Novel Advances and Updates in the Treatment of Colorectal Cancer

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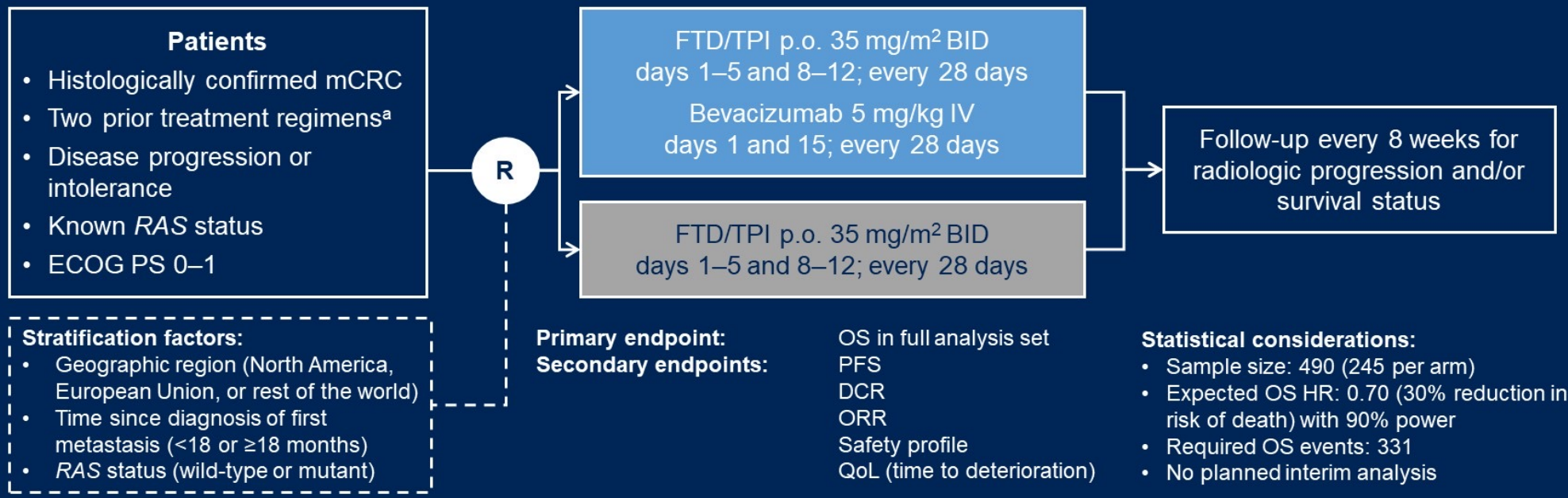
SUNLIGHT study design

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



Primary endpoint: OS in full analysis set

Secondary endpoints:
- PFS
- DCR
- ORR
- Safety profile
- QoL (time to deterioration)

Statistical considerations:
- Sample size: 490 (245 per arm)
- Expected OS HR: 0.70 (30% reduction in risk of death) with 90% power
- Required OS events: 331
- No planned interim analysis

[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.

Tabarnero et al: NEJM 2023

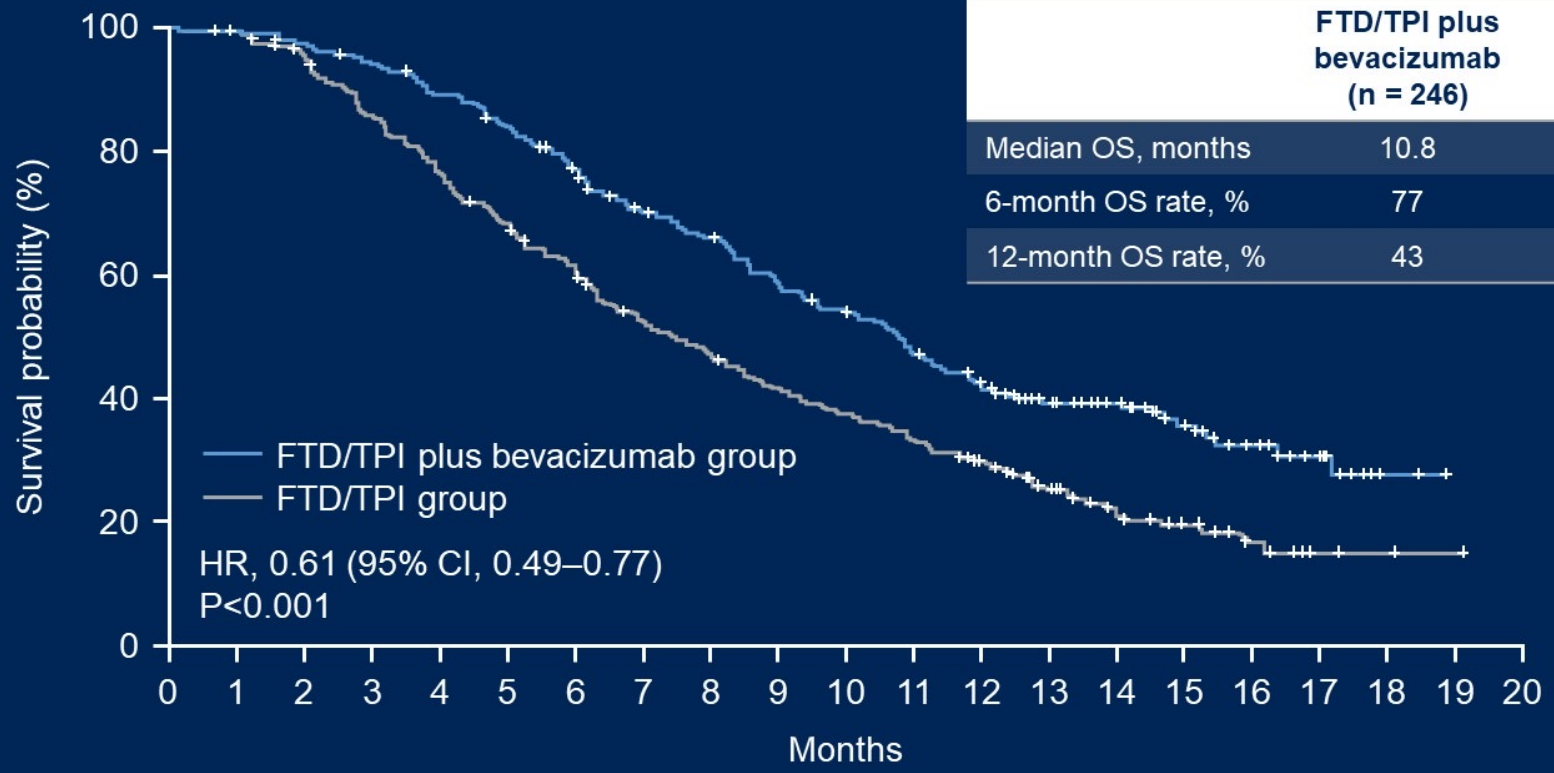
Key baseline characteristics

Characteristic		FTD/TPI plus bevacizumab (n = 246)	FTD/TPI (n = 246)
Age	Median (range), years	62 (20–84)	64 (24–90)
	<65 years, n (%)	146 (59)	129 (52)
	≥65 years, n (%)	100 (41)	117 (48)
Sex, n (%)	Male	122 (50)	134 (55)
Region	European Union	158 (64)	157 (64)
	North America	8 (3)	8 (3)
	Rest of the world	80 (33)	81 (33)
Primary tumor localization, n (%)	Right	62 (25)	77 (31)
	Left	184 (75)	169 (69)
Time from diagnosis of first metastasis to randomization,[a] n (%)	<18 months	104 (42)	105 (43)
	≥18 months	142 (58)	141 (57)
***RAS* status,[a] n (%)**	Mutant	171 (70)	170 (69)
	Wild-type	75 (31)	76 (31)
Prior treatment with bevacizumab, n (%)	No	68 (28)	70 (29)
	Yes	178 (72)	177 (72)
ECOG PS, n (%)	0	119 (48)	106 (43)
	1	127 (52)	139 (57)
	2	0	1 (0.4)[b]

[a] As documented in the Interactive Web Response System set for randomization. [b] Patient had an ECOG PS of 1 at randomization but was assessed as having an ECOG PS of 2 on day 1, cycle 1.
ECOG PS, Eastern Cooperative Oncology Group performance status; FTD/TPI, trifluridine/tipiracil.

Tabarnero 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

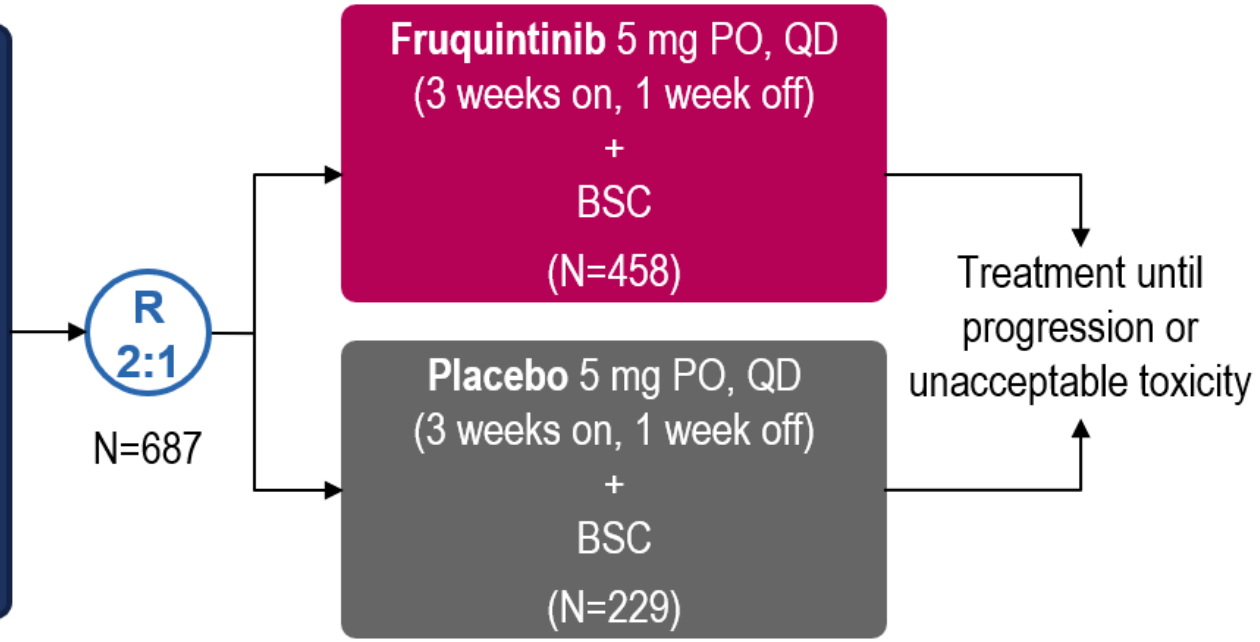
CI, confidence interval; FTD/TPI, trifluridine/tipiracil; HR, hazard ratio; OS, overall survival.

Tabarnero et al: NEJM 2023

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%)

Dasari et al: Lancet, 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)

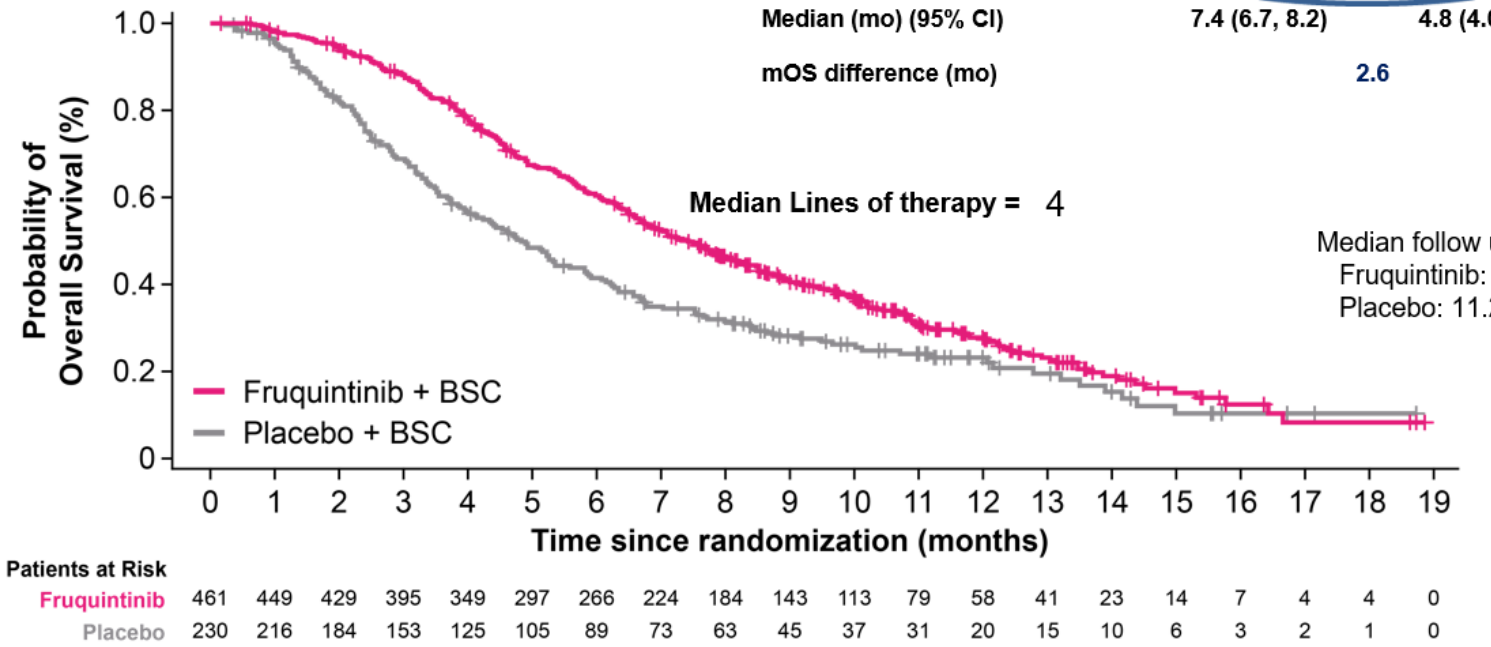
Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Duration of metastatic disease	≤ 18 mo	37 (8.0)	13 (5.7)
	> 18 mo	424 (92.0)	217 (94.3)
RAS status	WT	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	5 (11.5)	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%)

Dasari et al: Lancet, 2023

FRESCO-2: A global phase 3 multiregional clinical trial evaluating the efficacy and safety of fruquintinib in patients with refractory mCRC

(*FDA Approved 11/2023: 3rd line setting based on FRESCO and FRESCO2 trials*)

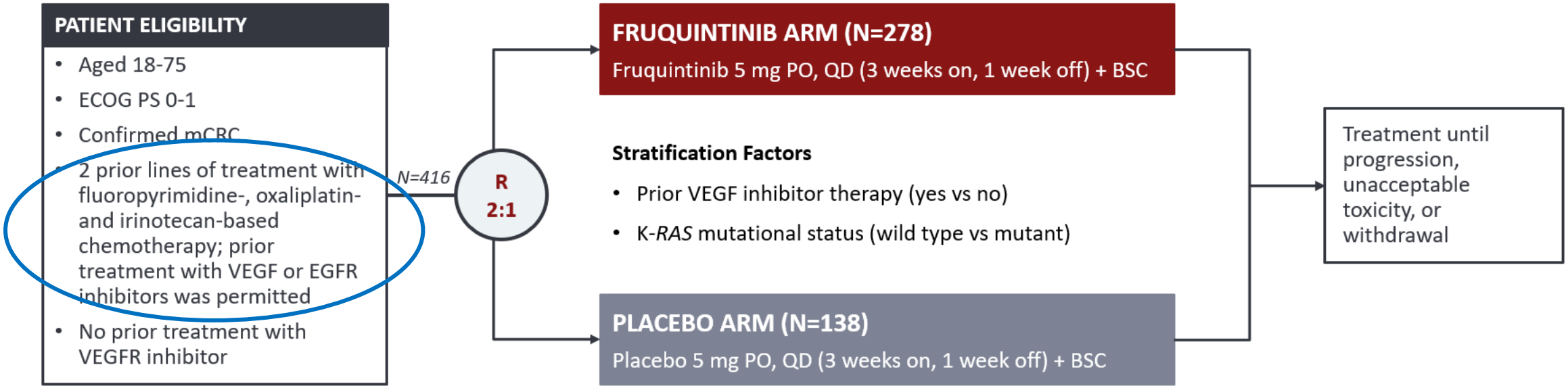
	Fruquintinib	Placebo
Events/Patients (%)	317/461 (68.8%)	173/230 (75.2%)
Stratified p-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.662 (0.549, 0.800)	
Median (mo) (95% CI)	7.4 (6.7, 8.2)	4.8 (4.0, 5.8)
mOS difference (mo)	2.6	



Dasari et al: Lancet, 2023

FRESCO (NCT02314819): Study Design

Phase 3, Conducted in China

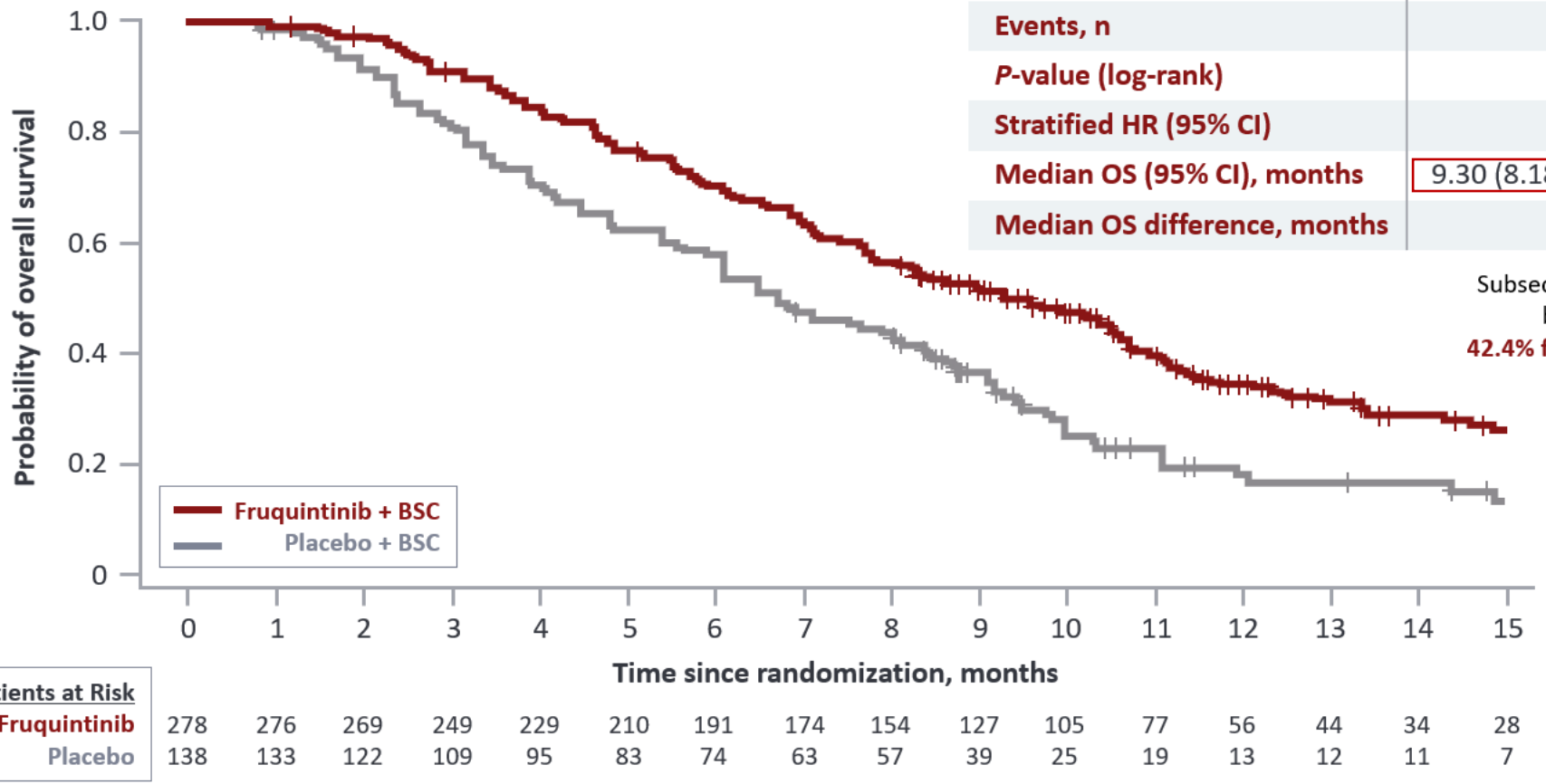


Primary endpoint	Secondary endpoints		Statistical assumptions
• Overall survival	**Key** • Progression-free survival • ORR • DCR	**Other** • DOR • Safety	**Sample size** • ~400 patients (280 OS events) would provide 80% power to detect a difference in OS with a HR of 0.70 at a 2-sided *P* value of 0.05 • Median OS assumption in the placebo arm is 6.3 months and median OS in fruquintinib arm is 9.0 months

Li et al: Jama, 2018

FRESCO: Primary Endpoint – Overall Survival (ITT Population)

	FRUQUINTINIB + BSC (N=278)	PLACEBO + BSC (N=138)
Median follow-up, months	13.3	13.2
Events, n	297	
P-value (log-rank)	<0.001	
Stratified HR (95% CI)	0.65 (0.51–0.83)	
Median OS (95% CI), months	9.30 (8.18–10.45)	6.57 (5.88–8.11)
Median OS difference, months	2.73	

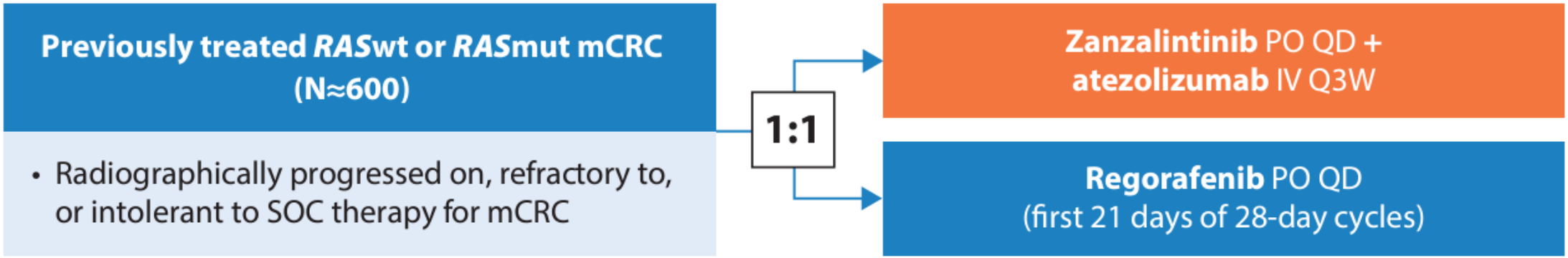


Patients at Risk																
Fruquintinib	278	276	269	249	229	210	191	174	154	127	105	77	56	44	34	28
Placebo	138	133	122	109	95	83	74	63	57	39	25	19	13	12	11	7

Subsequent anti-cancer medication between the two arms:
42.4% fruquintinib vs **50.7% placebo**

Li et al: Jama, 2018

Phase III Stellar 303: Refractory mCRC



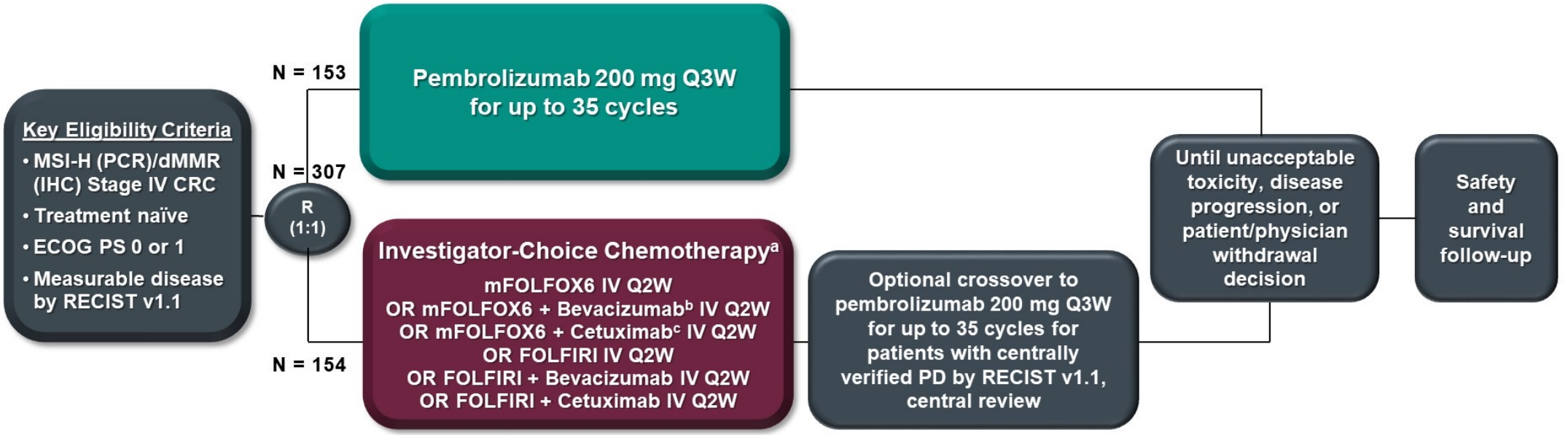
Endpoints N=874

Primary endpoint:	OS in the *RAS*wt population; OS in non-liver met pts (N=350)
Secondary endpoints:	PFS, ORR, and DOR per RECIST v1.1 by investigator, and OS in all randomized patients
Additional:	Safety

NCT05425940

Molecular Subsets in mCRC

KEYNOTE-177 Study Design
(NCT02563002)



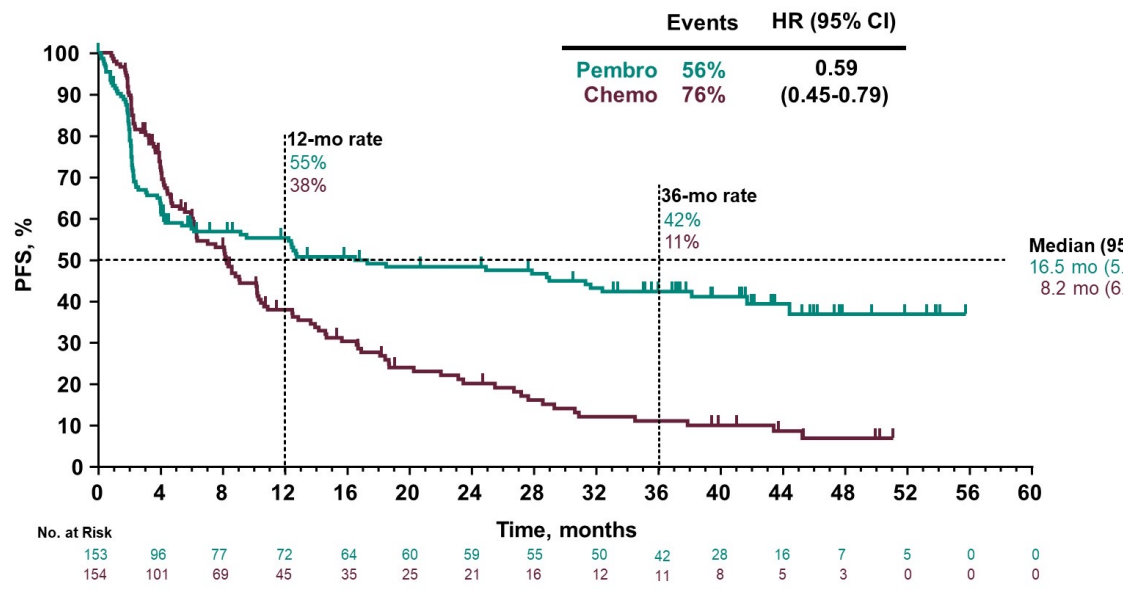
- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Andre et al: NEJM, 2022

Results of KN-177: MSI-High Tx Naïve mCRC

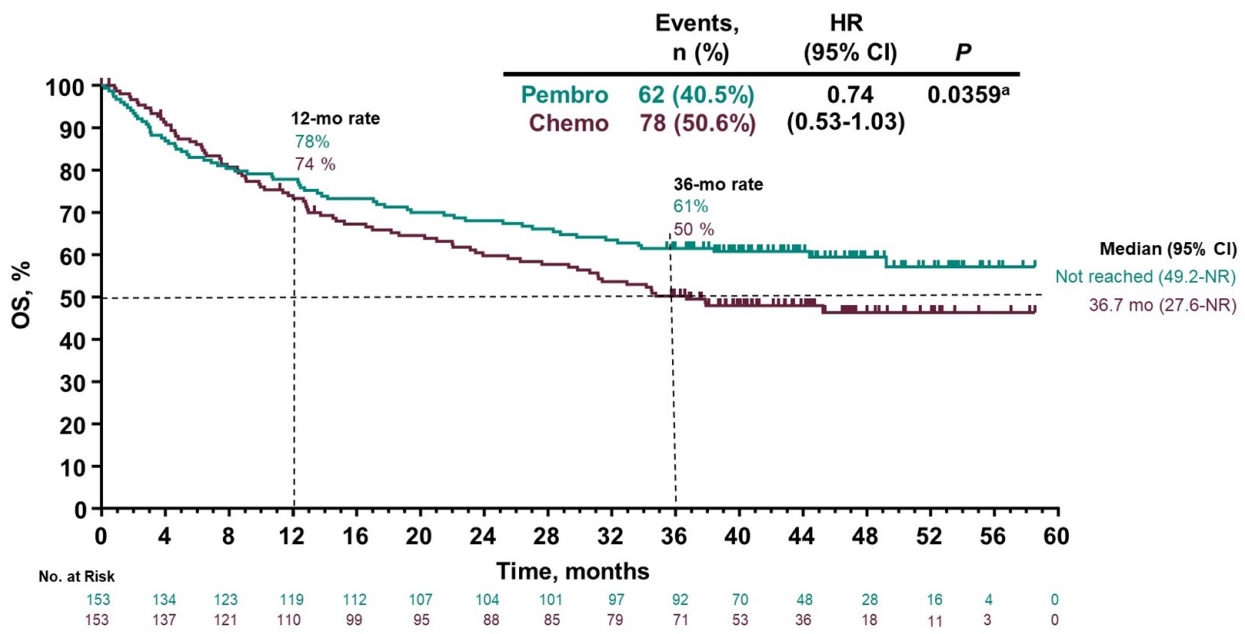
Progression-Free Survival



Data cut-off: 19Feb2021.

Andre KN177FA

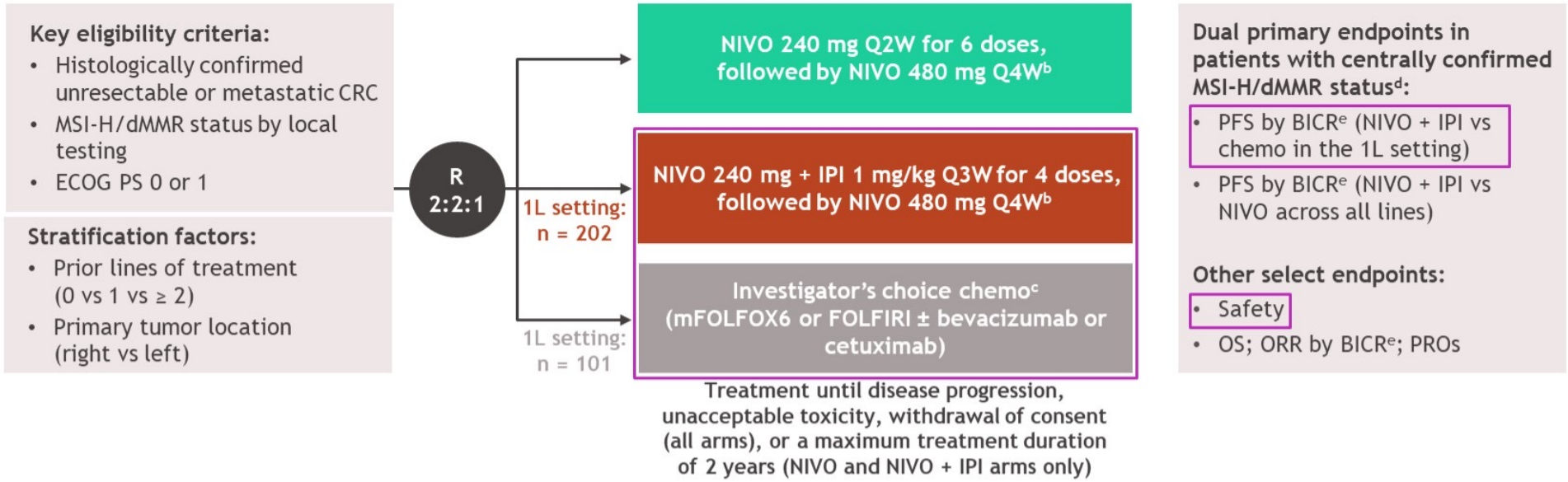
Overall Survival



Andre et al: NEJM, 2022

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

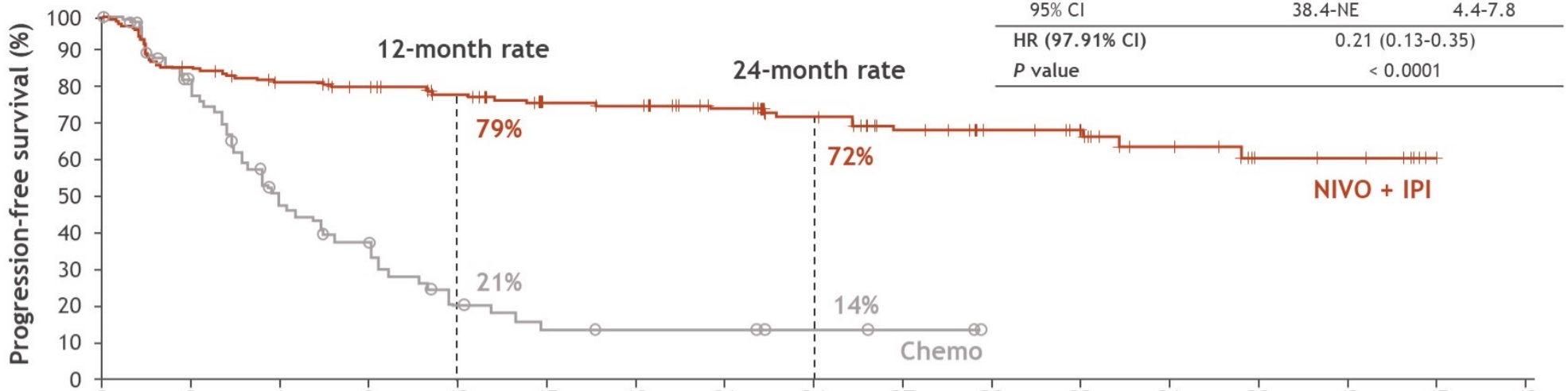


- At data cutoff (October 12, 2023), the median follow-up[f] was 24.3 months

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and last known date alive or death.

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	

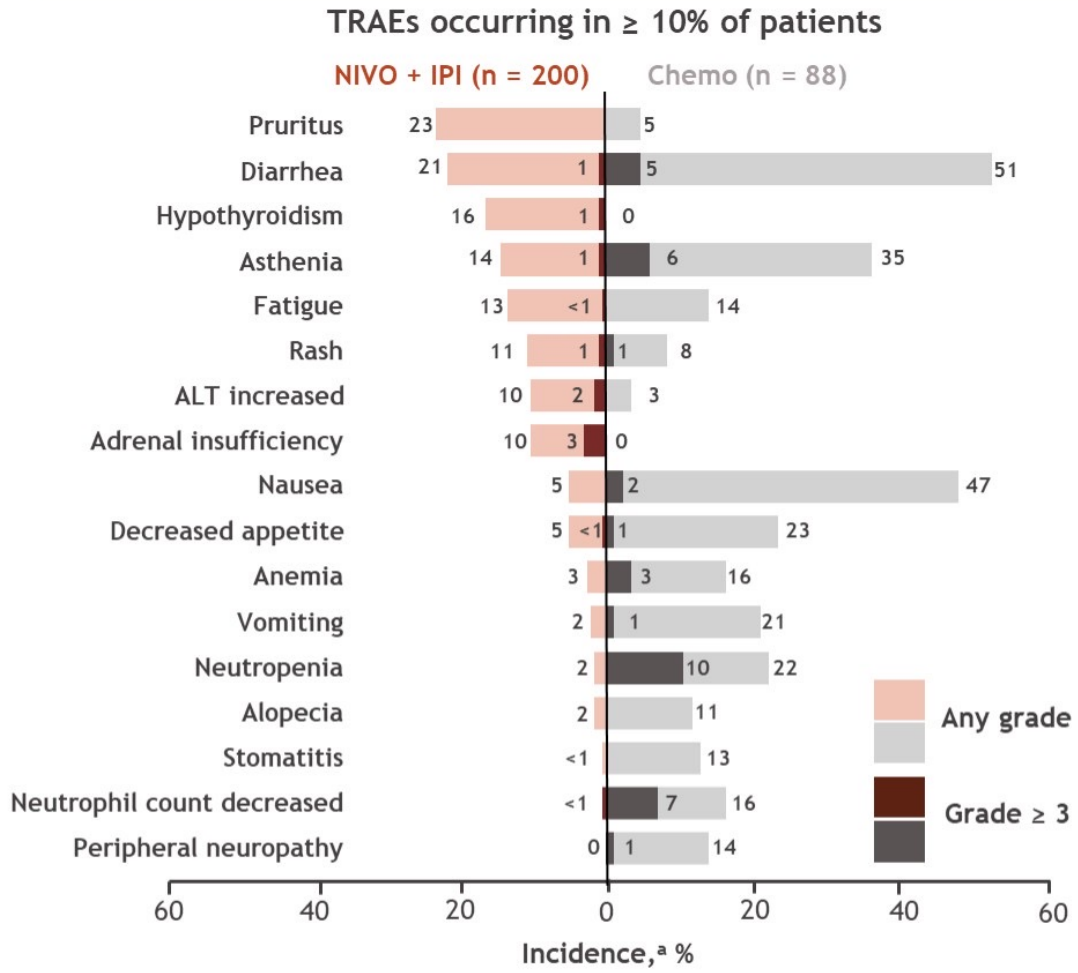


No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up, 24.3 months.

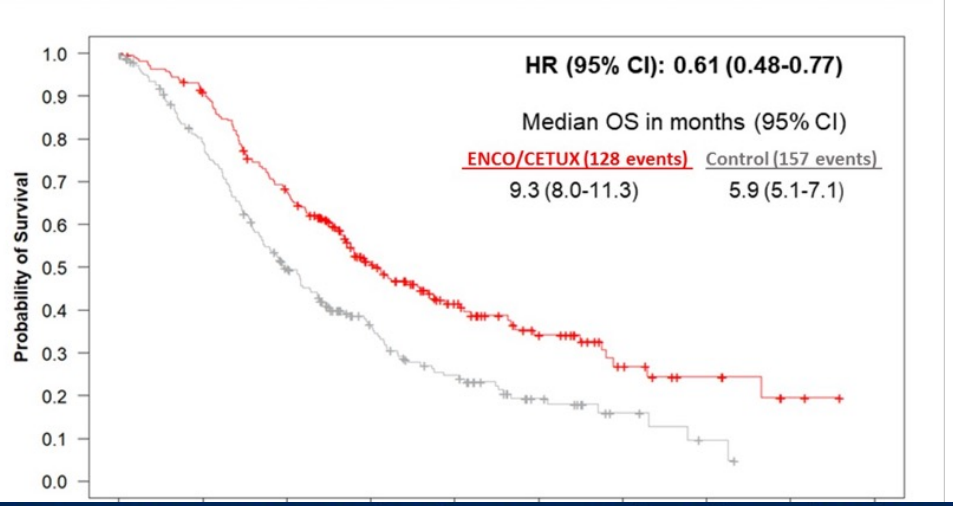
Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	
IMAEs,[d] n (%)				
Non-endocrine events				
Diarrhea/colitis	13 (7)	9 (5)	1 (1)	0
Hepatitis	11 (6)	6 (3)	0	0
Rash	11 (6)	3 (2)	0	0
Pneumonitis	4 (2)	3 (2)	0	0
Endocrine events				
Hypothyroidism/thyroiditis	34 (17)	3 (2)	1 (1)	0
Adrenal insufficiency	21 (11)	7 (4)	0	0
Hyperthyroidism	18 (9)	0	1 (1)	0
Hypophysitis	10 (5)	5 (3)	0	0

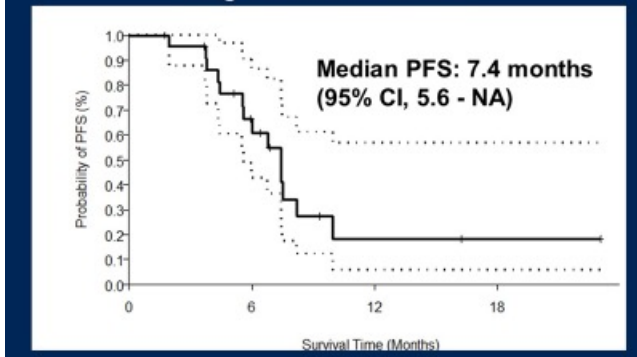
[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment. [d]Includes events reported within 100 days of last dose of study therapy reported in ≥ 2% of patients.

BRAF V600E MT Previously Treated MCRC

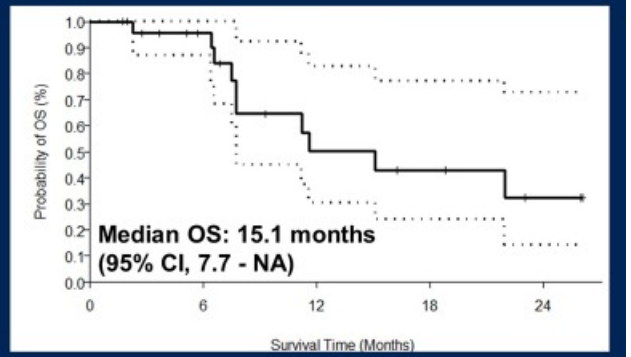


Survival outcomes: encorafenib + cetuximab + nivolumab

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

9

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

VANDERBILT-INGRAM CANCER CENTER

Study Design : Breakwater – Safety Lead In

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

***Arm B Folfox completed enrollment: FOLFIRI arm now enrolling**

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

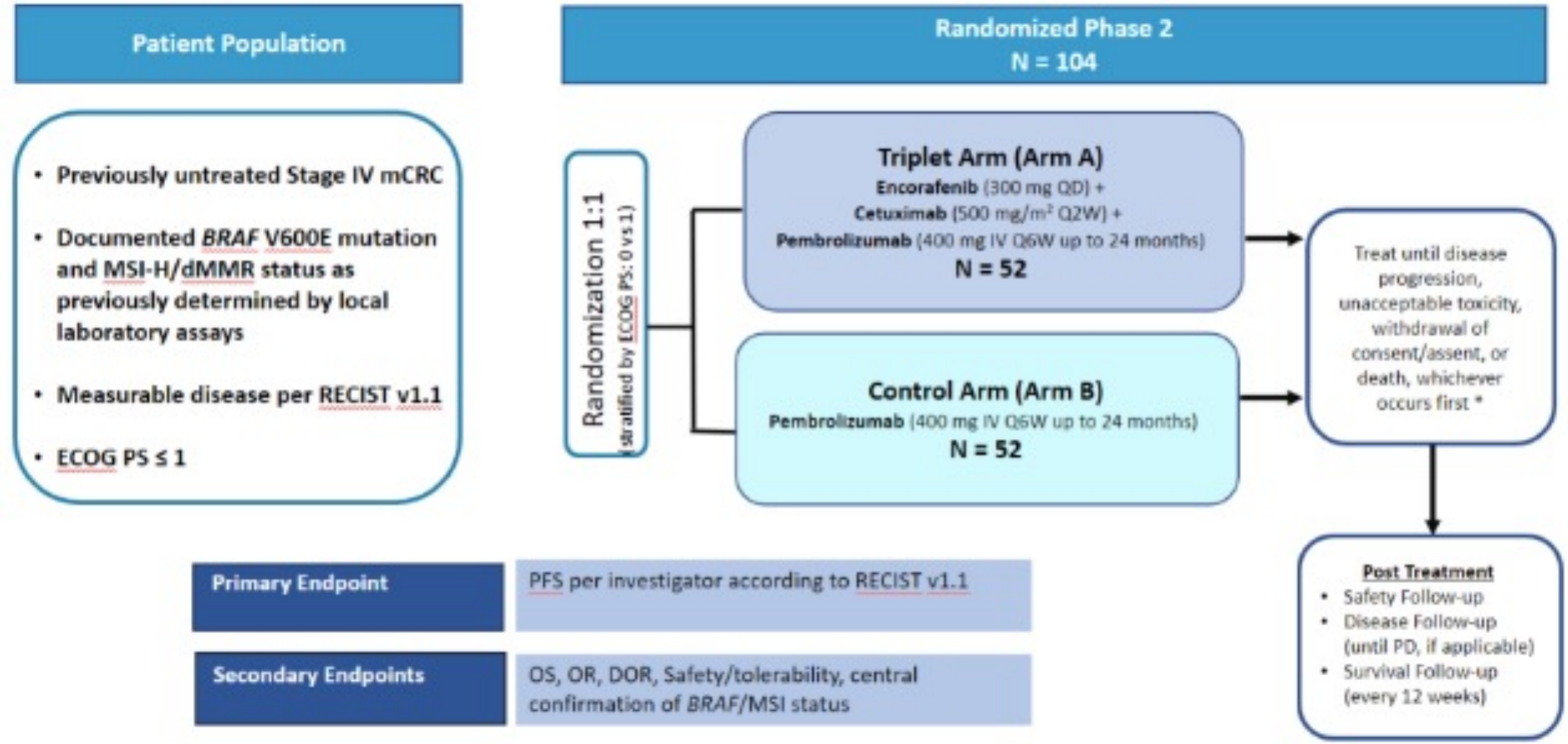
	1L		2L	
	EC + mFOLFOX6	EC + FOLFIRI	EC + mFOLFOX6	EC + FOLFIRI
Confirmed best overall response, n (%)	**n=19**	**n=12**	**n=8**	**n=18**
ORR, % (95% CI)	68.4 (46.0, 84.6)	75.0 (46.8, 91.1)	37.5 (13.7, 69.4)	44.4 (24.6, 66.3)
CR	1 (5.3)	2 (16.7)	0	1 (5.6)[a]
PR	12 (63.2)	7 (58.3)	3 (37.5)	7 (38.9)
SD	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.

MSI-H and BRAF V600E MT: SEAMARK



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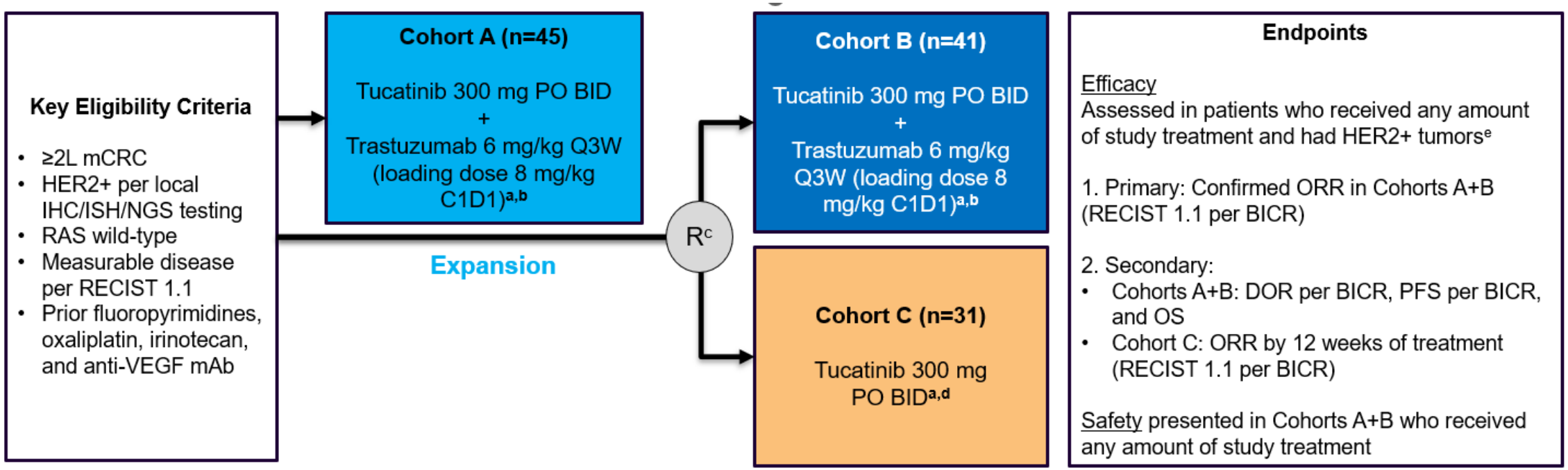
Moutaineer-02



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: NEJM, 2023

Tucatinib + Trastuzumab: Efficacy Outcomes

Responses	Tucatinib + Trastuzumab Cohorts A+B n=84
Best overall response per BICR[a], n (%)	
CR	3 (3.6)
PR	29 (34.5)
SD[b]	28 (33.3)
PD	22 (26.2)
Not available[c]	2 (2.4)
cORR per BICR, % (95% CI)[d]	**38.1 (27.7, 49.3)**
cORR per Investigator, % (95% CI)[d]	42.9 (32.1, 54.1)
Median time to objective response per BICR[e], months (range)	2.1 (1.2, 9.8)
DCR[f] per BICR, n (%)	60 (71.4)
Median DOR per BICR, months (95% CI)	**12.4 (8.5, 20.5)**

a Confirmed best overall response assessed per RECIST 1.1; b Includes SD and non-CR/non-PD; c Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e Time from the start of study treatment (Cohort A) or date of randomisation (Cohort B) to the first documentation of objective response (CR or PR that is subsequently confirmed); f Defined as sum of CR, PR, and SD

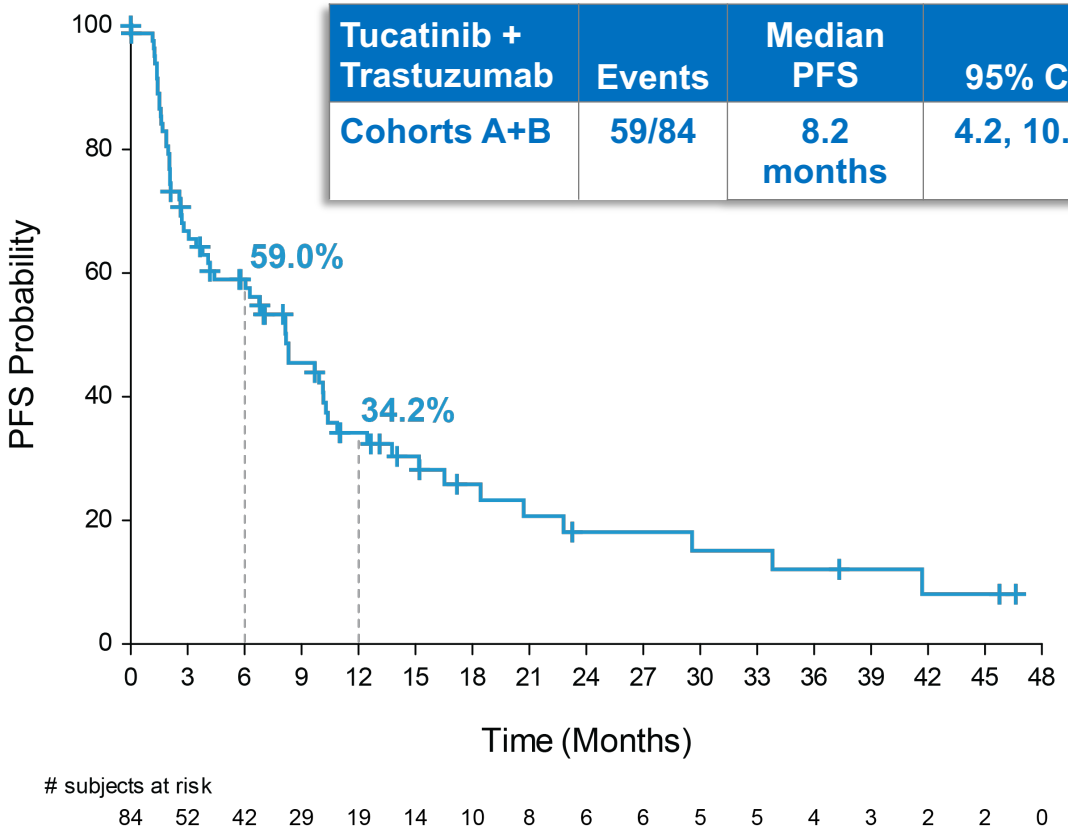
BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Data cutoff: 28 Mar 2022

Tucatinib + Trastuzumab: PFS and OS

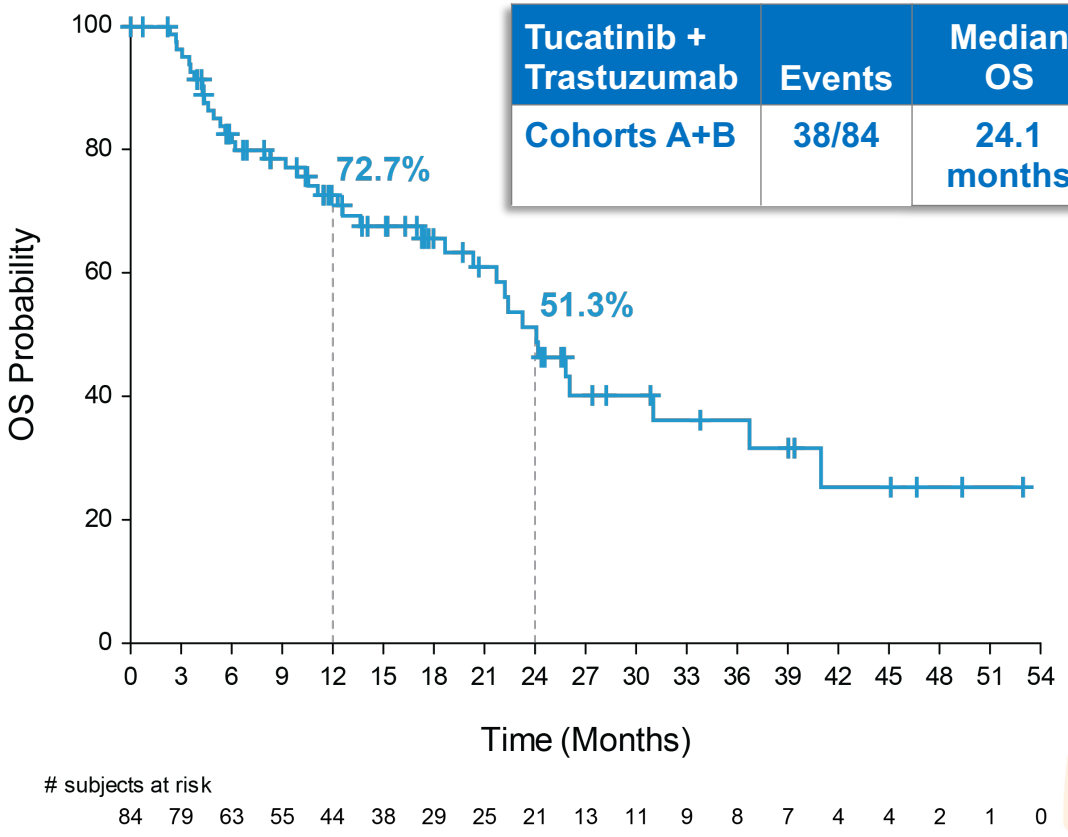
Progression-free Survival per BICR

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

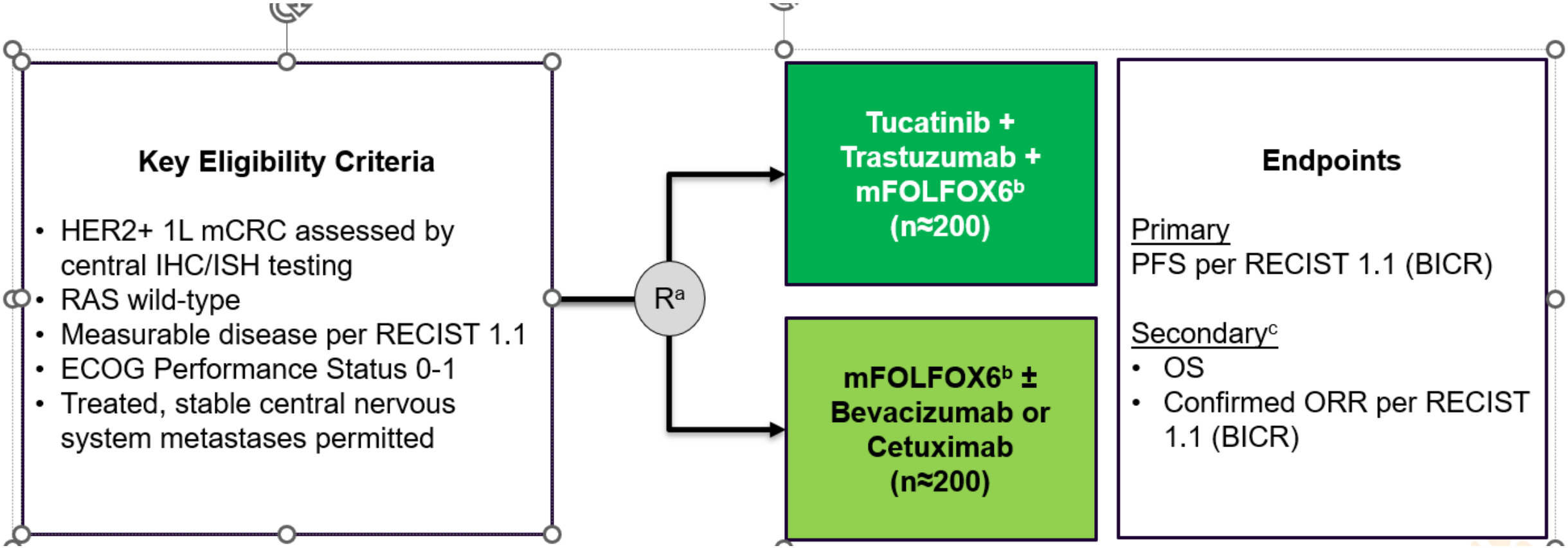


Median follow-up for Cohorts A+B was 20.7 months (IQR, 11.7, 39.0)

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

Data cutoff: 28 Mar 2022

Mountaineer - 03



https://clinicaltrials.gov/ct2/show/NCT05253651

CodeBreaK 300 Phase 3 Study Design

Global, randomized, open-label, active-controlled study of sotorasib + panitumumab in mCRC (NCT05198934)

Key eligibility criteria

- ≥ 18 years of age
- *KRAS* G12C–mutated mCRC, identified through central molecular testing
- ≥ 1 prior line of therapy for mCRC; progressed on or after fluoropyrimidine, irinotecan, and oxaliplatin*
- ECOG ≤ 2
- Measurable disease per RECIST 1.1
- No prior $KRAS^{G12C}$ inhibitor†

Stratified by: prior anti-angiogenic therapy (yes / no), **time from diagnosis of mCRC** (≥18 mo / <18 mo), **ECOG status** (0 or 1 / 2)

Randomization 1:1:1 (N = 160)

- **Sotorasib 960 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Sotorasib 240 mg daily + panitumumab 6 mg/kg 2QW (n = 53)**
- **Investigator's choice: trifluridine/tipiracil or regorafenib (n = 54)**

Treat until disease progression, start of another anti-cancer treatment, withdrawal of consent , or intolerance of treatment

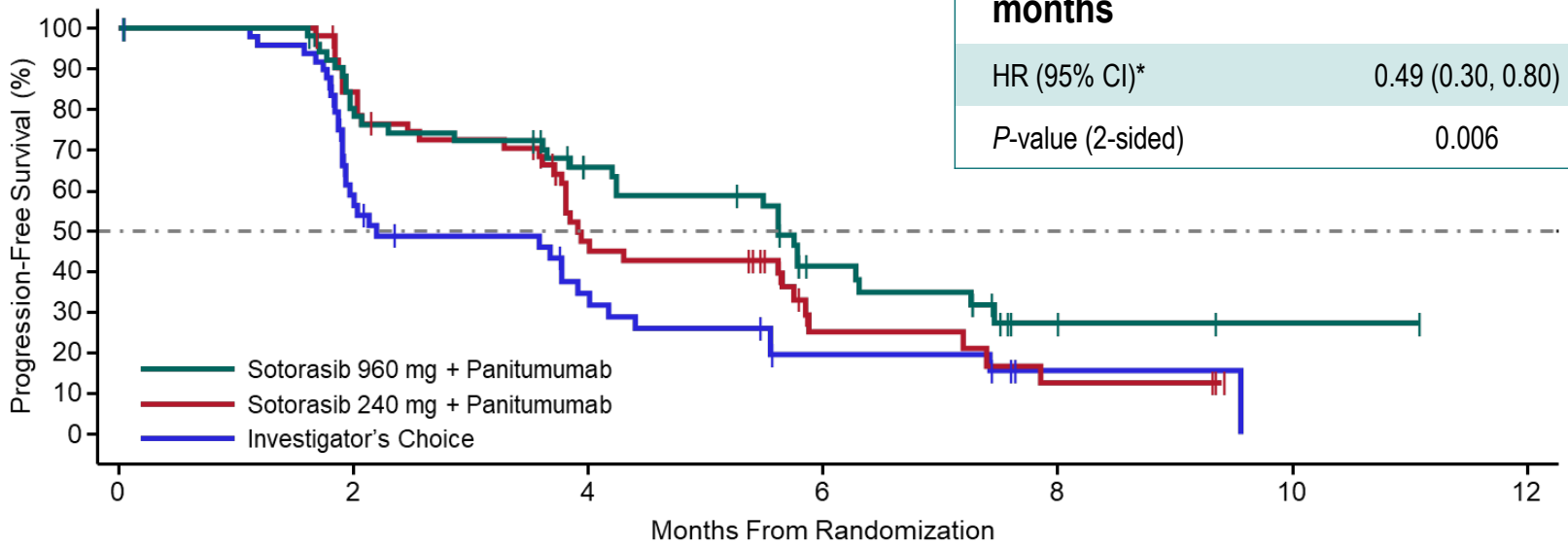
Primary endpoint: PFS by BICR (measured by CT / MRI and assessed by RECIST v1.1)
Key secondary endpoints: OS, ORR

*Patients deemed by the investigator not to be candidates for fluoropyrimidine, irinotecan, or oxaliplatin may still be eligible if ≥ 1 prior line of therapy was received for metastatic disease and trifluridine and tipiracil and/or regorafenib were deemed appropriate as 1st line of therapy. †Patients with prior treatment with trifluridine and tipiracil and with regorafenib were excluded, where the investigator's choice would be these agents.

2QW, every 2 weeks; BICR, blinded independent central review; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma; mCRC, metastatic colorectal cancer; MRI, magnetic resonance imaging; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary Endpoint: PFS in Intent-to-Treat Population

	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
Median PFS, months	**5.6**	**3.9**	**2.2**
HR (95% CI)*	0.49 (0.30, 0.80)	0.58 (0.36, 0.93)	–
P-value (2-sided)	0.006	0.030	–



Number of Patients at Risk:

Sotorasib 960 mg + Panitumumab	53	40	28	13	2	1	0
Sotorasib 240 mg + Panitumumab	53	43	20	6	3	0	
Investigator's Choice	54	24	12	5	1	0	

After a median follow-up of 7.8 months, sotorasib (960 mg and 240 mg) in combination with panitumumab significantly improved PFS by BICR versus investigator's choice

PFS was tested using stratified log-rank test. *HR is sotorasib 960 mg + panitumumab / investigator's choice therapy, or sotorasib 240 mg + panitumumab / investigator's choice therapy.
BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival.

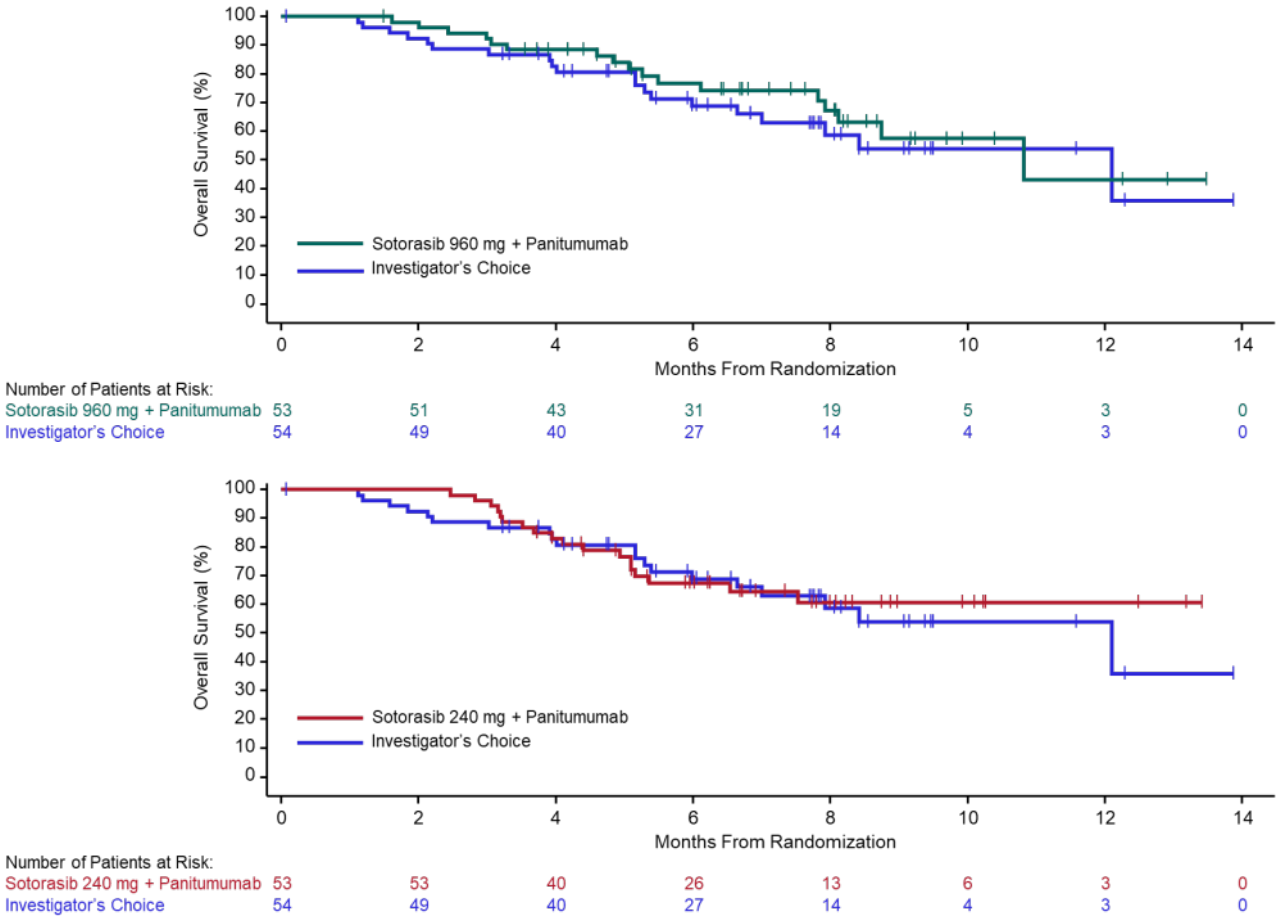
Activity Outcomes

Response by BICR	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
ORR, % (95% CI)*†	26 (15.3–40.3)	6 (1.2–15.7)	0 (0–6.6)
Complete response, n (%)	1 (2)	0	0
Partial response, n (%)	13 (25)	3 (6)	0
Stable disease, n (%)	24 (45)	33 (62)	25 (46)
Progressive disease, n (%)	12 (23)	13 (25)	17 (31)
Not evaluable / not done, n (%)	3 (6)	2 (4)	11 (20)
DCR, % (95% CI)*	72 (57.7–83.2)	68 (53.7–80.1)	46 (32.6–60.4)

ORR and DCR by BICR were higher with sotorasib (960 mg and 240 mg) + panitumumab versus investigator's choice

The intention-to-treat analysis set included all patients who underwent randomization.
*95% CIs were estimated using the Clopper-Pearson method. BICR, blinded independent central review; DCR, disease control rate; ORR, objective response rate
†Two patients (4%) in the 240 mg arm and 1 patient (2%) in the investigator's choice arm had non-complete response/non-progressive disease; these patients had BICR assessed non-target disease only

Overall Survival



	Sotorasib 960 mg + Panitumumab (n = 53)	Sotorasib 240 mg + Panitumumab (n = 53)	Investigator's Choice (n = 54)
HR (95% CI)*	**0.77 (0.41, 1.45)**	**0.91 (0.48, 1.71)**	–
Deaths, n (%)	17 (32)	18 (34)	20 (37)
Median follow-up, months (95% CI)	8.1 (6.7, 8.7)	7.7 (6.2, 8.3)	7.8 (6.5, 8.5)

Overall survival data were not mature at data cutoff, with 55 (34%) deaths observed

Survival rates were estimated using the Kaplan-Meier method.

*HR is sotorasib 960 mg + panitumumab / investigator's choice therapy, or sotorasib 240 mg + panitumumab / investigator's choice therapy. HR, hazard ratio.

The role of ctDNA in CRC

ASCO Gastrointestinal Cancers Symposium

Circulating tumor DNA (ctDNA) dynamics in colorectal cancer (CRC) patients with molecular residual disease: Updated analysis from GALAXY study in the CIRCULATE-JAPAN

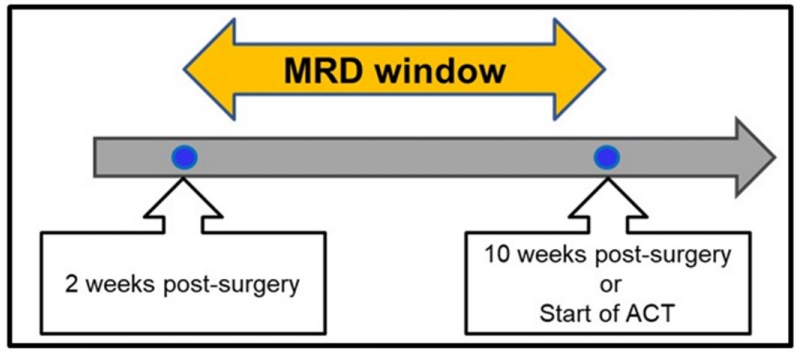
Presenting Author: Hiroki Yukami, MD, PhD

Co-authors: Yoshiaki Nakamura, Saori Mishima, Koji Ando, Hideaki Bando, Jun Watanabe, Keiji Hirata, Naoya Akazawa, Masataka Ikeda, Mitsuru Yokota, Kentaro Kato, George Laliotis, Vasily N. Aushev, Adham A. Jurdi, Minetta C. Liu, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Takayuki Yoshino

Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, Takatsuki, Japan; Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Colorectal Surgery, National Cancer Center Hospital East, Chiba, Japan; Department of Surgery, Gastroenterological Center, Yokohama City University Medical Center, Kanagawa, Japan; The Committee of Hereditary Colorectal Cancer of the Japanese Society for Cancer of the Colon and Rectum, Tokyo, Japan; Department of Gastroenterological Surgery, Sendai City Medical Center Sendai Open Hospital, Sendai, Japan; Division of lower GI surgery, Department of Gastroenterological Surgery, Hyogo Medical University, Nishinomiya, Japan; Department of General Surgery, Kurashiki Central Hospital, Okayama, Japan; Department of Surgery, Teine-Keijinkai Hospital, Sapporo, Japan; Natera, Inc., Austin, TX; National Cancer Center Hospital East, Kashiwa, Japan; Kyushu University, Fukuoka, Japan; Department of Surgery, Surgical Oncology and Science, Sapporo Medical University, Sapporo, Japan; National Hospital Organization, Osaka National Hospital, Osaka, Japan; Division of Drug and Diagnostic Development Promotion, Department for the Promotion of Drug and Diagnostic Development, National Cancer Center Hospital East, Kashiwa, Japan

Yukami et al: ASCO GI, 2024

DFS according to status in the MRD window in all stage

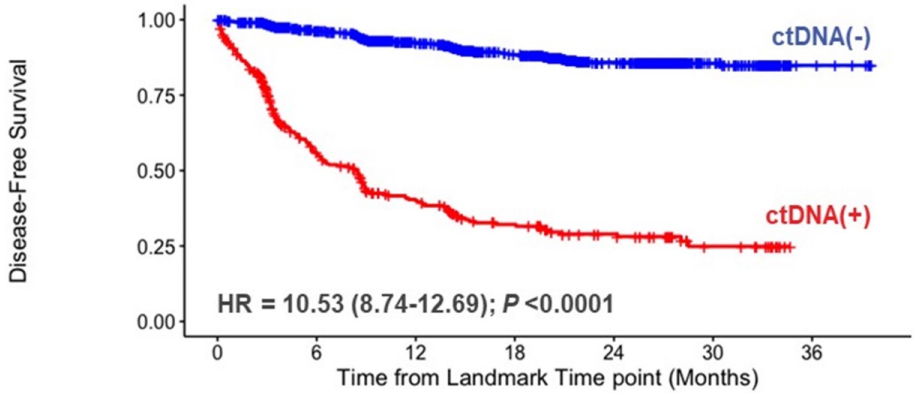


ACT: adjuvant chemotherapy

2,998 stage I-IV patients included in the outcome cohort

Excluded (N=138)
- DFS event prior to the 10 weeks landmark timepoint (n=138)

MRD Window analysis cohort (n=2,860)



Number at risk

ctDNA Negative	2491	2031	1441	1041	495	135	8
ctDNA Positive	369	165	98	59	35	13	0

ctDNA status	Negative	Positive
Events %	9.4 (235/2491)	58.8 (217/369)
24M-DFS % (95% CI)*	85.9 (83.9–87.7)	28.9 (23.4–34.8)

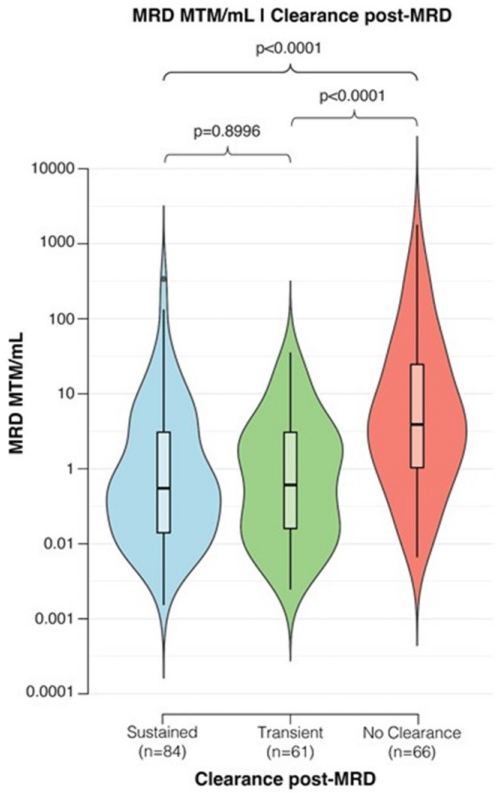
**DFS % from landmark time point*

MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

ctDNA-positive in the MRD window is predictive inferior DFS

Yukami et al: ASCO GI, 2024

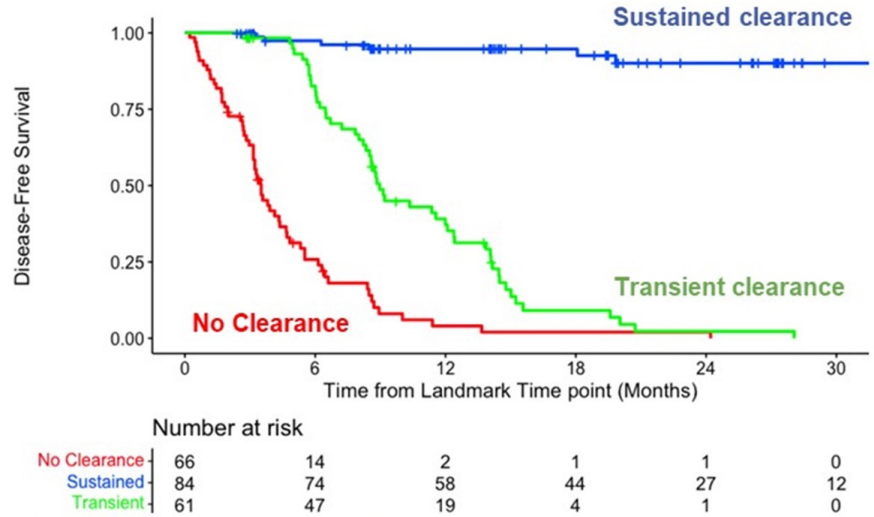
DFS according to ctDNA clearance in Patients with ctDNA positive in the MRD window



Group	Median MRD MTM/mL
Sustained	0.61
Transient	0.53
No Clearance	3.89

**P values from Wilcoxon rank-sum test*

Landmark 10 weeks post surgery



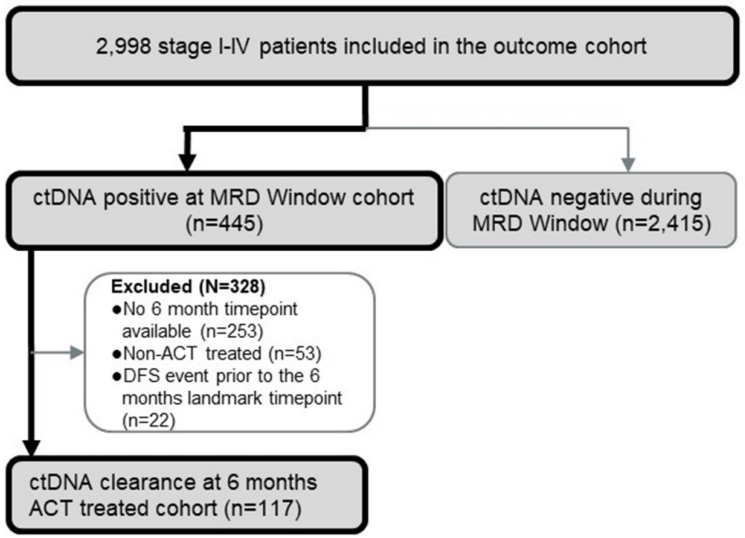
ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	7.1 (6/84)	85.2 (52/61)	89.4 (59/66)
Median DFS months (95% CI)	NR	9 (8.5–12.4)	3.5 (3.2–4.7)
24M-DFS % (95% CI)*	90.1 (78.6–95.6)	2.3 (0.02–10.3)	2 (0.02–9.2)
HR	**Reference**	**25.13**	**87.08**
95% CI	Not applicable	10.57–59.73	36.14–209.84
P	Not applicable	<0.0001	<0.0001

**DFS % from landmark time point*

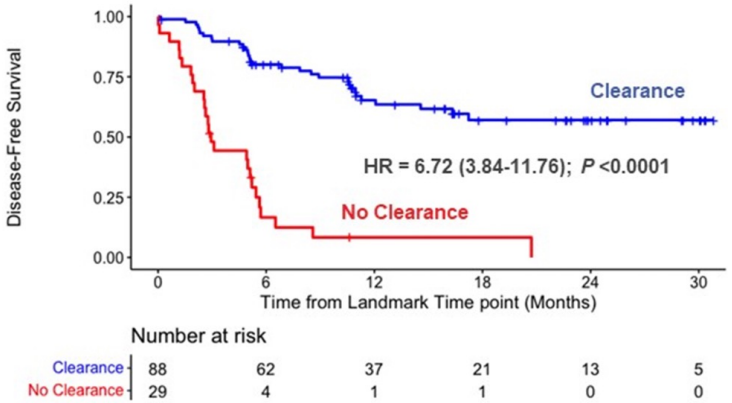
Sustained clearance indicates superior DFS compared to Transient or No clearance

Yukami et al: ASCO GI, 2024

Clearance and reduction in MTM/mL at 6 months in ACT treated patients

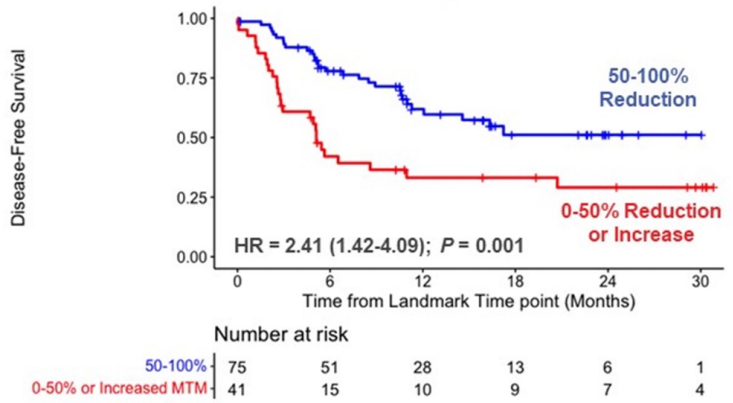


ctDNA clearance at 6 months



ctDNA Clearance	Clearance	No Clearance
Events %	35.2 (31/88)	89.7 (26/29)
24M-DFS % (95% CI)	57.1 (44–68.2)	NR

Positive at the MRD window to 6 months MTM/mL Reduction | ACT-treated



ctDNA Clearance	50-100% Reduction	0-50% Reduction or Increase
Events %	38.7 (29/75)	65.9 (27/41)
24M-DFS % (95% CI)	51.1 (36.4–64.1)	29 (15–44.6)

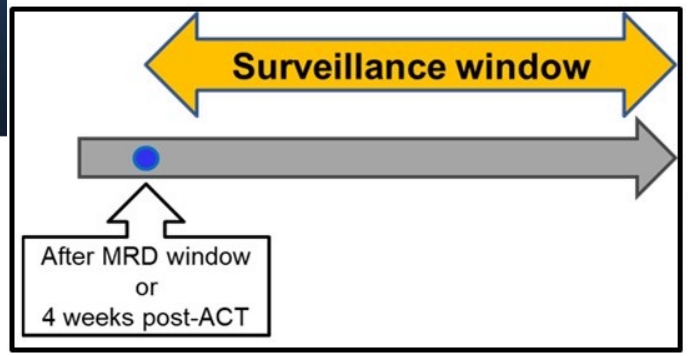
**DFS % from landmark time point*

Landmark 6 months post-surgery

ctDNA clearance and MTM/mL reduction on ACT is an indicator of treatment efficacy and results in better outcomes

Yukami et al: ASCO GI, 2024

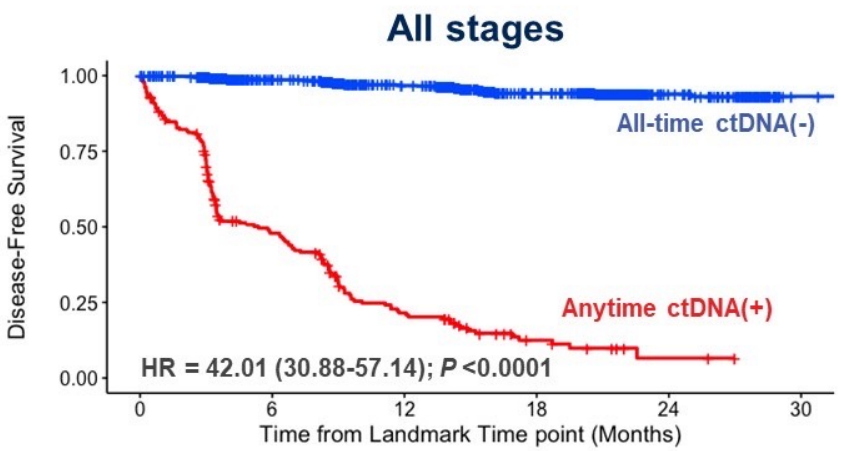
DFS according to ctDNA status in the Surveillance window



2,998 stage I-IV patients included in the outcome cohort

Excluded (N=1,212)
- No subsequent timepoints available (n=858)
- DFS event prior to the 8 months landmark timepoint (n=354)

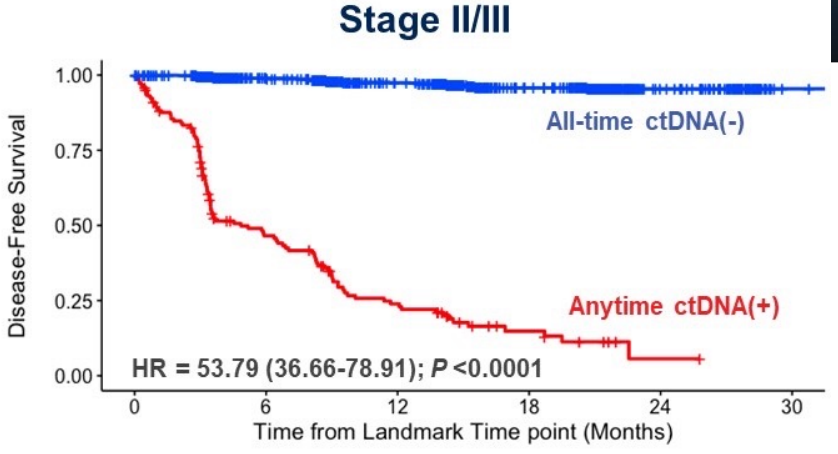
Surveillance Window analysis cohort (n=1,786)



Number at risk

ctDNA Negative	1582	1211	885	432	125	8
ctDNA Positive	204	84	33	10	2	0

ctDNA status	All-time Negative	Anytime Positive
Events %	3.7 (58/1582)	77.5 (158/204)
24M-DFS % (95% CI)*	93.9 (92–95.4)	6.6 (2–14.9)



Number at risk

ctDNA Negative	1326	1022	737	355	97	5
ctDNA Positive	146	57	26	9	1	0

ctDNA status	All-time Negative	Anytime Positive
Events %	2.7 (36/1326)	75.3 (110/146)
24M-DFS % (95% CI)*	95.4 (93.5–96.8)	5.6 (0.8–18.3)

DFS % from landmark time point

- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

ctDNA-positive in the surveillance window is predictive of inferior DFS

Yukami et al: ASCO GI, 2024

NRG ONCOLOGY

Advancing Research. Improving Lives.™

Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study

Van K. Morris[1], Greg Yothers[2], Scott Kopetz[1], Shannon L. Puhalla[3], Peter C. Lucas[2], Atif Iqbal[4], Patrick M Boland[5], Dustin A. Deming[6], Aaron J. Scott[7], Howard J Lim[8], Theodore S. Hong[9], Norman Wolmark[2], Thomas J. George[10]

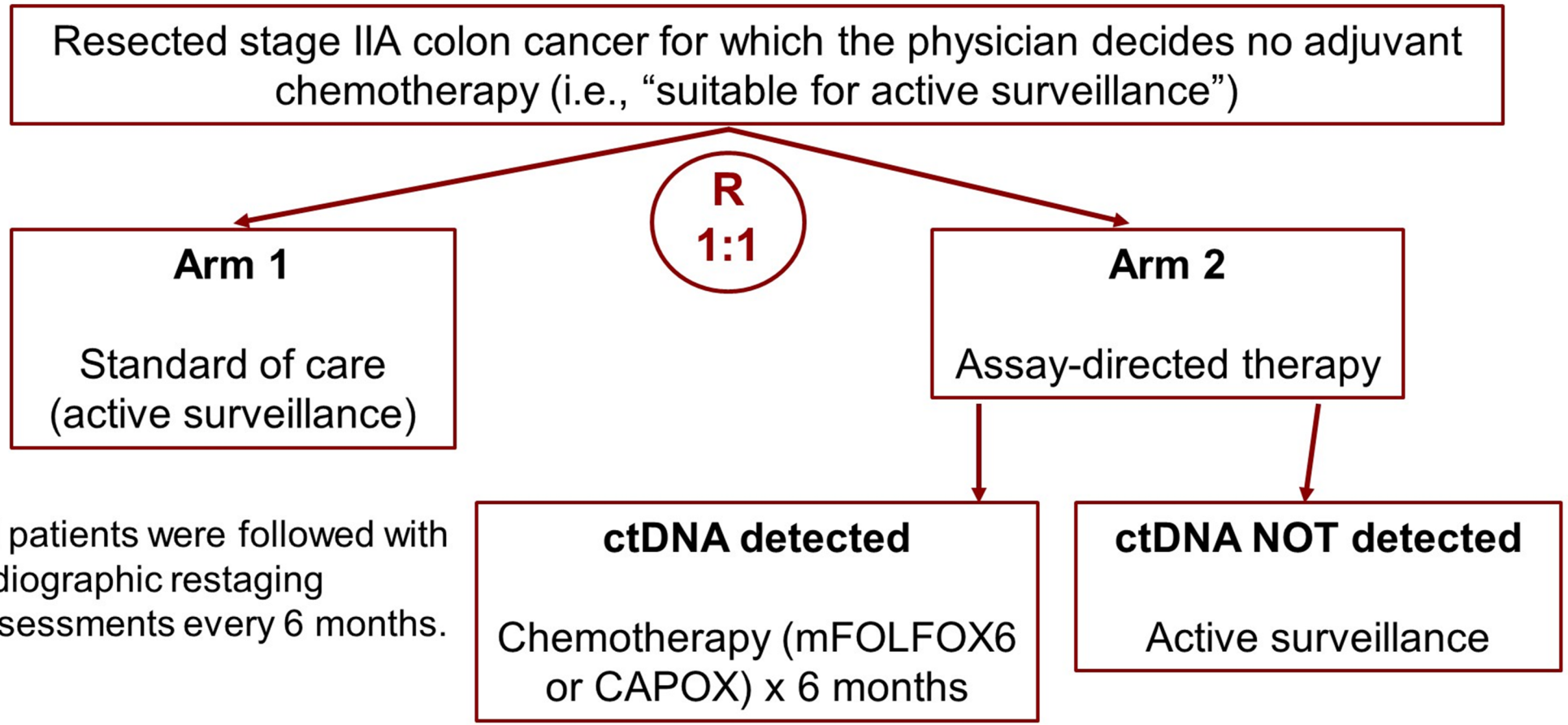
[1]The University of Texas -- MD Anderson Cancer Center; [2]NSABP Foundation, Inc.; [3]UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine; [4]Baylor College of Medicine; [5]Rutgers Cancer Institute of New Jersey; [6]University of Wisconsin; [7]University of Arizona Cancer Center; [8]BC Cancer - Vancouver, University of British Columbia; [9]Massachusetts General Hospital Cancer Center, Harvard Medical School; [10]UF Health Cancer Center, Gainesville, FL

January 20, 2024

NCI National Clinical Trials Network — a National Cancer Institute program

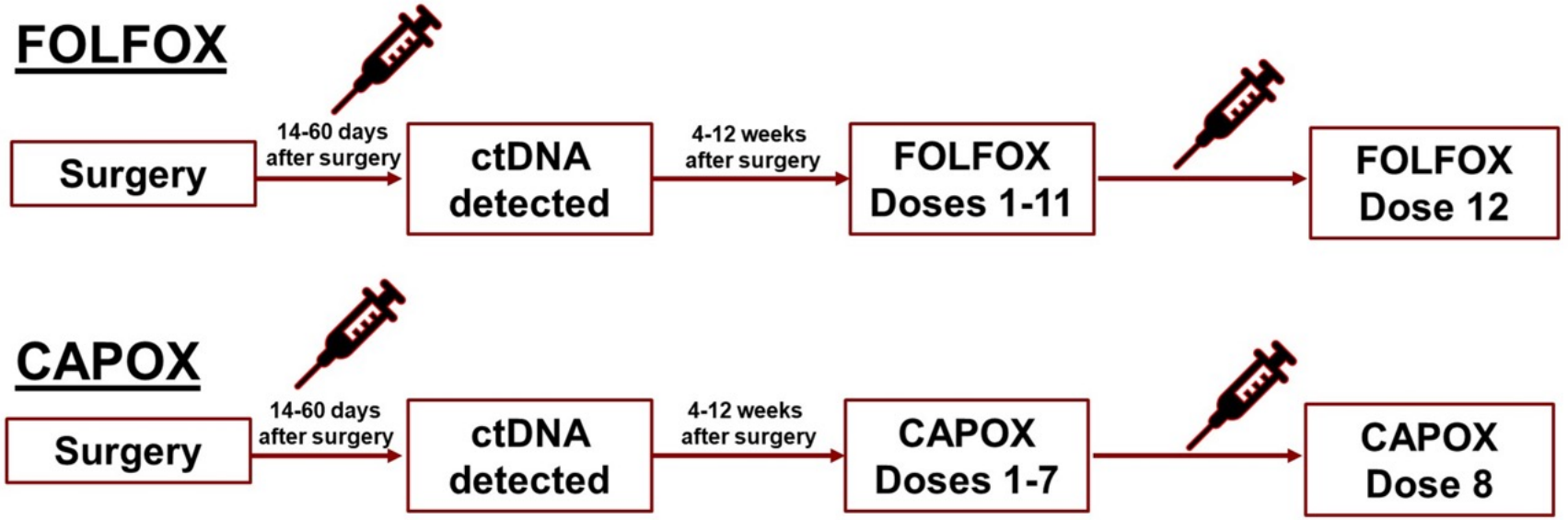
NCI Community Oncology Research Program — A program of the National Cancer Institute of the National Institutes of Health

NRG-GI005 (COBRA) Study Schema



Morris et al: ASCO GI 2024

Treatment schema: Arm 2 “ctDNA detected”



The 6-month timepoint was collected two weeks after prior dose of chemotherapy/ immediately prior to the administration of the last dose of chemotherapy.

Morris et al: ASCO GI 2024

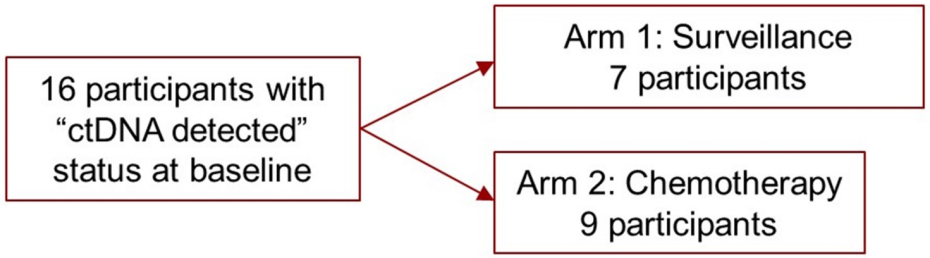
The assay and changes over time

	Guardant Reveal (original technology)	Guardant Reveal (updated technology)
Indication	CRC	CRC, Lung, Breast (others in development)
Bioinformatics MRD Calling	Combined genomic (CH filter) + epigenomic	Epigenomic only
Panel Size for MRD Calling	45kb genomic + 450 kb epigenomic	15 Mb epigenomic
CLIA Reporting	ctDNA detected vs. not detected	ctDNA detected vs. not detected & Quantification
Clinical Performance in CRC*:		
Sample Specificity	>93-100%[1,2]	>98%**[3]
Single Sample Post-Treatment Sensitivity	44-56% (landmark)[1,2]	45% (post-op)[3]
Longitudinal Sampling Sensitivity	62-91%[1,2]	80%[3]

*Data in breast cancer available: Janni et al. *SABCS 2023* (Abstract #PS06-06)
1 – Parikh et al *Clin Cancer Res (2021)* 27(20):5586-5594; 2 – Slater et al. *ASCO GI 2023* (Abstract #169) 3 – Nakamura et al. *ASCO GI 2024* (Abstract #180)

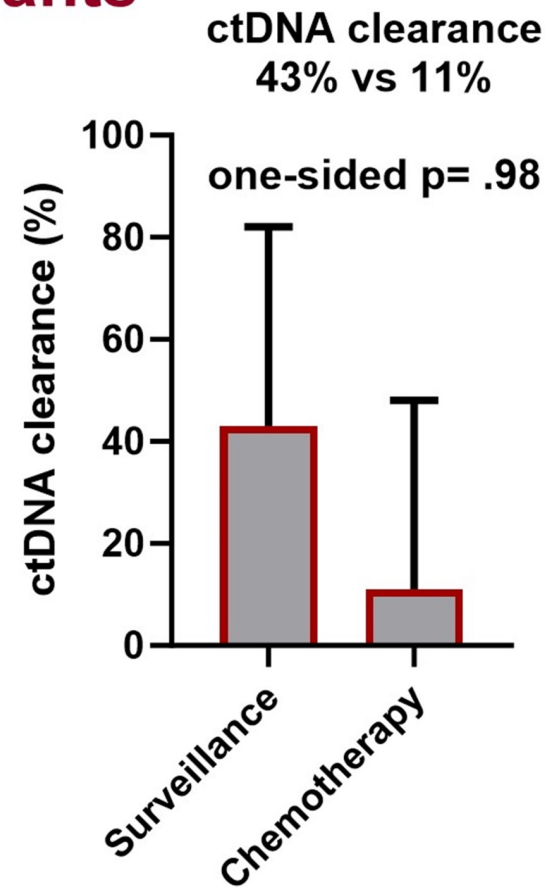
Phase II Endpoint Analysis: ctDNA(+) baseline participants

- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).

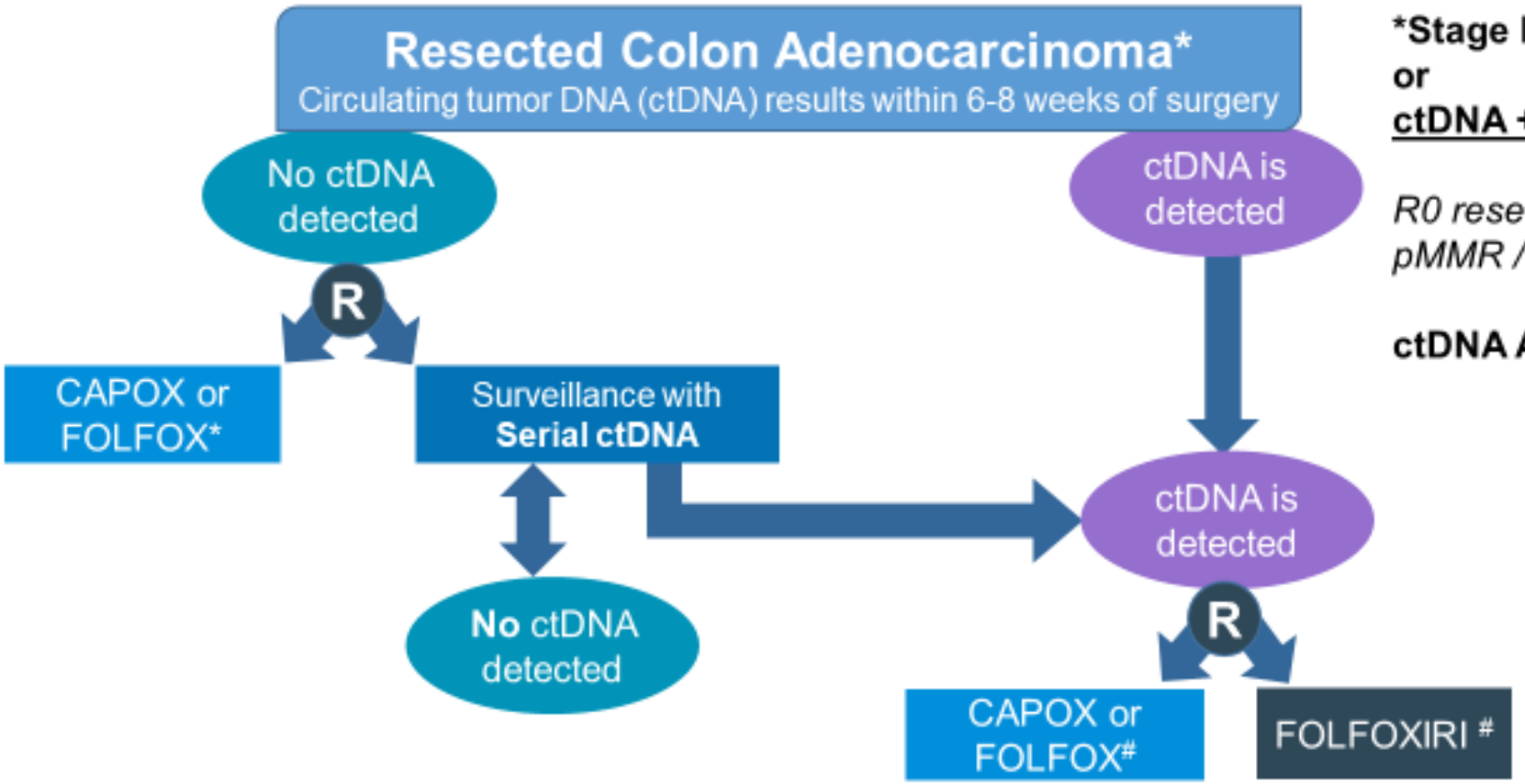


- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeded 0.35, H_o was not rejected, and the decision rule calls for early stopping due to futility.**



Morris et al: ASCO GI 2024



***Stage III (T1-3, N1/N1c)**
or
ctDNA +ve Stage II or Stage IIIC

R0 resection
pMMR / MSS

ctDNA Assay: Signatera

PIs:
Arvind Dasari (MDACC – NRG)
Christopher Lieu (UCCC – SWOG)

*: Duration and regimen per physician discretion
#: 6 months duration

NRG-GI008

NCT05174169

Thank you for your attention!

Contact Info: cathy.eng@vumc.org
Twitter: @cathyengmd
FB: cathy eng-mdcancer
www.youngadultswithcancer.com

NCT05174169

Conclusions:

- Molecular testing should be conducted in all patients
- COBRA demonstrates the challenges in an evolving field.
  - ctDNA remains exploratory but demonstrates the impact on prognosis