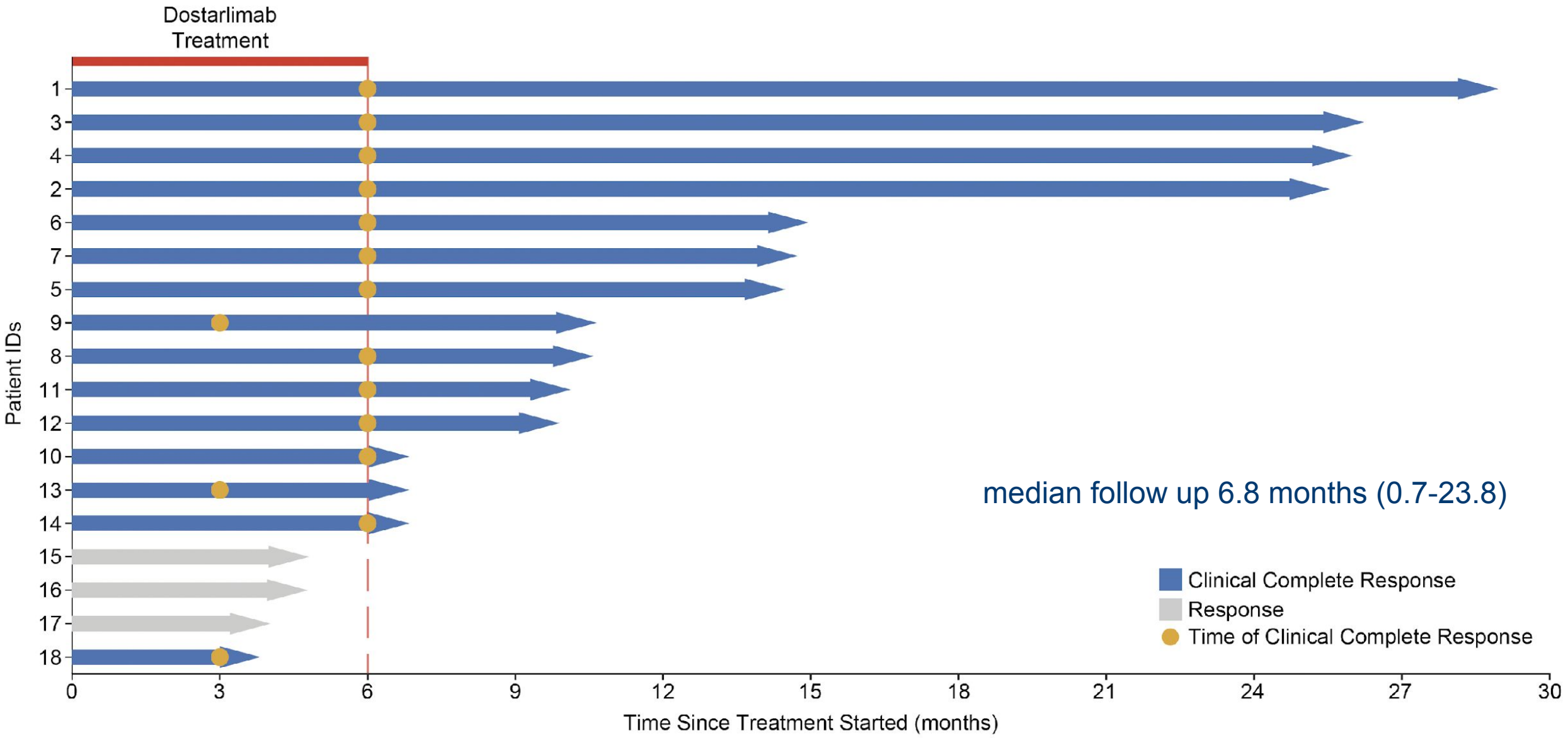
Individual responses to PD-1 blockade with dosta

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

Cercek et al: NEJM, 2022

Duration of response



Cercek et al: NEJM, 2022

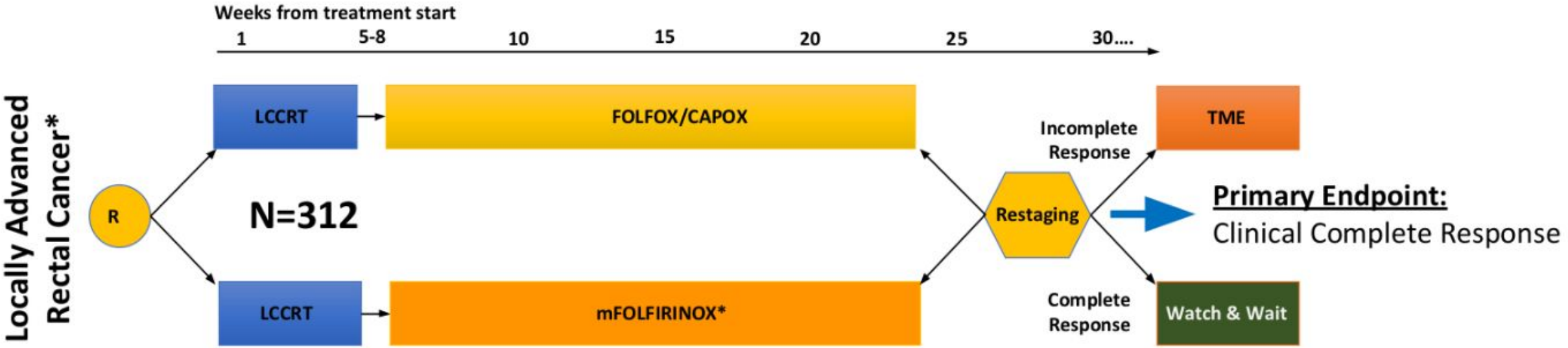
The Janus Rectal Cancer Study: A Randomized Phase II Trial

NCT05610163

A022104 – An Alliance, NRG & SWOG Study



Opened: 9 Nov 2022!



PI's: J. Smith, A. Dasari, W. Hall

Schema Legend: Randomization = R; LCCRT = long-course chemoradiation; Restaging determination = endoscopy, MRI and clinical exam 8-12 weeks post-completion of assigned TNT regimen

* <=12cm, cT4N0, anyT, N+; T3N0 that would require APR or coloanal anastomosis

Rectal Cancer Trials

Name of Trial	Phase	AJCC Stage	Location of tumor	DFS	OS	Mets	Other	Findings
OPRA	II	T3/T4N0; TxN+	Low-Lying	Equivocal	Equivocal	N/A	Sequence; W+W	ChemoXRT improves W+W
RAPIDO	III	T4a/b; N2	-	P= 0.048	P=0.50	P=0.011	5X5	High-risk recurrence
PRODIGE23	III	T3/T4N0; TxN+	-	-	P=0.033	P=0.011	FOLFOXIRI	Cancer Specific Survival (p=0.51)
PROSPECT	III	T3N0 or TxN+	Mid to high	Equivocal	Equivocal	-	Non-inferior	Omission of XRT
JANUS	II	T3/T4N0; TxN+	-	Pending	Pending	Pending	FOLFOXIRI	cCR
ACO/ARO/ AIO-18.1	III	T3/T4N0; TxN+ EMVI	Low-mid	Pending	Pending	Pending	Pending	W+W

W+W = Active surveillance

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Metastatic Colorectal Cancer

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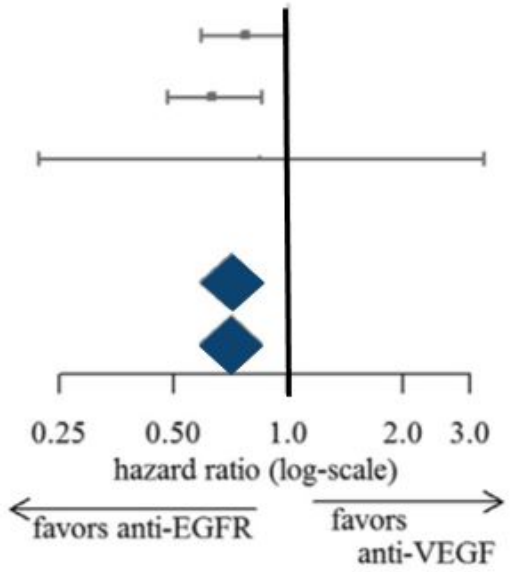
Meta-Analysis of PEAK, FIRE-3 and CALGB 80405: OS

A

Left-sided mCRC

study	n	Weight (%)	OS HR	95% CI	P-value
CALGB/SWOG 80405	325	53.8	0.77	(0.59 , 0.99)	
FIRE-3	306	44.2	0.63	(0.48 , 0.85)	
PEAK	107	2	0.84	(0.22 , 3.27)	
Summary (FE)			**0.71**	**(0.58 , 0.85)**	**0.0003**
Summary (RE)			**0.71**	**(0.58 , 0.85)**	**0.0003**

Heterogeneity: I^2 = 0%, 95% CI = (0% , 95.1%)
P-value = 0.575 (χ^2 test)



Tejpar et al: JAMA Oncol, 2017

PARADIGM Trial Design: All RAS in Left Sided Tumors

Phase 3, randomized, open-label, multicenter study (NCT02394795)

Patients with *RAS* WT mCRC

- Unresectable disease
- No previous chemotherapy[a]
- Age: 20–79 years
- ECOG performance status 0–1
- At least 1 evaluable lesion
- Adequate organ function
- Life expectancy ≥ 3 months

N=823

R 1:1

Panitumumab +mFOLFOX6[b]

Bevacizumab +mFOLFOX6[b]

Primary endpoint

- OS: left-sided[c] population; if significant, analyzed in overall population

Secondary endpoints

- PFS, RR, DOR, R0 resection: left-sided[c] and overall populations
- Safety: all treated patients

Exploratory endpoints

- ETS, depth of response, DCR: left-sided[c] and overall populations

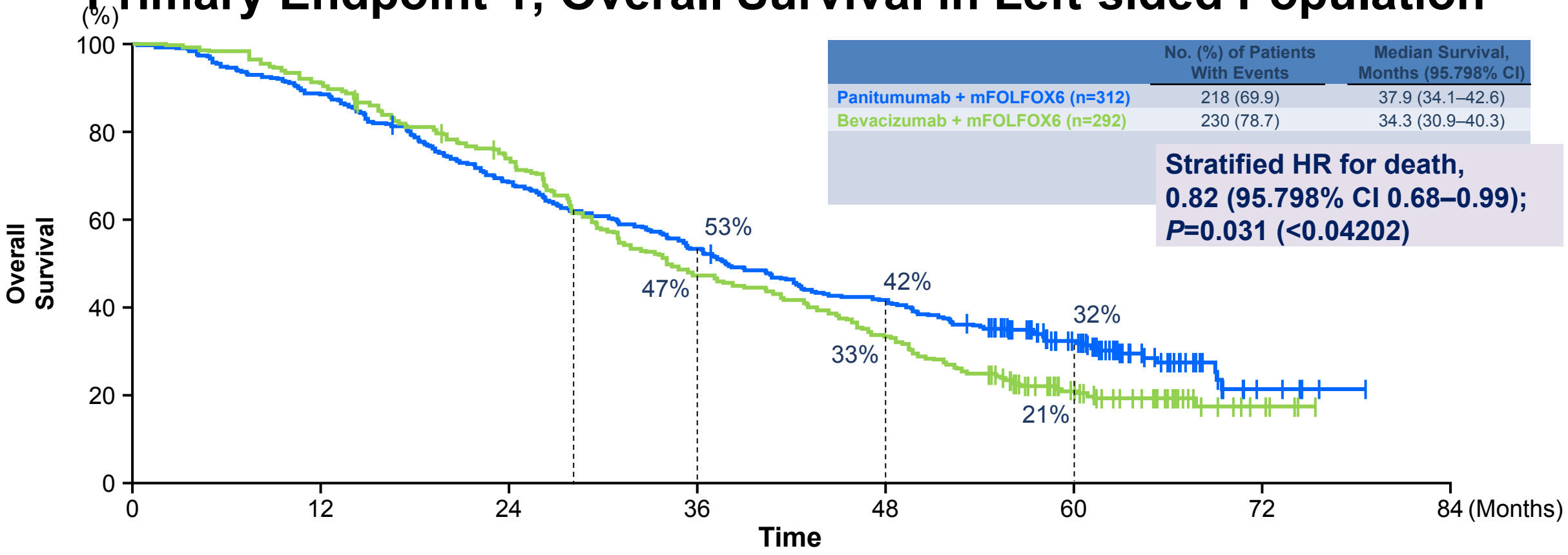
Stratification factors

- Institution
- Age: 20–64 vs 65–79 years
- Liver metastases: present vs absent

DCR, disease control rate; DOR; duration of response; ECOG, Eastern Cooperative Oncology Group; ETS, early tumor shrinkage; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; RR, response rate; R0, curative resection; WT, wild type.
[a]Adjuvant fluoropyrimidine monotherapy allowed if completed > 6 months before enrollment. [b]Until disease progression, unacceptable toxicity, withdrawal of consent or investigator's judgement or curative intent resection.
[C]Primary tumor in descending colon, sigmoid colon, rectosigmoid, and rectum.

Watanabe et al: Jama Network, 2023

Primary Endpoint-1; Overall Survival in Left-sided Population



	No. (%) of Patients With Events	Median Survival, Months (95.798% CI)
Panitumumab + mFOLFOX6 (n=312)	218 (69.9)	37.9 (34.1–42.6)
Bevacizumab + mFOLFOX6 (n=292)	230 (78.7)	34.3 (30.9–40.3)

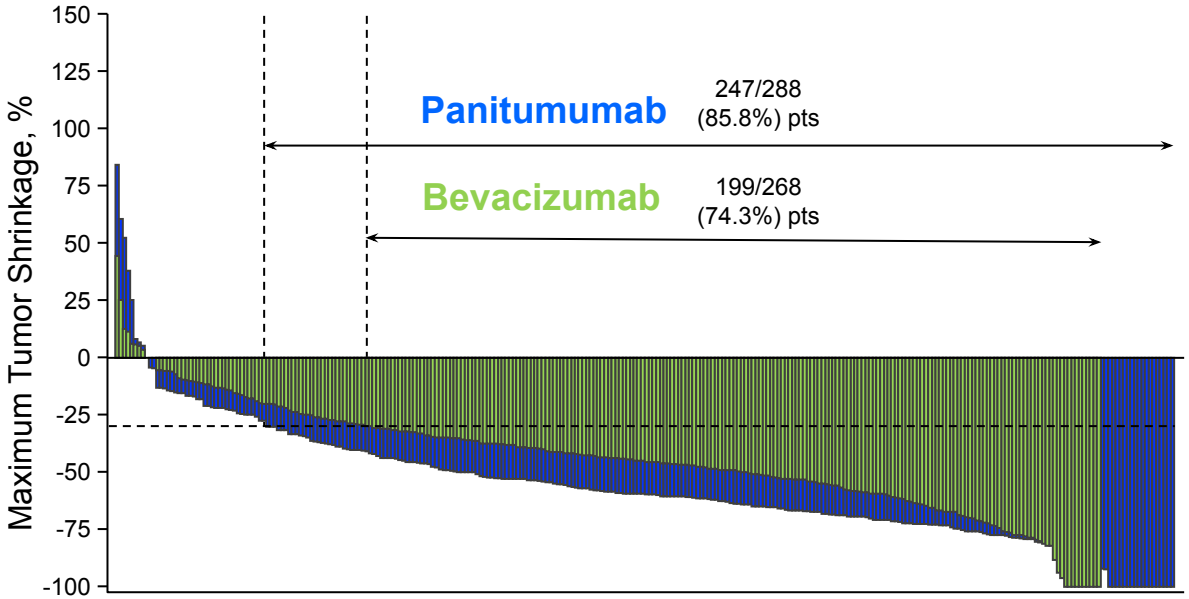
Stratified HR for death, 0.82 (95.798% CI 0.68–0.99); *P*=0.031 (<0.04202)

No. at risk								
Panitumumab	312	276	213	166	129	68	5	0
Bevacizumab	292	266	212	136	96	40	5	0

Watanabe et al: Jama Network, 2023

PARADIGM: Depth of Response and RR

Left-Sided Population



Horizontal dotted line at 30% indicates response per RECIST v1.1.

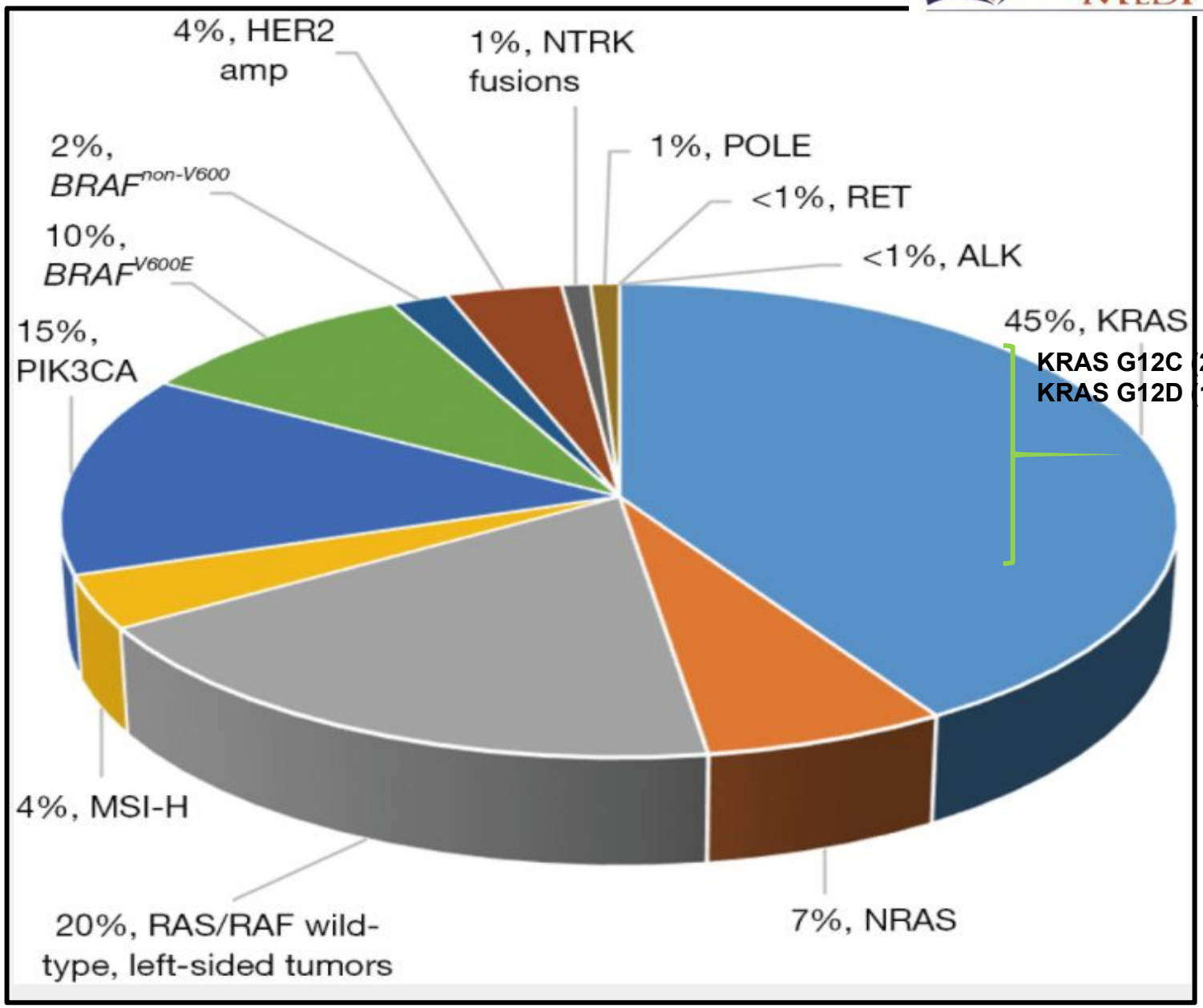
Parameter	Left-sided Population	
	Panitumumab + mFOLFOX6 (n=308)	Bevacizumab + mFOLFOX6 (n=287)
Response rate, % (95% CI)	80.2 (75.3–84.5)	68.6 (62.9–74.0)
Difference, % (95% CI)	11.2 (4.4–17.9)	
DCR, % (95% CI)	97.4 (94.9–98.9)	96.5 (93.7–98.3)
Median DOR,[a] months (95% CI)	13.1 (11.1–14.8)	11.2 (9.6–13.1)
R0 rate,[b] % (95% CI)	18.3 (14.1–23.0)	11.6 (8.2–15.9]

	Left-sided Population	
	Panitumumab + mFOLFOX6 (n=288)	Bevacizumab + mFOLFOX6 (n=268)
Median, %	-59.4	-43.6

Depth of response was assessed in patients with measurable lesions at baseline.

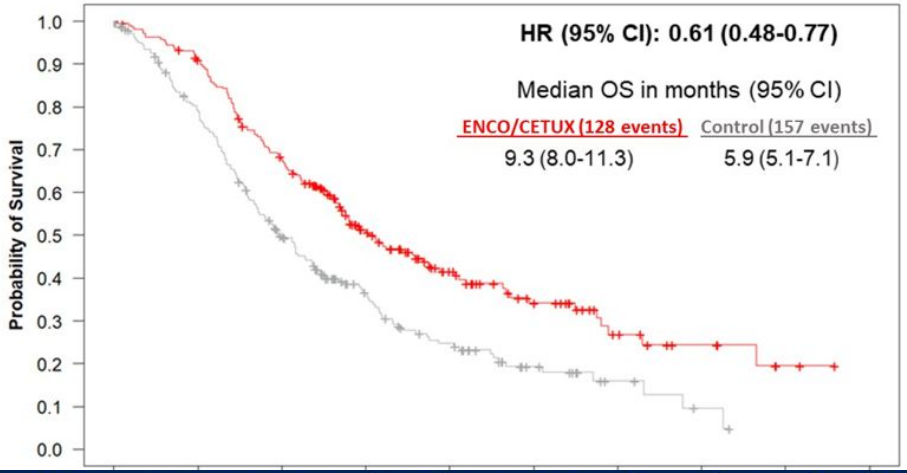
Watanabe et al: Jama Network, 2023

Molecular Subsets: Precision Oncology



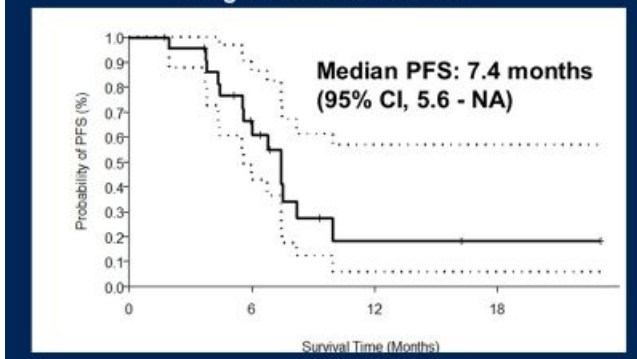
Henry et al, CCO, 2019

BRAF V600E MT Previously Treated MCRC

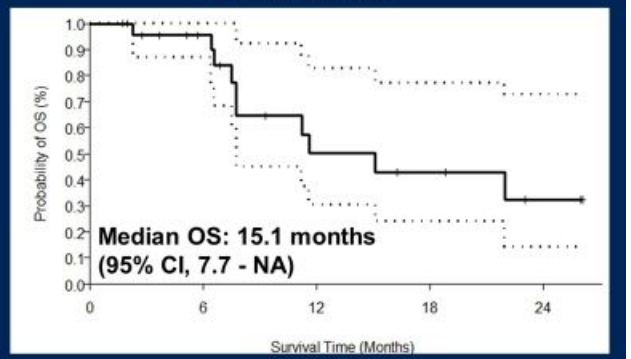


Survival outcomes: encorafenib + cetuximab + nivolumab

Progression-free survival



Overall survival



Median follow-up time: 16.3 months (95% CI, 6.9 –NA)
Median duration of response: 7.7 months (95% CI, 3.8 – NA)

Encorafenib + cetuximab: median PFS 4.2 months (95% CI, 3.7-5.4), median OS 8.4 months (95% CI, 7.5-11.0) [1]

[1]Kopetz S et al. NEJM 2019

ASCO Gastrointestinal Cancers Symposium #GI22 PRESENTED BY: Van Morris, MD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

SWOG 2107

Pts with MSS, *BRAF*^{V600E} metastatic CRC, AND
- 1-2 prior lines of systemic therapy
- ECOG PS 0-1
- No prior (1) BRAF, MEK, ERK; (2) anti-EGFR; or (3) immune checkpoint therapy

R

2:1

N=75

Encorafenib + cetuximab + nivolumab

Encorafenib + cetuximab

PI: V. Morris

SWOG
Leading cancer research. Together.

PI: V. Morris

Study Design

BREAKWATER (NCT04607421) is an ongoing, open-label, global, multicenter, randomized phase 3 study evaluating 1L EC ± chemotherapy vs SOC chemotherapy alone in participants with BRAF V600E-mutant mCRC

Safety Lead-In

Participants who have received ≤1 prior treatment for mCRC

Cohort 1 (n=30)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m^2 Q2W
+ FOLFIRI Q2W in 28-day cycles

Cohort 2 (n=27)
Encorafenib 300 mg QD
+ cetuximab 500 mg/m^2 Q2W
+ mFOLFOX6 Q2W in 28-day cycles

Primary Endpoint

- Safety (frequency of DLTs)

Secondary Endpoints

- Safety (AEs, dose interruptions/ modifications/discontinuations)
- PKs
- Antitumor activity by investigator (ORR, DOR, TTR, PFS, OS)

Inclusion Criteria	Exclusion Criteria
• BRAF V600E-mutant mCRC (blood or tumor tissue) • ≤1 prior systemic treatment for mCRC • Evaluable disease (RECIST 1.1) • ECOG PS 0 or 1 • Adequate BM, hepatic, and renal function	• Prior treatment with BRAF or EGFR inhibitors or both oxaliplatin and irinotecan • Symptomatic brain metastases • MSI-H or dMMR tumors[a]

Phase 3

Participants who have not received prior systemic treatment for mCRC

R

Arm A (n≈235)
Encorafenib + cetuximab

Arm B (n≈235)
Encorafenib + cetuximab
+ mFOLFOX6

Control (n≈235)
mFOLFOX6/FOLFOXIRI/
CAPOX ± bevacizumab

Primary Endpoint

- PFS by BICR

Secondary Endpoints

- OS
- ORR, DOR, and TTR by BICR and by investigator
- PFS by investigator
- Safety
- PROs
- Biomarkers

Here we present an updated analysis from the BREAKWATER SLI, including updated safety and antitumor activity data by BICR, as well as preliminary biomarker data

Data cutoff: September 5, 2022.

[a]Unless patient ineligible to receive immune checkpoint inhibitors due to pre-existing medical condition.

BICR, blinded independent central review; BM, bone marrow; DLT, dose-limiting toxicity; dMMR, deficient mismatch repair; EC, encorafenib + cetuximab; MSI-H, microsatellite instability-high; PK, pharmacokinetic; Q2W, every 2 weeks; QD, once daily; SLI, safety lead-in; SOC, standard of care.

PRESENTED BY: Scott Kopetz, MD, PhD

Overview of Response by BICR

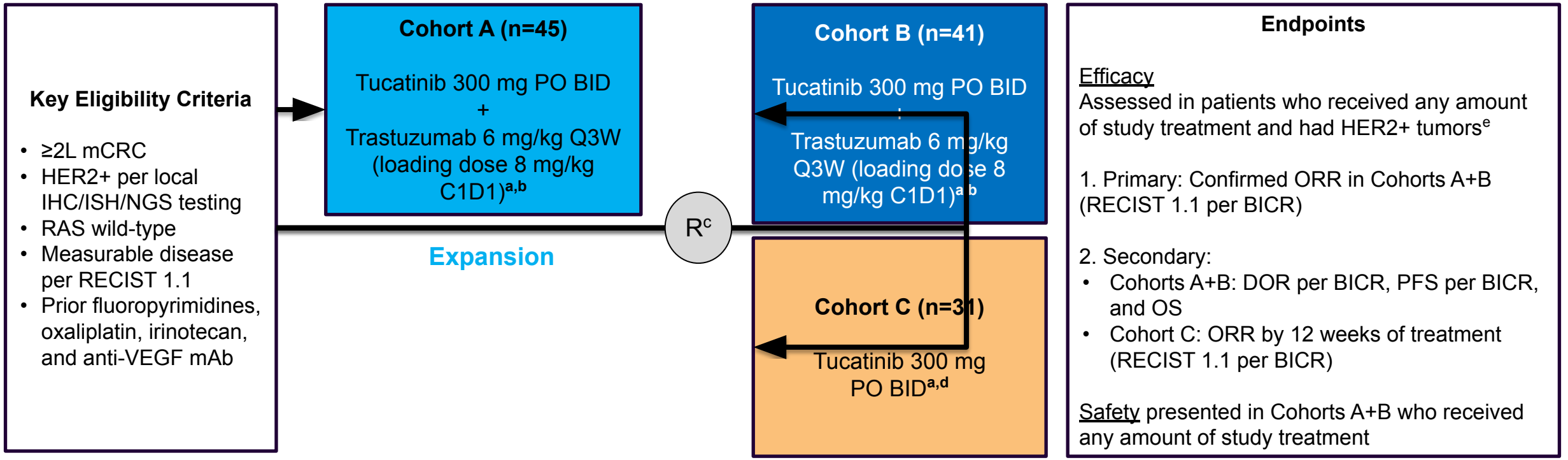
	1L		2L	
	EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
Confirmed best overall response, n (%)	**n=19**	**n=12**	**n=8**	**n=18**
ORR, % (95% CI)	68.4 (46.0, 84.6)	75.0 (46.8, 91.1)	37.5 (13.7, 69.4)	44.4 (24.6, 66.3)
CR	1 (5.3)	2 (16.7)	0	1 (5.6)[a]
PR	12 (63.2)	7 (58.3)	3 (37.5)	7 (38.9)
SD	4 (21.1)	2 (16.7)	5 (62.5)	7 (38.9)
PD	1 (5.3)	0	0	0
Non-CR/non-PD[b]	0	1 (8.3)	0	2 (11.1)
Not evaluable[c]	1 (5.3)	0	0	1 (5.6)
Responders	**n=13**	**n=9**	**n=3**	**n=8**
mTTR, weeks (range)	6.9 (5.9–30.0)	7.0 (6.1–42.7)	6.9 (6.4–23.1)	13.0 (6.1–47.3)
mDOR, months (95% CI)	9.8 (6.9, NE)	12.4 (6.9, NE)	NE (5.6, NE)	9.9 (5.5, NE)
≥6 months, n (%)	7 (53.8)	6 (66.7)	1 (33.3)	4 (50.0)

Data cutoff: September 5, 2022.

[a]This participant with CR only had nontarget lesions at baseline. [b]Participants with only nontarget lesions at baseline. [c]Reasons included SD <6 weeks after treatment start date (1 patient in the EC + mFOLFOX6 cohort in the 1L setting) and early death (1 patient in the EC + FOLFIRI cohort in the 2L setting).

BICR, blinded independent central review; EC, encorafenib and cetuximab; NE, not estimable.

MOUNTAINEER: Global, Open-Label, Phase 2 Trial



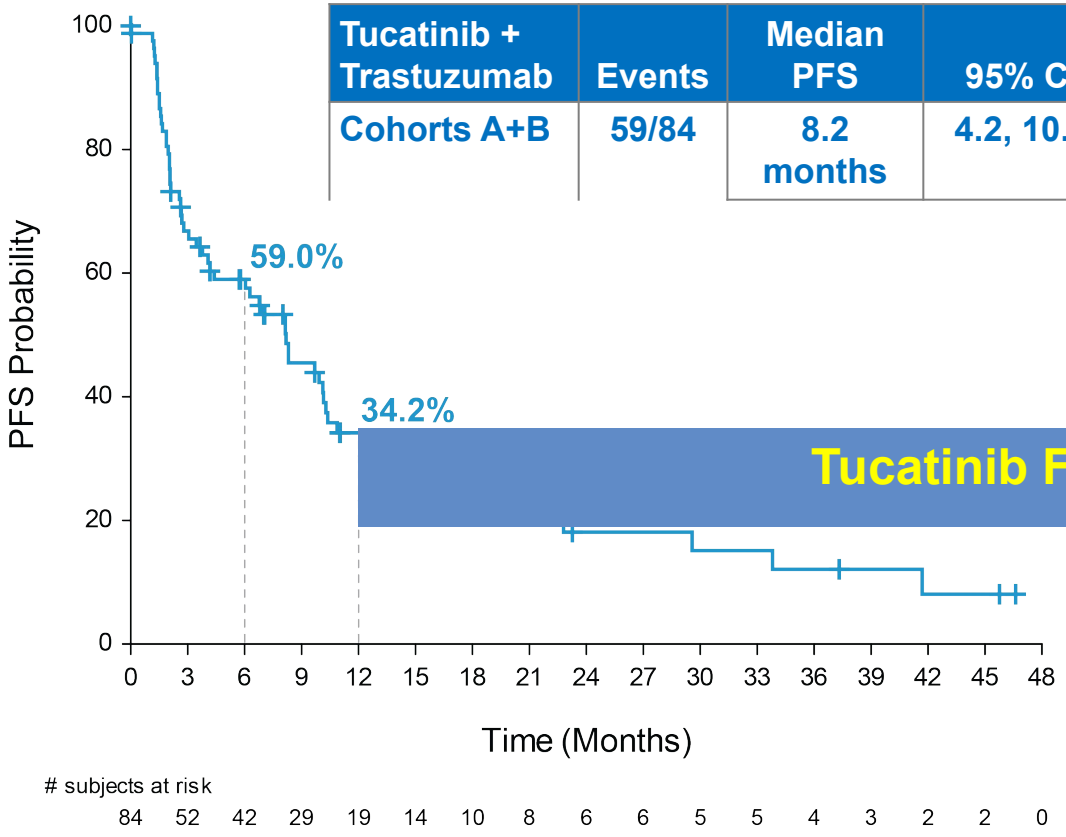
MOUNTAINEER began as a US Investigator-Sponsored Trial and initially consisted of a single cohort (Cohort A) and was expanded globally to include patients randomised to receive tucatinib + trastuzumab (Cohort B) or tucatinib monotherapy (Cohort C)

Strickler et al: Lanc Onc, 2023

Tucatinib + Trastuzumab: PFS and OS

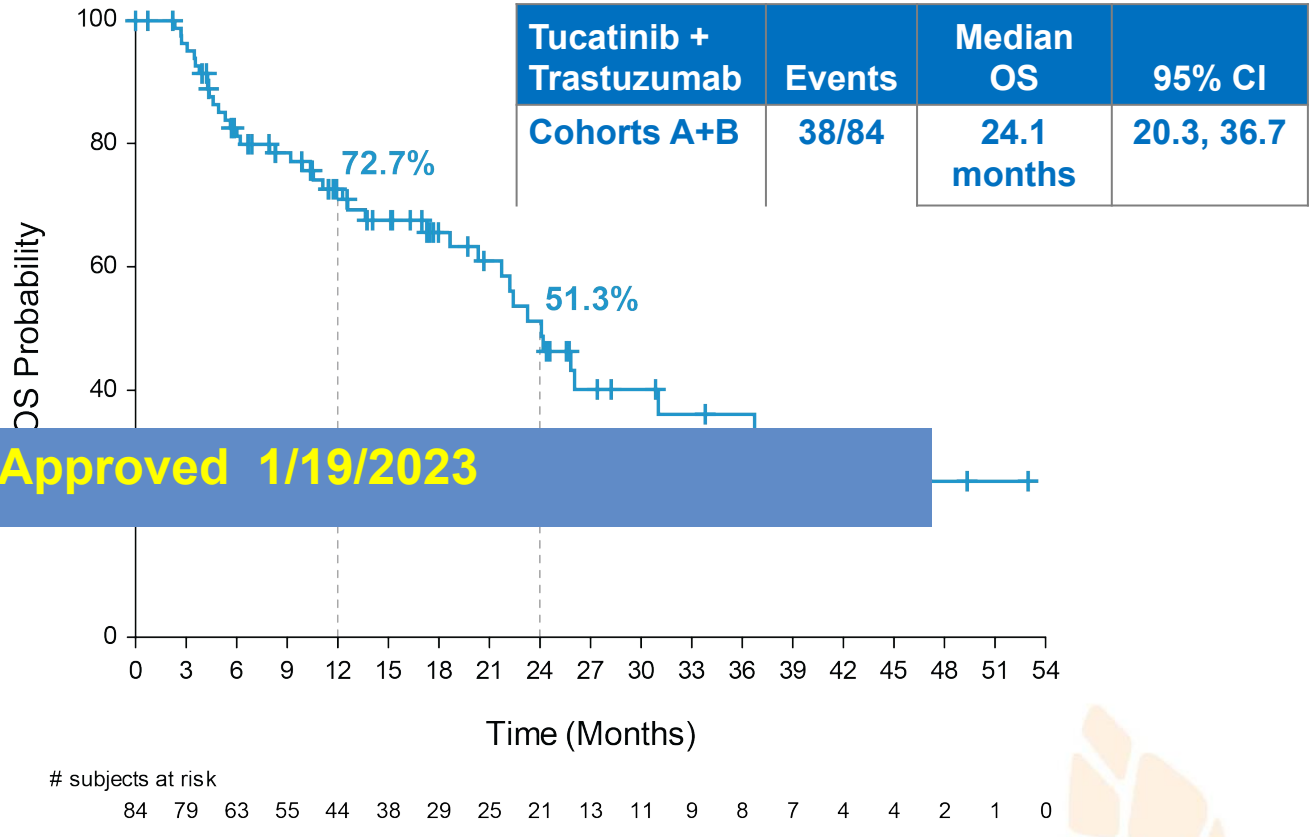
Progression-free Survival per BICR

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



Overall Survival

Tucatinib + Trastuzumab	Events	Median OS	95% CI
Cohorts A+B	38/84	24.1 months	20.3, 36.7

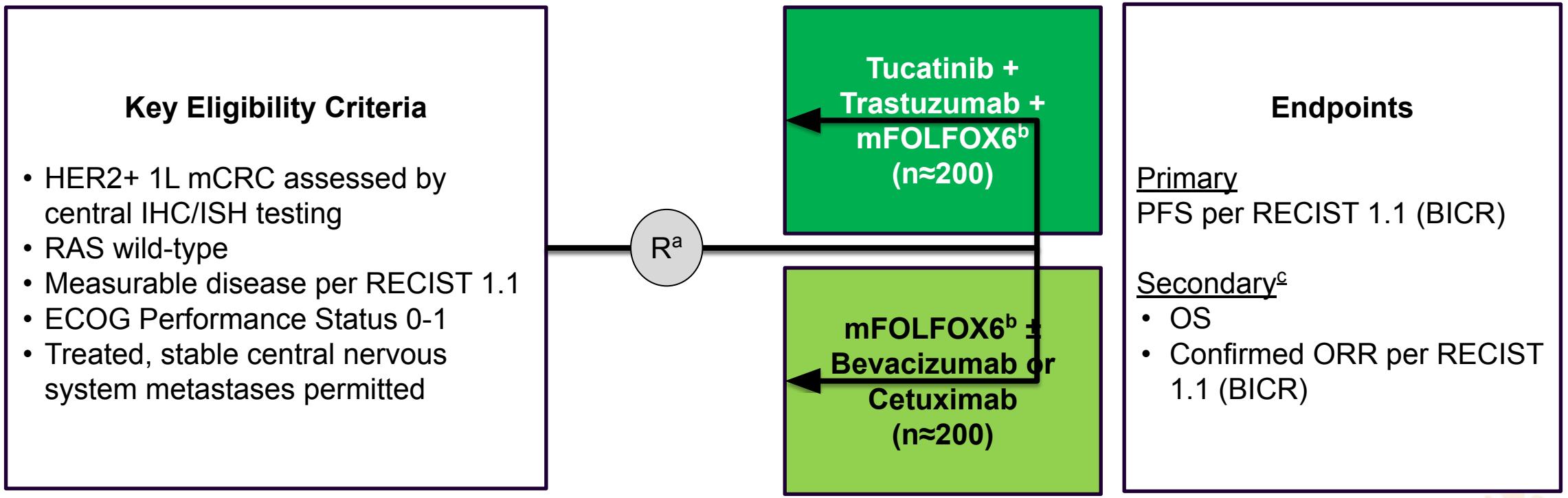


Tucatinib FDA Approved 1/19/2023

Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

Strickler et al: Lanc Onc, 2023

MOUNTAINEER-03: Global, Randomised, Open-Label, Phase 3 Trial

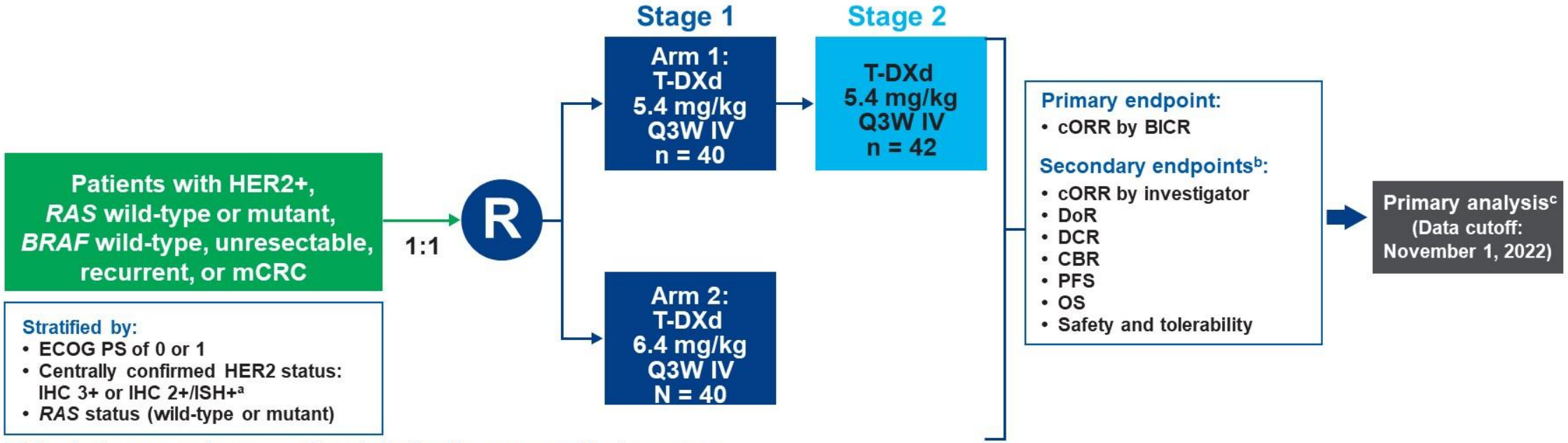


NCT05253651

DESTINY-CRC02 Study Design

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

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



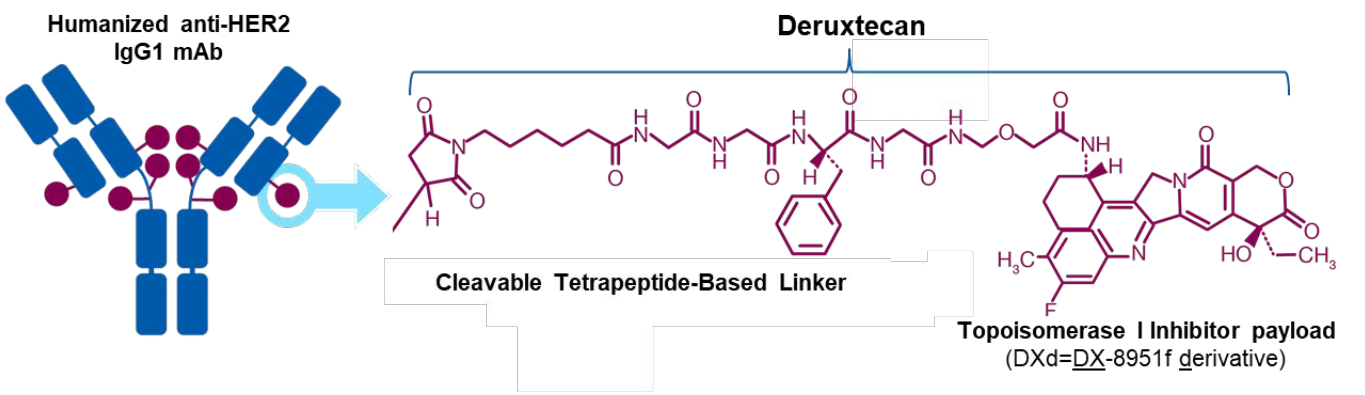
This study was not powered to statistically compare the two arms.

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

PRESENTED BY: Kanwal Raghav, MD

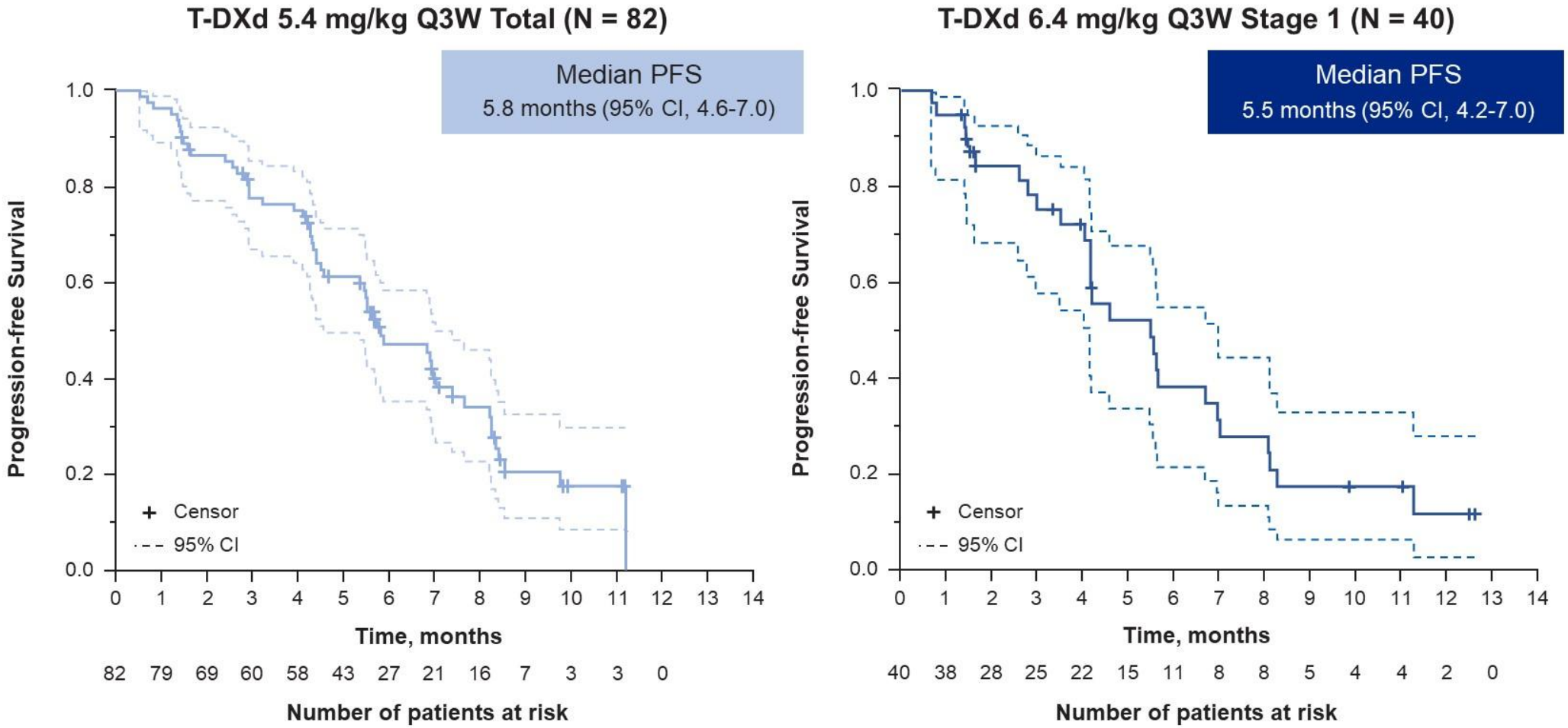
Trastuzumab deruxtecan (T-DXd; DS-8201)

- Trastuzumab deruxtecan is an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor.
- Survival benefits of the drug have been proven in HER2-positive breast and gastric cancers.[1,2]



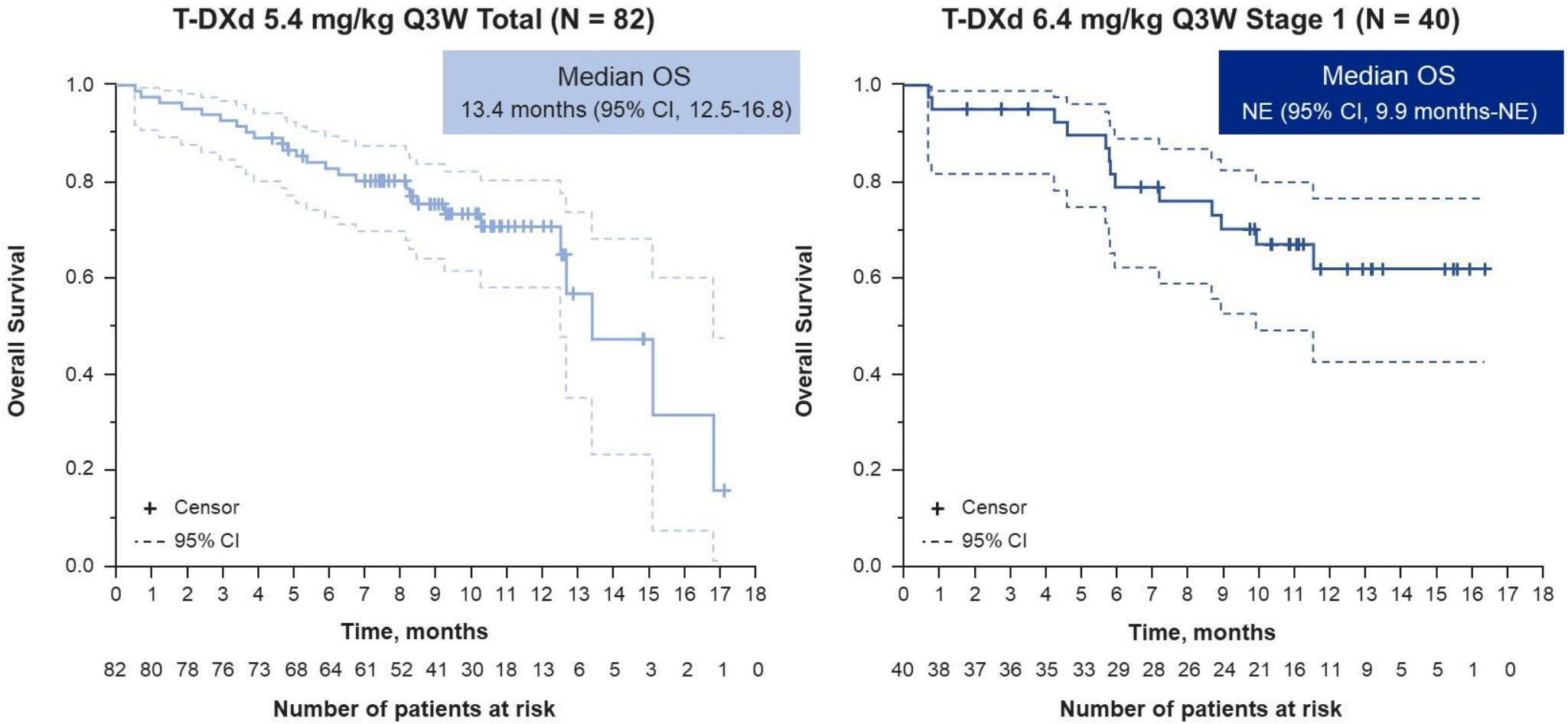
1. NEJM 2022;386:1143. 2. NEJM 2020;382:2419.

Median Progression-Free Survival by BICR



BICR, blinded independent central review; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Median Overall Survival

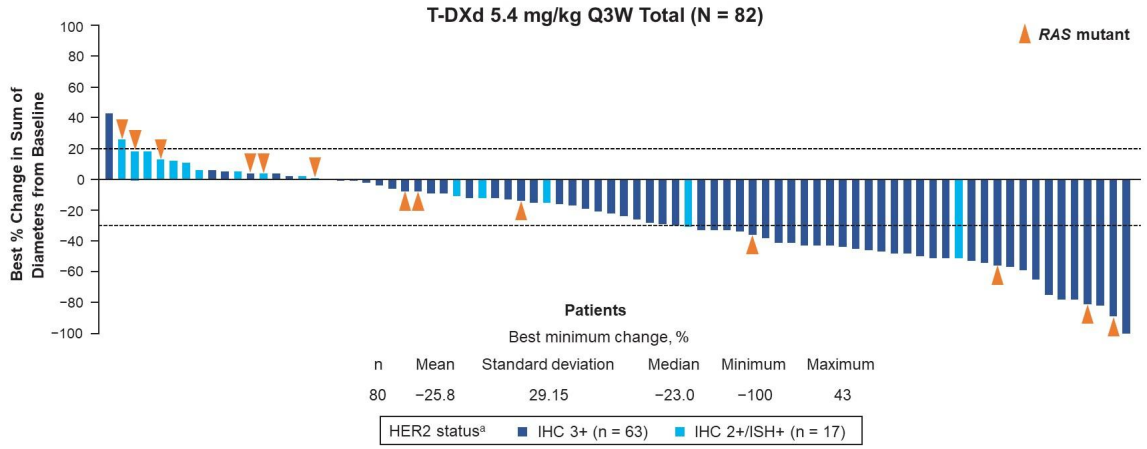


NE, not evaluable; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Overall Response Rate by Dose

DESTINY-CRC02

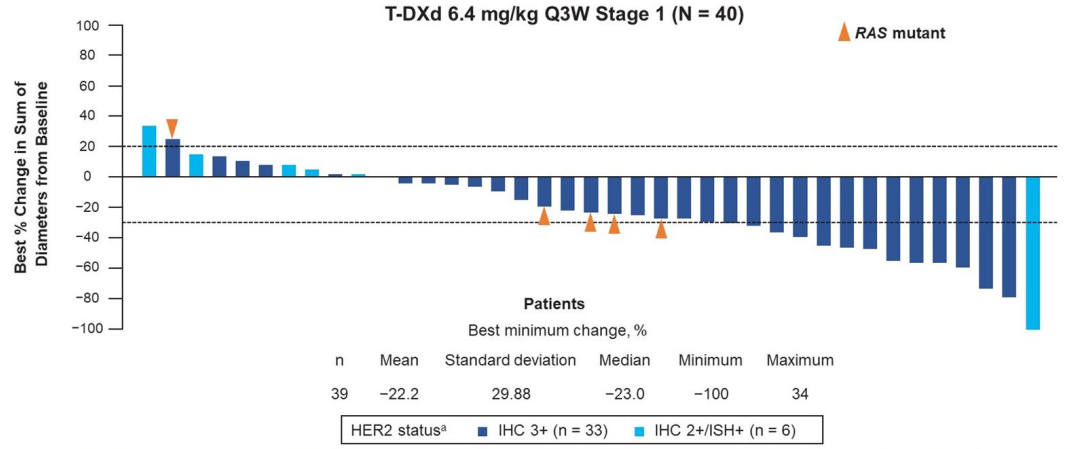
Best Percentage Change in Sum of Diameters by BICR for T-DXd 5.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

DESTINY-CRC02

Best Percentage Change in Sum of Diameters by BICR for T-DXd 6.4 mg/kg



BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.
Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the waterfall graphs.
[a]HER2 status was assessed by central laboratory.

Raghav et al: ASCO 2023

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)[b]

ILD, interstitial lung disease; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.
[a]1 patient randomized to receive T-DXd 6.4 mg/kg was mistakenly given T-DXd 5.4 mg/kg and counted in the 5.4 mg/kg arm safety analysis set. [b]There was 1 adjudicated, drug-related, grade 5 ILD/pneumonitis event, which was reported as respiratory failure, which was considered unrelated to study drug by investigator.

PRESENTED BY: Kanwal Raghav, MD

Ongoing KRAS G12C MT Phase I and III Trials

Phase 3: Sotorasib + Panitumumab

Patients
- > 1 prior line of treatment for mCRC
- KRAS G12C MT
- ECOG PS 0-2
- **N=193**
- ***Not yet recruiting**

NCT05198934

Arms A: Sotorasib 960 mg + Panitumumab or
Arm B: Sotorasib (240 mg) + PMab

1:1 Randomization

Physician's Choice: Regorafenib or TAS-102

Primary Endpoint: PFS

- **Metastatic CRC**
- ***KRAS* G12C in tumor**
  - Local test acceptable for enrollment; central confirmation req'd w/in 30d
- **PD on 1L fluoropyrimidine + oxaliplatin or irinotecan**
- **No prior anti-EGFR or direct KRAS G12Ci**

1:1
N~420

Adagrasib 600 mg BID + Cetuximab 500 mg/m² Q2W

FOLFIRI or mFOLFOX6§

§Anti-VEGF/VEGFR allowed per Investigator discretion

Phase 1a

Dose escalation of LY3537982†

Primary endpoints:
Dose-limiting toxicities (DLTs),
Adverse Events (AEs), and Serious Adverse Events (SAEs)

Phase 1b

Dose expansion:

LY3537982† monotherapy

LY3537982† + abemaciclib‡

LY3537982† + erlotinib§

LY3537982† + pembrolizumab||

LY3537982† + temuterkib¶

LY3537982† + LY3295668 (AurA inhibitor)#

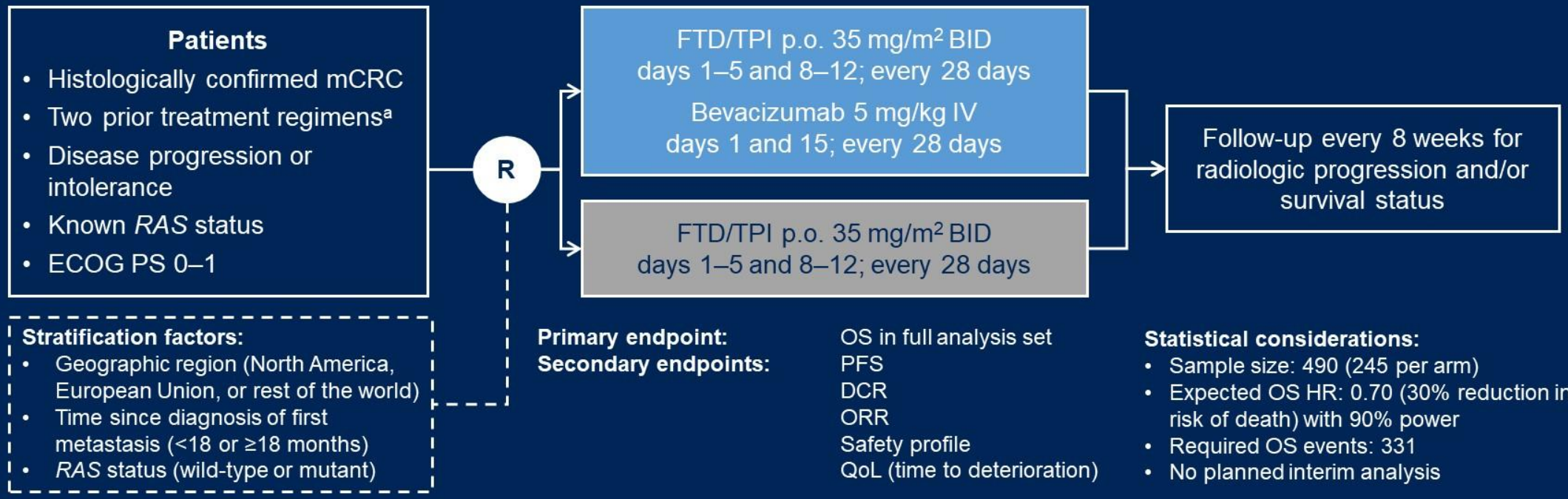
LY3537982† + cetuximab**

LY3537982† + TNO155††

Primary endpoints:
DLTs, AEs, and SAEs

SUNLIGHT study design - 3rd Line

- An open-label, randomized, phase 3 study in patients with refractory mCRC (NCT04737187)

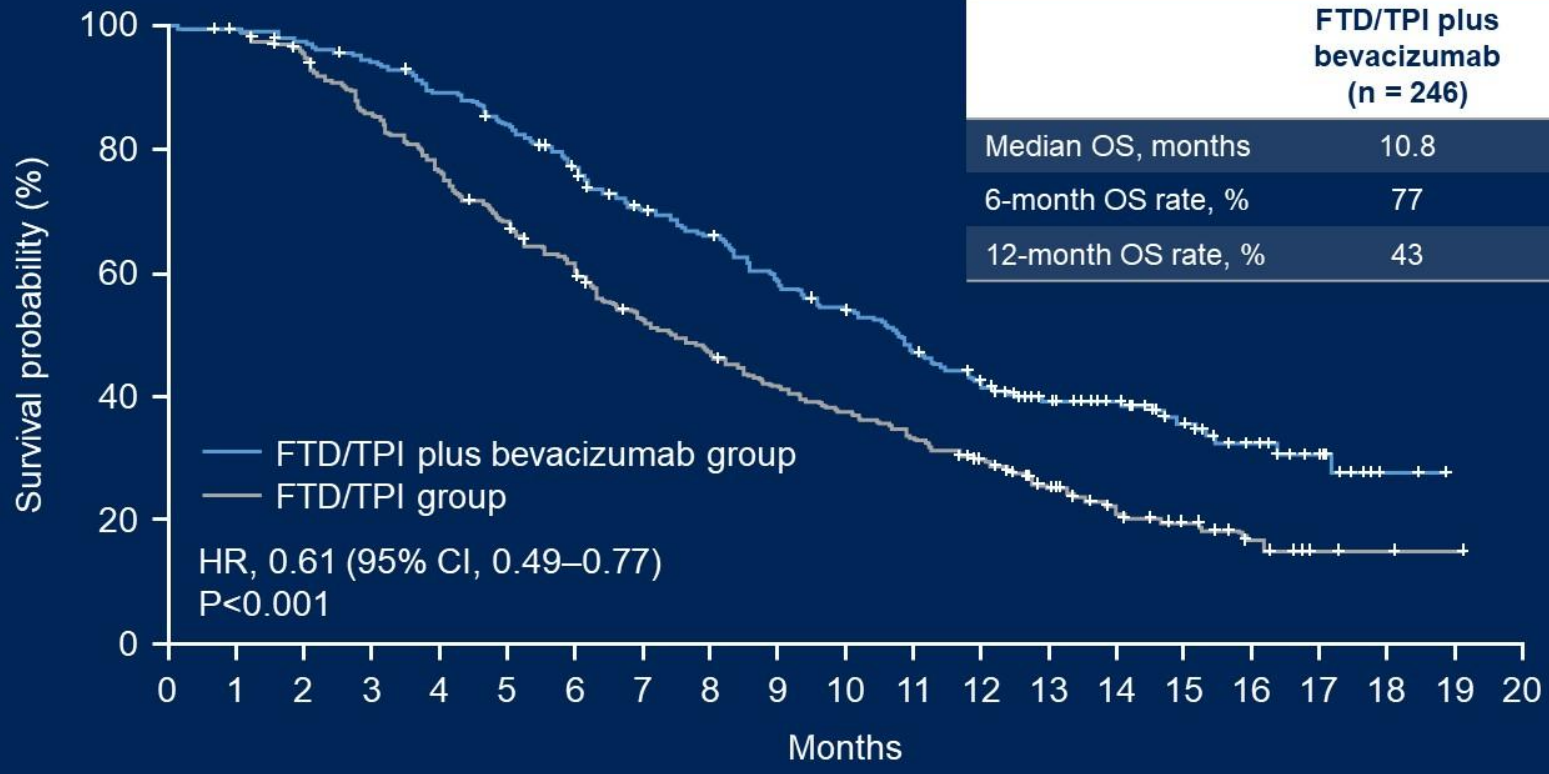


[a] Prior treatment must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody (not necessarily bevacizumab), and/or an anti-EGFR monoclonal antibody for patients with *RAS* wild-type and could have included (neo)adjuvant chemotherapy if disease had recurred during treatment or within 6 months of the last administration of (neo)adjuvant therapy. BID, twice daily; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EFGR, epidermal growth factor receptor; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; IV, intravenous; mCRC, metastatic colorectal cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., orally; QoL, quality of life; R, randomization; VEGF, vascular endothelial growth factor.

PRESENTED BY: Prof. Josep Tabernero

Tabanero et al: NEJM 2023

OS in full analysis set (primary endpoint)



	FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Median OS, months	10.8	7.5
6-month OS rate, %	77	61
12-month OS rate, %	43	30

No. at risk

FTD/TPI plus bevacizumab group	246	244	239	230	217	203	183	160	149	131	119	104	88	69	52	37	24	13	2	0	0
FTD/TPI group	246	242	230	205	184	163	143	120	108	95	85	76	63	44	24	16	10	5	2	1	0

CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

PRESENTED BY: Prof. Josep Tabernero

Tabanero et al: NEJM 2023

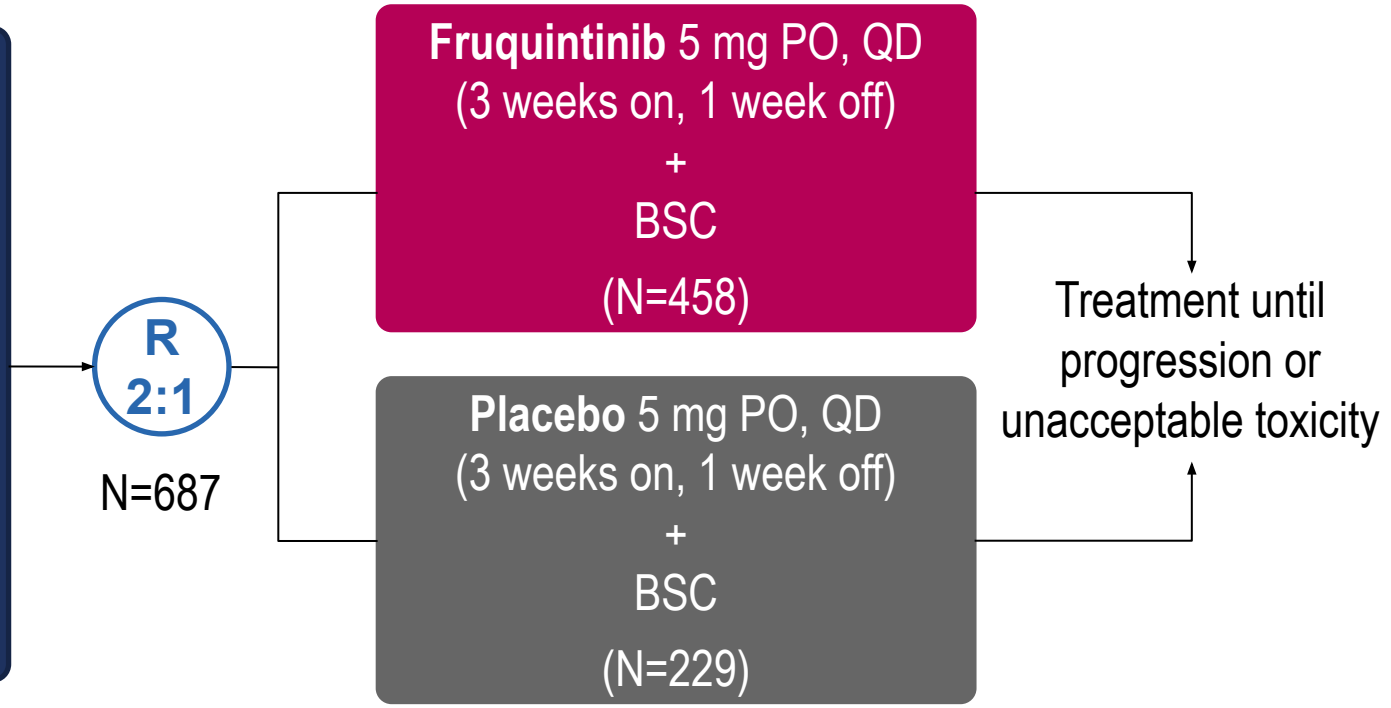
Fast Facts about FRESCO-2

- Approved in China (2018)
- Only phase III trial opened at that time
- Due to lack of trials, we wanted to be able to offer to all possible patients
- Placebo arm due to no other treatments available after lonsurf and/or rego
- Completed enrollment quicker than expected despite COVID-19
  - Unmet need
- Supply chain issue resulted in ↓tubes for ctDNA correlatives

FRESCO-2 Study Design

Patient Eligibility

- Prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild type, an anti-EGFR therapy
- Progression on, or intolerance to, TAS-102 and/or regorafenib
- Prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated



Stratification Factors

- Prior therapy (TAS-102 vs regorafenib vs TAS-102 and regorafenib)
- *RAS* mutational status (wild-type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Mechanism of action: Highly selective oral tyrosine kinase inhibitor of VEGFRs-1, -2, and -3

Note: To ensure the patient population is reflective of clinical practice, the number of patients treated with prior regorafenib was limited to 344 patients (50%)

BSC, best supportive care.
NCT04322539.

PARIS 2022 ESMO congress

Dasari A .....Eng et al. ESMO 2022; Dasari et al: Lancet, June 15, 2023

Patient and Disease Characteristics

ITT Population

Enrollment: Sep 2020 to Dec 2021

Data Cutoff: 24 June 2022

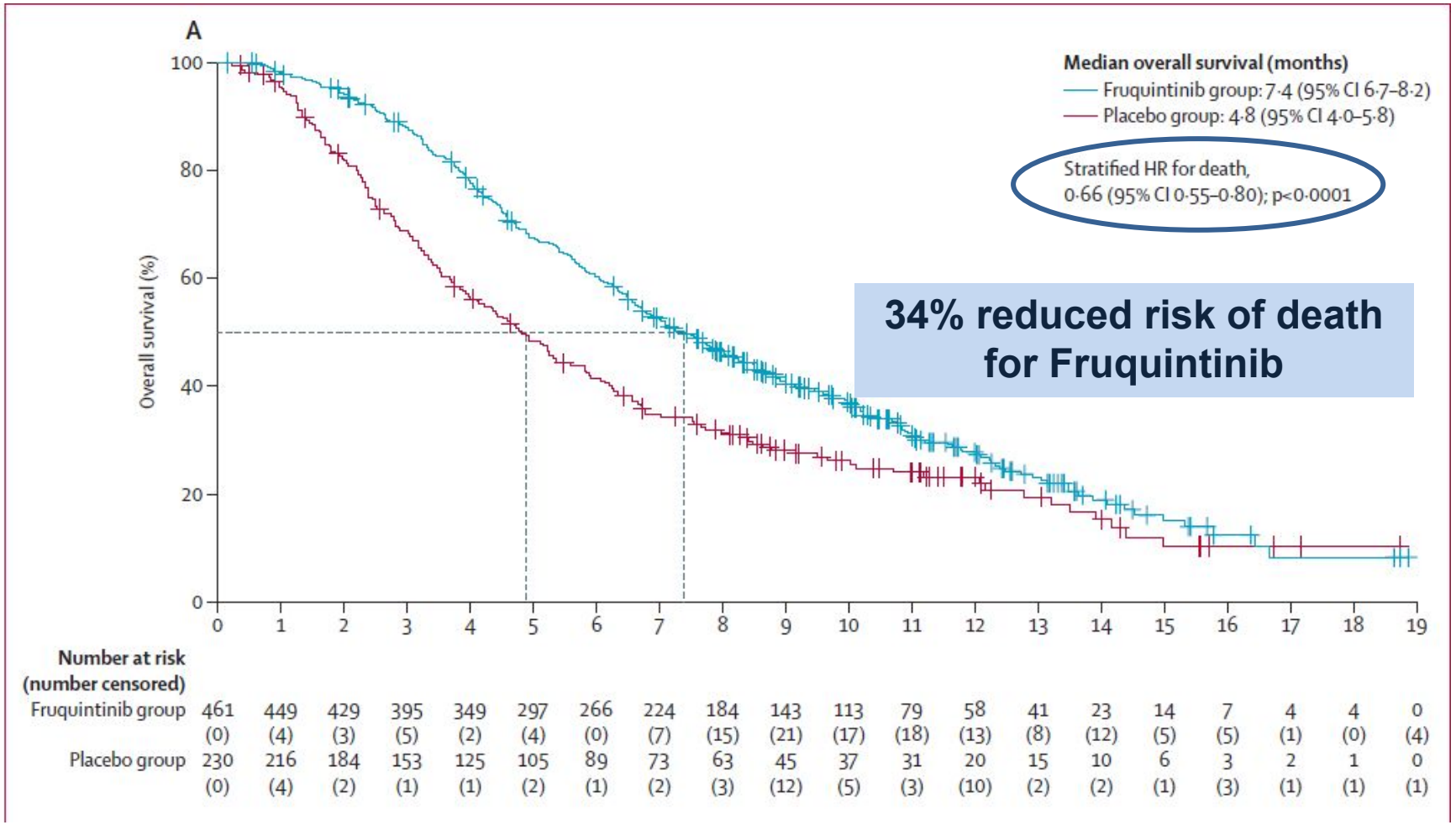
Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Age, y	Median (range)	64 (25, 82)	64 (30, 86)
	≥ 65	214 (46.4)	111 (48.3)
Sex	Female	216 (46.9)	90 (39.1)
	Male	245 (53.1)	140 (60.9)
Region	North America	82 (17.8)	42 (18.3)
	Europe	329 (71.4)	166 (72.2)
	Asia Pacific	50 (10.8)	22 (9.6)
ECOG PS	0	196 (42.5)	102 (44.3)
	1	265 (57.5)	128 (55.7)
Primary site at 1st diagnosis	Colon left	192 (41.6)	92 (40.0)
	Colon right	97 (21.0)	53 (23.0)
	Colon left and right	4 (0.9)	2 (0.9)
	Colon unknown	25 (5.4)	13 (5.7)
	Rectum only	143 (31.0)	70 (30.4)
Liver metastases	Yes	339 (73.5)	156 (67.8)

Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Duration of metastatic disease	≤ 18 mo	37 (8.0)	13 (5.7)
	> 18 mo	424 (92.0)	217 (94.3)
RAS status	WT	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	5 (11.5)	22 (9.6)
Number of previous treatment lines in metastatic disease			
Median		4 (3–6)	4 (3–6)
≤3		125 (27%)	64 (28%)
>3		336 (73%)	166 (72%)
Previous therapies			
VEGF inhibitor		445 (97%)	221 (96%)
EGFR inhibitor		180 (39%)	88 (38%)
Immune checkpoint inhibitor		21 (5%)	11 (5%)
BRAF inhibitor		9 (2%)	7 (3%)
Previous trifluridine–tipiracil or regorafenib			
Trifluridine–tipiracil		240 (52%)	121 (53%)
Regorafenib		40 (9%)	18 (8%)
Both		181 (39%)	91 (40%)

PARIS 2022 ESMO congress

Dasari A .....Eng et al. ESMO 2022; Dasari et al: The Lancet, June 15, 2023

FRESCO-2: Primary Endpoint - OS

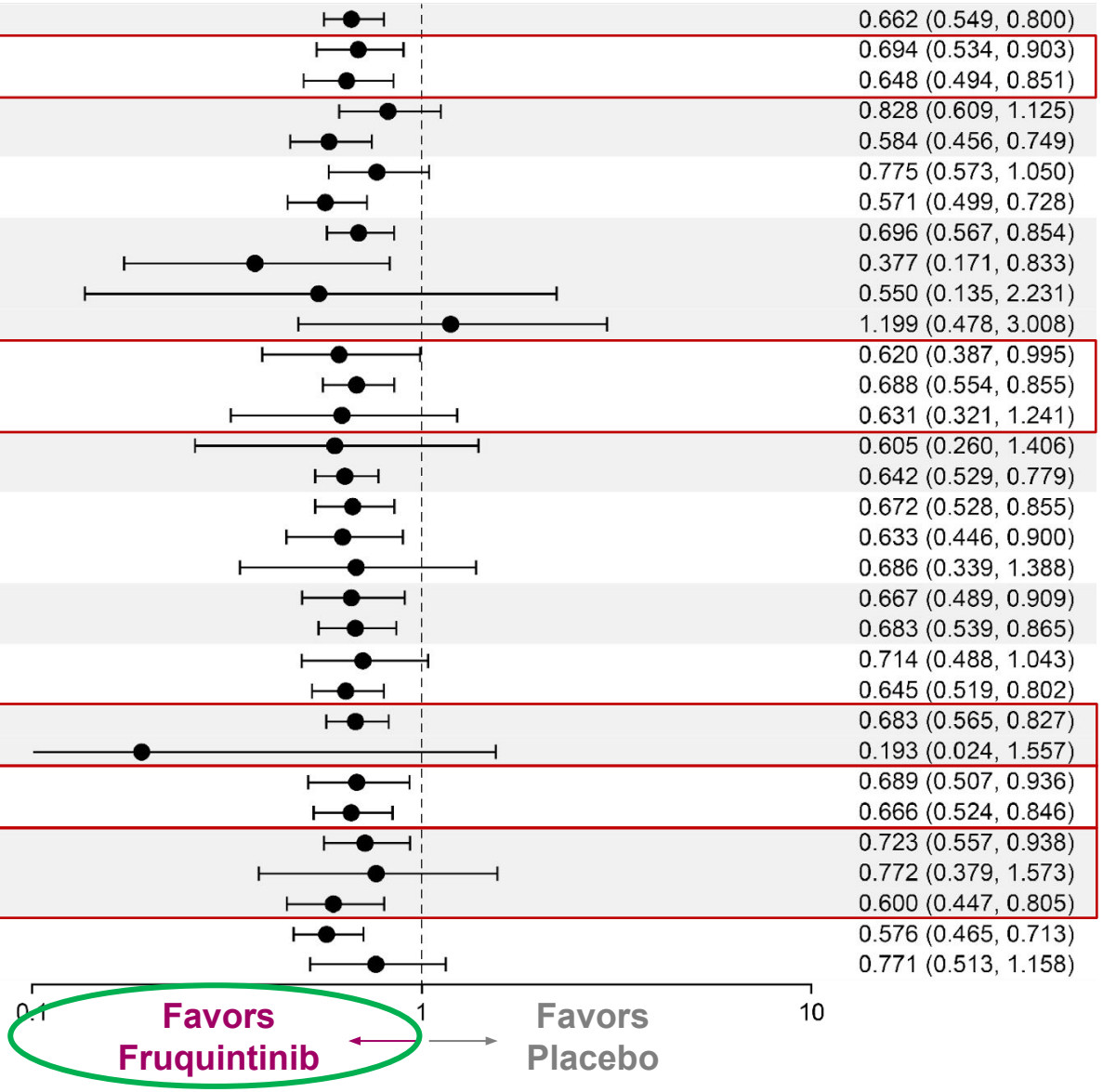


Dasari…Eng et al: The Lancet, 2023

OS Subgroup Analysis

ITT Population

Subgroup		Fruquintinib n/N	Placebo n/N	HR (95% CI)
ITT population		317/461	173/230	0.662 (0.549, 0.800)
Age	< 65	171/247	89/119	0.694 (0.534, 0.903)
	≥ 65	146/214	84/111	0.648 (0.494, 0.851)
Sex	Female	149/216	61/90	0.828 (0.609, 1.125)
	Male	168/245	112/140	0.584 (0.456, 0.749)
ECOG PS	0	121/196	67/102	0.775 (0.573, 1.050)
	1	196/265	106/128	0.571 (0.499, 0.728)
Race	Caucasian	260/367	145/192	0.696 (0.567, 0.854)
	Asian	24/43	14/18	0.377 (0.171, 0.833)
	African American	7/13	5/7	0.550 (0.135, 2.231)
	Other	26/38	9/13	1.199 (0.478, 3.008)
Region	North America	50/82	29/42	0.620 (0.387, 0.995)
	Europe	237/329	130/166	0.688 (0.554, 0.855)
	Asia Pacific	30/50	14/22	0.631 (0.321, 1.241)
Duration of metastatic disease	≤ 18 mo	30/37	8/13	0.605 (0.260, 1.406)
	> 18 mo	287/424	165/217	0.642 (0.529, 0.779)
Primary tumor site at 1st diagnosis	Colon	195/279	109/137	0.672 (0.528, 0.855)
	Rectum	99/143	49/70	0.633 (0.446, 0.900)
	Colon and Rectum	23/39	15/23	0.686 (0.339, 1.388)
RAS status	WT	119/170	62/85	0.667 (0.489, 0.909)
	Mutant	198/291	111/145	0.683 (0.539, 0.865)
# of prior treatment lines in metastatic disease	≤ 3	80/125	45/64	0.714 (0.488, 1.043)
	>3	237/336	128/166	0.645 (0.519, 0.802)
Prior VEGFi	Yes	306/445	167/221	0.683 (0.565, 0.827)
	No	11/16	6/9	0.193 (0.024, 1.557)
Prior EGFRi	Yes	127/180	64/88	0.689 (0.507, 0.936)
	No	190/281	109/142	0.666 (0.524, 0.846)
Prior TAS-102 and Regorafenib	TAS-102	165/240	88/121	0.723 (0.557, 0.938)
	Regorafenib	25/40	12/18	0.772 (0.379, 1.573)
	Both	127/181	73/91	0.600 (0.447, 0.805)
Liver metastases	Yes	255/339	132/156	0.576 (0.465, 0.713)
	No	62/122	41/74	0.771 (0.513, 1.158)



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Dasari A .....Eng et al. ESMO 2022; Dasari et al: Lancet, June 15, 2023

Analysis of Fruquintinib Adverse Events of Special Interest from The Phase 3 FRESCO-2 study

Table 3: Treatment-emergent AESIs (any grade, PT occurring in ≥5% patients)

AESI category, n (%)* PT	Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension†	179 (38.4)	65 (14.0)	20 (8.7)	2 (0.9)
Hypertension	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Dermatological toxicity	157 (34.4)	31 (6.8)	27 (11.7)	1 (0.4)
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Liver function test abnormality	113 (24.8)	38 (8.3)	44 (19.1)	21 (9.1)
AST increased	48 (10.5)	10 (2.2)	11 (4.8)	3 (1.3)
ALT increased	47 (10.3)	14 (3.1)	9 (3.9)	1 (0.4)
Blood bilirubin increased	36 (7.9)	11 (2.4)	11 (4.8)	6 (2.6)
Thyroid dysfunction	123 (27.0)	2 (0.4)	4 (1.7)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Thyroid-stimulating hormone increased	32 (7.0)	0	3 (1.3)	0
Infection	96 (21.1)	30 (6.6)	29 (12.6)	13 (5.7)
Proteinuria	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Hemorrhage	65 (14.3)	8 (1.8)	22 (9.6)	4 (1.7)

Analysis of Fruquintinib Adverse Events of Special Interest from The Phase 3 FRESCO-2 study

Table 4: Selected treatment-emergent AESIs leading to dose reduction and dose discontinuation

	Patients with AESI PT leading to dose reduction				Patients with AESI PT leading to dose discontinuation			
	Fruquintinib (n=456)		Placebo (n=230)		Fruquintinib (n=456)		Placebo (n=230)	
PT, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	17 (3.7)	15 (3.3)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)	0	0
Palmar-plantar erythrodysesthesia syndrome	24 (5.3)	14 (3.1)	0	0	3 (0.7)	2 (0.4)	0	0
AST increased	1 (0.2)	0	0	0	0	0	1 (0.4)	0
ALT increased	2 (0.4)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	1 (0.4)	0
Blood bilirubin increased	6 (1.3)	0	0	0	1 (0.2)	0	0	0
Proteinuria	8 (1.8)	2 (0.4)	1 (0.4)	1 (0.4)	4 (0.9)	1 (0.2)	0	0

Conclusions:

- **Rectal Cancer**
  - Several options based on location of primary tumor and T and N stage
  - Increased incidence in EOCRC to focus on sphincter preservation
- **MCRC**
  - **PARADIGM**: FOLFOX + anti-EGFR therapy in left sided all RAS WT tumors may be considered for OS
  - BRAF V600E MT
    - Phase III - **BREAKWATER** trial
  - HER2+: Consider tucatinib + traszutuzumab for refractory pts
    - Phase III – **Mountaineer 3**
    - **DESTINY CRC–02**: TDXd – Appropriate dose is 5.4 mg/kg
  - Refractory
    - 3rd line: **Sunlight** (TAS-102 + bevacizumab)
    - **FRESCO-2**: Single agent Fruquintinib
- **ctDNA**: COBRA and CIRCULATE (stage II and III colon CA)