Recent Practice Changing Clinical Trials in Colorectal Cancer

April 12, 2025

South Florida GI Cancer Symposium

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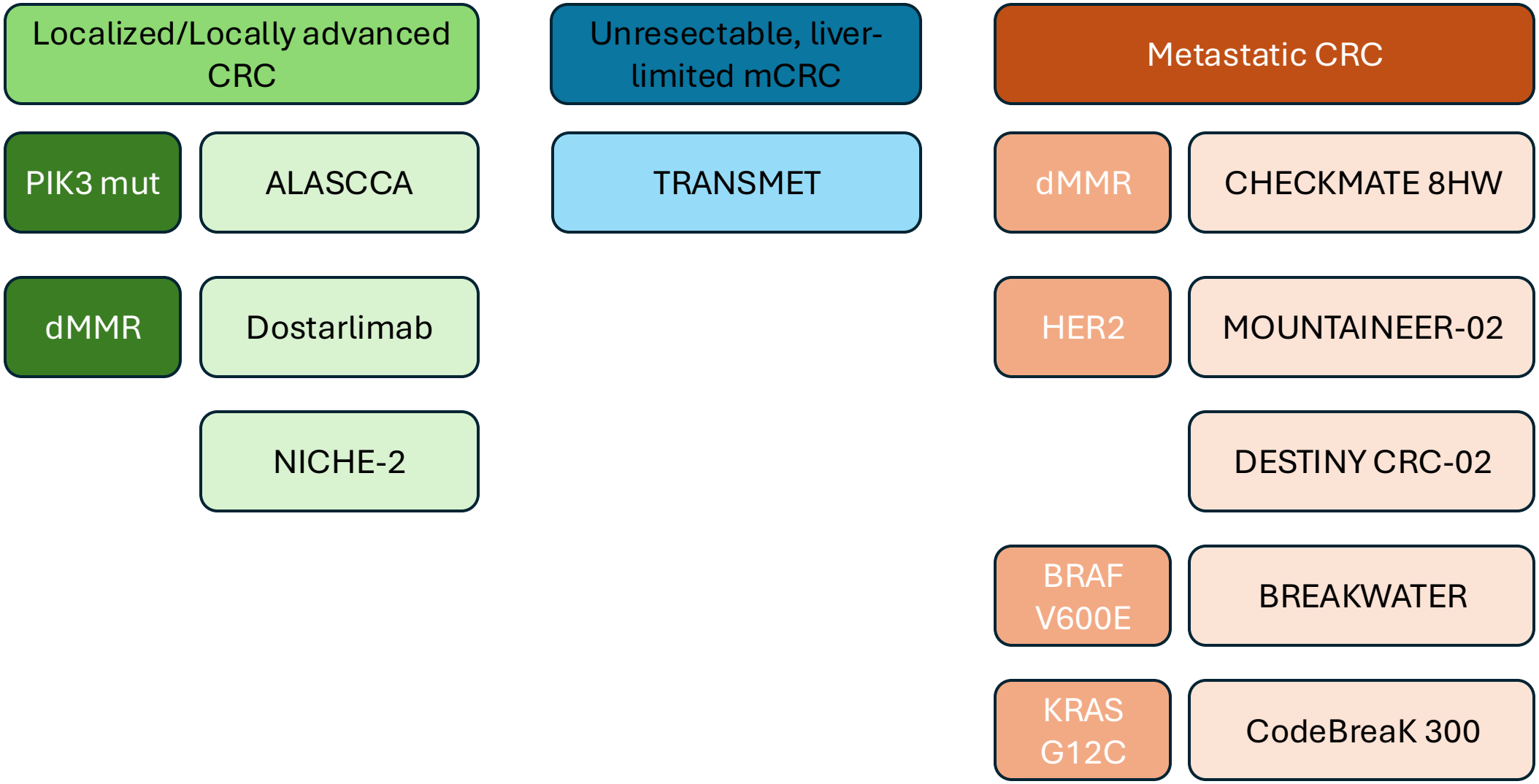
Outline


Localized/Locally advanced CRC
PIK3 mut
ALASCCA
dMMR
Dostarlimab
NICHE-2
Unresectable, liver-limited mCRC
TRANSMET
Metastatic CRC
dMMR
CHECKMATE 8HW
HER2
MOUNTAINEER-02
DESTINY CRC-02
BRAF V600E
BREAKWATER
KRAS G12C
CodeBreaK 300

The ALASCCA Trial (NCT02647099)

ALASCCA
Adjuvant ASA vid kolorektalcancer

N=3,508 screened for alteration in PI3K pathway: Rectal cancer pTNM I-III, Colon cancer pTNM II-III, 18-80y

37%

N=515 PIK3CA exon 9/20

N=314 Randomized Group A

N=157 Aspirin 160 mg daily for 3 years

N=157 Placebo daily for 3 years

N=588 PIK3R1/PTEN/ other PIK3CA

N=312 Randomized Group B

N=156 Aspirin 160 mg daily for 3 years

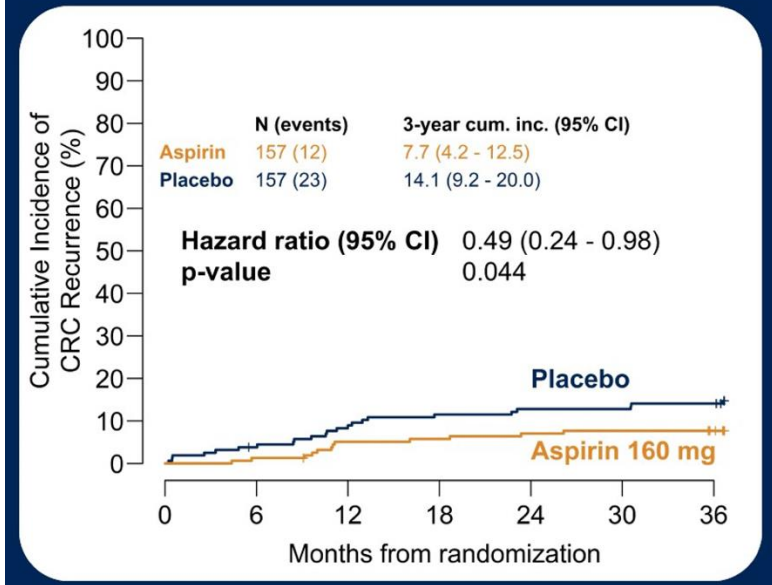
N=156 Placebo daily for 3 years

Primary outcome:
Time to CRC recurrence (TTR) in Group A

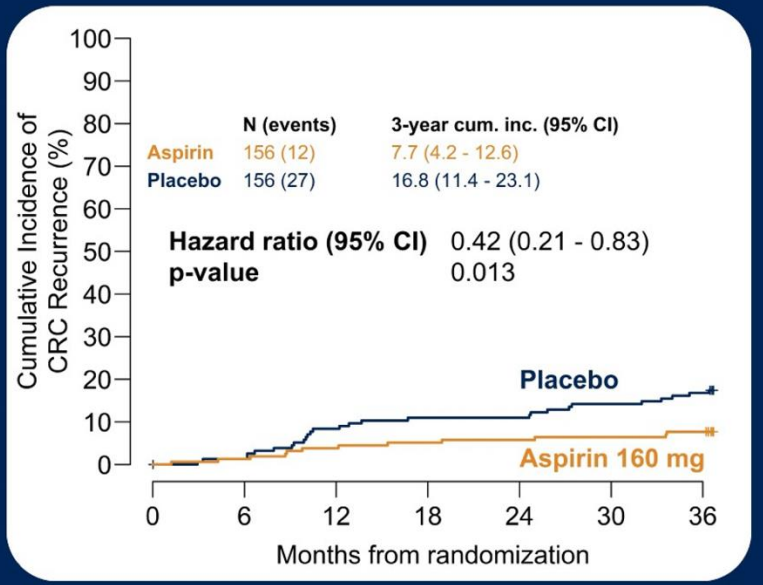
Secondary outcomes:
- Disease-Free Survival (DFS) in Group A
- TTR in Group B
- DFS in Group B
- Safety

Primary Outcome: CRC Recurrence

Group A (PIK3CA Exons 9/20)



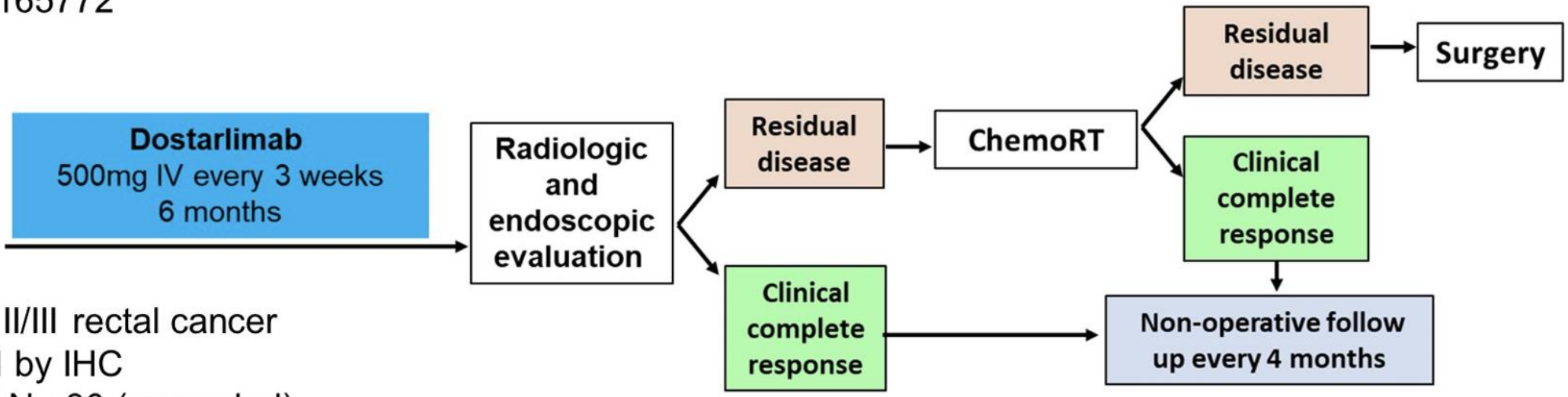
Group B (PIK3R1/PTEN/Other PIK3CA)



Slides: ASCO GI 2025

Neoadjuvant PD-1 blockade in Locally Advanced Mismatch Repair–Deficient Rectal Cancer

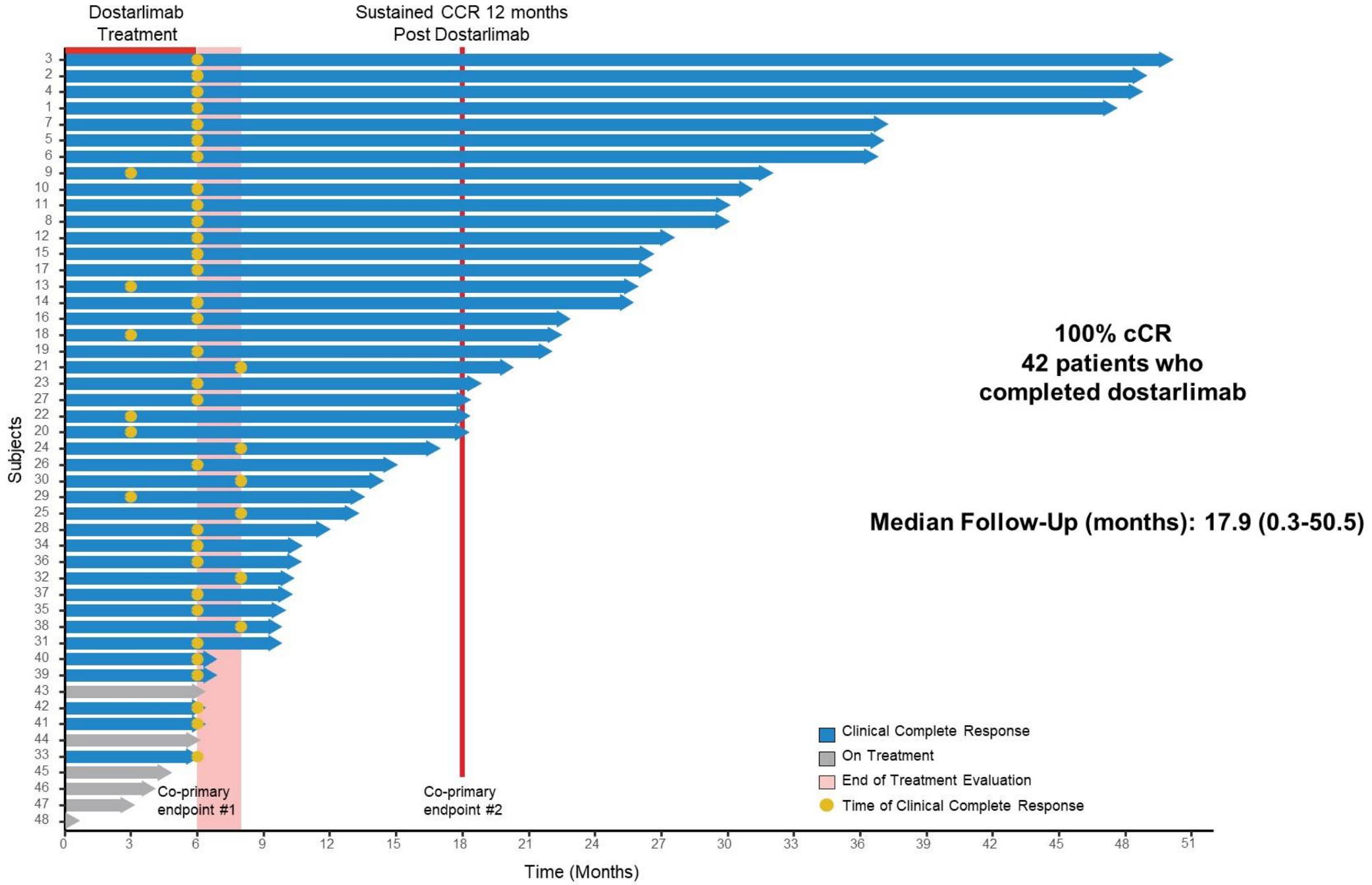
NCT04165772



Stage II/III rectal cancer
MMRd by IHC
Target N= 30 (expanded)

Primary Endpoints:

- ORR after completion of PD-1 alone or in combination with chemoRT
- pCR or sustained cCR for 12 mo after completion of PD1 alone or in combination with chemoRT



Slide: ASCO 2024

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer (NICHE-2)

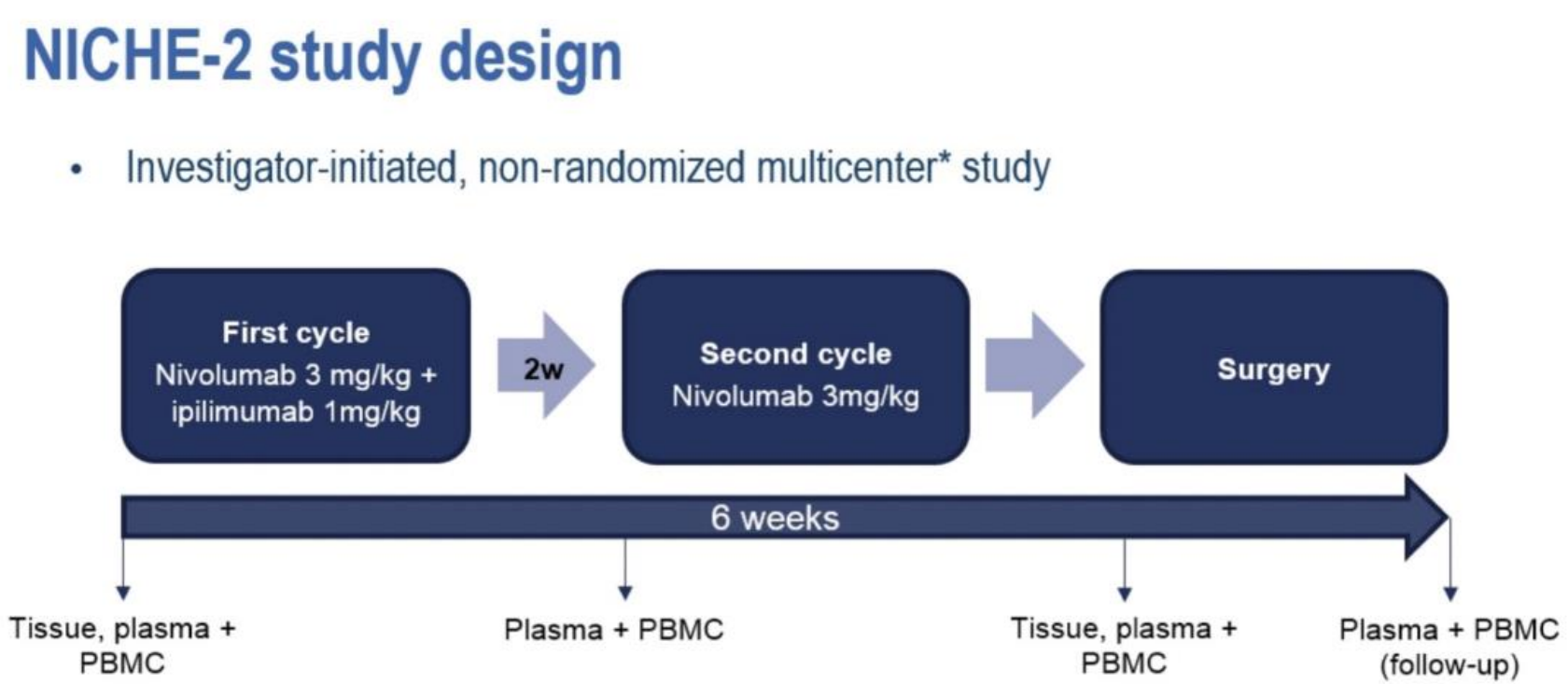


Figure: ESMO 2022

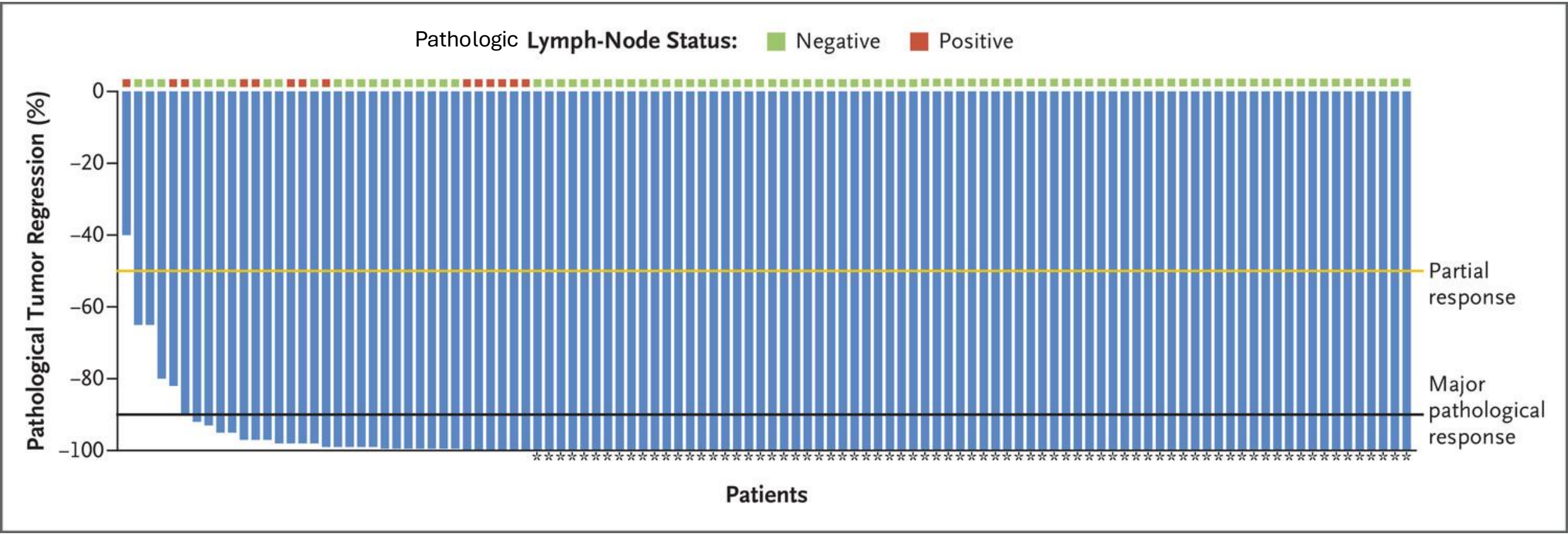
Table 1. Demographic and Disease Characteristics of the Patients.

Characteristic	Patients (N=115)
Female sex — no. (%)	67 (58)
Median age (range) — yr	60 (20–82)
WHO performance-status score — no. (%)*	
0	100 (87)
1	15 (13)
Race or ethnic group — no. (%)†	
White	97 (84)
Asian	6 (5)
Black	5 (4)
Other	7 (6)
Tumor stage — no. (%)‡	
cT2	17 (15)
cT3 or cT3–T4a	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status — no. (%)§	
cN–	38 (33)
cN+	77 (67)
Primary tumor location — no. (%)	
Right	78 (68)
Transverse	17 (15)
Left	20 (17)
Lynch syndrome — no. (%)	37 (32)
Unexplained dMMR — no. (%)¶	2 (2)
Non–Lynch syndrome dMMR — no. (%)	76 (66)

* The World Health Organization (WHO) performance-status score ranges from 0 to 5, with higher scores indicating greater disability.
† Race or ethnic group was reported by the patients or inferred on the basis of the country of birth if patient-reported data were unavailable. The category "Other" includes patients of Hispanic, Middle Eastern, and North African descent.
‡ Tumor stage was classified according to the American Joint Committee on Cancer staging system, version 8, with higher numbers indicating a more advanced tumor.
§ Nodal status indicates the presence (cN+) or absence (cN–) of cancer cells in the lymph nodes.
¶ Unexplained mismatch repair deficiency (dMMR) was specified as dMMR that could not be explained by characteristic germline alterations, biallelic somatic inactivation of the MMR protein, or *MLH1* promoter hypermethylation.

Table: NEJM 2024

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer (NICHE-2)



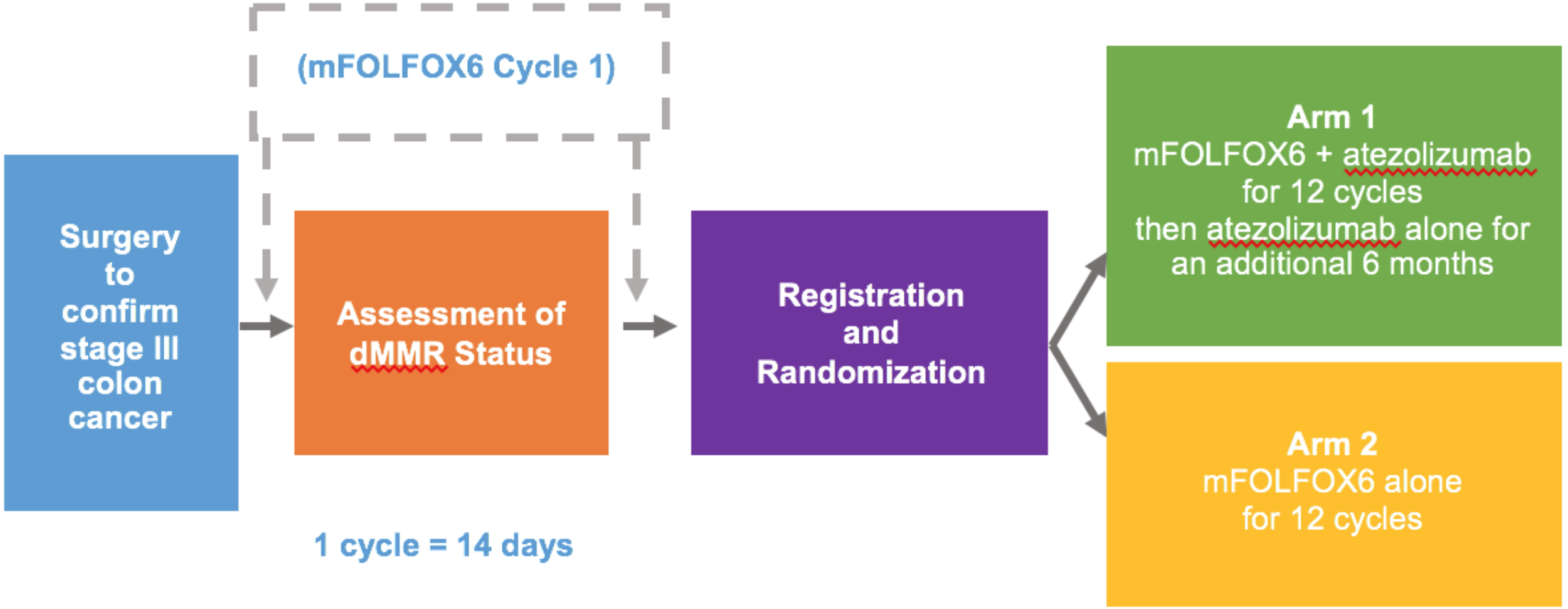
- 3 patients received adjuvant chemotherapy
- With a median follow-up of 26.2 months (range, 9.1 to 65.3), no disease recurrences have been observed.
- All 37 patients with a follow-up of longer than 36 months remain disease-free.

N Engl J Med 2024;390:1949-58. DOI: 10.1056/NEJMoa2400634

Neoadjuvant IO for dMMR localized CRC: remaining questions

- Neoadjuvant versus adjuvant treatment
- Dual versus single-agent immune checkpoint inhibitor
  - Novel checkpoint inhibitors
- Optimal duration of treatment
- Non-operative management in colon cancer

Awaiting results: ATOMIC trial



NEOPRISM-CRC Study Design

32 Patients
- Radiological high-risk stage II or stage III CRC
- ECOG PS 0-1
- dMMR by IHC or MSI-H by PCR

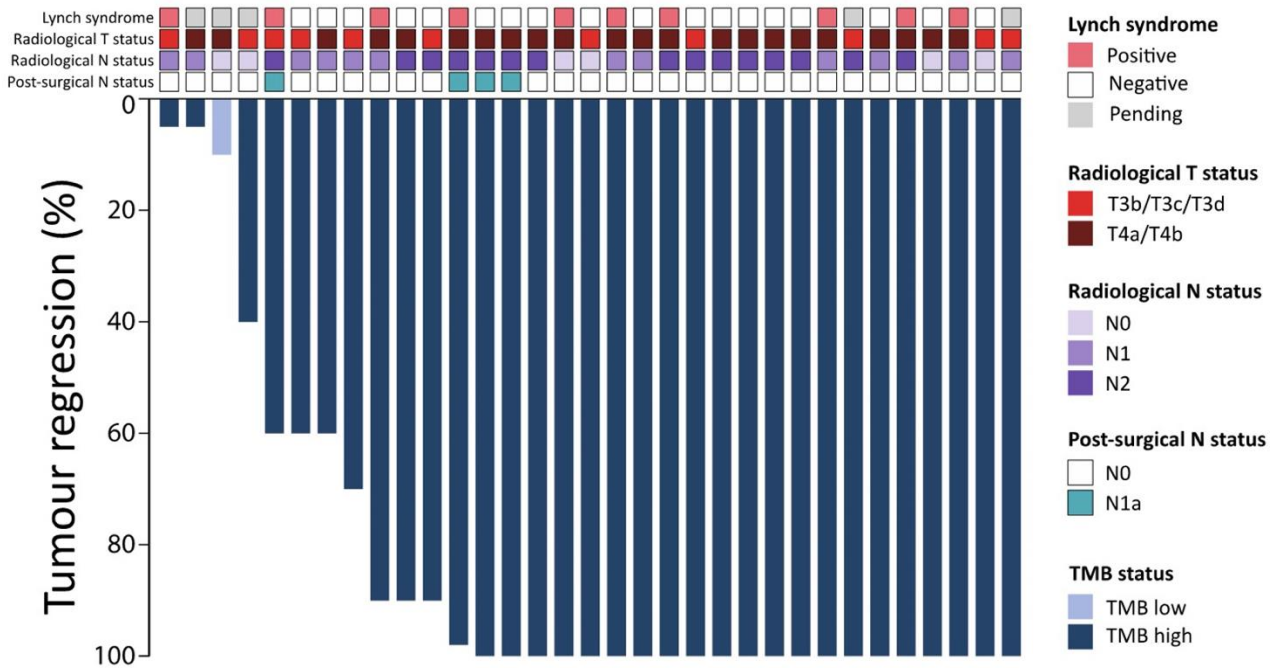
Yes → Pembrolizumab 200 mg Q3W Cycle 1

- TMB high or medium → Pembrolizumab 200mg Q3W C2+3
- TMB low

→ Surgery 4-6 weeks after last cycle → +/- adjuvant FOLFOX or CAPOX

3 year follow up
- EOT CT, CEA, ctDNA, PMBCs
- 3m CEA y1-3
- CT CAP at 6/12/24/36m

pCR seen in 59% of 32 TMB-high resected primaries

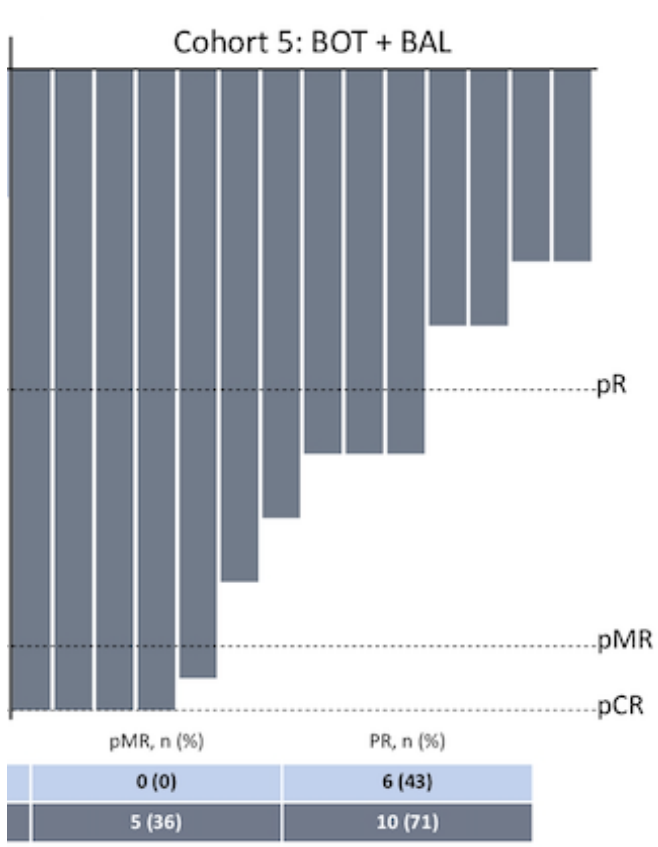


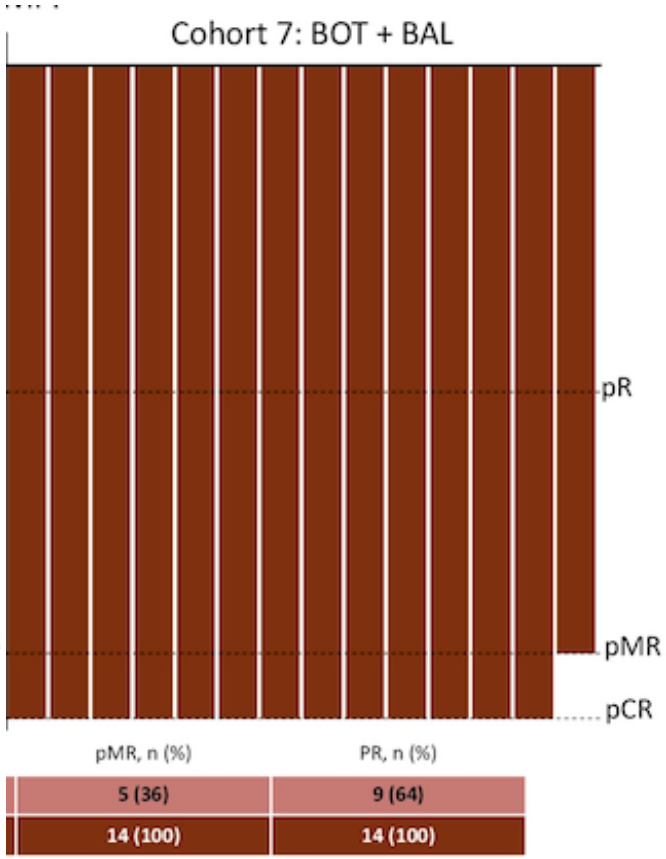
No disease relapse with median follow up of 9.7 months (range 5.3-19.0) and only 2 patients had adjuvant CAPOX

UNICORN by GONO

Cohort 5: resectable pMMR colon cancer
IV BOT 1mg/kg on day 1 and BAL 3mg/kg on days 1 and 15 → resection on day 35 +/- 5 days

Cohort 7: resectable dMMR colon cancer
IV BOT at 1mg/kg on day 1 and BAL 3mg/kg on days 1 and 15 → resection on day 35 +/- 5 days

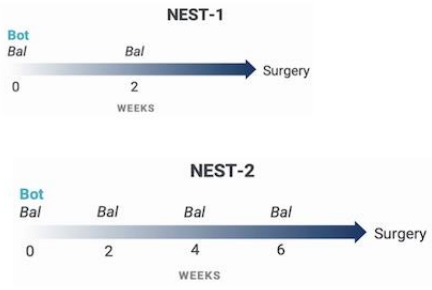


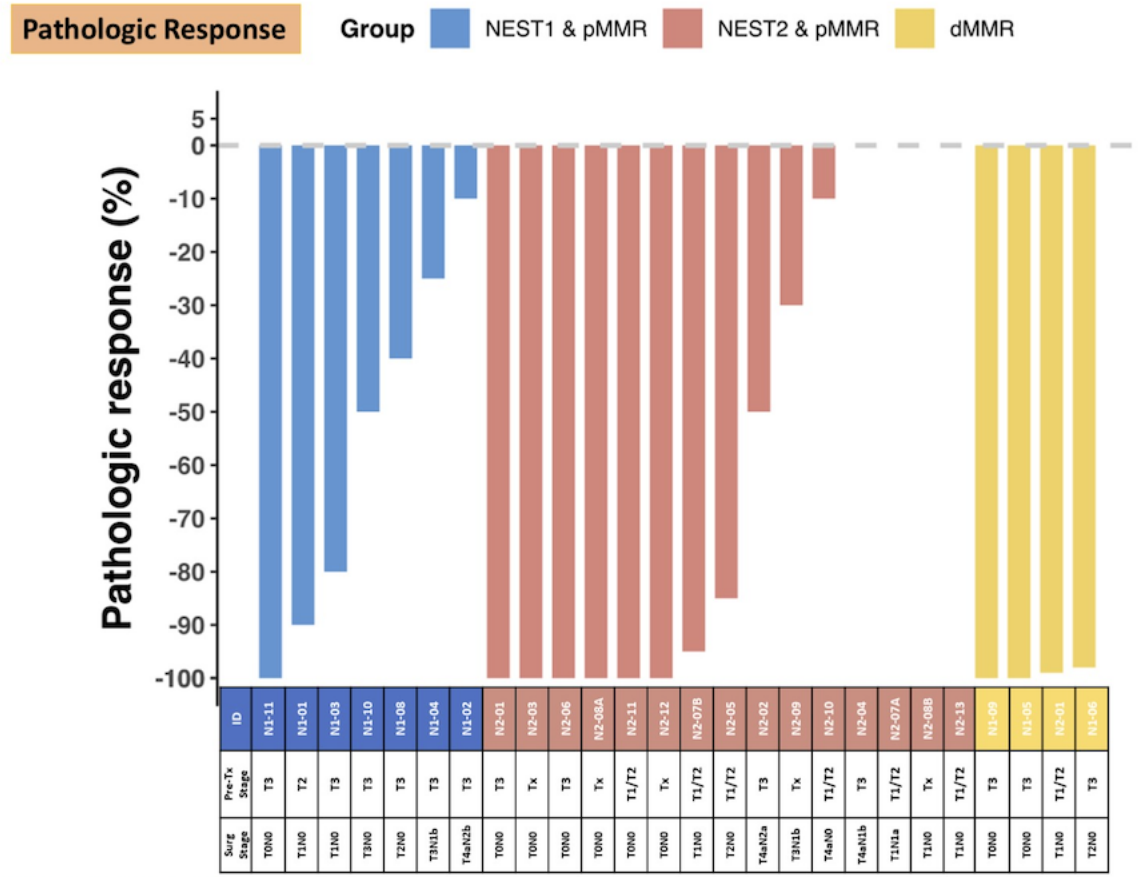


NEST-1 and NEST-2

NEST-1
1 dose of 75mg Botensilimab (BOT)
2 doses of 240mg Balstilimab (BAL) 2 weeks apart

NEST-2
1 dose of 75mg Botensilimab (BOT)
Up to 4 doses of 240mg Balstilimab (BAL) 2 weeks apart





TransMet: liver transplant for liver-limited mCRC

<=65 years
Unresectable LM-CRC
1-3 prior lines of systemic therapy
Gold Standard Resection of the primary
No extra-hepatic disease
BRAF WT
CEA<80 prior to transplant

1:1 randomization

Chemotherapy + Liver Transplant

Chemotherapy
+
Any locoregional therapies except transplant

Primary Endpoint:
Overall Survival at 5 years

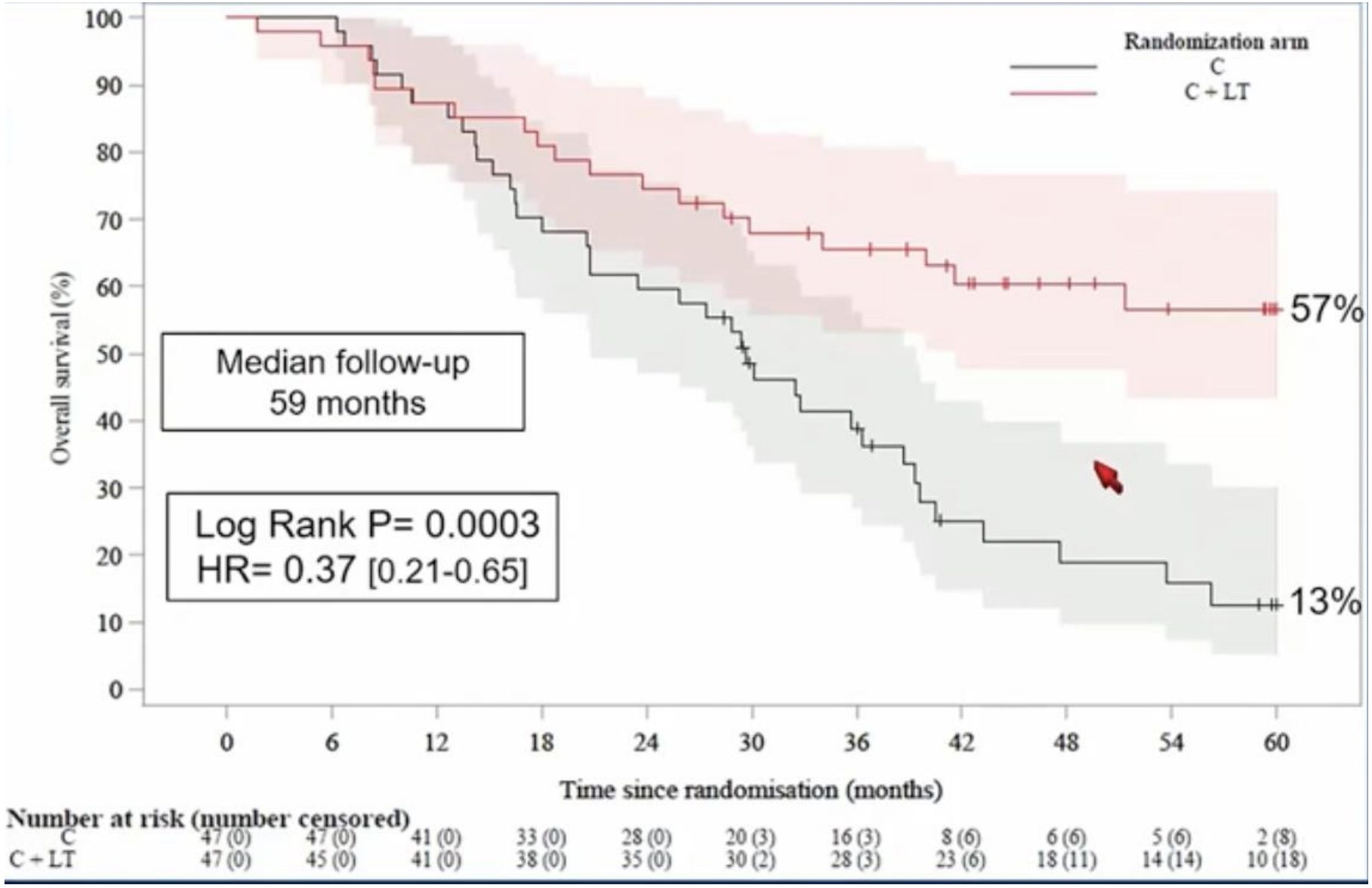
Secondary Endpoints:
Overall survival at 3 years
Progression Free Survival at 3 and 5 years
Recurrence free survival at 3 and 5 years

Presented at ASCO Annual Meeting 2024

TransMet Trial: Baseline Characteristics

	LT+C (n=47)	C alone (n=47)
Age (years)	52.0 (47-59)	55.0 (47-59)
Male	27 (57%)	28 (60%)
Right-sided primary	7 (15%)	7 (15%)
RAS mut	11 (23%)	12 (26%)
Median number of liver lesions	20 (14-25)	20 (12-25)
Fong's clinical risk score >2	42 (89%)	42 (89%)
Number of lines of chemotherapy prior to randomization		
1	19 (40%)	22 (47%)
2	20 (43%)	22 (47%)
3	8 (17%)	3 (6%)
Previous Liver surgery or ablation	4 (9%)	12 (26%)
Median time between diagnosis of liver metastases and randomization (months)	16 (12–26)	14 (9–19)

TRANSMET: Primary Endpoint 5-year OS (ITT)



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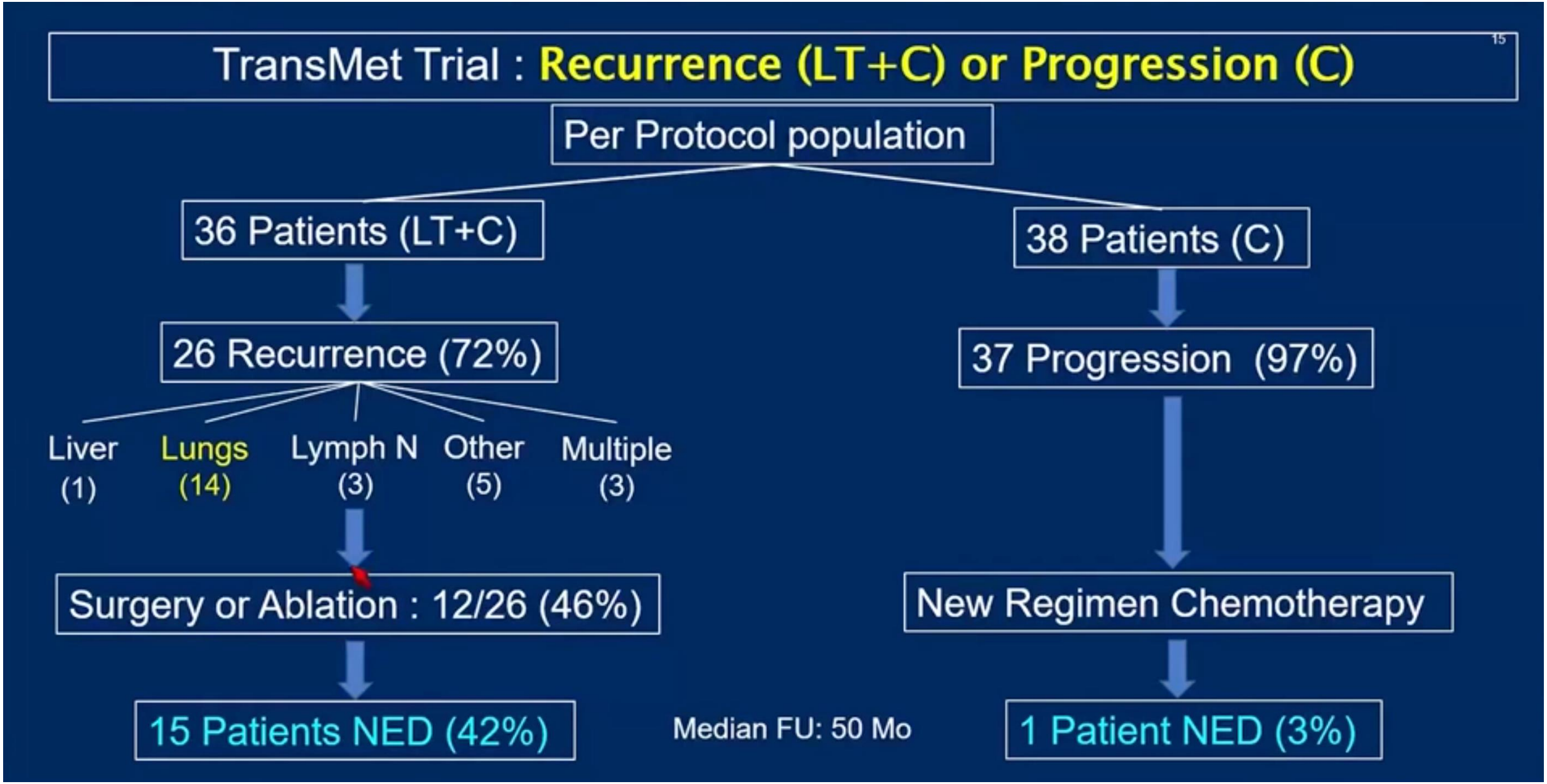
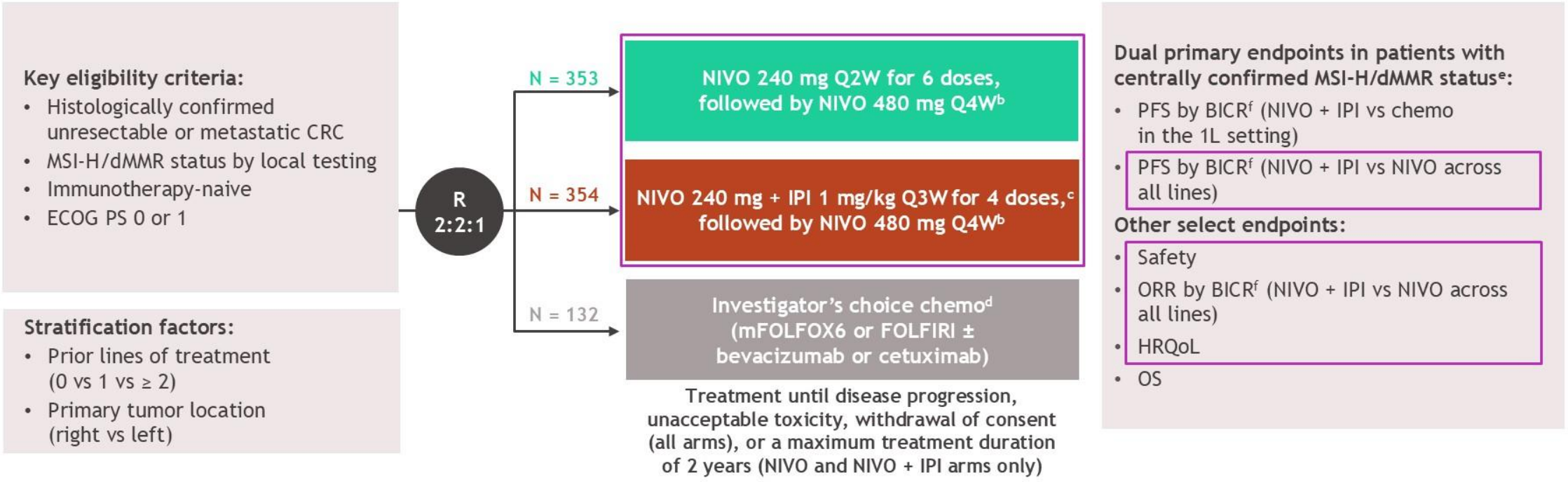


Presented at ASCO Annual Meeting 2024

Nivolumab plus ipilimumab vs nivolumab monotherapy or chemotherapy for dMMR metastatic CRC (CheckMate 8HW)



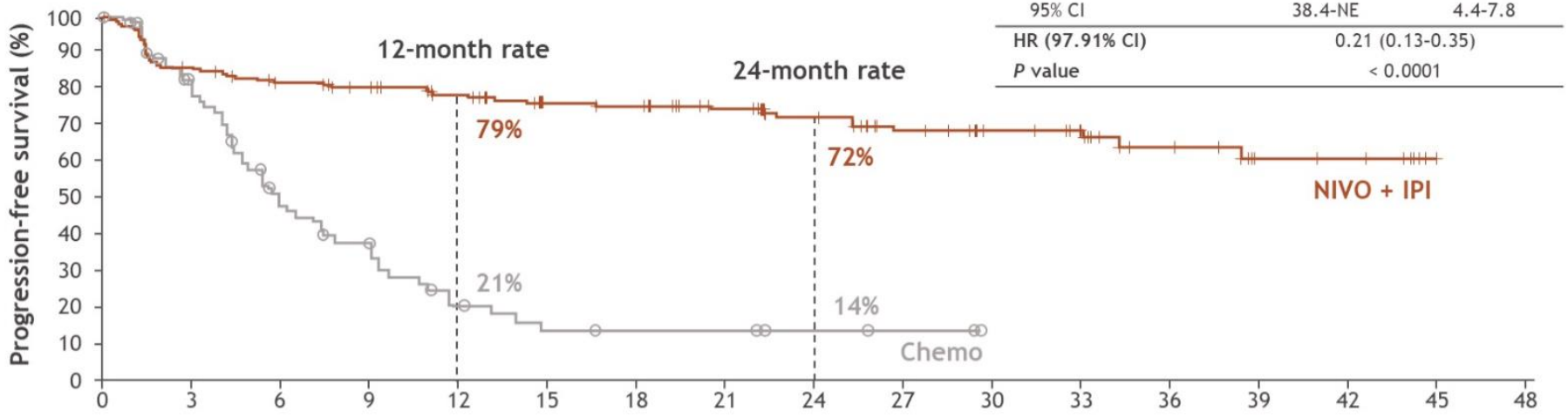
- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7–60.5)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either IHC and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

Nivolumab plus ipilimumab vs chemotherapy for dMMR metastatic CRC (CheckMate 8HW)

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)

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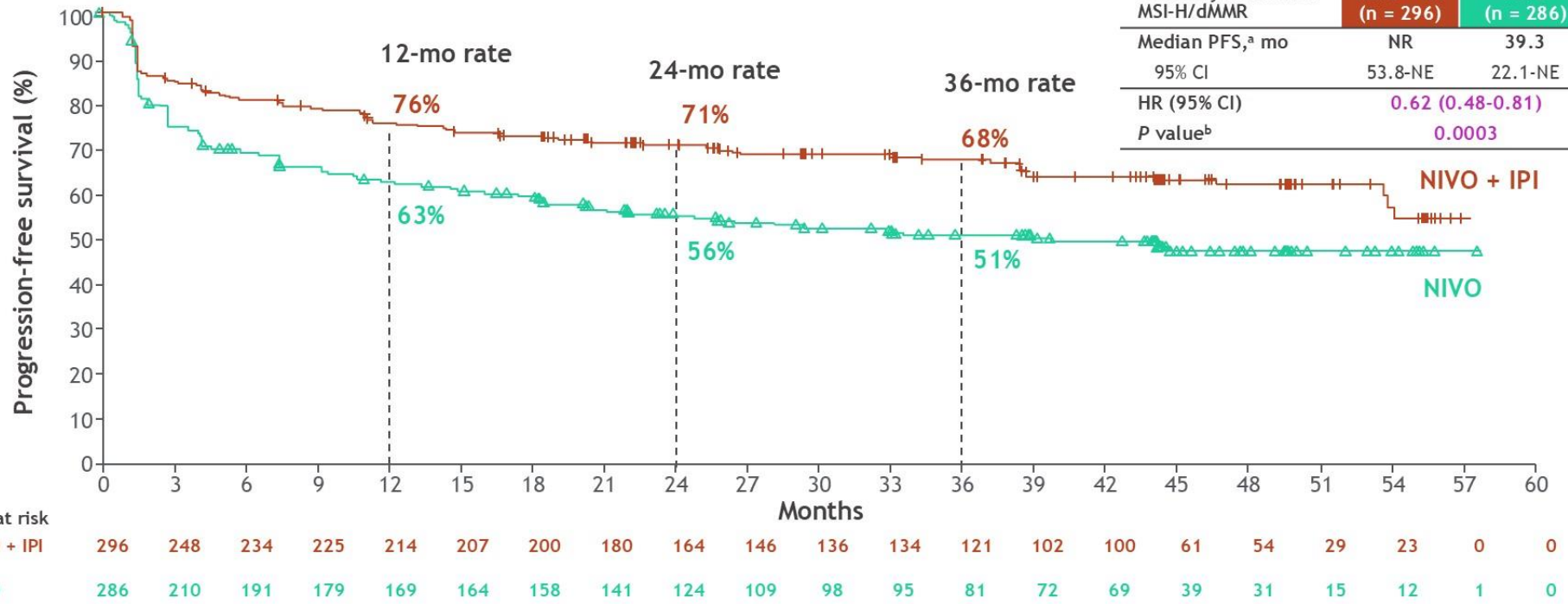
Nivolumab plus ipilimumab vs nivolumab monotherapy for dMMR metastatic CRC (CheckMate 8HW)

CheckMate 8HW

Progression-free survival



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy
  - PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (median PFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52-0.79])

[a]Per BICR. [b]Boundary for statistical significance, p < 0.0095.

Slide: GI ASCO 2025

Lancet 2025 https://doi.org/10/1016/S0140-6736(24)02848-4

Single vs dual IO in metastatic dMMR

CheckMate 8HW

Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 352)		NIVO (n = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs[a]				
Any TRAEs	285 (81)	78 (22)	249 (71)	50 (14)
Serious TRAEs	65 (18)	55 (16)	29 (8)	24 (7)
TRAEs leading to discontinuation[b]	48 (14)	33 (9)	21 (6)	14 (4)
Treatment-related deaths[c]	2 (< 1)[d]		1 (< 1)[e]	
TRAEs[a] reported in ≥ 10% of patients				
Pruritus	91 (26)	0	63 (18)	0
Diarrhea	71 (20)	3 (< 1)	59 (17)	2 (< 1)
Hypothyroidism	61 (17)	2 (< 1)	31 (9)	0
Asthenia	58 (16)	2 (< 1)	44 (13)	2 (< 1)
Fatigue	42 (12)	1 (< 1)	35 (10)	1 (< 1)
Hyperthyroidism	40 (11)	0	16 (5)	0
Arthralgia	38 (11)	1 (< 1)	23 (7)	0
Rash	34 (10)	3 (< 1)	29 (8)	1 (< 1)
Adrenal insufficiency	34 (10)	8 (2)	12 (3)	3 (< 1)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Discontinuation of any component of the combination regimen was counted as a drug discontinuation event. [c]Treatment-related deaths were reported regardless of timeframe. [d]Includes 1 event each of myocarditis and pneumonitis. No new treatment-related deaths were reported since the previous interim analysis. [e]One event of pneumonitis.

BREAKWATER: Study Design

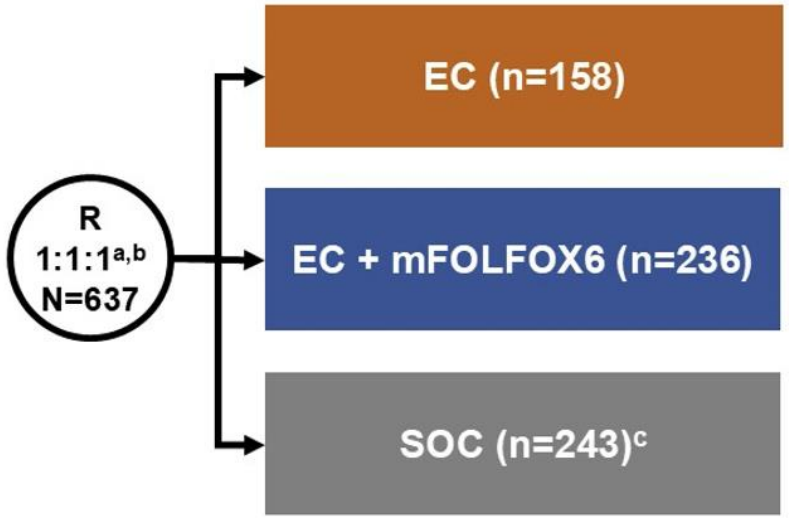
- BREAKWATER (NCT04607421) is an open-label, multicenter, phase 3 study in first line BRAF V600E-mutant mCRC

Inclusion criteria

- Age ≥16 years (or ≥18 years based on country)
- No prior systemic treatment for metastatic disease
- Measurable disease (RECIST 1.1)
- BRAF V600E-mutant mCRC by local or central laboratory testing
- ECOG PS 0 or 1
- Adequate bone marrow, hepatic, and renal function

Exclusion criteria

- Prior BRAF or EGFR inhibitors
- Symptomatic brain metastases
- MSI-H/dMMR tumors (unless patients were ineligible to receive immune checkpoint inhibitors due to a pre-existing medical condition)
- Presence of a *RAS* mutation



Stratified by regions (US/Canada vs Europe vs Rest of World) and ECOG PS (0 vs 1)

Dual primary endpoints:
PFS and ORR[d] by BICR
(EC + mFOLFOX6 vs SOC)

Key secondary endpoint:
OS (EC + mFOLFOX6 vs SOC)

Here we present the primary analysis of ORR by BICR (one of the dual primary endpoints), an interim analysis of OS, and safety in the EC + mFOLFOX6 and SOC arms

[a]Following a protocol amendment, enrollment to the EC arm was stopped and patients were randomized 1:1 to the EC+mFOLFOX6 or SOC arms; data in the EC arm will be reported at a later date. [b]Patients were enrolled between November 16, 2021, and December 22, 2023. [c]mFOLFOX6/FOLFOXIRI/CAPOX ± bevacizumab. [d]In the first 110 patients in each of the EC+mFOLFOX6 and SOC arms.

CAPOX, capecitabine/oxaliplatin; BICR, blinded independent central review; dMMR, deficient mismatch repair; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; FOLFOXIRI, fluorouracil/leucovorin/oxaliplatin/irinotecan; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

BREAKWATER: Baseline Characteristics

	EC + mFOLFOX6 n=236	SOC n=243	Total N=479
Age, median (range), years	60.0 (24-81)	62.0 (28-84)	61.0 (24-84)
Sex, n (%)			
Male	123 (52.1)	119 (49.0)	242 (50.5)
Female	113 (47.9)	124 (51.0)	237 (49.5)
ECOG PS, n (%)			
0	129 (54.7)	131 (53.9)	260 (54.3)
1	103 (43.6)	98 (40.3)	201 (42.0)
Side of tumor, n (%)			
Left	89 (37.7)	98 (40.3)	187 (39.0)
Right	147 (62.3)	145 (59.7)	292 (61.0)
No. of organs involved, n (%)[a]			
≤2	122 (51.7)	129 (53.1)	251 (52.4)
≥3	114 (48.3)	114 (46.9)	228 (47.6)
Liver metastases, n (%)[a]	144 (61.0)	156 (64.2)	300 (62.6)
CEA at baseline, n (%)			
≤5 µg/L	65 (27.5)	63 (25.9)	128 (26.7)
>5 µg/L	166 (70.3)	163 (67.1)	329 (68.7)
CRP at baseline, n (%)			
≤10 mg/L	125 (53.0)	119 (49.0)	244 (50.9)
>10 mg/L	105 (44.5)	107 (44.0)	212 (44.3)

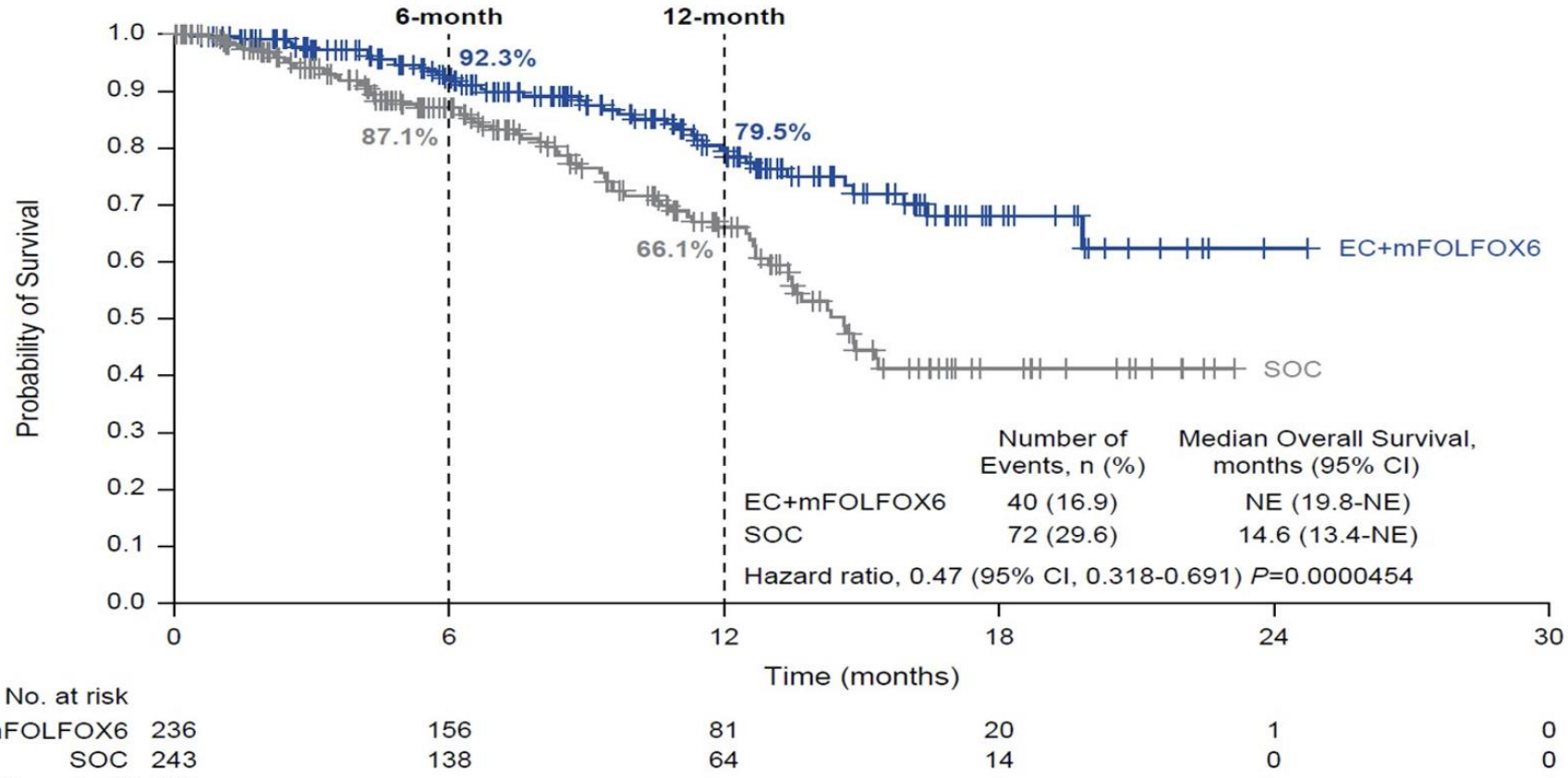
Data cutoff: December 22, 2023.

[a]Based on BICR.

BICR, blinded independent central review; CEA, carcinoembryonic antigen; CRP, C-reactive protein; EC, encorafenib plus cetuximab; ECOG PS, Eastern Cooperative Oncology Group performance status; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care.

Slide: GI ASCO 2025

BREAKWATER: Interim Overall Survival



Data cutoff: December 22, 2023.

[a]OS was tested following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001. Statistical significance was not achieved at this time.

EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; NE, not estimable; SOC, standard of care.

These results also formed the basis for the accelerated approval by the FDA (as part of Project FrontRunner) of EC + mFOLFOX6 for the treatment of patients with BRAF V600E-mutant mCRC—including in the first line setting

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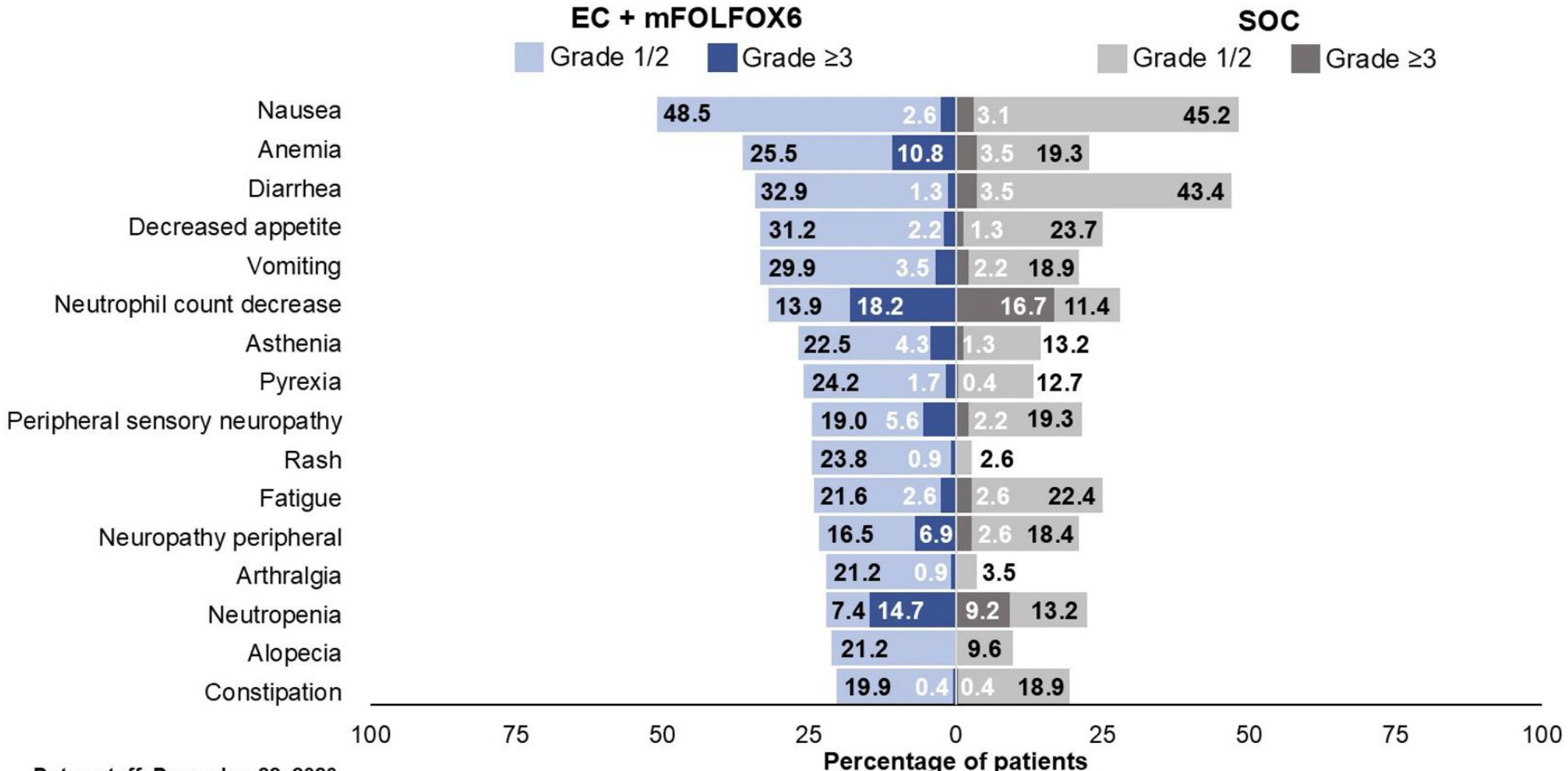
Most Frequent (≥20%)[a] All-Causality TEAEs



Data cutoff: December 22, 2023.

[a]Frequency is based on the EC + mFOLFOX6 arm.

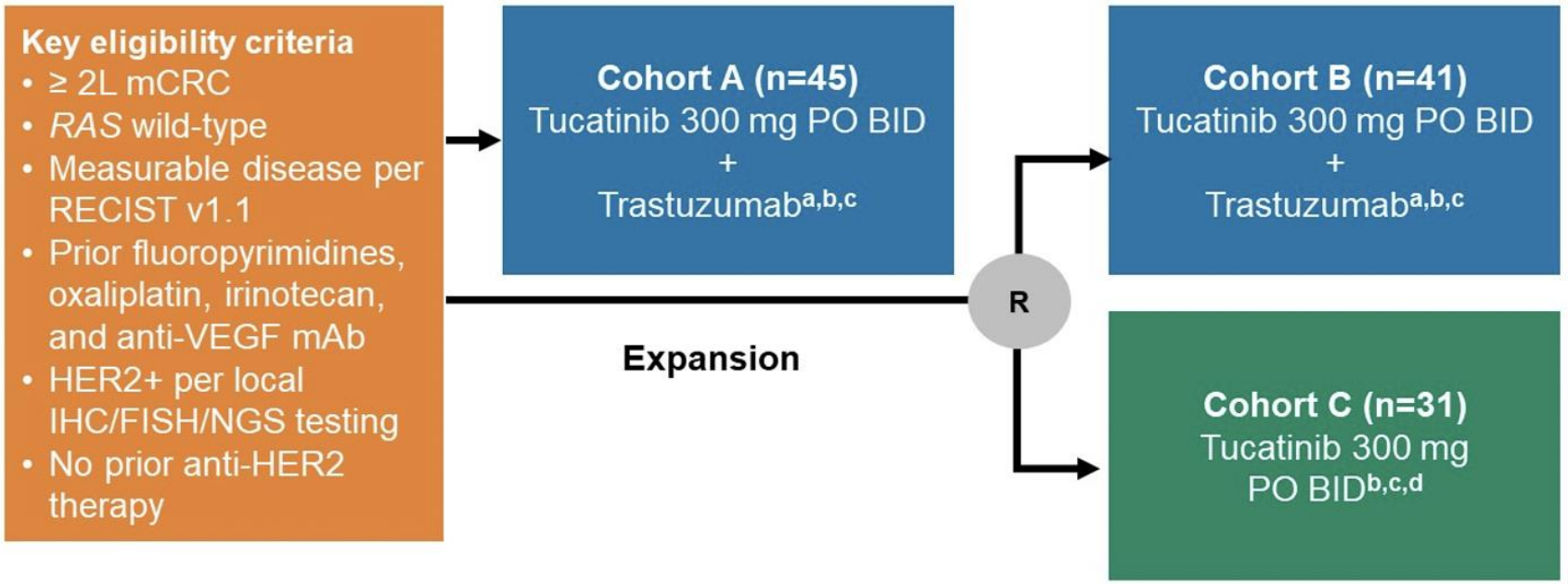
EC, encorafenib plus cetuximab; mFOLFOX6, modified fluorouracil/leucovorin/oxaliplatin; SOC, standard of care; TEAE, treatment-emergent adverse event.

Slide: GI ASCO 2025

BRAF V600E mutated mCRC

- Triplet chemotherapy versus targeted therapy + doublet
- Maintenance targeted therapy alone versus targeted therapy + chemo
- Tolerability

MOUNTAINEER: Multi-Center, Open-Label, Phase 2 Trial (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

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

[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.
≥ 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.

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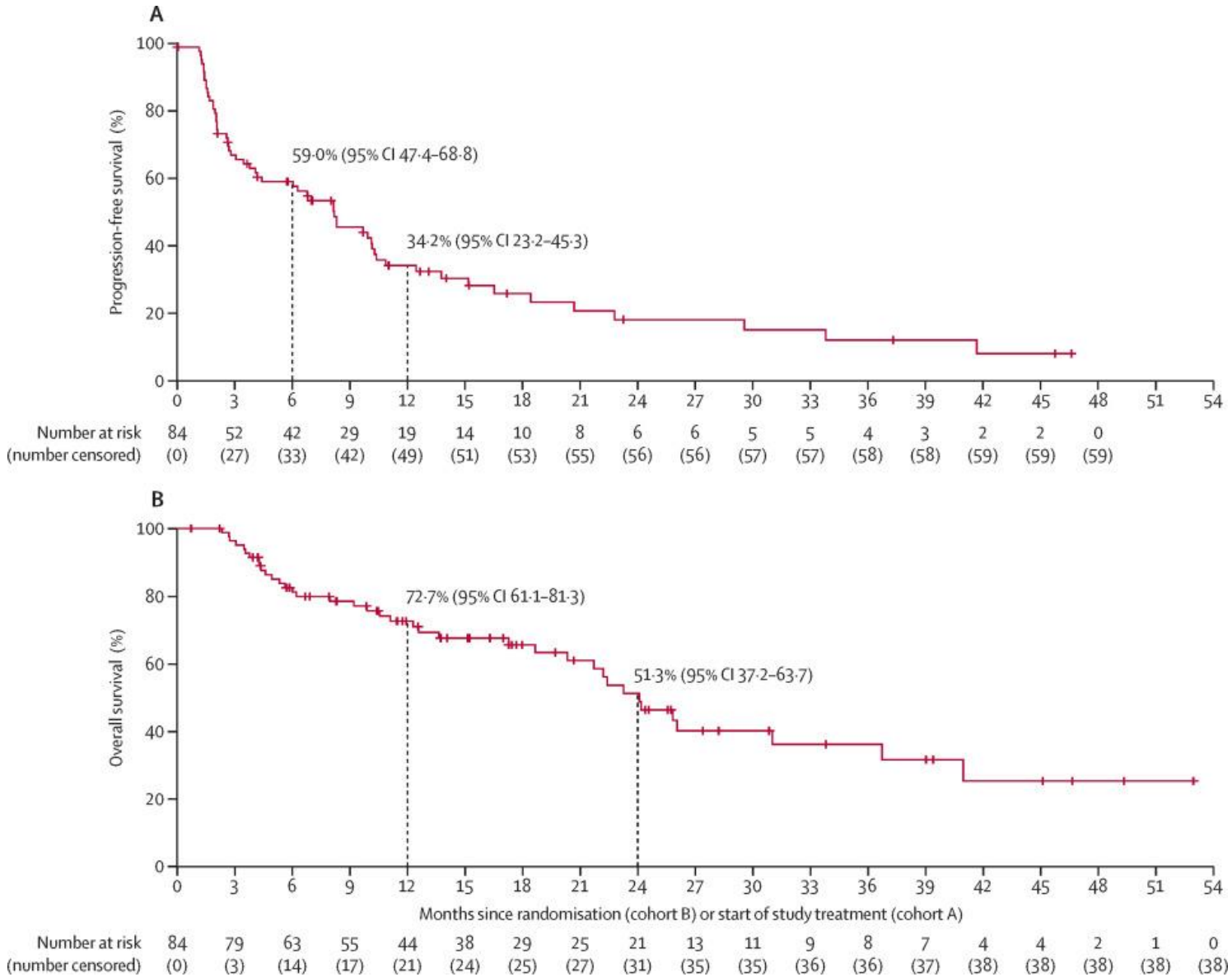
Figure 3: Kaplan-Meier estimates of progression-free survival by blinded independent central review (A) and overall survival (B) in patients treated with tucatinib plus trastuzumab, full analysis set (n=84)



The median progression-free survival was 7·0 months (95% CI 4·3–9·7)

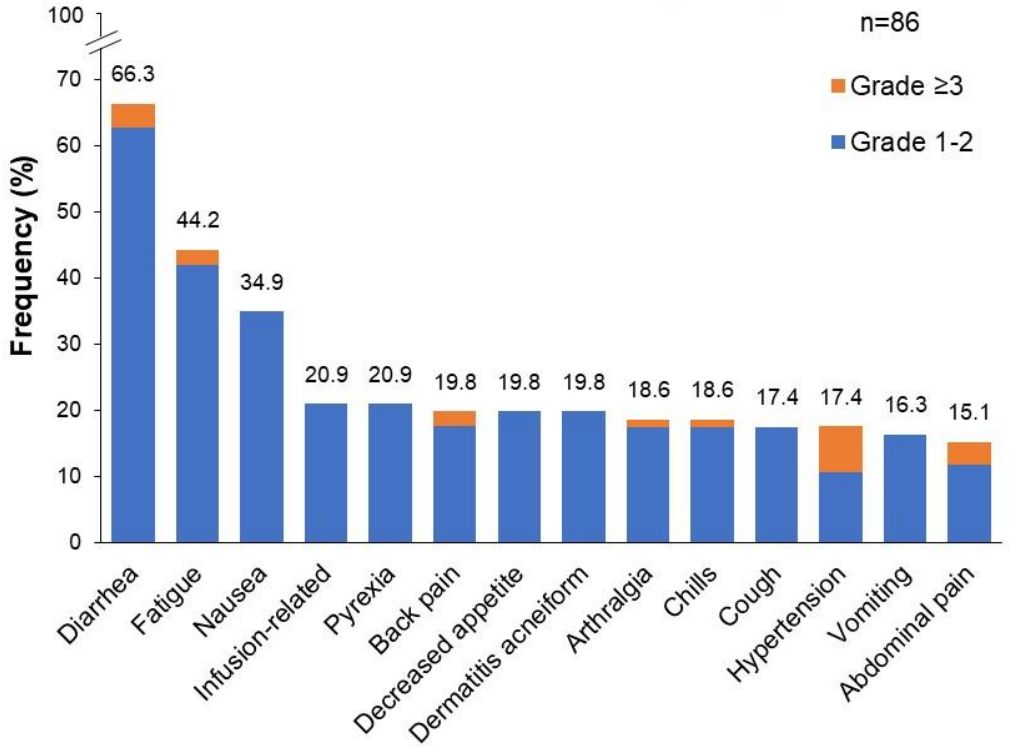
The median overall survival was 24·1 months (95% CI 20·3–36·7)

The Lancet Oncology
Volume 24, Issue 5, May 2023, Pages 496-508

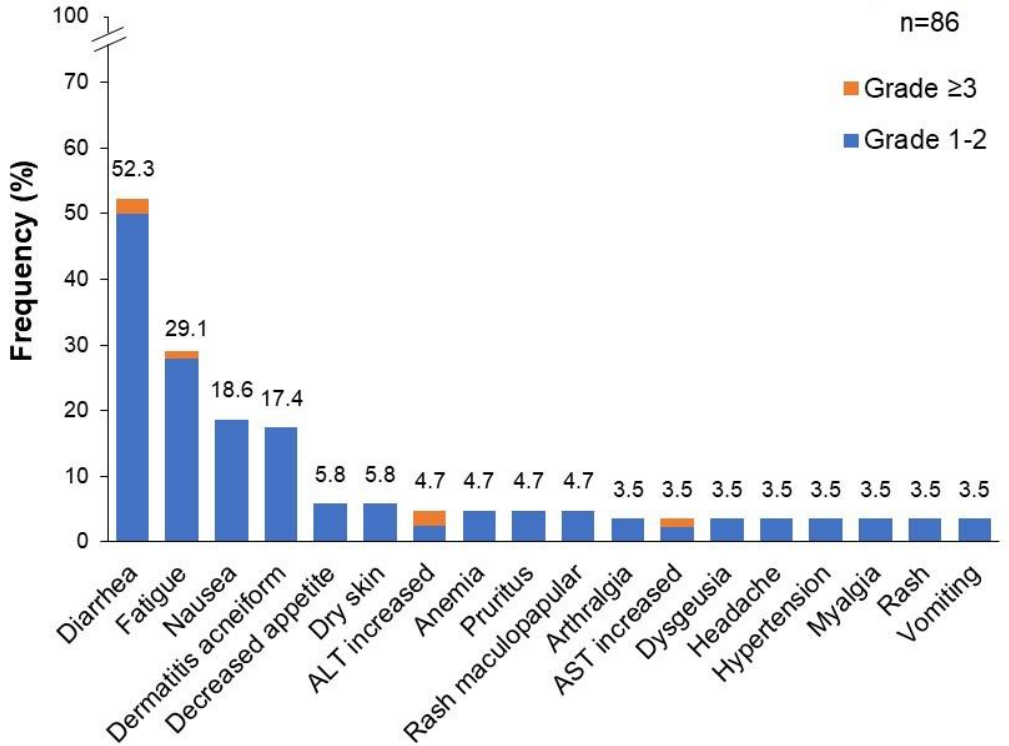
TEAEs in Cohorts A+B

- 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

Most Common TEAEs (≥15%)



Most Common Tucatinib-related TEAEs (≥3%)



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

PRESENTED BY: John H. Strickler

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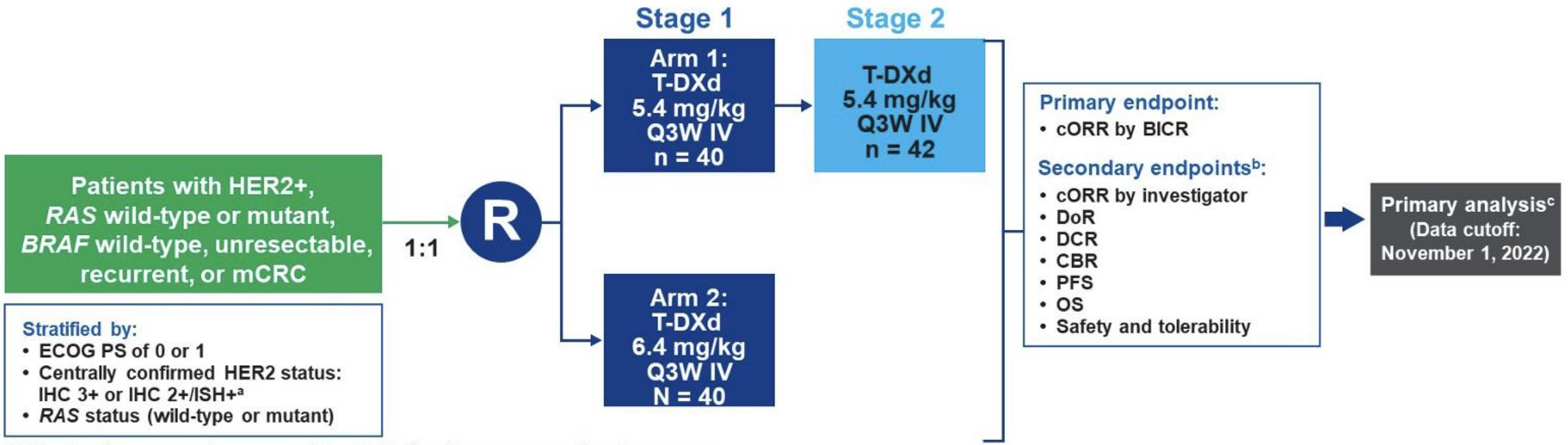
DESTINY-CRC02 Study Design

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.

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Baseline Characteristics

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median age, years (range)	58.2 (26-78)	60.6 (30-84)	59.1 (26-84)	62.3 (35-81)
Sex, n (%)				
Male	21 (52.5)	24 (57.1)	45 (54.9)	19 (47.5)
Region, n (%)				
Asia-Pacific	25 (62.5)	22 (52.4)	47 (57.3)	24 (60.0)
US	5 (12.5)	1 (2.4)	6 (7.3)	2 (5.0)
Europe	10 (25.0)	19 (45.2)	29 (35.4)	14 (35.0)
HER2 status, n (%)				
IHC 3+	32 (80.0)	32 (76.2)	64 (78.0)	34 (85.0)
IHC 2+/ISH+	8 (20.0)	10 (23.8)	18 (22.0)	6 (15.0)
ECOG PS, n (%)				
0	22 (55.0)	24 (57.1)	46 (56.1)	22 (55.0)
1	18 (45.0)	18 (42.9)	36 (43.9)	18 (45.0)
***RAS* status, n (%)**				
Wild-type	34 (85.0)	34 (81.0)	68 (82.9)	34 (85.0)
Mutant	6 (15.0)	8 (19.0)	14 (17.1)	6 (15.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

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Prior Treatment

	T-DXd 5.4 mg/kg Q3W			T-DXd 6.4 mg/kg Q3W
	Stage 1 n = 40	Stage 2 n = 42	Total N = 82	Stage 1 N = 40
Median prior lines of systemic therapy, n (range)	4 (1-12)	3 (1-7)	3 (1-12)	4 (1-8)
Systemic chemotherapy, n (%)	**40 (100)**	**42 (100)**	**82 (100)**	**40 (100)**
Irinotecan	39 (97.5)	40 (95.2)	79 (96.3)	40 (100)
Fluoropyrimidines[a]	40 (100)	42 (100)	82 (100)	40 (100)
Oxaliplatin	40 (100)	41 (97.6)	81 (98.8)	40 (100)
Anti-EGFR, n (%)	29 (72.5)	28 (66.7)	57 (69.5)	31 (77.5)
Anti-HER2, n (%)	**11 (27.5)**	**6 (14.3)**	**17 (20.7)**	**10 (25.0)**
HER2 TKI[b]	6 (15.0)	4 (9.5)	10 (12.2)	7 (17.5)
Anti-HER2 antibodies[c]	10 (25.0)	6 (14.3)	16 (19.5)	10 (25.0)
Anti-VEGF, n (%)	36 (90.0)	38 (90.5)	74 (90.2)	38 (95.0)
Regorafenib and tipiracil/trifluridine, n (%)	20 (50.0)	14 (33.3)	34 (41.5)	13 (32.5)
Other systemic therapy, n (%)	5 (12.5)	6 (14.3)	11 (13.4)	10 (25.0)

5FU, fluorouracil; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

[a]Includes 5FU, capecitabine, S1, or tegafur. [b]Includes tucatinib and lapatinib. [c]Includes trastuzumab, trastuzumab duocarmazine, trastuzumab emtansine, pertuzumab, and zanidatamab (ZW25).

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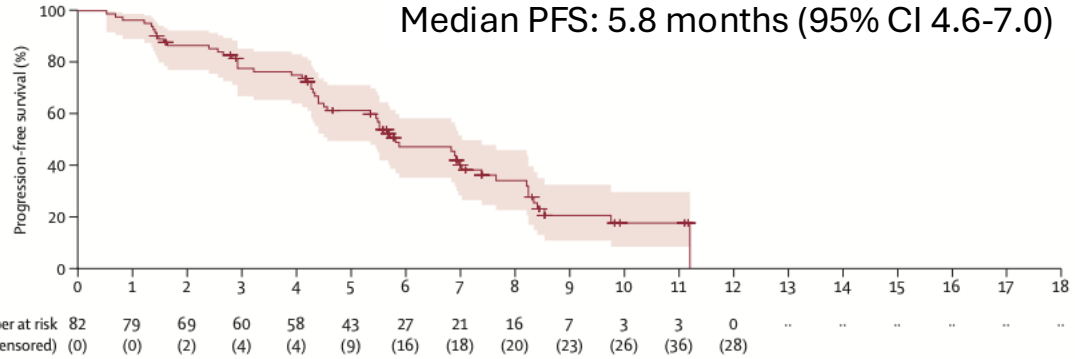
DESTINY-CRC02: PFS and OS

Trastuzumab deruxtecan 5·4 mg/kg dose group (n=82)

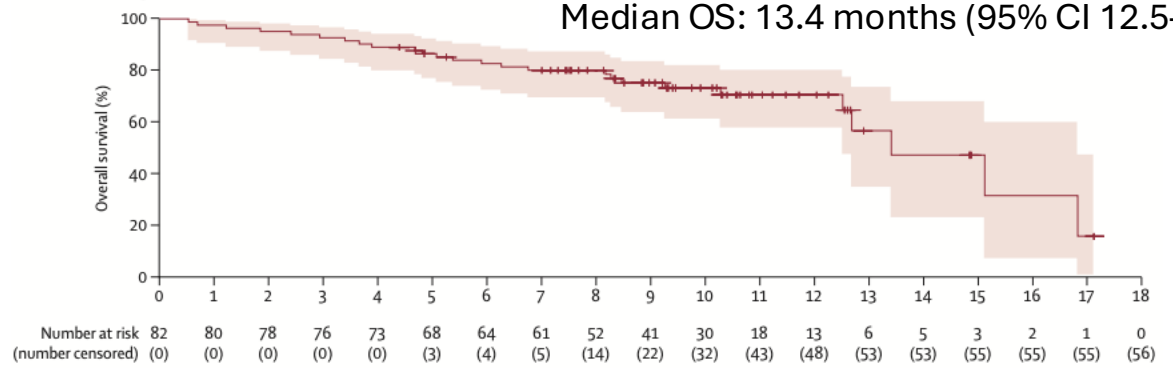
A

Median PFS: 5.8 months (95% CI 4.6-7.0)



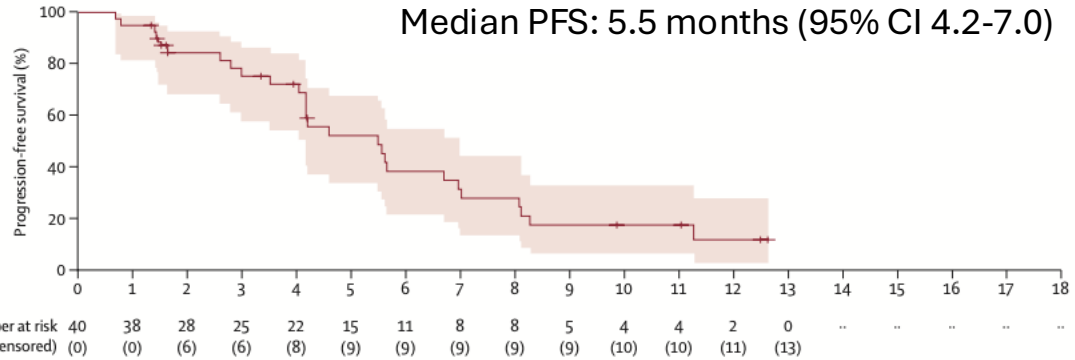
C

Median OS: 13.4 months (95% CI 12.5-16.8)



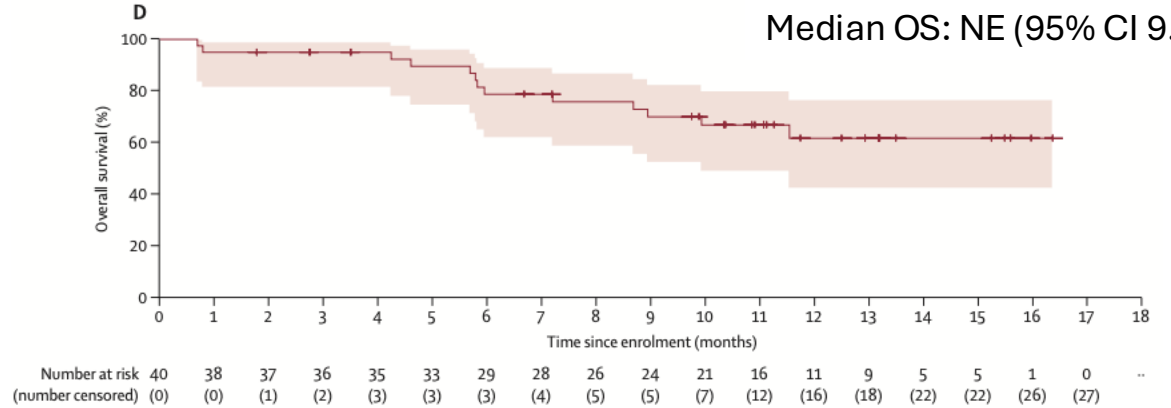
B

Median PFS: 5.5 months (95% CI 4.2-7.0)



D

Median OS: NE (95% CI 9.9-NE)

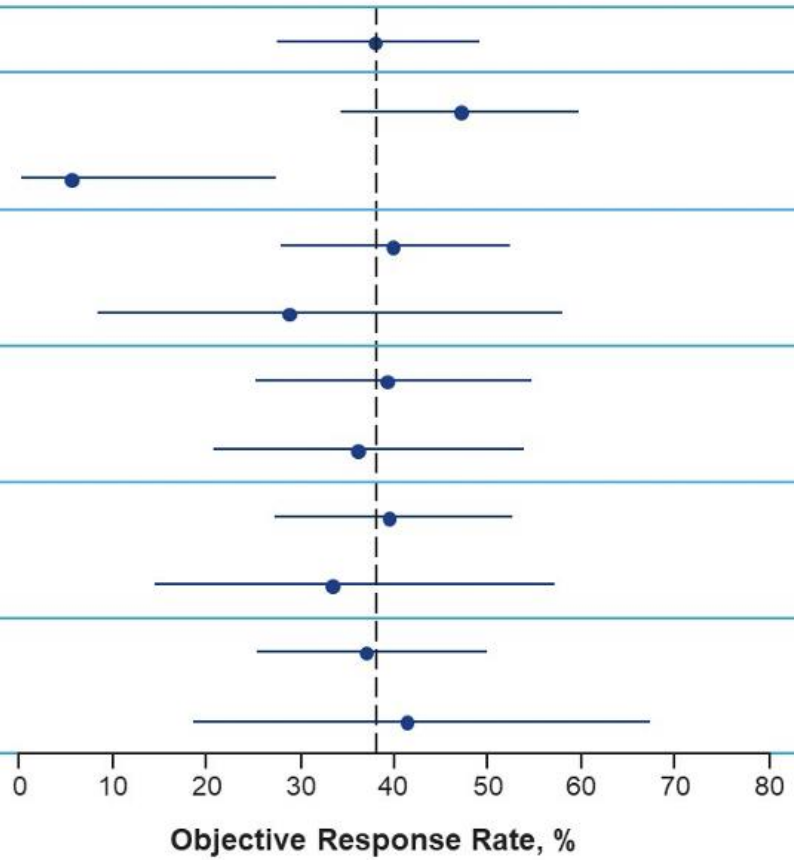


Trastuzumab deruxtecan 6·4 mg/kg dose group (n=40)

Lancet Oncol 2024; 25: 1147–62

Best Overall Response by BICR by Subgroup With T-DXd 5.4 mg/kg

		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



BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; *RAS*, rat sarcoma; T-DXd, trastuzumab deruxtecan.

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

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CODEBREAK 300

Inclusion Criteria:

- KRAS G12C mutated mCRC
- Received ≧1 prior line of therapy for mCRC, including oxaliplatin, irinotecan, 5FU if eligible
- No prior KRAS inhibitor

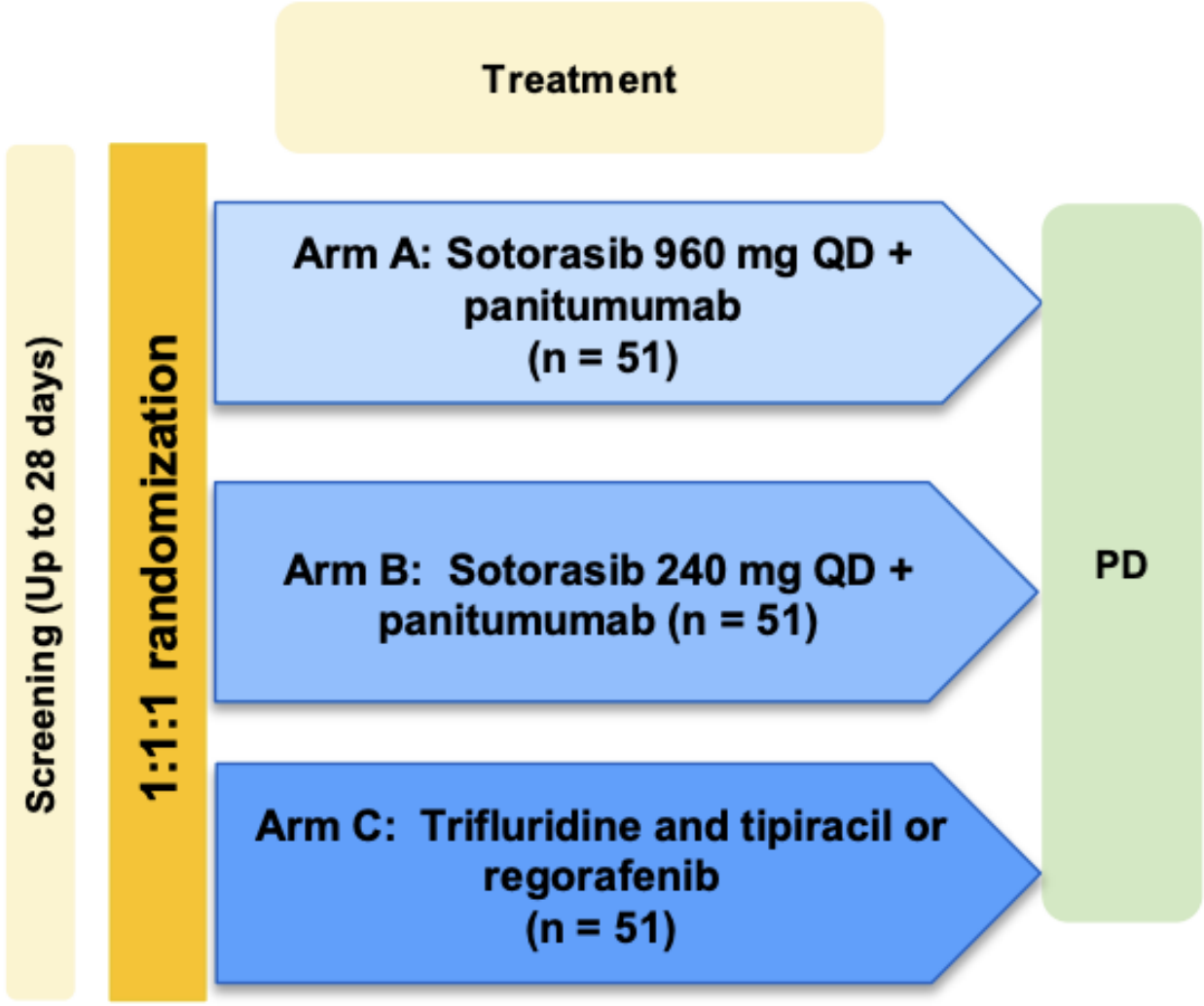
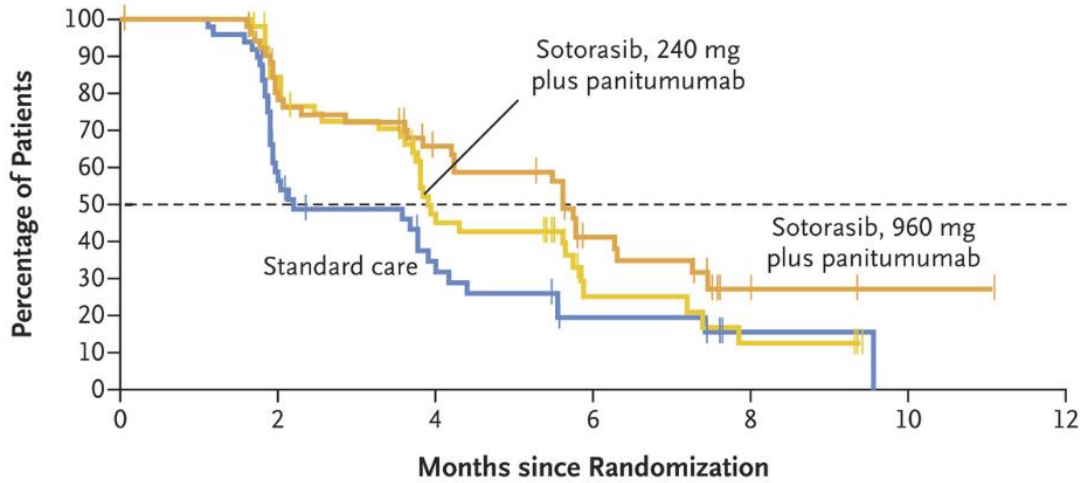


Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	960-mg Sotorasib–Panitumumab (N=53)	240-mg Sotorasib–Panitumumab (N=53)	Standard Care (N=54)
Median age (range) — yr	63.0 (37–79)	58.0 (35–82)	64.5 (34–81)
Age category — no. (%)			
<65 yr	32 (60.4)	39 (73.6)	27 (50.0)
≥65 yr	21 (39.6)	14 (26.4)	27 (50.0)
Male sex — no. (%)	29 (54.7)	26 (49.1)	24 (44.4)
Geographic region of enrollment — no. (%)			
North America	5 (9.4)	5 (9.4)	7 (13.0)
Europe	41 (77.4)	28 (52.8)	36 (66.7)
Asia	6 (11.3)	19 (35.8)	11 (20.4)
Rest of the world	1 (1.9)	1 (1.9)	0
Race — no. (%)†			
Asian	6 (11.3)	22 (41.5)	12 (22.2)
Black	0	1 (1.9)	0
White	43 (81.1)	30 (56.6)	37 (68.5)
Other	4 (7.5)	0	5 (9.3)
Previous antiangiogenic therapy — no. (%)	45 (84.9)	47 (88.7)	48 (88.9)
Time from initial diagnosis of metastatic disease to randomization — no. (%)			
≥18 mo	29 (54.7)	29 (54.7)	31 (57.4)
<18 mo	24 (45.3)	22 (41.5)	23 (42.6)
Unknown	0	2 (3.8)	0
ECOG performance-status score — no. (%)‡			
0	32 (60.4)	29 (54.7)	35 (64.8)
1	19 (35.8)	22 (41.5)	18 (33.3)
2	2 (3.8)	2 (3.8)	1 (1.9)
Body site at initial diagnosis — no. (%)			
Colon	37 (69.8)	32 (60.4)	37 (68.5)
Rectum	16 (30.2)	21 (39.6)	17 (31.5)
Location of tumor — no. (%)			
Left side	28 (52.8)	36 (67.9)	37 (68.5)
Right side	24 (45.3)	17 (32.1)	16 (29.6)
Unknown	1 (1.9)	0	1 (1.9)
No. of lines of previous anticancer therapy			
1 — no. (%)	7 (13.2)	8 (15.1)	9 (16.7)
≥2 — no. (%)	46 (86.8)	45 (84.9)	45 (83.3)
Median	2	2	2
Previous treatment with oxaliplatin, irinotecan, and fluoropyrimidine — no. (%)	49 (92.5)	50 (94.3)	51 (94.4)
Previous treatment with trifluridine and tipiracil — no. (%)	7 (13.2)	7 (13.2)	6 (11.1)
Previous treatment with regorafenib — no. (%)	4 (7.5)	1 (1.9)	2 (3.7)
Microsatellite instability status — no. (%)			
High	1 (1.9)	0	0
Stable	42 (79.2)	42 (79.2)	43 (79.6)
Low	3 (5.7)	2 (3.8)	3 (5.6)
Unknown or not tested	7 (13.2)	9 (17.0)	8 (14.8)

* Percentages may not sum to 100 because of rounding.
† Race was either reported by the patient or determined by the investigator.
‡ The Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

A Progression-free Survival (Intention-to-Treat Population)

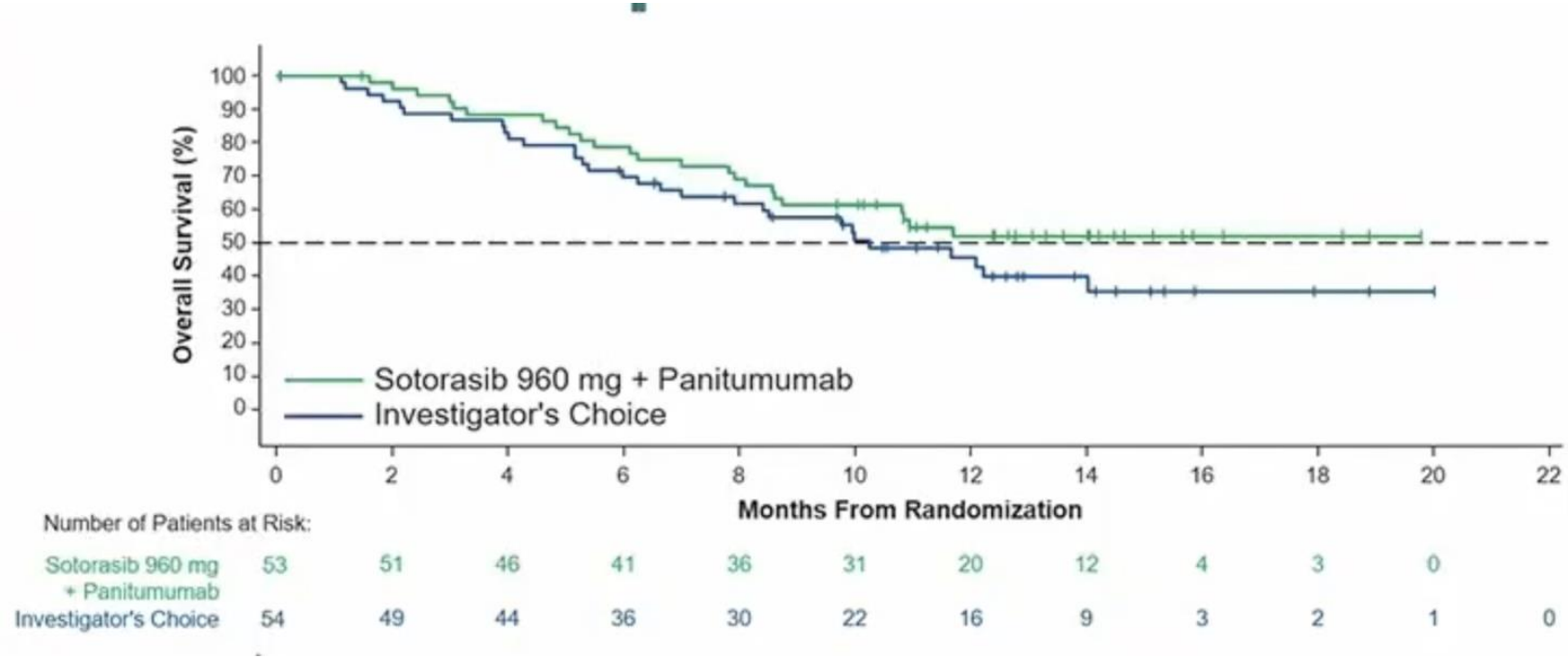


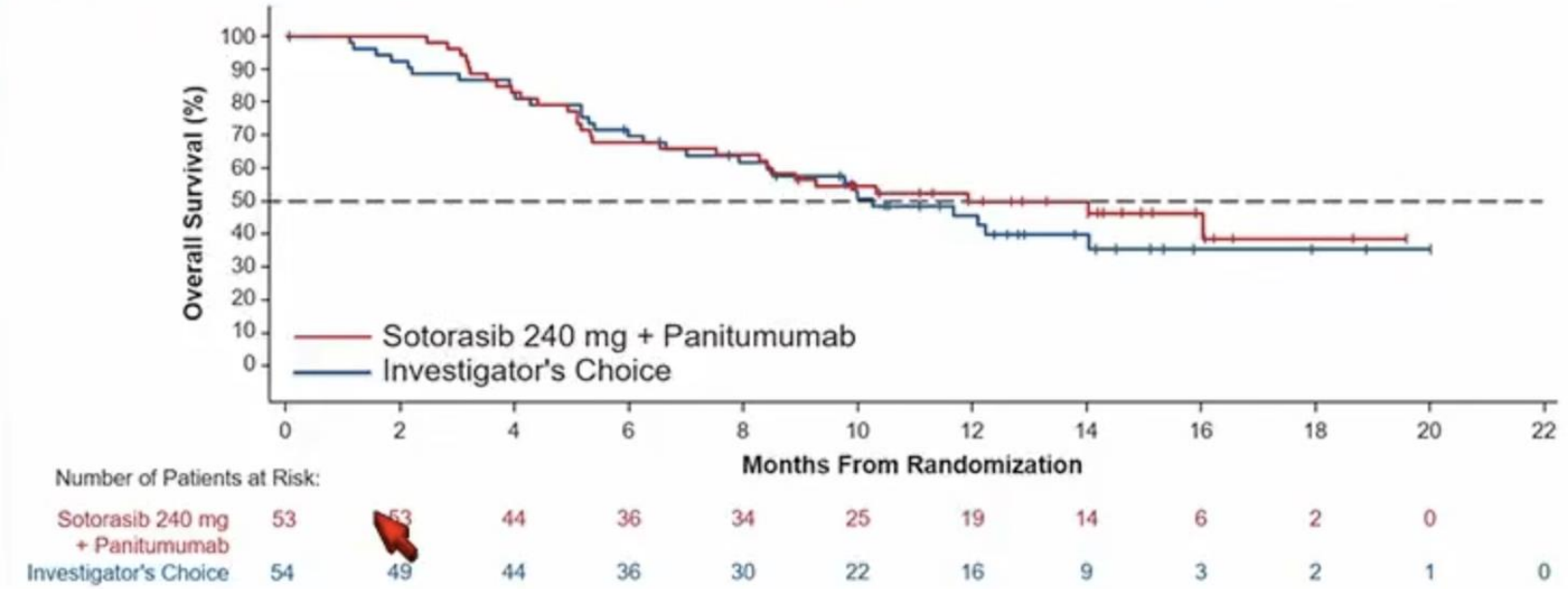
No. at Risk

Sotorasib, 960 mg plus panitumumab	53	40	28	13	2	1	0
Sotorasib, 240 mg plus panitumumab	53	43	20	6	3	0	
Standard care	54	24	12	5	1	0	

	Median Progression-free Survival	Hazard Ratio for Disease Progression or Death (95% CI)	Two-Sided P Value
	mo		
Sotorasib, 960 mg plus Panitumumab	5.62	0.48 (0.30–0.78)	0.005
Sotorasib, 240 mg plus Panitumumab	3.91	0.59 (0.37–0.95)	0.036
Standard Care	2.04		

N Engl J Med 2023;389:2125-2139
DOI: 10.1056/NEJMoa2308795
VOL. 389 NO. 23





	Soto960 +Pani (N=53)	Soto240+Pani (N=53)	Investigator Choice (N=54)
Median OS (mo)	NE (8.6, NE)	11.9 (7.5,NE)	10.2 (7.0,NE)
HR	0.70 (0.41,1.18)	0.83 (0.49,1.39)	
Median FU (mo)	13.6	14.0	12.9
ORR%	30.2 (18.3,44.3)	7.5 (21,18.2)	1.9 (0.0,9.9)
Median DOR (mo)	10.1 (3.1,12.9+)	NR (5.6,11.2+)	NR (5.2,5.2)

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Will MOUNTAINEER-3 and CodeBreaK-301 be the new BREAKWATER?

MOUNTAINEER-3

Study population

Measurable disease per RECIST v1.1
ECOG PS 0–1
HER2+, *RAS* WT locally advanced unresectable or metastatic CRC

Patients may have received chemotherapy for CRC in the adjuvant treatment if completed > 6 months prior to enrollment (Cycle 1 Day 1).

Patients may have received up to two doses of mFOLFOX6 in the locally advanced unresectable or metastatic setting prior to randomization.

1:1 randomization

Tucatinib experimental arm

Tucatinib 300 mg PO BID

Trastuzumab 8 mg/kg loading dose, then 6 mg/kg IV (Q3W)

mFOLFOX6 (Q2W)

N=200

Standard of care control arm

mFOLFOX6 (Q2W), or

mFOLFOX6 (Q2W) + bevacizumab (Q2W), or

mFOLFOX6 (Q2W) + cetuximab (QW)

N=200

Primary endpoint:
PFS (assessed by BICR)

Key secondary endpoint:
OS

CodeBreaK-301

Study Population
Measurable disease per RECIST v1.1
KRAS G12C mut
Treatment naïve in metastatic setting

1:1 randomization

Sotorasib experimental arm
Sotorasib 960 mg + panitumumab 6mg/kg (Q2W) + FOLFIRI

N=225

FOLFIRI + bev

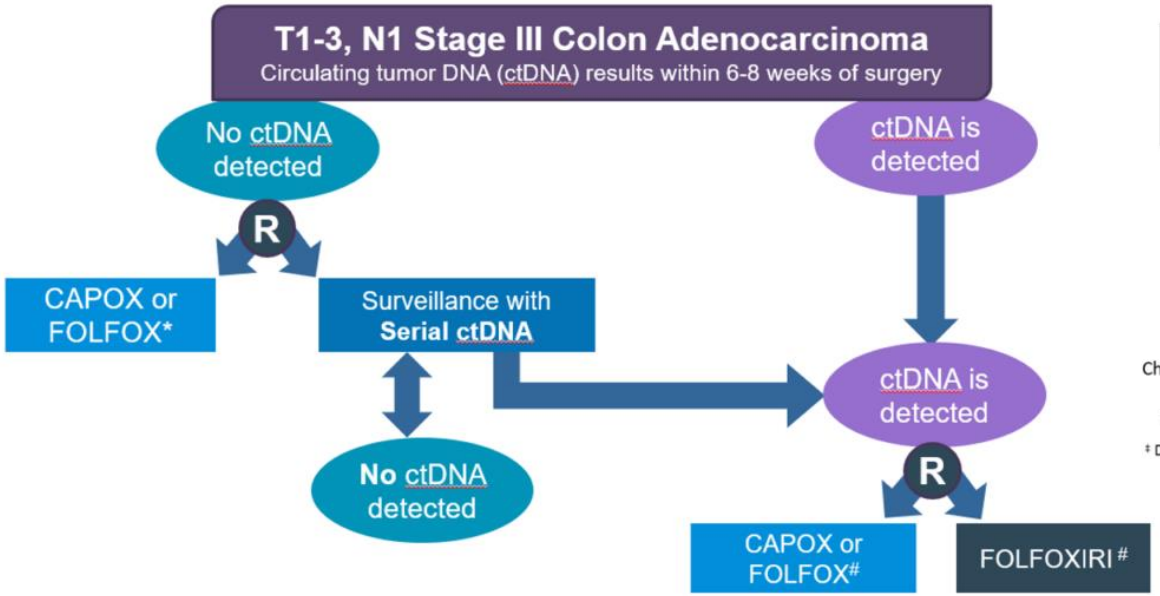
N=225

Primary endpoint:
PFS (assessed by RECIST)

Key secondary endpoint:
OS

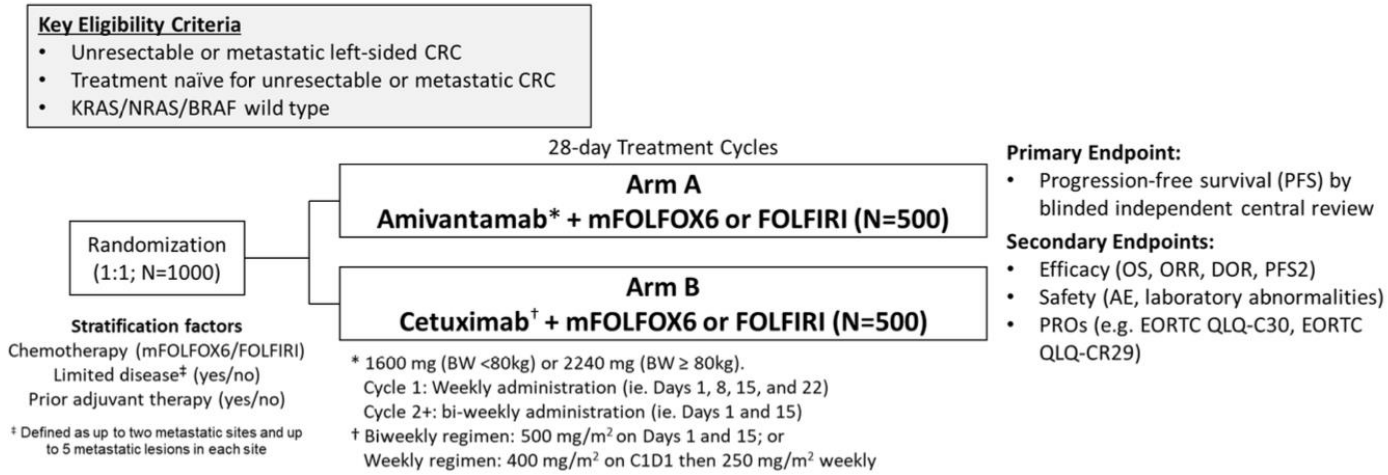
Looking ahead…

CIRCULATE-US



Primary endpoint: DFS

OrigAMI-2



Pan-KRAS inhibitors:

- In combination with cetuximab/panitumumab
- In combination with chemotherapy
- In 1st, 2nd, and 3rd line

A Randomized, Phase 3, Open-Label Study Comparing Botensilimab Plus Balstilimab with Investigator Choice Standard of Care Therapy in Participants with Previously Treated Metastatic Colorectal Cancer and No Active Liver Metastases

Questions?