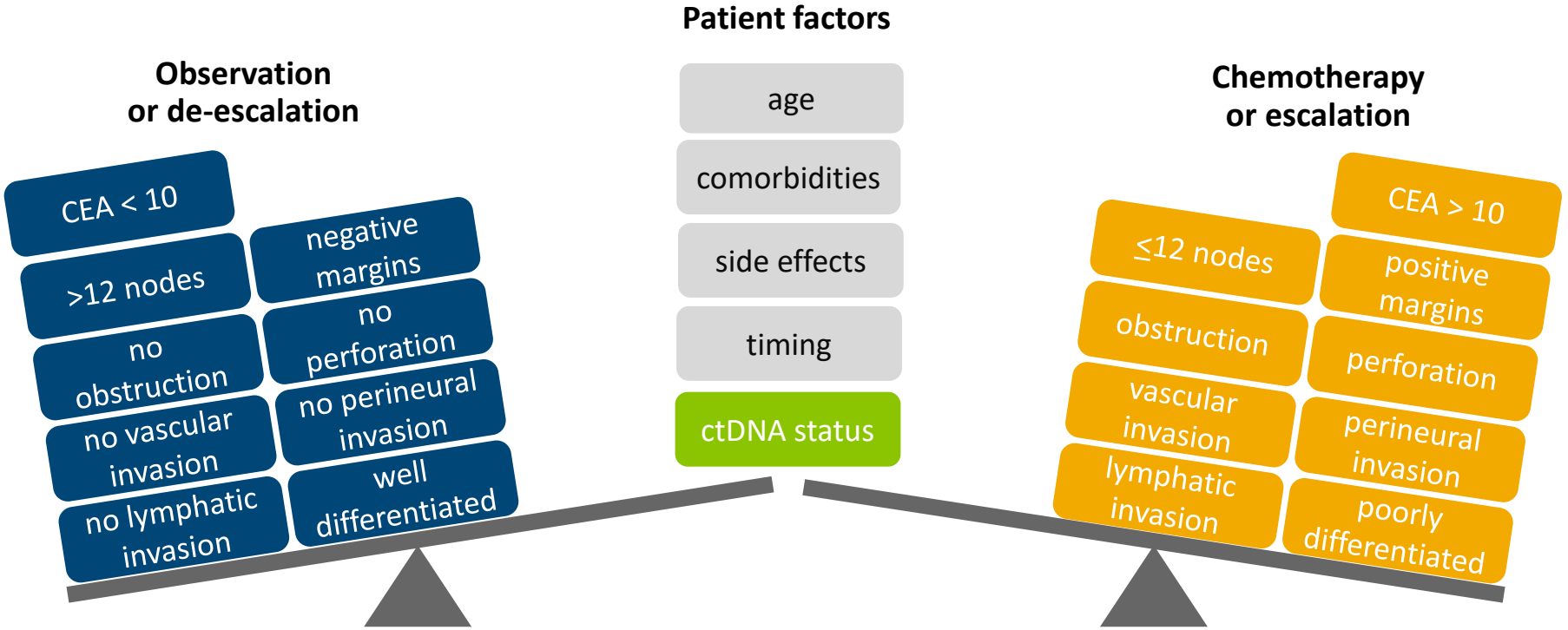
Advances in the Management of Colorectal Cancer: Recent Evidence and Emerging Treatment Paradigms

John Strickler, MD
Professor of Medicine
Duke University
February 10, 2026

Question: My patient has resected stage II/III colon cancer (MSS).
Can MRD testing be used to guide decisions?

Factors that influence adjuvant chemotherapy: T3N0 colon cancer



DYNAMIC Study Design

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

Tie et al., N Engl J Med 2022;386:2261-72.Presented at 2022 ASCO Annual Meeting

DYNAMIC: Adjuvant chemotherapy given less in the ctDNA-guided management group

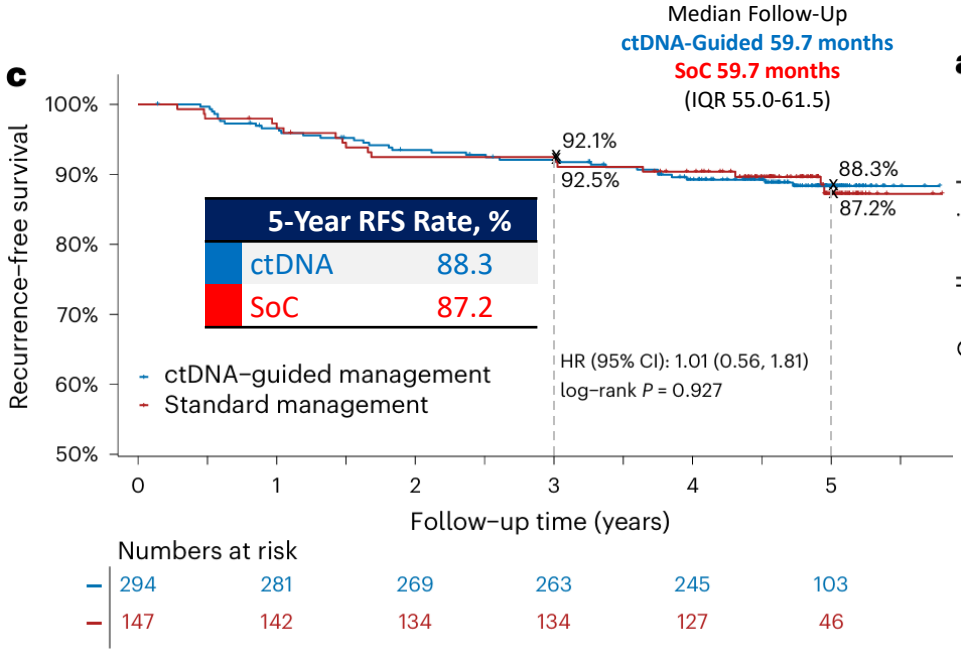
Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Tie et al., N Engl J Med 2022;386:2261-72.Presented at 2022 ASCO Annual Meeting

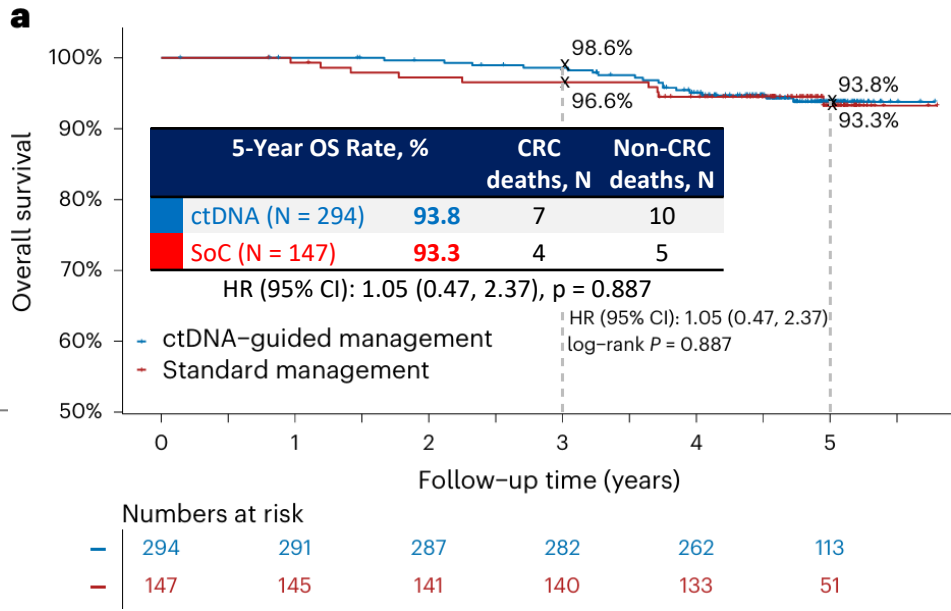
DYNAMIC: Updated 5-year RFS and Overall survival

Difference in 5-year RFS rate +1.1%
(95% CI for difference, -5.8 to 8.0%)

Updated 5-Year RFS Analysis



Overall Survival



- **ctDNA-guided MRD-based adjuvant therapy significantly reduced the proportion of patients receiving postoperative adjuvant therapy compared to SOC based on conventional clinicopathological factors, while demonstrating non-inferiority in 5-year RFS/OS.**

Tie J, et al. Nature Medicine 2025

DYNAMIC-III Study Design

Randomized phase II/III trial: ctDNA-informed escalation versus standard management

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumor-Informed ctDNA Analysis
(SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- **ctDNA-Negative → De-escalate**
- **ctDNA-Positive → Escalate**

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

Stratified by clinical risk (low vs high) and sites

Pre-Planned SoC → Escalation

No chemotherapy → 5FU/Cape
5FU/Cape → 6M Oxaliplatin doublet
3M Oxaliplatin doublet → 6M Doublet or ≥ 3M FOLFOXIRI
6M Oxaliplatin doublet → ≥ 3M FOLFOXIRI

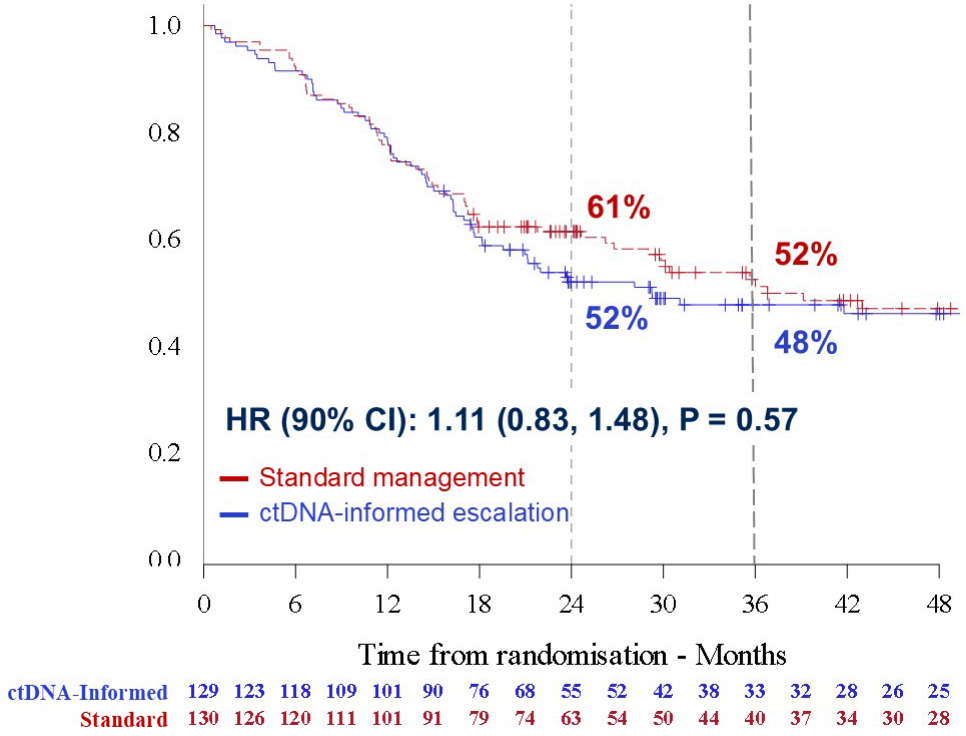
Primary Analysis of ctDNA-Positive Cohort: Endpoints to be Presented

Primary: 2 years RFS	**Secondary:** safety, end-of-treatment (EoT) ctDNA clearance
	Exploratory: post-operative ctDNA levels

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ASCO Annual Meeting

DYNAMIC-III: Recurrence-Free Survival for ctDNA+

Randomized phase II/III trial: ctDNA-informed escalation versus standard management



	Total	Events	Median RFS (mths)	2-year RFS (90% CI)	3-year RFS (90% CI)
ctDNA	129	66	29.24	52% (44, 59)	48% (40, 55)
SoC	130	62	36.80	61% (54, 68)	52% (44, 60)

Median follow-up 42.2 months (0.78 - 63.0)

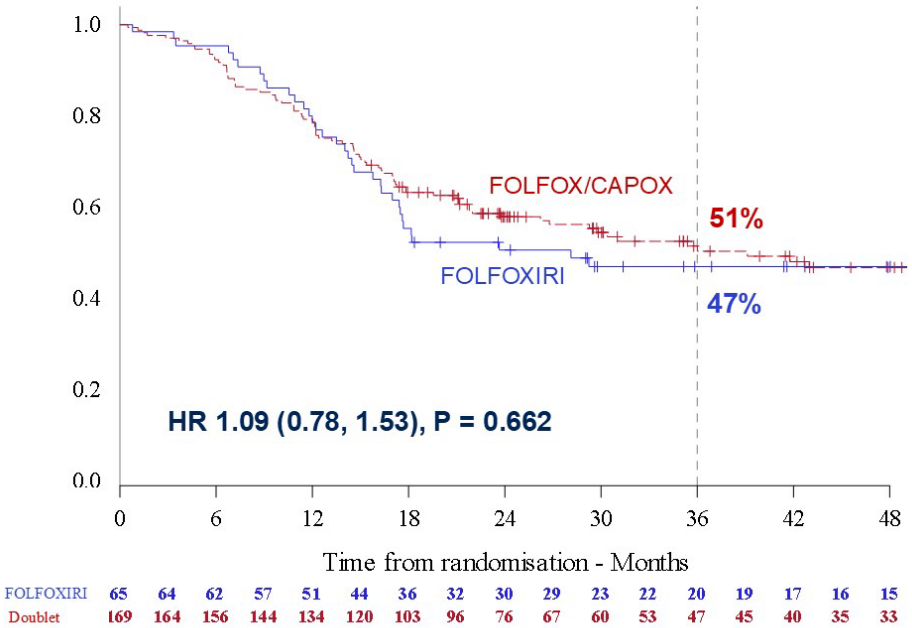
Data cut-off: 14 Nov 2024

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ASCO Annual Meeting

DYNAMIC-III: FOLFOXIRI vs FOLFOX/CAPOX

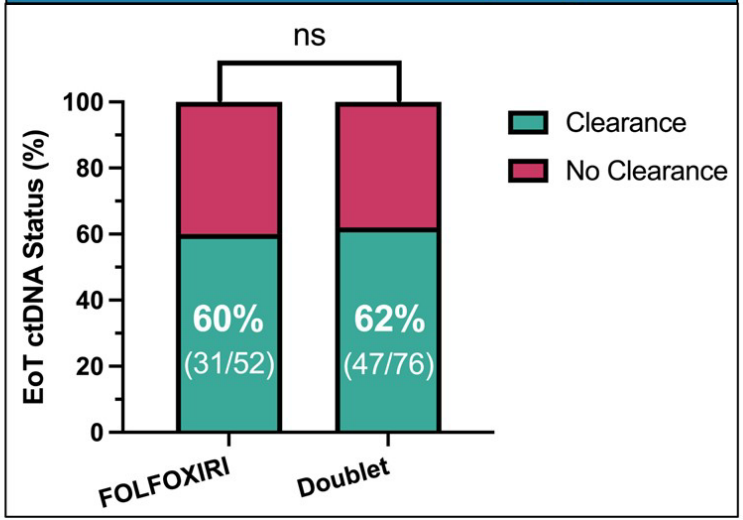
Randomized phase II/III trial: ctDNA-informed escalation versus standard management

Recurrence free survival



	TDMM/mL, median (IQR)	P
FOLFOXIRI	0.28 (0.06, 1.78)	0.236
Doublet	0.15 (0.06, 0.97)	

ctDNA Clearance Rate by Regimen



Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ASCO Annual Meeting

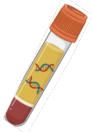
DYNAMIC-III Study Design

Randomized phase II/III trial: ctDNA-informed de-escalation versus standard management

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumour-Informed ctDNA Analysis
(SaferSeqS[1] targeted CRC panel)



W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- ctDNA-Negative ➔ De-escalate
- ctDNA-Positive ➔ Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Pre-Planned SoC ➔ De-escalation

6M FP	➔ No chemo or 3M FP
3M Oxaliplatin + FP	➔ 3-6M FP
6M Oxaliplatin + FP	➔ 3M Oxaliplatin + FP or 6M FP

FP = fluoropyrimidine

Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

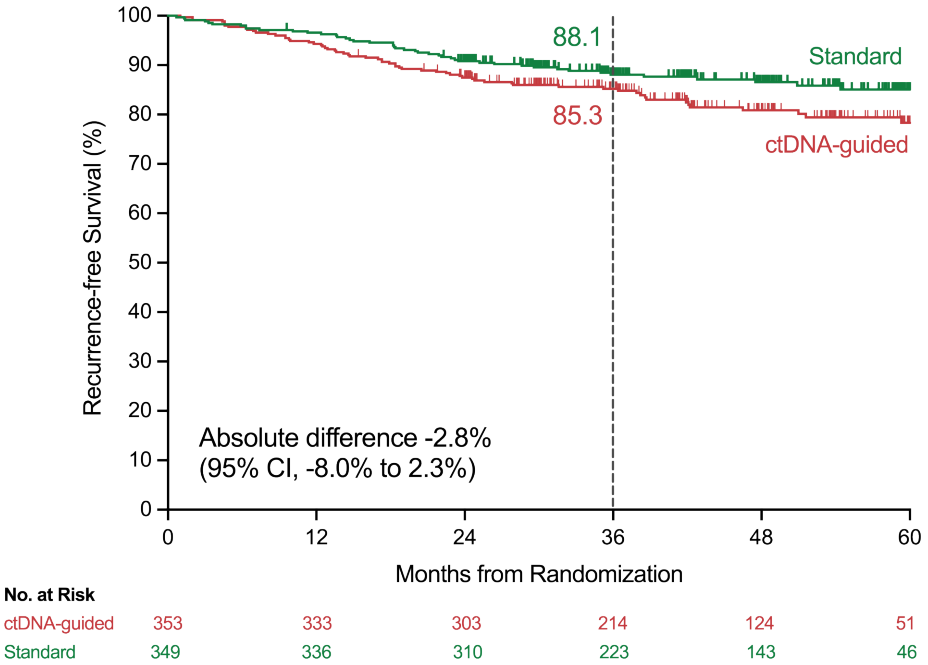
Stratified by clinical risk (low vs high) and sites

Primary Analysis of ctDNA-Negative Cohort: Endpoints to be Presented Here	
Primary: 3-year recurrence-free survival (RFS)	Secondary: treatment adherence, safety

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ESMO Congress

DYNAMIC-III: RFS for ctDNA negative

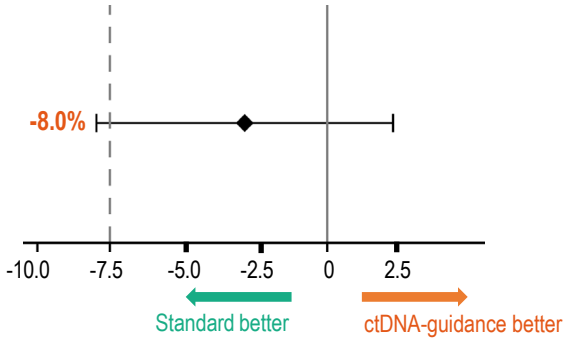
Randomized phase II/III trial: ctDNA-informed de-escalation versus standard management



Median follow-up 47 months (0.68 - 67.0)

Arm	Total	Events	3-year RFS (95% CI)
ctDNA	353	63	85.3% (81, 89)
Standard	349	45	88.1% (84, 91)

Absolute Difference in 3-year RFS (95% CI)

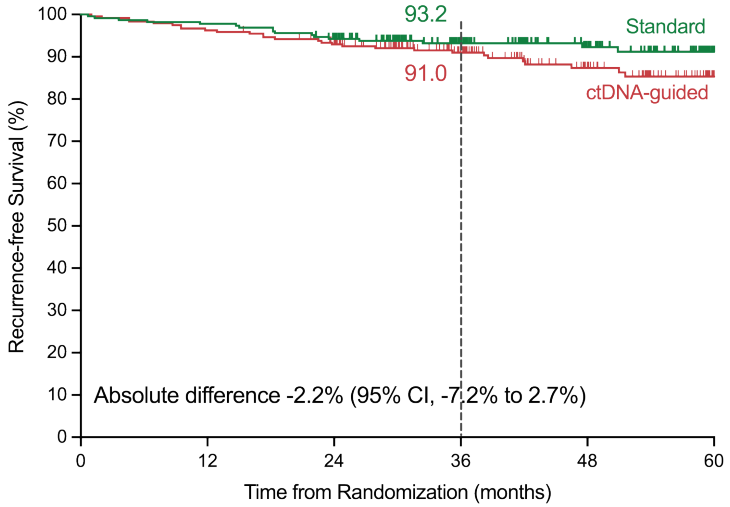


Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ESMO Congress

DYNAMIC-III: RFS for ctDNA negative

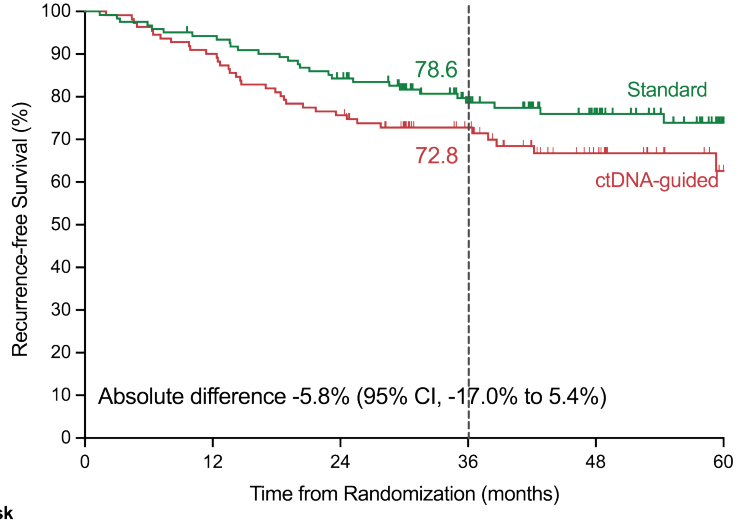
Randomized phase II/III trial: ctDNA-informed de-escalation versus standard management

Clinical Low Risk (T1-3N1)



No. at Risk						
ctDNA-guided	242	233	219	160	93	39
Standard	227	222	209	152	95	32

Clinical High Risk (T4 and/or N2)



No. at Risk						
ctDNA-guided	111	100	84	54	31	12
Standard	122	114	101	71	48	14

Tie et al., Nature Med 2025 Dec; 31(12):4291-4300. Presented at 2025 ESMO Congress

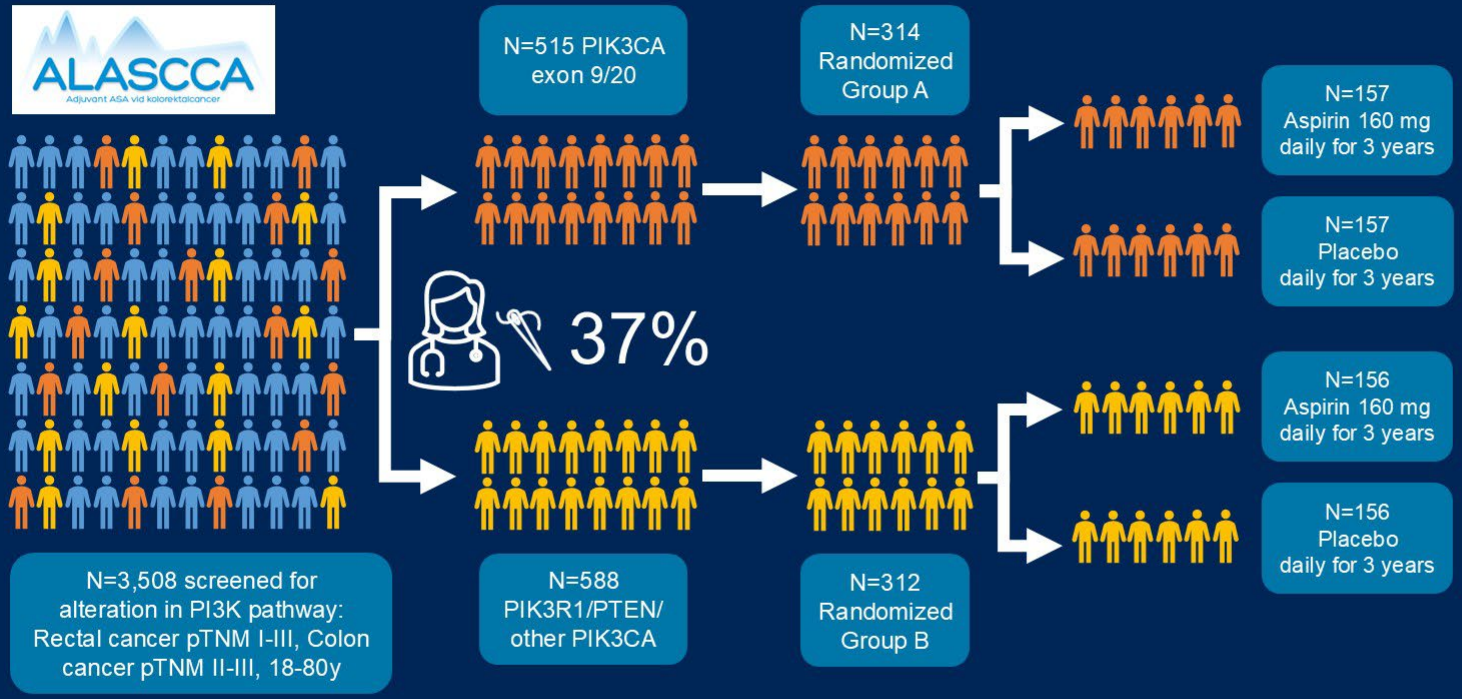
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 18, 2025 VOL. 393 NO. 11

Low-Dose Aspirin for PI3K-Altered Localized Colorectal Cancer

A. Martling,[1,2] I. Hed Myrberg,[3] M. Nilbert,[4] H. Grönberg,[5] F. Granath,[3] M. Eklund,[5] T. Öresland,[6,7] L.H. Iversen,[8] C. Haapamäki,[9] M. Janson,[10] K. Westberg,[1,11] J. Segelman,[1,12] U. Ersson,[13] M. Prytz,[14,15] E. Angenete,[15,16] R. Bergström,[5] M. Mayrhofer,[5,17] B. Glimelius,[18] and J. Lindberg,[19] for the ALASCCA Study Group*

The ALASCCA Trial (NCT02647099)



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

April 2016: Start of screening

July 2016: First patient randomized

July 2021: Last patient randomized

July 2024: Complete 3-year follow-up

Patient Characteristics

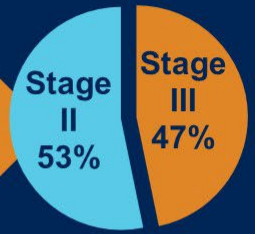
626 patients randomized

Median age 66 years (range 31-80)

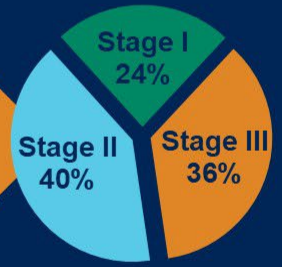
52% Females

67% Colon cancer
33% Rectal cancer

pTNM Stage in colon cancer patients



pTNM Stage in rectal cancer patients

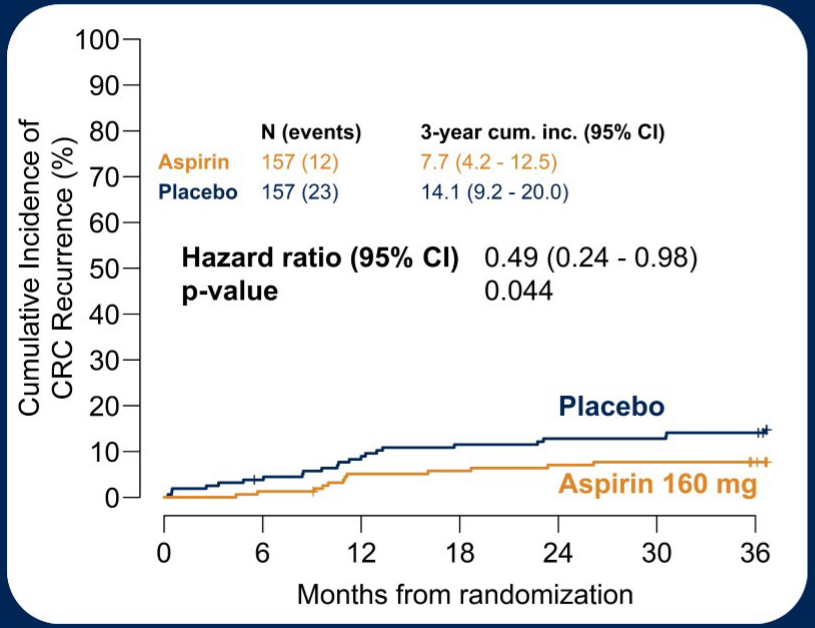


50% of rectal cancer patients given neoadjuvant therapy

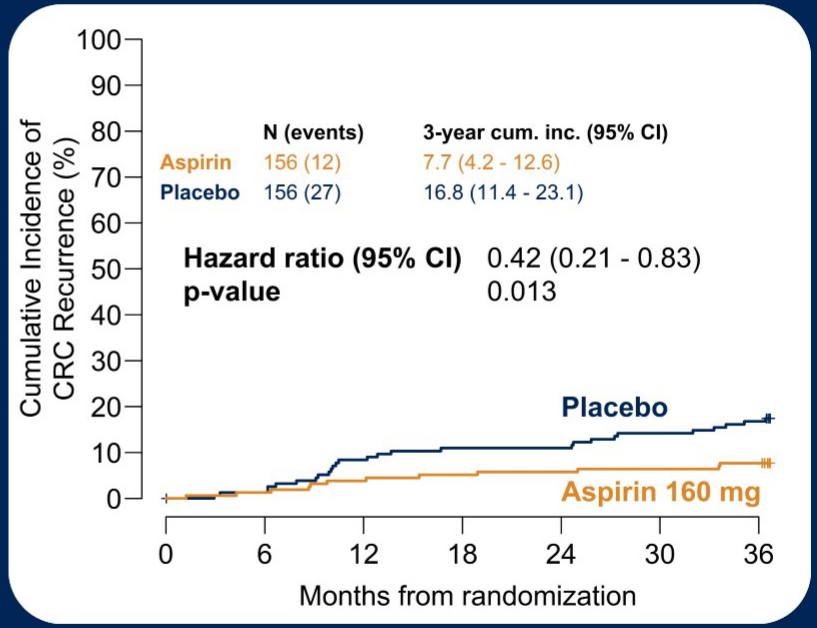
50% of colon cancer patients given adjuvant therapy

Primary Outcome: CRC Recurrence

Group A (PIK3CA Exons 9/20)

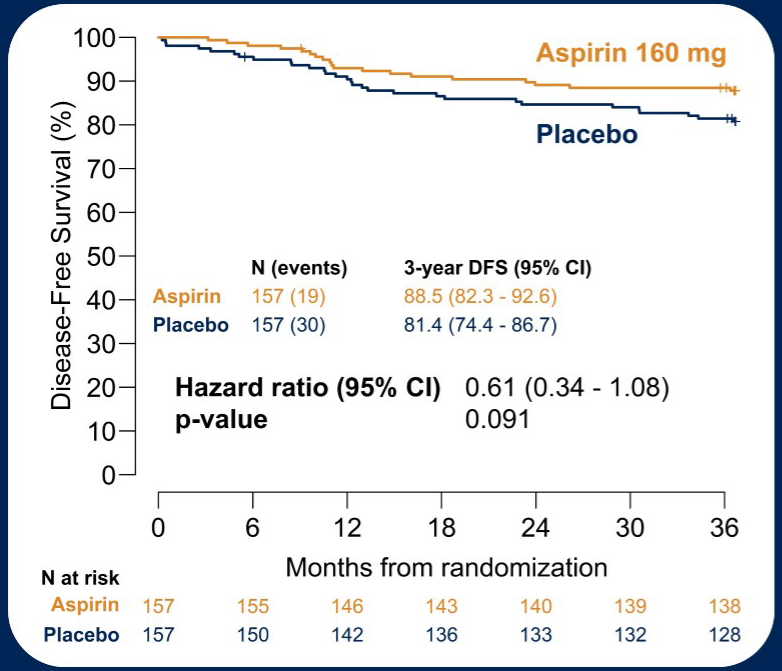


Group B (PIK3R1/PTEN/Other PIK3CA)



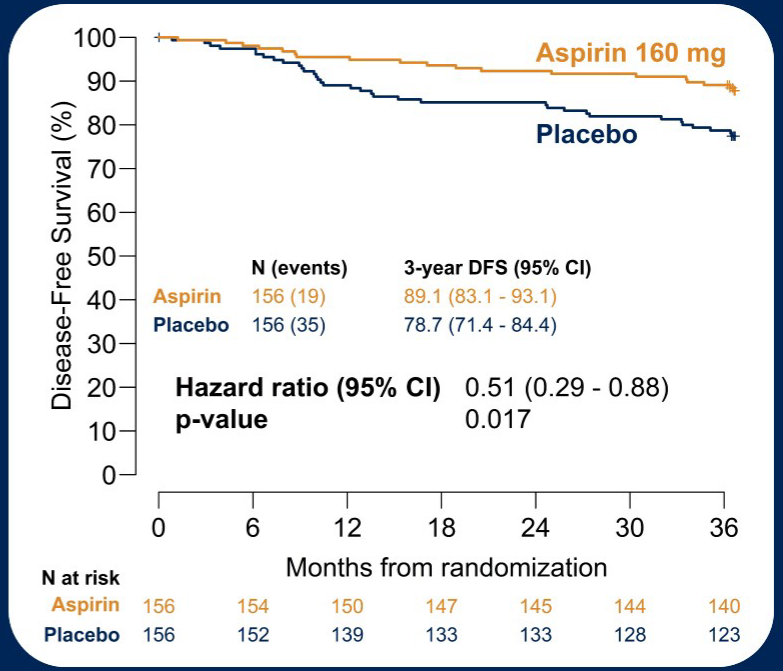
Secondary Outcome: Disease-Free Survival*

Group A (PIK3CA Exons 9/20)



*Events: CRC local recurrence, CRC distant metastases, new other primary cancer, death of any cause

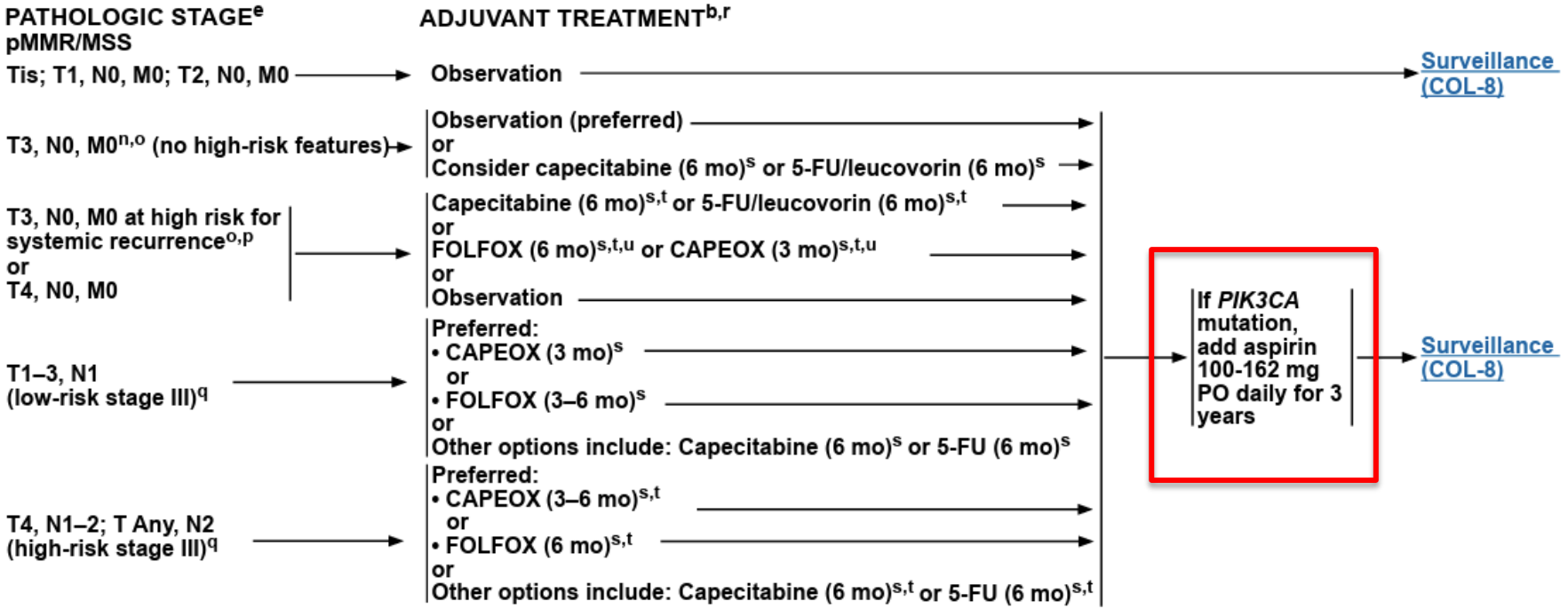
Group B (PIK3R1/PTEN/Other PIK3CA)



National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2025
pMMR/MSS Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion



Research

JAMA Oncology | Original Investigation

Predictive Role of Circulating Tumor DNA in Stage III Colon Cancer Treated With Celecoxib

A Post Hoc Analysis of the CALGB (Alliance)/SWOG 80702 Phase 3 Randomized Clinical Trial

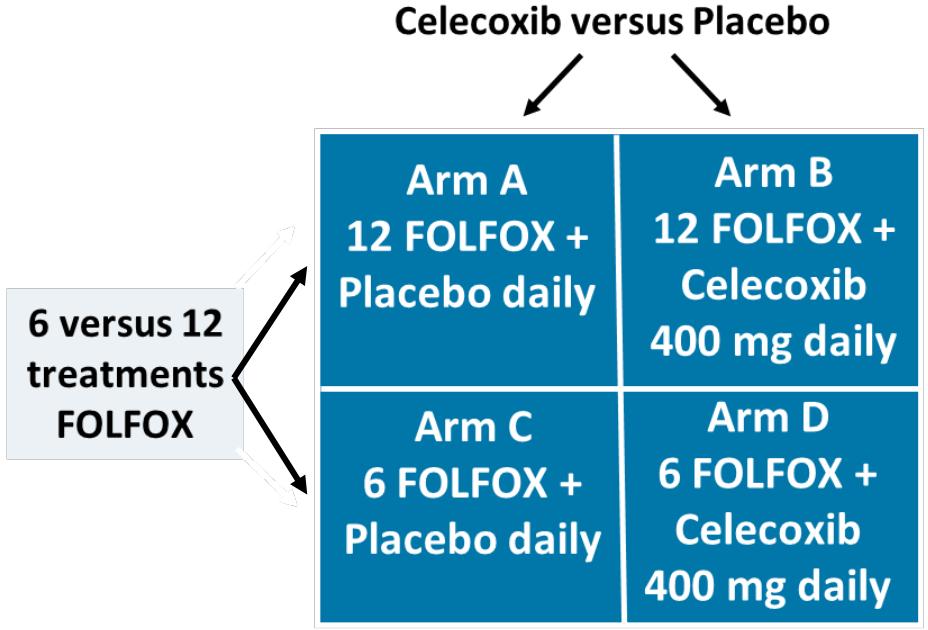
George Q. Zhang, MD, MPH; Jeffrey A. Meyerhardt, MD, MPH; Qian Shi, PhD; Tyler Twombly, BS; Levi Pederson, MS; Chao Ma, MS; Juha P. Väyrynen, MD, PhD; Melissa Zhao, MD, MS; Yasutoshi Takashima, MD, PhD; Ardaman Shergill, MD; Pankaj Kumar, MD; Felix Couture, MD; Philip Kuebler, MD; Smitha Krishnamurthi, MD; Benjamin Tan, MD; Eileen M. O'Reilly, MD; Marios Giannakis, MD, PhD; Shuji Ogino, MD, PhD; Adham Jurdi, MD; Shruti Sharma, PhD; Alexey Aleshin, MD; Anthony F. Shields, MD, PhD; Jonathan A. Nowak, MD, PhD

Zhang et al., *JAMA Oncol*. Published online December 4, 2025. doi:10.1001/jamaoncol.2025.5144

CALGB/SWOG 80702 trial design

Key eligibility criteria

- Resected adenocarcinoma of the colon without metastatic disease
- At least one pathologically confirmed positive lymph node or N1c disease as defined in AJCC version 7
- Patients ineligible if they use NSAIDs at any dose more than 2x / week or aspirin at more than 325 mg 3x / week. Low-dose aspirin not exceeding 100 mg/day *permitted*

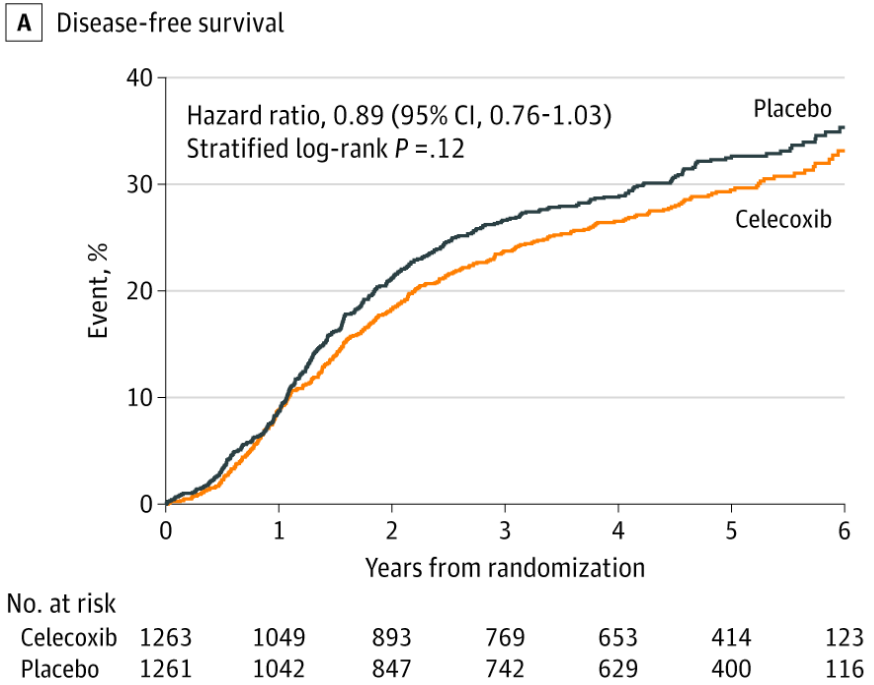


Celecoxib/placebo continued for a total of 3 years from the day study drug was initiated

Target sample size = 2,500
Actual final accrual = 2,526

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

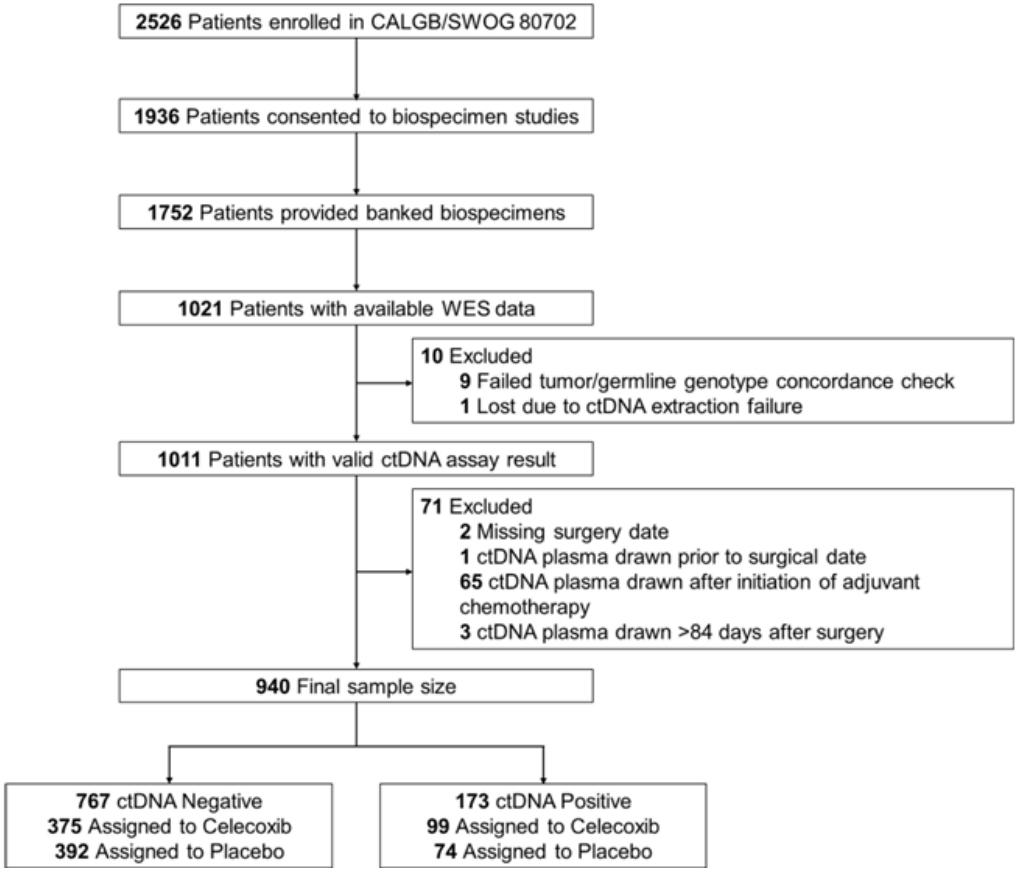
CALGB/SWOG 80702: Survival according to adjuvant celecoxib



- Effect of celecoxib treatment did not significantly differ according to assigned duration of adjuvant chemotherapy
- However, the HR of 0.89 and the Kaplan-Meier curve separation implied a potential benefit in subgroups of participants
- Post-hoc analysis: Investigators evaluated the predictive utility of ctDNA to identify patients who may benefit from celecoxib

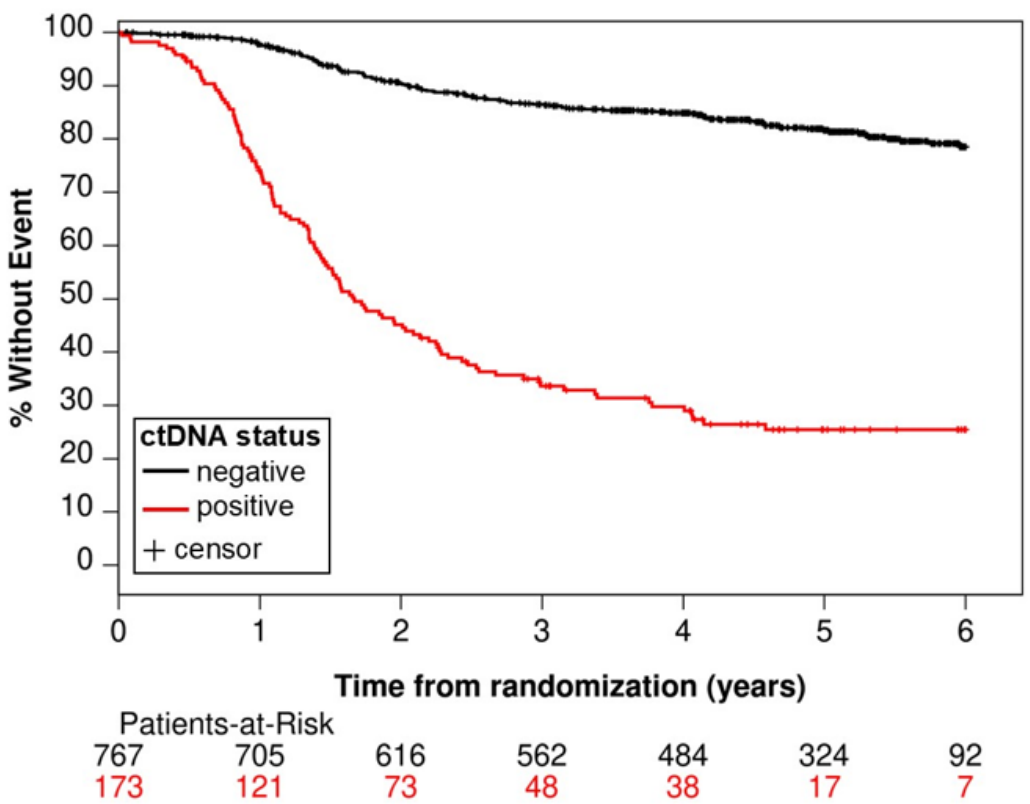
Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

Study composition for ctDNA analysis



Zhang et al., *JAMA Oncol*. Published online December 4, 2025. doi:10.1001/jamaoncol.2025.5144

Disease-free survival by ctDNA status

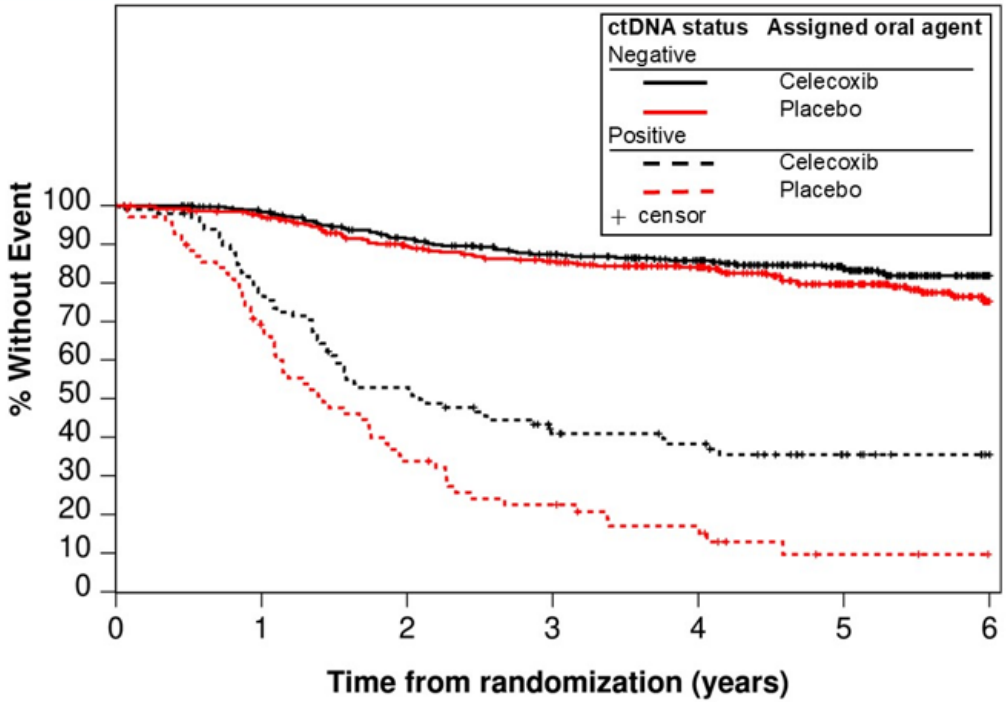


ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]
Negative	131/767	Reference	86.5 (84.0-89.1%)
Positive	118/173	7.14 (5.54-9.21)	33.7 (27.1-41.8%)
Logrank P-value: <0.0001[3]			

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Log-rank test

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

Disease-free survival by ctDNA status and celecoxib use

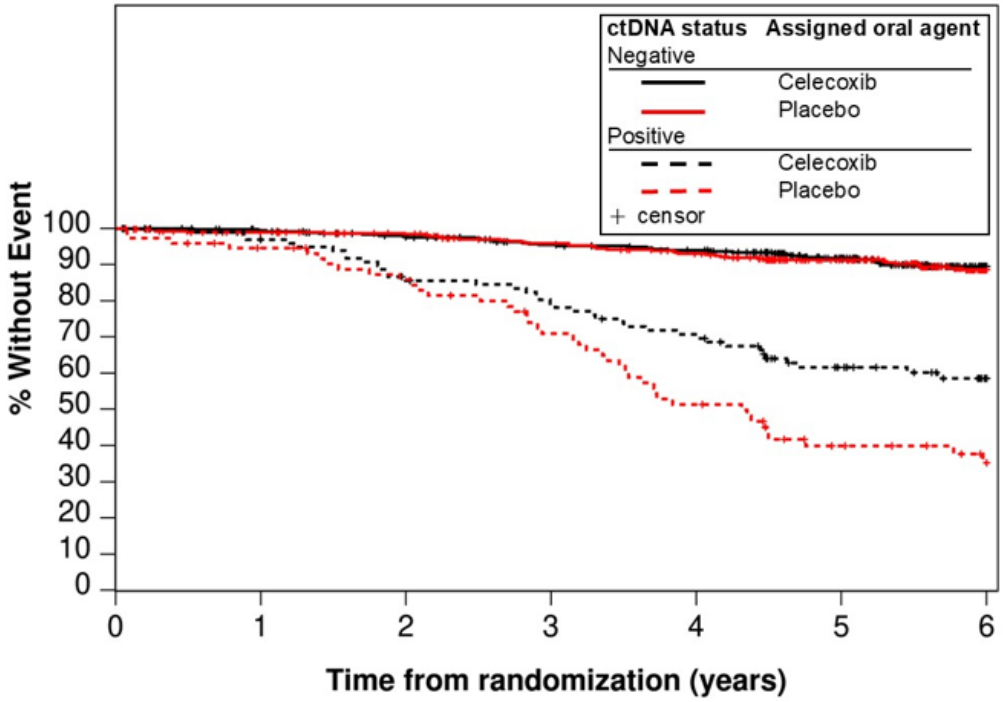


Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)	
Placebo	57/74	Reference	22.6 (14.3-35.5%)	
Interaction P-value: 0.1359[3]				

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

Overall survival by ctDNA status and celecoxib use



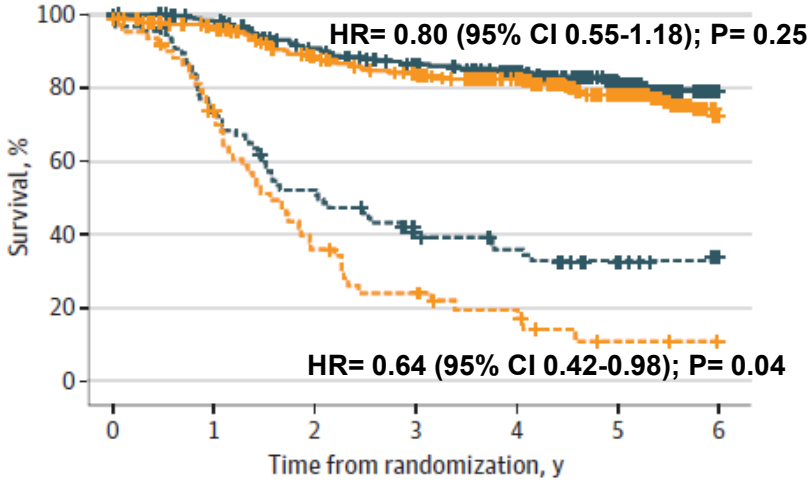
Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	5 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.5098[4]
Celecoxib	36/375	0.86 (0.55-1.35)	91.8 (88.9-94.7%)	
Placebo	41/392	Reference	91.3 (88.4-94.3%)	
Positive				0.0135[4]
Celecoxib	41/99	0.58 (0.38-0.90)	61.6 (52.4-72.4%)	
Placebo	44/74	Reference	39.9 (29.6-53.8%)	
Interaction P-value: 0.2061[3]				

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

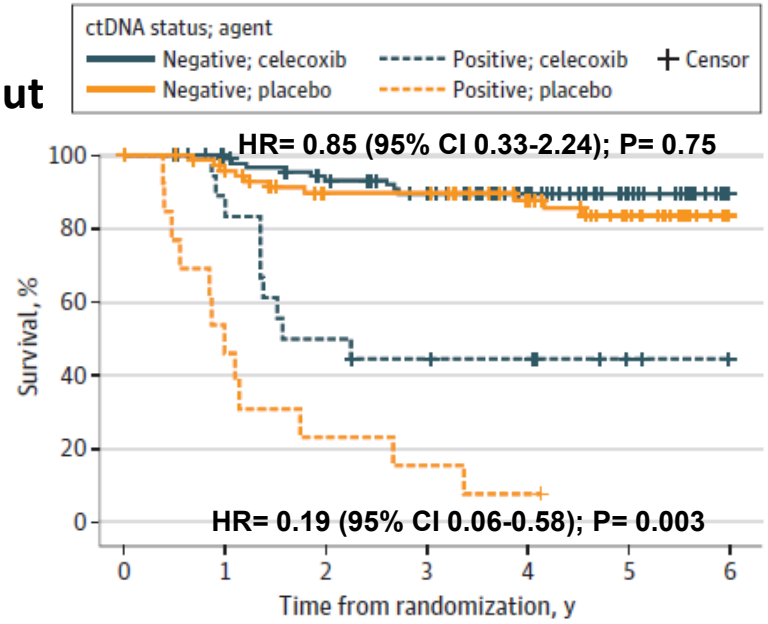
DFS by ctDNA status and celecoxib use: PIK3CA status

PIK3CA wild-type



No. at risk							
Negative; celecoxib	278	260	229	207	184	124	33
Negative; placebo	318	292	252	228	195	132	35
Positive; celecoxib	81	60	42	27	23	13	6
Positive; placebo	61	39	19	12	8	2	0

PIK3CA mut

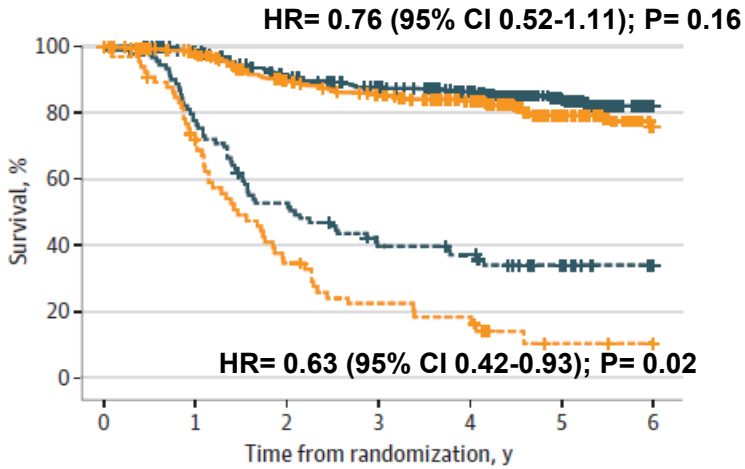


No. at risk							
Negative; celecoxib	97	88	80	72	59	38	16
Negative; placebo	74	65	55	55	46	30	8
Positive; celecoxib	18	16	9	7	6	2	1
Positive; placebo	13	6	3	2	1	0	0

Zhang et al., *JAMA Oncol*. Published online December 4, 2025. doi:10.1001/jamaoncol.2025.5144

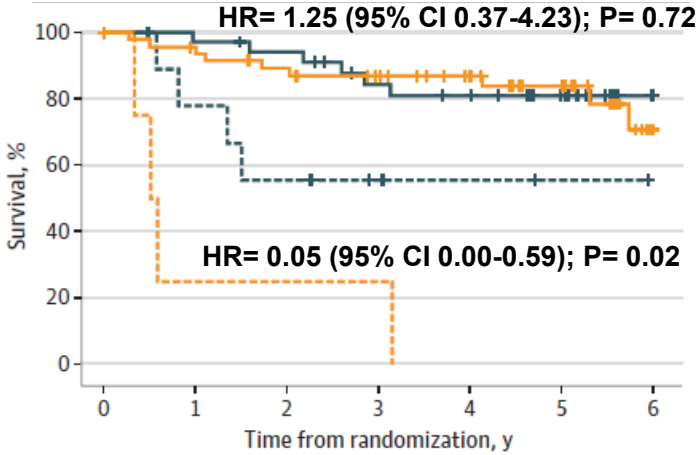
DFS by ctDNA status and celecoxib use: MSI status

Non-MSI-high



No. at risk							
Negative; celecoxib	340	315	278	254	220	147	47
Negative; placebo	344	313	267	247	212	140	40
Positive; celecoxib	89	69	46	31	27	14	7
Positive; placebo	70	44	21	13	9	2	0

MSI-H



No. at risk							
Negative; celecoxib	35	33	31	25	23	15	2
Negative; placebo	48	44	40	36	29	22	3
Positive; celecoxib	10	7	5	3	2	1	0
Positive; placebo	4	1	1	1	0	0	0

Zhang et al., *JAMA Oncol*. Published online December 4, 2025. doi:10.1001/jamaoncol.2025.5144

CALGB/SWOG 80702: Limitations

- Post hoc analysis
- ctDNA status not used to select patients for adjuvant celecoxib
- ctDNA status only measured at one timepoint- no measure of ctDNA clearance
- Only a subset of patients in CALGB/SWOG 80702 tested – may not be representative of general population
- Aspirin = celecoxib?

Zhang et al., *JAMA Oncol*. Published online December 4, 2025. doi:10.1001/jamaoncol.2025.5144

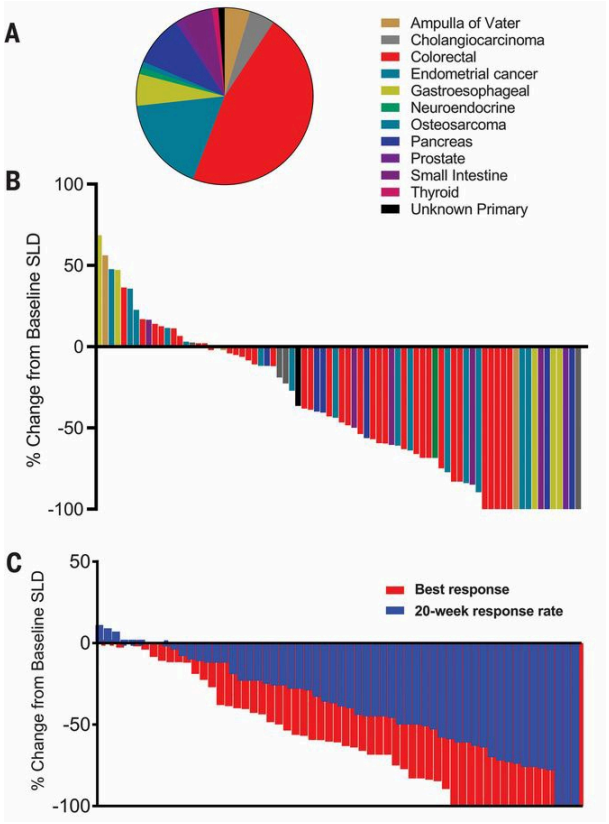
Question: My patient has resected stage II/III colon cancer (MSS). Can MRD testing be used to guide decisions?

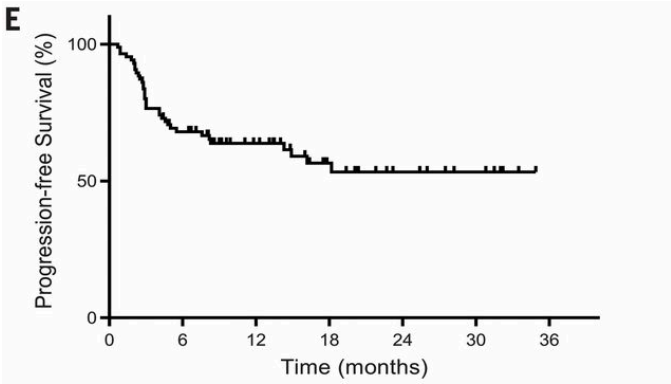
- MRD testing has demonstrated clinical utility for patients with stage II (T3N0, MSS) colon cancer
- For patients with stage III colon cancer, there is not yet evidence we can de-escalate treatment based on a negative result, or escalate treatment based on a positive result
- Aspirin reduces the risk of recurrence in patients with CRC who have a PI3K mutated tumor (and is part of the guidelines)
- Celecoxib can be considered for patients with MRD+ stage III colon cancer

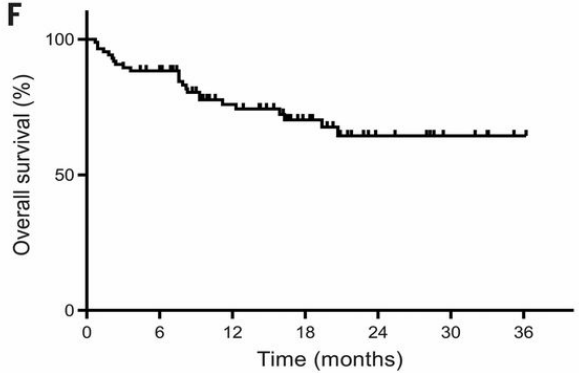
Question: What is the optimal management of MSI-High/ dMMR colorectal cancer?

Long-term response to immunotherapy (MSI-H)

Clinical response to pembrolizumab across 12 different tumor types with dMMR



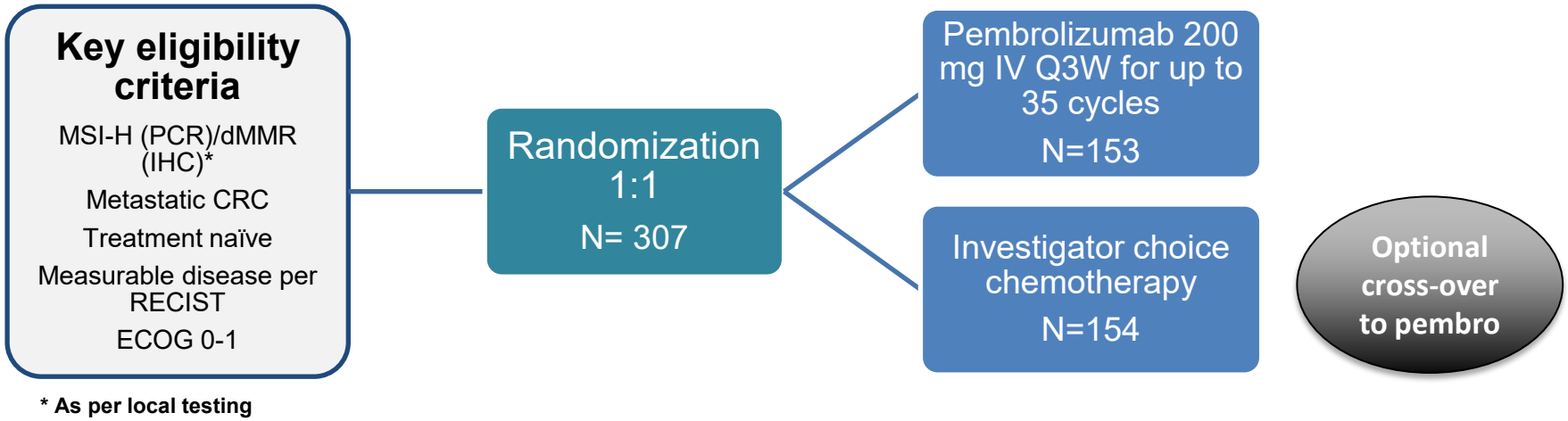




Le et al. *Science* 2017;357:409-413

KEYNOTE-177: 1L Pembrolizumab versus Chemotherapy

Phase 3, randomized, open-label, global multicenter study for 1L treatment of metastatic CRC (NCT02563002)



* As per local testing

Primary endpoints: Progression-free survival and overall survival
Secondary endpoints: ORR and safety

Andre et al., NEJM 2020; 383: 2207-2218

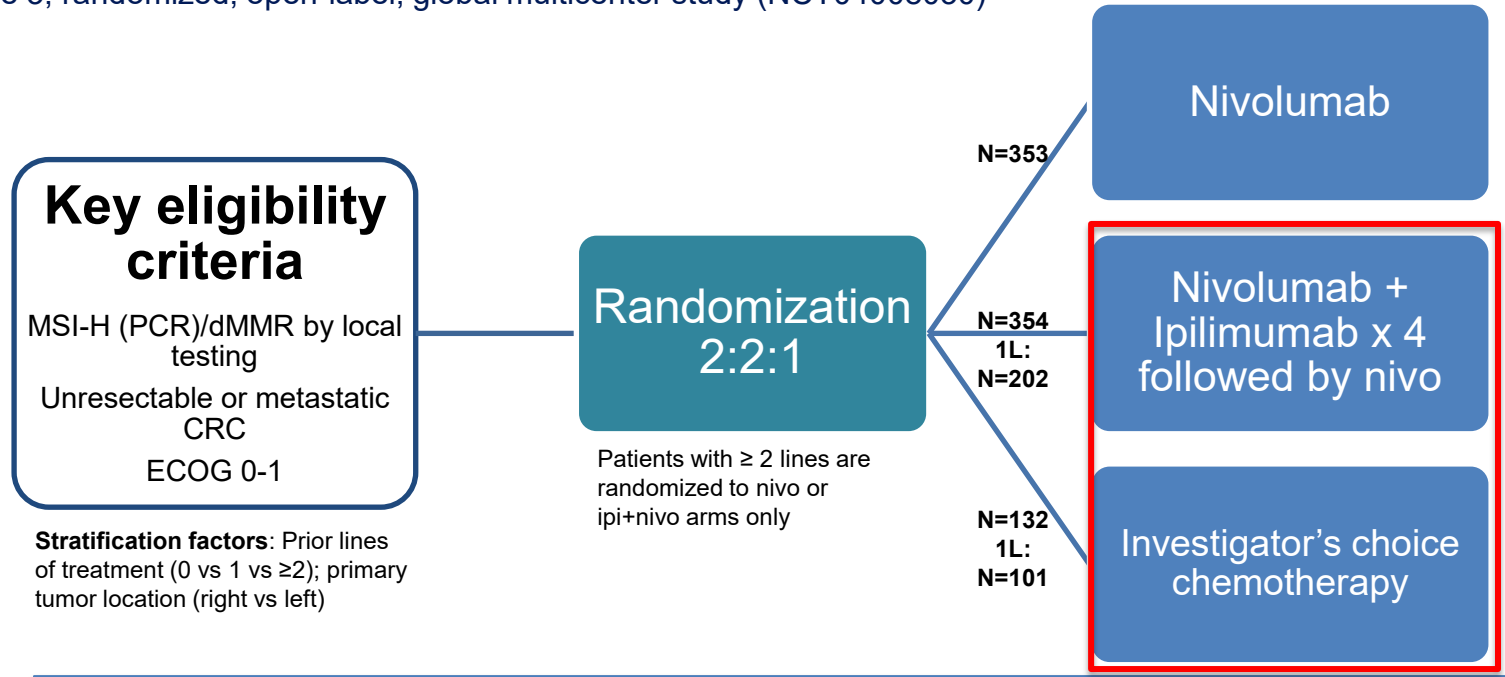
KEYNOTE-177: Key efficacy outcomes favor pembrolizumab

	Pembrolizumab (N= 153)	Chemotherapy (N= 154)	HR (95% CI)	*P*-value
PFS, months (95% CI)	**16.5 (5.4-38.1)**	**8.2 (6.1-10.2)**	**0.59 (0.45-0.79)**	**<0.001**
OS, months (95% CI)	Not reached	36.7 (27.6-NR)	0.74 (0.53-1.03)	0.036
ORR (95% CI)	43.8% (35.8-52.0)	33.1% (25.8-41.1)		
DOR, months (95% CI)	Not reached (2.3-41.4+)	10.6 (2.8-37.5+)		

Andre et al., NEJM 2020; 383: 2207-2218
Diaz et al., Lancet Oncol 2022; 23(5) 659-670.

CheckMate 8HW: Study Design

Phase 3, randomized, open-label, global multicenter study (NCT04008030)



Primary endpoint: In patients with centrally confirmed MSI-H/dMMR status PFS for nivo+ipi vs chemo in 1L and PFS for nivo+ipi vs nivo across all lines
Key secondary endpoints: OS, ORR, patient reported outcomes, safety

Andre et al., NEJM 2024; 391; 21: 2014-2026
Presented by Lenz et al at ASCO AM 2025

CheckMate 8HW: Ipi+nivo superior to chemotherapy (centrally confirmed MSI-H/dMMR)*

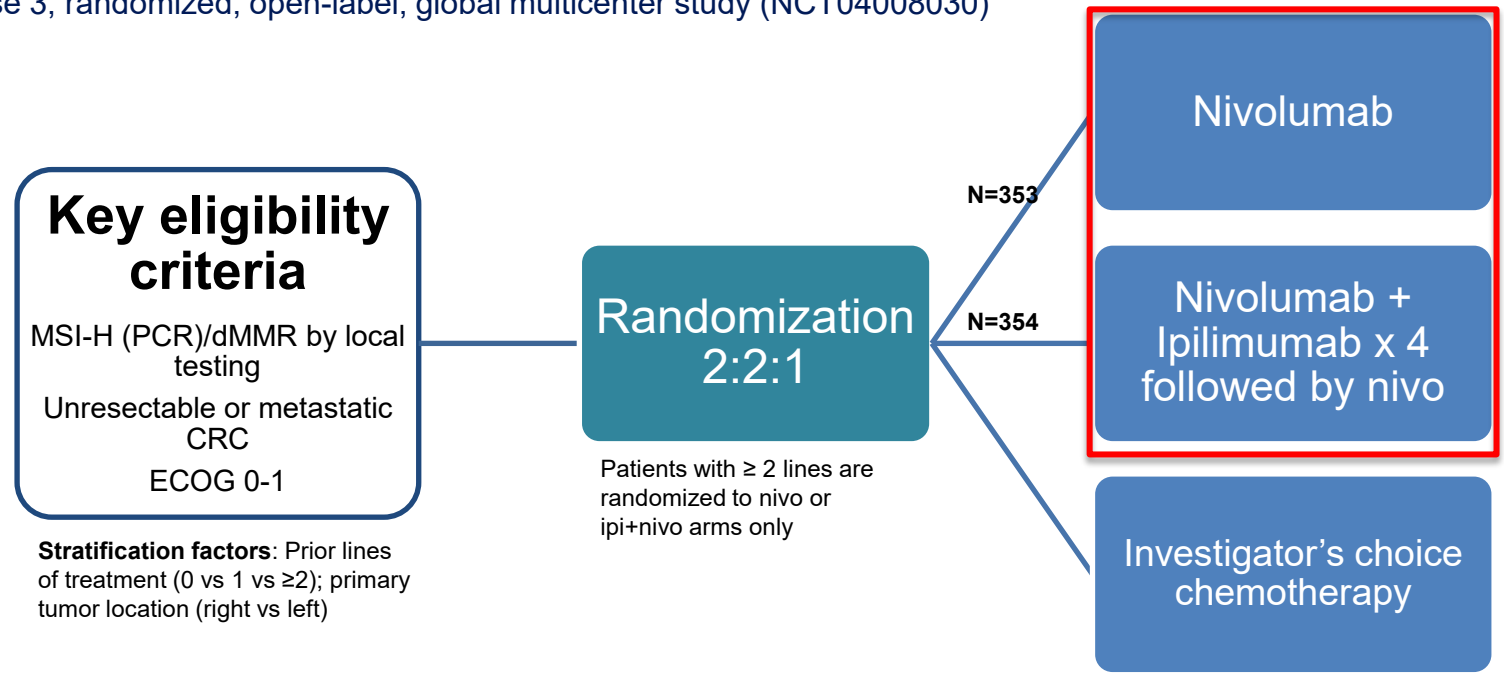
	1L NIVO + IPI (N= 171)	1L Chemo (N= 84)	HR (95% CI)	*P*-value
PFS, months (95% CI)	NR (54.1-NE)	5.9 (4.4-7.8)	0.21 (0.14-0.31)	< 0.0001
PFS2, months (95% CI)	NR (NE-NE)	30.3 (15.2-NE)	0.28 (0.18-0.44)	< 0.0001

* Per BICR

Andre et al., NEJM 2024; 391; 21: 2014-2026
Presented by Lenz et al at ASCO AM 2025

CheckMate 8HW: Study Design

Phase 3, randomized, open-label, global multicenter study (NCT04008030)



Primary endpoint: In patients with centrally confirmed MSI-H/dMMR status PFS for nivo+ipi vs chemo in 1L and PFS for nivo+ipi vs nivo across all lines
Key secondary endpoints: OS, ORR, patient reported outcomes, safety

Andre et al., Lancet 2025; online ahead of print
Presented by Lenz et al at ASCO AM 2025

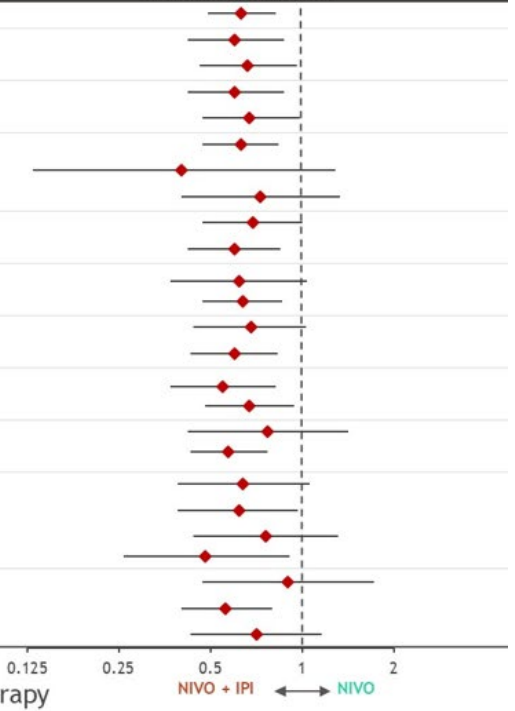
CheckMate 8HW: Ipi+nivo superior to nivolumab alone

	NIVO + IPI (N= 352)	NIVO (N= 351)	HR (95% CI)	*P*-value
PFS, months (95% CI)	NR (53.8-NE)	39.3 (22.1-NE)	0.62 (0.48-0.81)	0.0003
ORR (95% CI)	71% (65-76)	58% (52-64)		0.0011

Andre et al., Lancet 2025; online ahead of print
Presented by Andre et al at ASCO GI 2025; J Clin Oncol 43, 2025 (suppl 4; abstr LBA143)

CheckMate 8HW: PFS subgroup analysis

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	NIVO	
Overall (N = 582)		NR	39.3	0.63
Age, years	< 65 (n = 321)	NR	NR	0.60
	≥ 65 (n = 261)	NR	29.4	0.66
Sex	Male (n = 284)	NR	28.2	0.60
	Female (n = 298)	NR	NR	0.67
Region	US/Canada/Europe (n = 415)	NR	29.4	0.63
	Asia (n = 52)	NR	NR	0.40
	Rest of world (n = 115)	NR	NR	0.73
ECOG PS	0 (n = 313)	54.1	NR	0.69
	1 (n = 269)	NR	18.2	0.60
Tumor sidedness	Left (n = 152)	NR	NR	0.62
	Right (n = 430)	NR	33.2	0.64
Liver metastases[a,b]	Yes (n = 210)	NR	NR	0.68
	No (n = 368)	NR	33.2	0.60
Peritoneal metastases[a,b]	Yes (n = 226)	54.1	24.8	0.55
	No (n = 352)	NR	NR	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77
	< 1% (n = 427)	NR	24.8	0.57
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 156)	NR	44.3	0.64
	BRAF mutant (n = 179)	NR	25.9	0.62
	KRAS or *NRAS* mutant (n = 125)	NR	NR	0.76
	Unknown (n = 114)	54.1	38.1	0.48
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90
	No (n = 334)	NR	44.3	0.56
	Unknown (n = 156)	NR	33.2	0.71



- PFS consistently favored NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

[a]Per BICR. [b]Patients may have had more than one site of metastasis.

Andre et al., Lancet 2025; online ahead of print
Presented by Andre et al at ASCO GI 2025; J Clin Oncol 43, 2025 (suppl 4; abstr LBA143)

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.

Andre et al., Lancet 2025; online ahead of print
Presented by Andre et al at ASCO GI 2025; J Clin Oncol 43, 2025 (suppl 4; abstr LBA143)

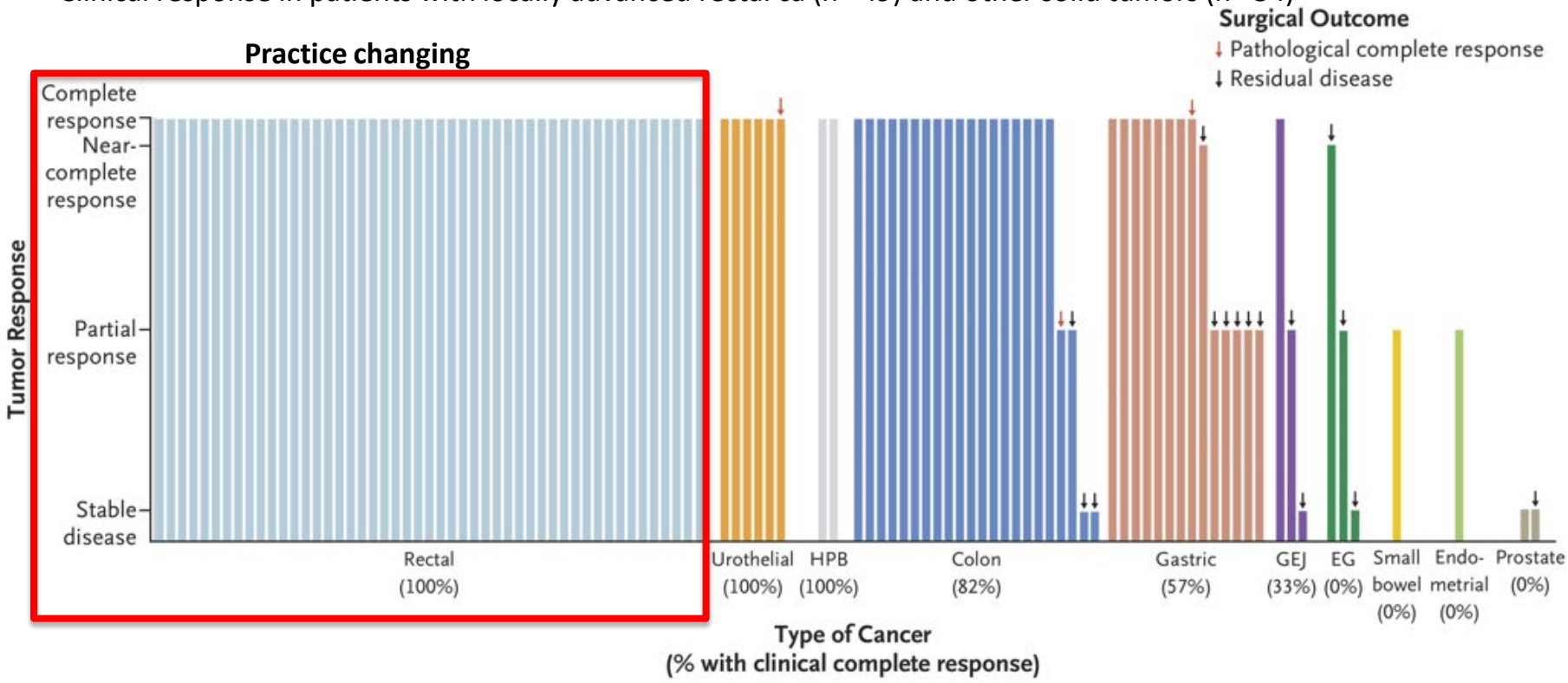
Immunotherapy for MSI-H metastatic CRC: Key points

- MSI-H disease is chemotherapy-resistant
- Immunotherapy (pembrolizumab and nivolumab +/- ipilimumab) is superior to conventional chemotherapy
- Nivolumab + ipilimumab is superior to nivolumab
- All patients with mCRC should received MSI testing at the moment of diagnosis and receive immunotherapy if they have MSI-H disease (unless contraindicated)

How should patients with non-metastatic MSI-H CRC be managed?

Dostarlimab (anti-PD-1) for MSI-H solid tumors

Clinical response in patients with locally advanced rectal ca (n= 49) and other solid tumors (n= 54)



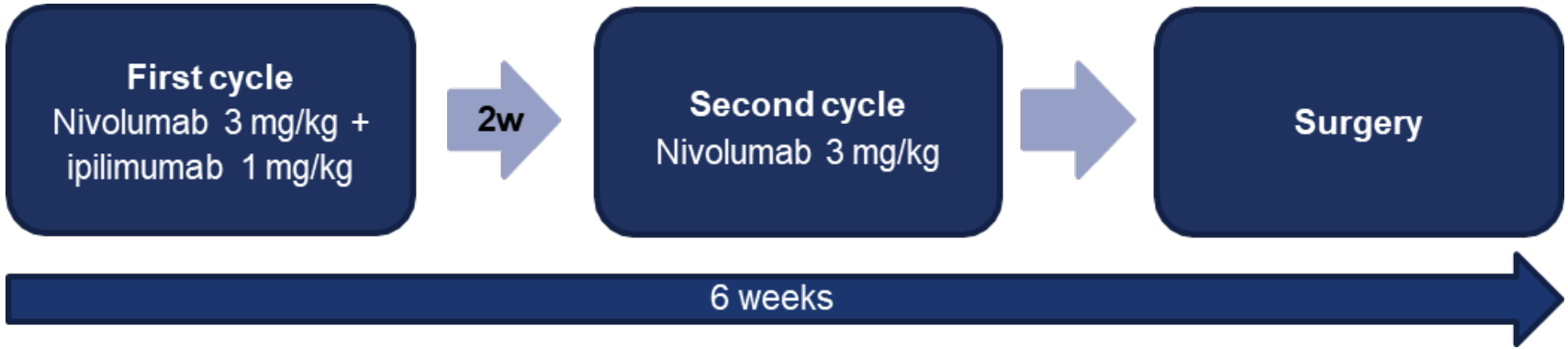
Cercek et al., *N Engl J Med* 2025;392:2297-2308

NICHE-2 Study Design

Investigator-initiated, non-randomized multicenter study

Key eligibility criteria

- Non-metastatic dMMR colon cancer, previously untreated
- cT3 and/or N+ based on radiographic staging
- No clinical or radiologic signs of obstruction or perforation



Chalabi et al., *Annals of Oncology* (2024) 35 (suppl_2): 1-72. Presented at ESMO 2024

Pathologic responses in NICHE-2

Pathologic response in **98%** of 111 patients in efficacy analysis

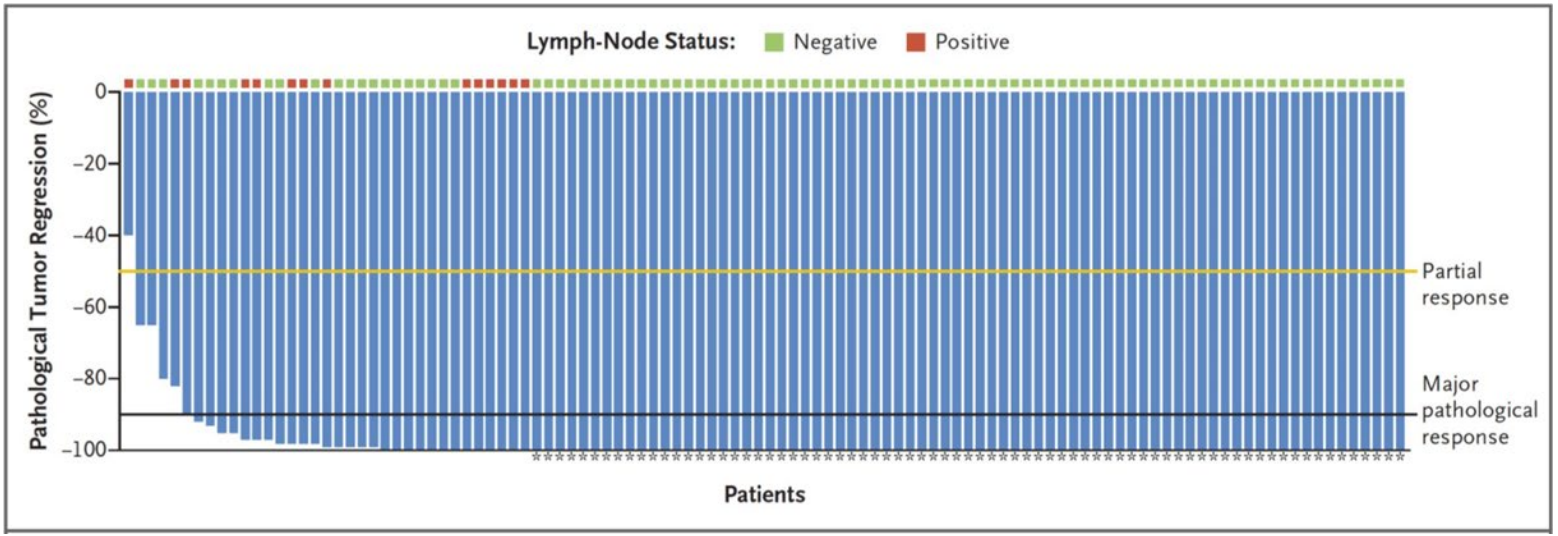
- Major pathologic response (≤10% residual viable tumor): **95%**
- Pathologic complete response: **68%**

Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease

- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

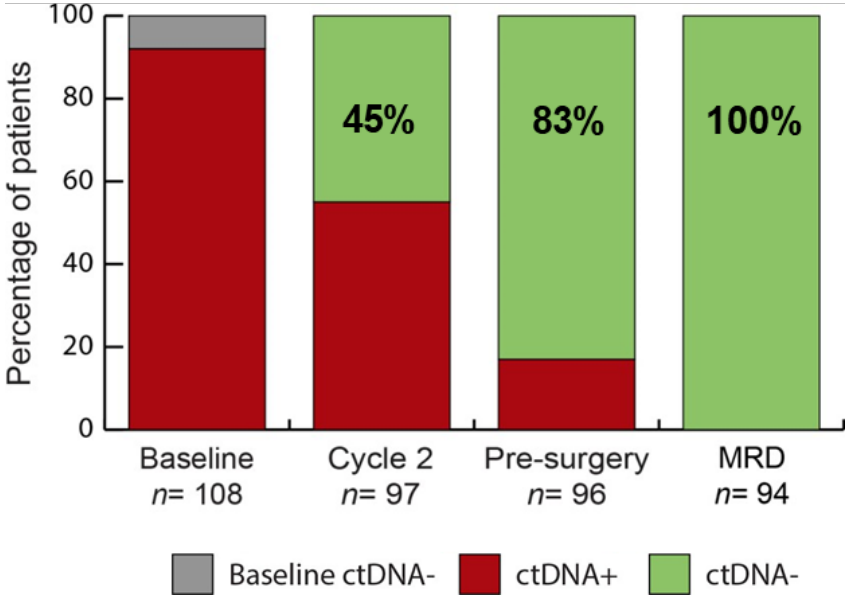
* 1 non-responder, 1 partial responder and 1 MPR

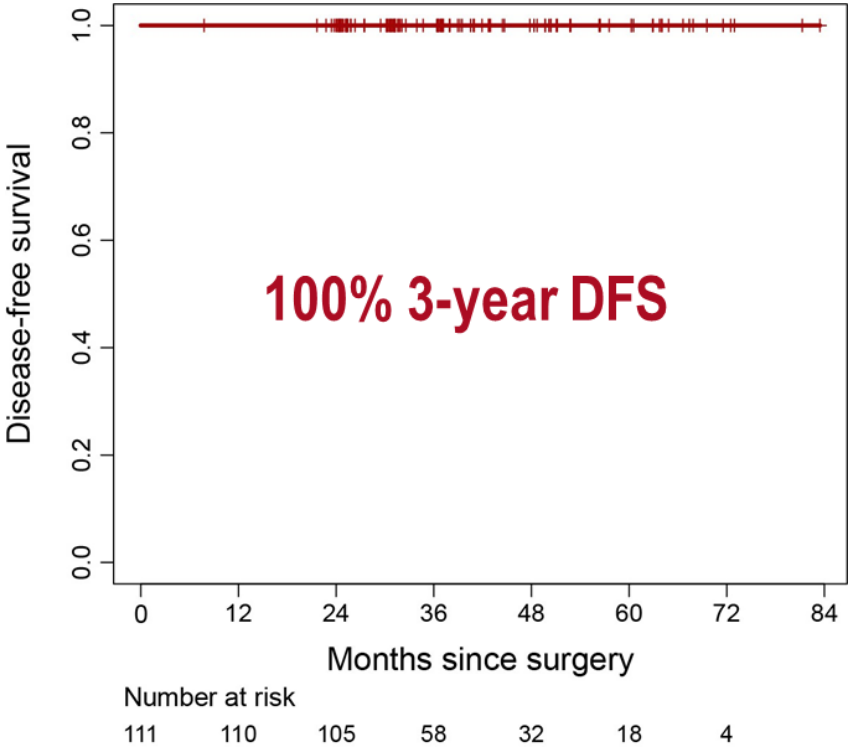


Chalabi et al., *Annals of Oncology* (2024) 35 (suppl_2): 1-72. Presented at ESMO 2024

Pathologic responses and MRD in NICHE-2

All patients were ctDNA negative at the MRD time point (3 weeks after surgery)

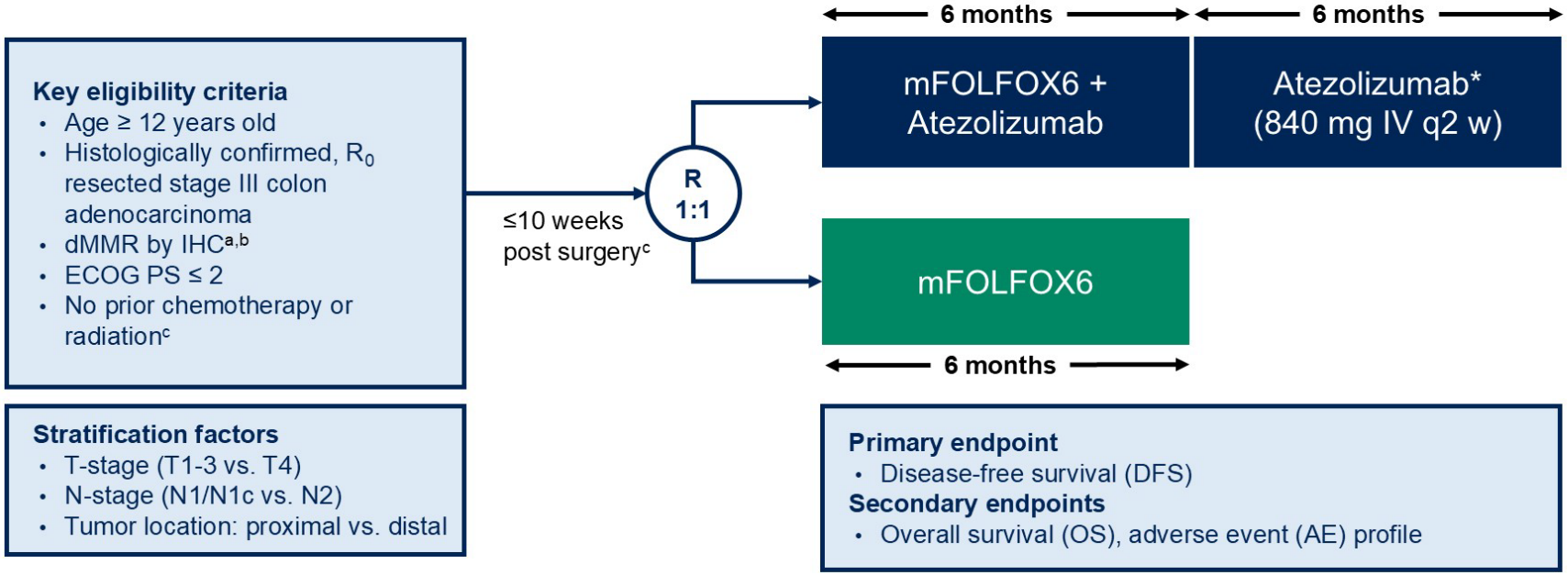




Chalabi et al., *Annals of Oncology* (2024) 35 (suppl_2): 1-72. Presented at ESMO 2024

ATOMIC Study Design

ATOMIC is a randomized, multicenter, open label phase 3 study

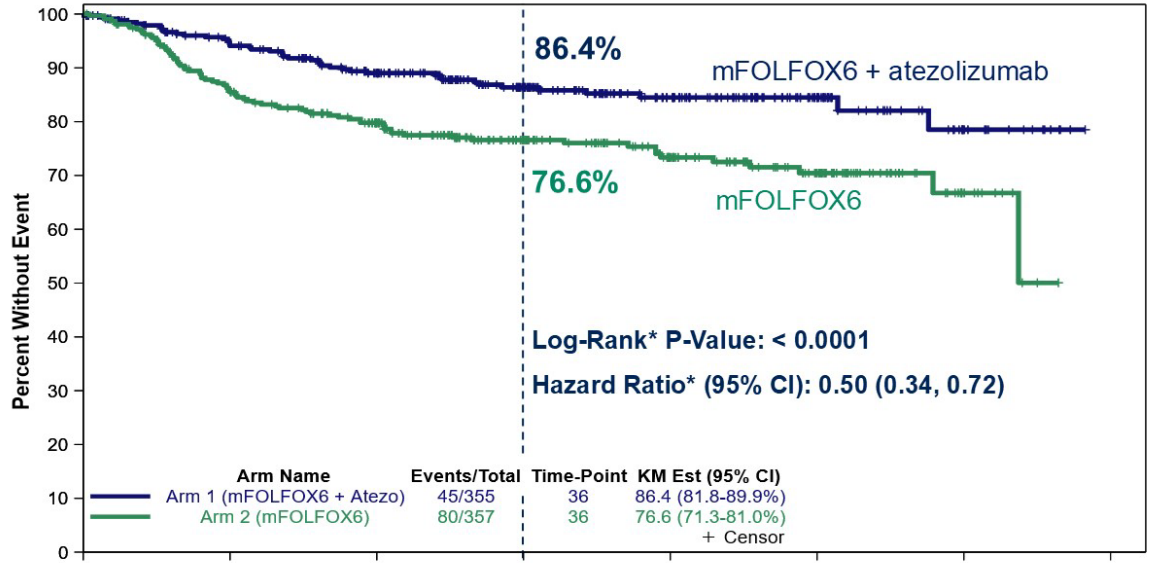


[a] **dMMR by immunohistochemistry (IHC) locally or at site-selected reference laboratory. Retrospective central confirmation of dMMR also performed.**
[b] Lynch syndrome included.
[c] One cycle of mFOLFOX6 prior to randomization permitted.

*Atezolizumab (anti-PD-L1)

Sinicrope et al., *J Clin Oncol* 43, 2025 (suppl 17; abstr LBA1). Presented at ASCO 2025

ATOMIC: DFS (primary endpoint)



Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

*Stratified by randomization factors

Median follow-up = 37.2 mos

Sinicrope et al., *J Clin Oncol* 43, 2025 (suppl 17; abstr LBA1). Presented at ASCO 2025

Question: What is the optimal management of MSI-High/ dMMR colorectal cancer?

- Stage IV disease: Nivolumab + ipilimumab
- Locally advanced rectal cancer: Neoadjuvant anti-PD-1
- Locally advanced colon cancer: 2 options
  - Neoadjuvant nivolumab + ipilimumab
  - Adjuvant FOLFOX + atezolizumab (stage III)

Question: What is the optimal management of chemotherapy refractory metastatic colorectal cancer?

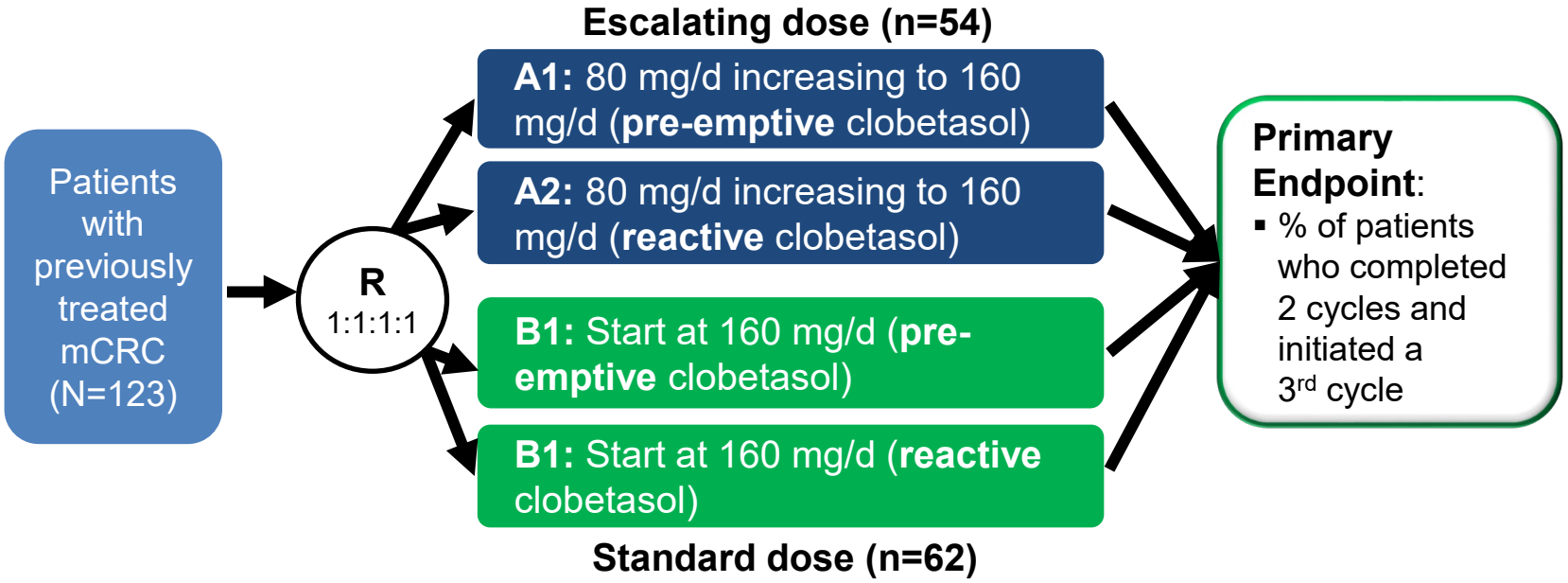
Single agent activity of anti-EGFR therapies, regorafenib and TAS-102

	N	ORR (%)	Median PFS (months) (95% CI)	Median OS (months) (95% CI)
Panitumumab vs Cetuximab*	499 500	22.0% 19.8%	4.1 (3.2-4.8) 4.4 (3.2-4.8)	10.4 (9.4-11.6) 10.0 (9.3-11.0)
Regorafenib vs Placebo	505 255	1.0% 0.4%	1.9 (n/a) 1.7 (n/a)	6.4 (n/a) 5.0 (n/a)
TAS-102 vs Placebo	534 266	1.6% 0.4%	2.0 (1.9-2.1) 1.7 (1.7-1.8)	7.1 (6.5-7.8) 5.3 (4.6-6.0)

* EGFR treatment naïve, *RAS* WT

Grothey et al., Lancet. 2013 Jan; 381(9863): 303-12.
Mayer et al., NEJM. 2015 May 14;372(20):1909- 19.
Price, et al., Lancet Oncol. 2014;15:569-79.

ReDOS: Regorafenib dose optimization study

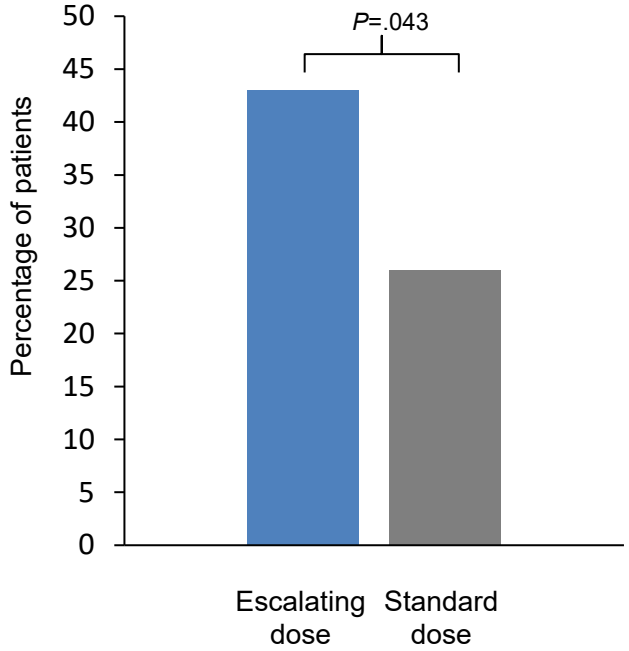


Secondary Endpoints	PFS, OS, Time-to-Progression (TTP)

Bekaii-Saab TS et al. *Lancet Oncol.* 2019; 20(8):1070-1082.

ReDOS: Escalating dose superior to standard dose

Percentage of patients starting Cycle 3 (primary endpoint)

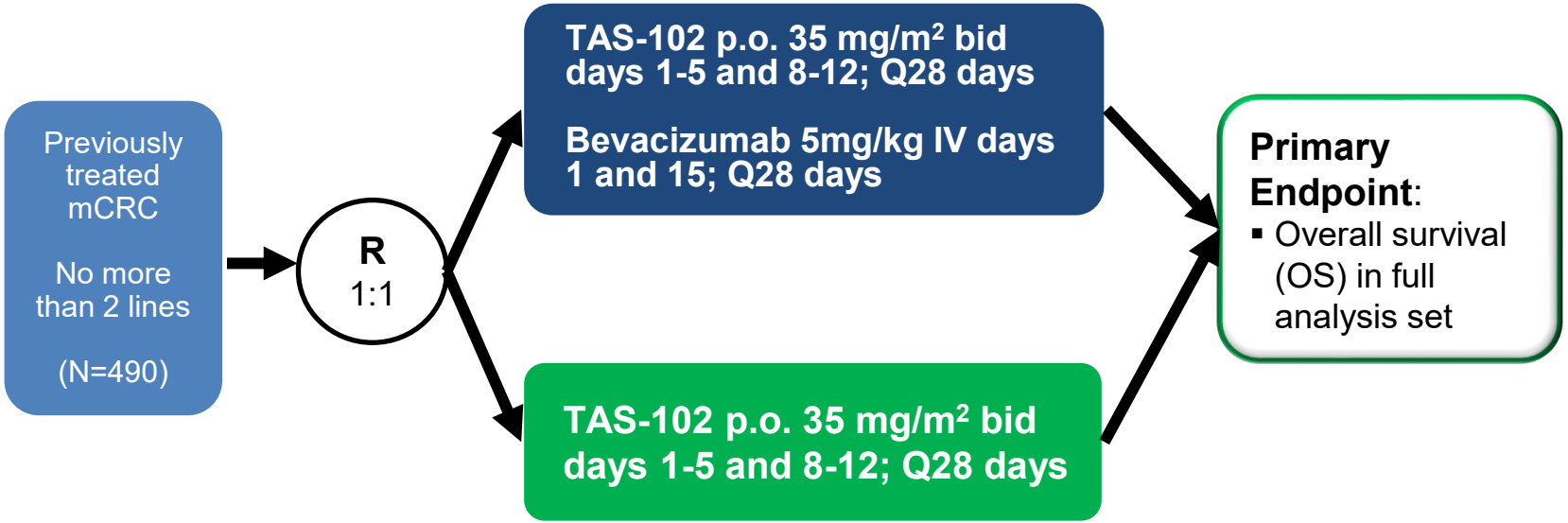


	Escalating Dose (n=54)	Standard Dose (n=62)
Median OS (95% CI), months	9.8 (7.5-11.9)	6.0 (4.9-10.2)
	HR 0.72 (95% CI 0.47-1.10), *P*=.12	
Median PFS (95% CI), months	2.8 (2.0-5.0)	2.0 (1.8-2.8)
	HR 0.84 (95% CI 0.57-1.24), *P*=.38	

	Escalating dose (n=54)		Standard dose (n=62)	
n (%)[a]	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	7 (13)	0	11 (18)	0
HFSR	8 (15)	0	10 (16)	0
Abdominal pain	9 (17)	0	4 (6)	0
Hypertension	4 (7)	0	9 (15)	0
Hyponatremia	2 (4)	1 (2)	4 (6)	1 (2)
Bilirubin increased	2 (4)	0	5 (8)	0
Alkaline phosphatase increased	3 (6)	0	1 (2)	1 (2)
AST increased	1 (2)	0	4 (6)	0
Dehydration	0	0	5 (8)	0
Dyspnea	1 (2)	1 (2)	4 (6)	0
Lymphocyte count decreased	4 (7)	0	0	0
Maculopapular rash	0	0	3 (5)	0

[a]Grade 3 or 4 AEs occurring in ≥5% of patients.
CI, confidence interval; HFSR, hand-foot skin reaction.
Bekaii-Saab TS et al. *Lancet Oncol*. 2019; 20(8):1070-1082.

SUNLIGHT: TAS-102 +/- bevacizumab



Secondary Endpoints	PFS, DCR, ORR, safety profile, QoL

Prager G et al. *NEJM.* 2023; 388: 1657-1667.

SUNLIGHT: TAS-102 + bevacizumab improves survival

	TAS-102 + bev (95% CI)	TAS-102 (95% CI)	HR (95% CI) P-value
Overall Survival (full analysis set)	10.8 months (9.4-11.8)	7.5 months (6.3-8.6)	0.61 (0.49-0.77) P<0.001
Prior bevacizumab sub-population	9.0 months (8.3-10.8)	7.1 months (6.0-8.5)	0.72 (0.56-0.92) NR
PFS	5.6 months (4.5-5.9)	2.4 months (2.1-3.2)	0.44 (0.36-0.53) P<0.001
Prior bevacizumab sub-population	4.5 months (4.1-5.5)	2.2 months (2.1-3.4)	0.51 (0.41-0.63) NR
ORR	6.3%	0.9%	P=0.004
DCR	76.6%	47.0%	P<0.001

Prager G et al. *NEJM.* 2023; 388: 1657-1667.

SUNLIGHT: Safety Summary

Adverse events occurring in at least 20% of patients that received TAS-102

	TAS-102 + bevacizumab (n=246)		TAS-102 (n=246)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	62.2%	43.1%	51.2%	32.1%
Nausea	37.0%	1.6%	27.2%	1.6%
Anemia	28.9%	6.1%	31.7%	11.0%
Asthenia	24.4%	4.1%	22.4%	4.1%
Fatigue	21.5%	1.2%	16.3%	3.7%
Diarrhea	20.7%	0.8%	18.7%	2.4%
Decreased appetite	20.3%	0.8%	15.4%	1.2%

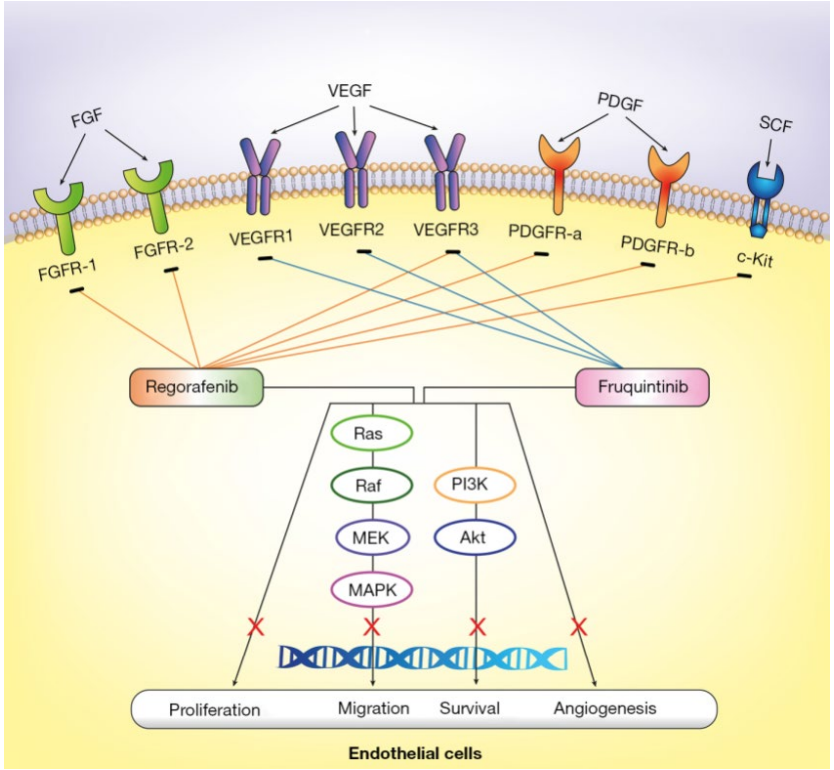
Prager G et al. *NEJM.* 2023; 388: 1657-1667.

TAS-102+bevacizumab: Real world strategies to manage toxicity

- Dose reductions
- Alternate dosing strategies (7 days on/ 7 days off)
- Growth factor support(?)
- Hold bevacizumab
- Others?

Fruquintinib: Inhibitor of VEGFR1-3

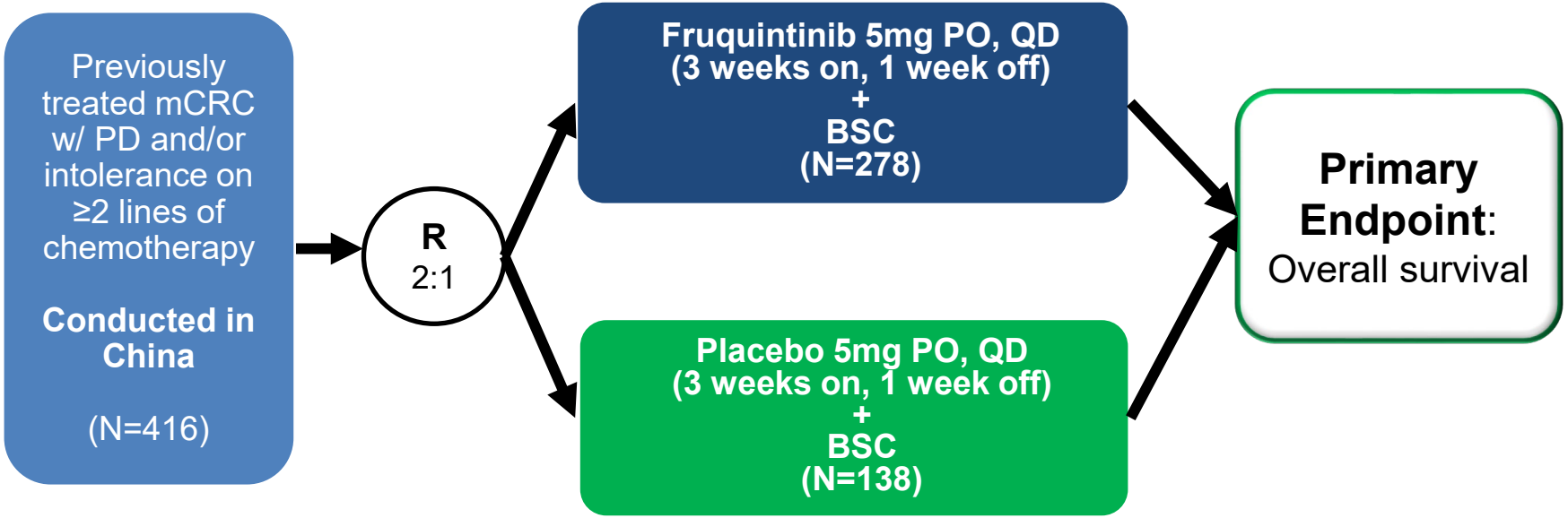
- Highly selective and potent oral tyrosine kinase inhibitor of VEGFRs-1, -2, and -3
- Dosing: 5mg po daily for the first 21 days each 28-day cycle
- Mean elimination half-life is ~42H
- PKs are not significantly altered by age, sex, race, ethnicity, mild to moderate renal impairment, or mild hepatic impairment



Source: Xu et al., Transl Cancer Res 2022;11(1):276-287

Dasari et al., Presented at 2022 ESMO Congress
Dasari et al., Lancet 2023; 402(10395) p 41-53

FRESCO: Fruquintinib vs placebo



Secondary Endpoints	PFS, DCR, ORR, Safety

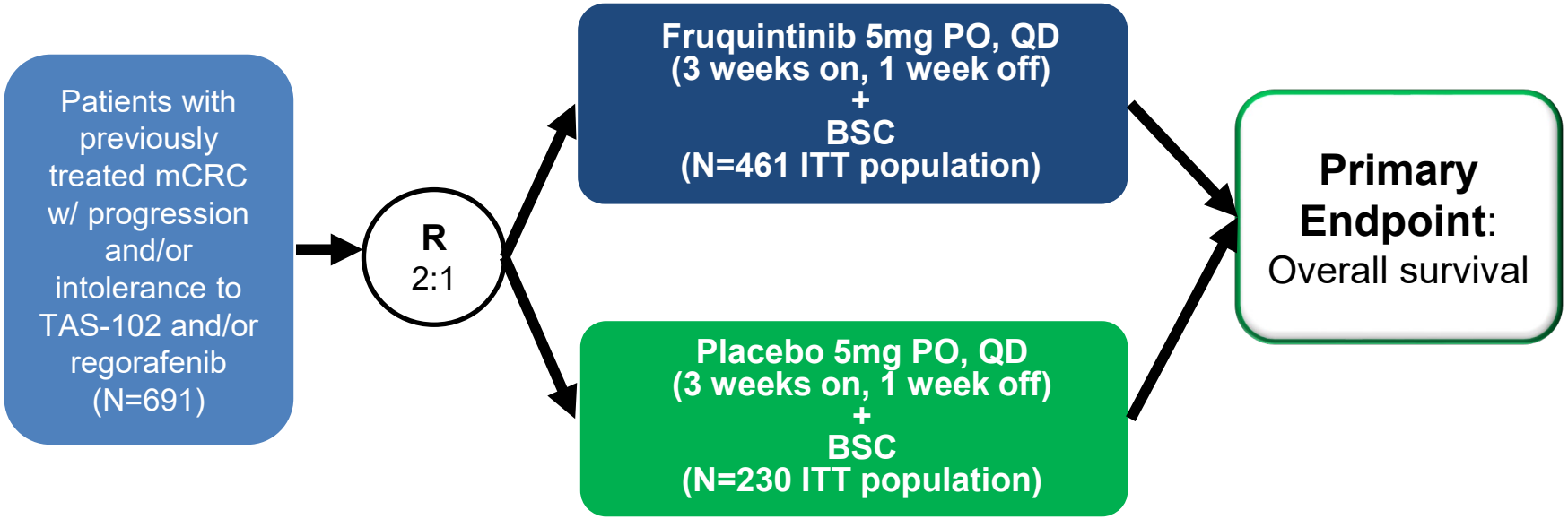
Li J et al. *JAMA*. 2018; 319(24): 2486-2496.

FRESCO: Fruquintinib improves survival, PFS

	Fruquintinib (95% CI)	Placebo (95% CI)	HR (95% CI) P-value
Overall Survival	9.3 months (8.2-10.4)	6.6 months (5.9-8.1)	0.65 (0.51-0.83) P<0.001
PFS	3.7 months (3.6-4.6)	1.8 months (1.8-1.8)	0.26 (0.21-0.34) P<0.001
ORR	4.7%	0%	P=0.01

Li J et al. *JAMA*. 2018; 319(24): 2486-2496.

FRESCO-2: Fruquintinib vs placebo



Secondary Endpoints	PFS, DCR, ORR, Safety

Dasari A et al. *Lancet*. 2023 Jun 15:S0140-6736(23)00772-9.

FRESCO-2: Fruquintinib improves survival, PFS

	Fruquintinib (95% CI)	Placebo (95% CI)	HR (95% CI) P-value
Overall Survival	7.4 months (6.7-8.2)	4.8 months (4.0-5.8)	0.66 (0.55-0.80) P<0.0001
PFS	3.7 months (3.5-3.8)	1.8 months (1.8-1.9)	0.32 (0.27-0.39) P<0.0001
ORR	2% (0.6-3.1)	0% (0.0-1.6)	P=0.059
DCR	56% (50.9-60.1)	16% (11.6-21.5)	P<0.0001

Dasari A et al. *Lancet*. 2023 Jun 15:S0140-6736(23)00772-9.

FRESCO-2: Patient and Disease Characteristics

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)

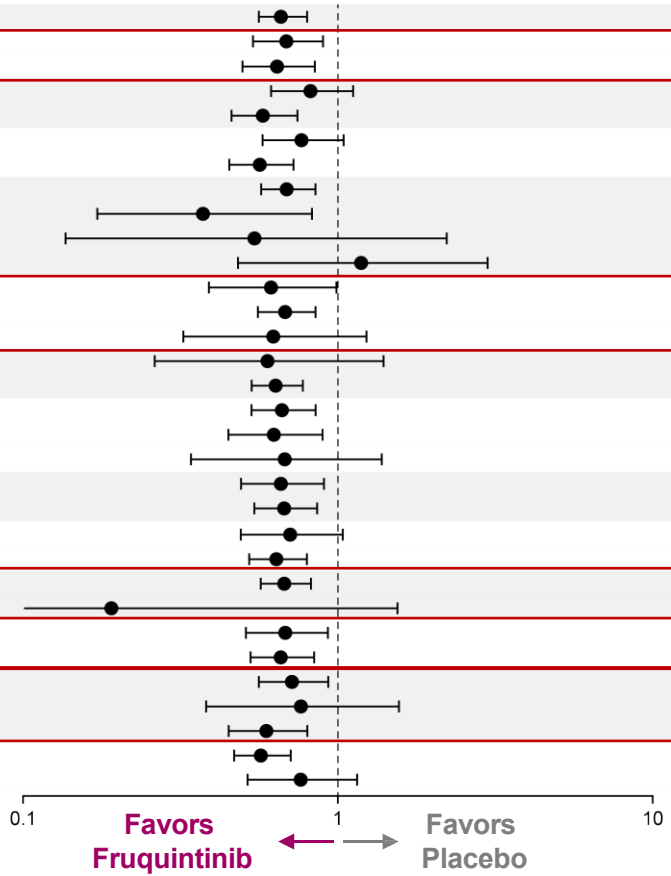
Characteristic, n (%)		Fruquintinib (N=461)	Placebo (N=230)
Duration of metastatic disease	≤ 18 mo	37 (8.0)	13 (5.7)
	> 18 mo	424 (92.0)	217 (94.3)
RAS status	WT	170 (36.9)	85 (37.0)
	Mutant	291 (63.1)	145 (63.0)
BRAF V600E mutation	No	401 (87.0)	198 (86.1)
	Yes	7 (1.5)	10 (4.3)
	Other/Unknown	5 (11.5)	22 (9.6)
Number of prior treatment lines in metastatic disease	Median (range)	5 (2, 16)	5 (2, 12)
	≤ 3	125 (27.1)	64 (27.8)
	> 3	336 (72.9)	166 (72.2)
Prior therapies	VEGF inhibitor	445 (96.5)	221 (96.1)
	EGFR inhibitor	180 (39.0)	88 (38.3)
Prior TAS-102 and/or regorafenib	TAS-102	240 (52.1)	121 (52.6)
	Regorafenib	40 (8.7)	18 (7.8)
	Both	181 (39.3)	91 (39.6)

Dasari A et al. *Lancet.* 2023 Jun 15:S0140-6736(23)00772-9.
Dasari A et al. ESMO 2022, Presentation LBA25. Presented at ESMO 2022.

FRESCO-2: 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)



Dasari A et al. *Lancet.* 2023 Jun 15:S0140-6736(23)00772-9.
Dasari A et al. ESMO 2022, Presentation LBA25. Presented at ESMO 2022.

FRESCO-2: Safety summary

Adverse events occurring in at least 20% of patients that received fruquintinib

	Fruquintinib (n=456)		Placebo (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	37%	14%	9%	1%
Asthenia	34%	8%	23%	4%
Decreased appetite	27%	2%	17%	1%
Diarrhea	24%	4%	10%	0%
Hypothyroidism	21%	<1%	<1%	0%
Fatigue	20%	4%	16%	1%

Dasari A et al. *Lancet*. 2023 Jun 15:S0140-6736(23)00772-9.

Fruquintinib: Real world strategies to manage toxicity

- Dose reductions
- Lower starting dose (ReDOS strategy?)
- Structured exercise/ physical therapy
- Others?

Stacking up the 3L+ options for metastatic CRC

Agent	Regorafenib		TAS-102+bev		Fruquintinib	
Trial	**ReDOS**		**SUNLIGHT**		**FRESCO-2**	
	Escalating	Standard	TAS+Bev	TAS only	Fruquintinib	Placebo
Overall Survival	9.8	6.0	Overall 10.8 Prior bev 9.0	Overall 7.5 Prior bev 7.1	7.4	4.8
PFS	2.8	2.0	Overall 5.6 Prior bev 4.5	Overall 2.4 Prior bev 2.2	3.7	1.8

Factors that influence treatment choice:
- Prior therapies
- Comorbidities
- Tolerability
- Clinical activity
- Access (reimbursement)

Bekaii-Saab TS et al. *Lancet Oncol.* 2019; 20(8):1070-1082.
Prager G et al. *NEJM.* 2023; 388: 1657-1667.
Dasari A et al. *Lancet.* 2023 Jun 15:S0140-6736(23)00772-9.

Updated analysis of a phase 2 study of fruquintinib plus trifluridine/tipiracil (TAS-102) asthird-line treatment in patients with metastatic colorectal adenocarcinoma.

Jianjun Peng[1], Jianting Long[1], Ling Huang[2], Yong Li[3], Jianjun Xiao[4], Jianhua Liu[2], Haibo Zhang[3], Derong Xie[5], Wei Wang[6], Chengyin Weng[7], Zongcheng Zhang[8], Xiaoshu Chai[9]
1. The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; 2. Guangdong Provincial People's Hospital, Guangzhou, China; 3. Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; 4. Zhongshan City People's Hospital, Zhongshan, China; 5. Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China; 6. Foshan First People's Hospital, Foshan, China; 7. First People's Hospital, Guangzhou, China; 8.Liwan District People's Hospital of Guangzhou, Guangzhou, China; 9. University Town Branch, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China

❑ **Eligibility**

- Metastatic or recurrent colorectal adenocarcinoma
- 18-75 years old
- ECOG PS 0-1
- At least one measurable lesions (RECIST v1.1)
- Failed at least 2 regimens
- No prior anti-VEGFR treatment

N=54

- **NCT05004831**

Fruquintinib (4mg, qd, d1-21, q4w) + TAS-102 (35mg/m², bid, d1-5, 8-12, q4w)

Until disease progression or unacceptable toxicity

❑ **Primary endpoint**

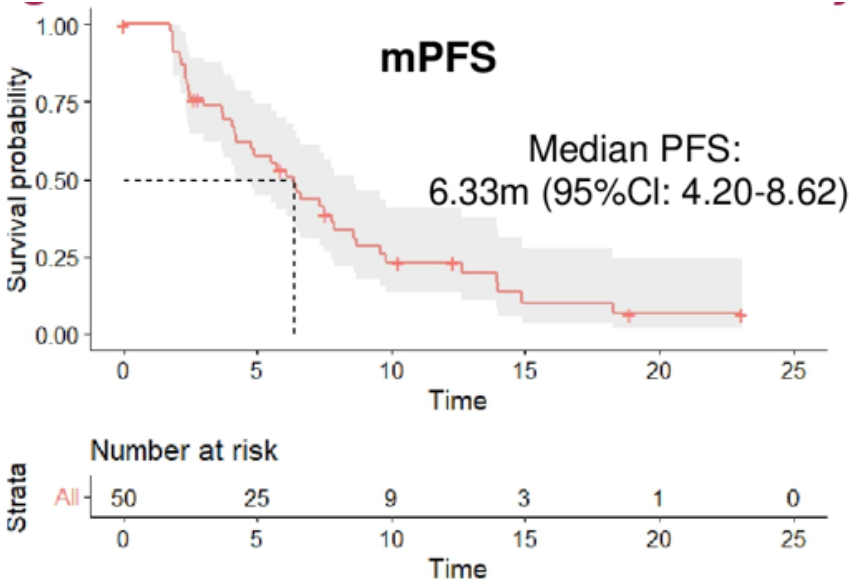
Progression-free survival (PFS)

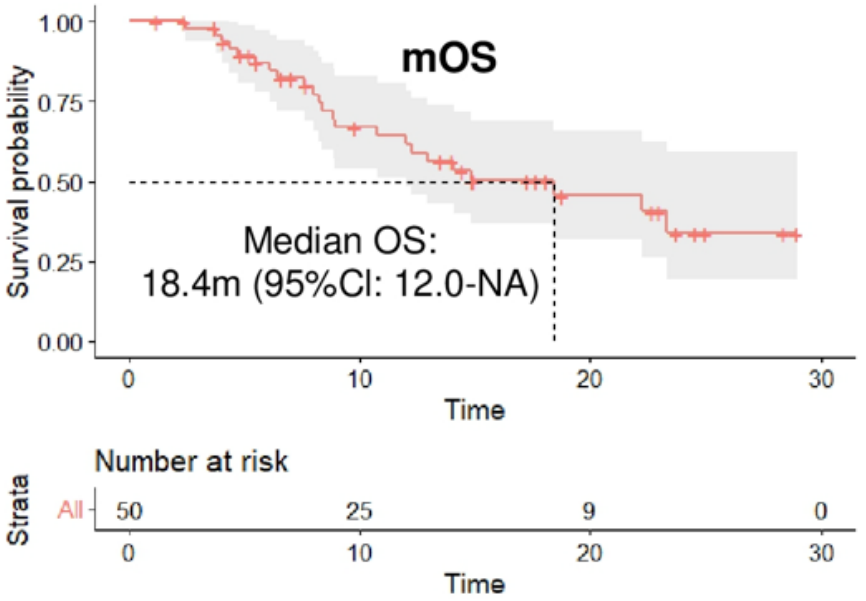
❑ **Secondary endpoints**

Objective response rate (ORR)
Disease control rate (DCR)
Overall survival (OS)
Safety and tolerability

Peng et al., J Clin Oncol 43, 2025 (suppl 4; abstr 145). Presented at ASCO GI 2025

Phase 2 Study of Fruquintinib + TAS-102 for 3rd line treatment of mCRC: Efficacy





Peng et al., J Clin Oncol 43, 2025 (suppl 4; abstr 145). Presented at ASCO GI 2025

FRUITION: FRUquInTInib and TAS-102 In CombinatiON in refractory MSS CRC

Randomized, multicenter* Phase 2 trial in 3L mCRC (NCT06992258)

Key eligibility criteria

- Aged ≥18 years
- Histologically/cytologically confirmed advanced or metastatic MSS/pMMR CRC
- Prior treatment with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab/panitumumab†
- PD or intolerance to last regimen
- No prior fruquintinib, TAS-102, or regorafenib
- ECOG PS 0 or 1

R 1:1

FRUQUINTINIB + TAS-102 (n=74)

- **Fruquintinib** 5 mg PO, QD, D1–21 Q4W +
- **TAS-102** 35 mg/m^2 PO BID D1–5; D15–19 Q4W

N=120 subjects

FRUQUINTINIB (n=74) 5 mg PO, QD D1–21 Q4W

Until disease progression, unacceptable toxicity, or other protocol-defined reason for discontinuation‡

Randomization stratified by:

- *RAS* status (WT vs mutated)
- Primary tumor site (left vs right)

Accrual time: 18 months; follow-up: 12 months

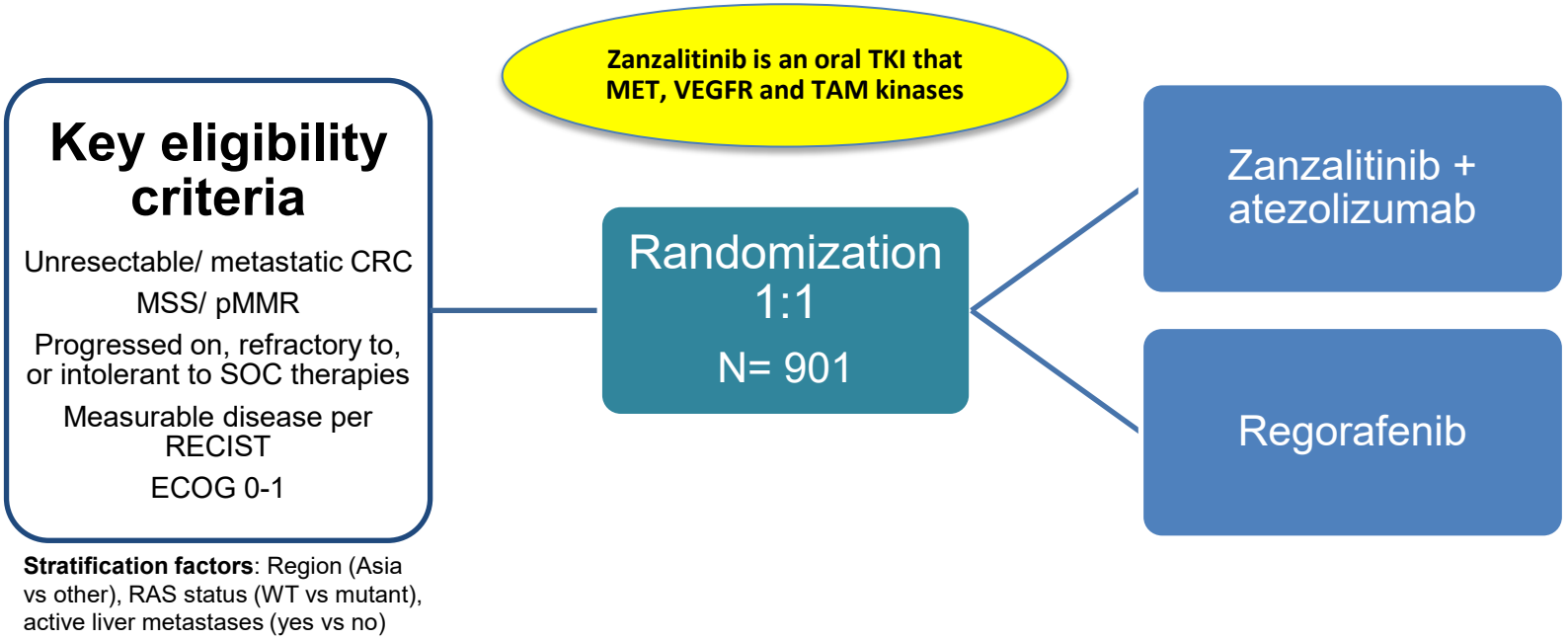
Primary endpoint	Secondary endpoints	
PFS	• ORR • DCR • DOR • CBR • OS	• Incidence of Grade ≥3 TRAEs • Dose reductions or delays due to TRAEs • Treatment discontinuation due to TRAEs • ctDNA growth rate/velocity

*15 sites in the US; †For *RAS* WT disease; ‡Death, patient or physician decision to withdraw, or pregnancy, whichever occurs first

3L, third-line; BID, twice daily; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; D#, Day #; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; (m)CRC, (metastatic) colorectal cancer; pMMR, proficient mismatch repair; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; Q4W, every 4 weeks; QD, once daily; R, randomization; TRAE, treatment-related adverse event; WT wild type

STELLAR-303: Zanzalitinib + Atezolizumab vs Regorafenib

Phase 3, randomized, open-label, global, multicenter study for previously treated metastatic CRC (NCT05425940)



Stratification factors: Region (Asia vs other), RAS status (WT vs mutant), active liver metastases (yes vs no)

Dual primary endpoints: 1) OS in the ITT population; 2) OS in patients without active liver metastases
Secondary endpoints: PFS, ORR, DOR, safety

Saeed et al., Future Oncology 2024; 20(24): 1733-1743

STELLAR-303: Zanzalitinib + Atezolizumab vs Regorafenib

	Zanzalitinib + atezolizumab (N=451)	Regorafenib (N= 450)	HR (95% CI)	*P*-value
ORR	4%	1%		
PFS, months (95% CI)	3.7	2.0	0.68 (0.59-0.79)	NR
OS, months (95% CI)	10.9	9.4	0.80 (0.69-0.93)	0.0045

The interim analysis in the nlm ITTpopulation (dual primary endpoint) showed a trend in OS favoring the combination (stratified HR, 0.79 [95% CI, 0.61–1.03; P=0.087]; median, 15.9 versus 12.7 months with regorafenib)

*Two-sided alpha = 0.015. CI, confidence interval; HR, hazard ratio; ITT, intention to treat; OS, overall survival.

Elez et. al., NEJM 2025 DOI: 10.1056/NEJMoa2501912
Presented at ASCO 2025

STELLAR-303: Zanzalitinib + Atezolizumab vs Regorafenib

Event, n (%)	Zanzalintinib + Atezolizumab (n=446)	Regorafenib (n=434)
Treatment-related adverse events		
Any-grade	423 (95)	399 (92)
Grade 3	248 (56)	143 (33)
Grade 4	15 (3)	17 (4)
Serious adverse events	255 (57)	184 (42)
Serious treatment-related adverse events	118 (26)	45 (10)
Adverse events leading to discontinuation of all treatment	82 (18)	64 (15)
Dose modification due to an adverse event*		
Dose reduction of zanzalintinib/regorafenib	270 (61)	174 (40)
Dose delay of atezolizumab	193 (43)	NA

- Most frequent AEs leading to discontinuation of zanzalintinib + atezolizumab: abdominal pain, asthenia, and general physical health deterioration (4 [1%] patients each)
- Deaths considered related to treatment by investigators: intestinal perforation (n=2) for zanzalintinib, pneumonitis and renal failure (n=1 each) for atezolizumab, altered state of consciousness (n=1) for zanzalintinib + atezolizumab, and jejunal perforation (n=1) for regorafenib

*Based on exposure case report form.

Elez et. al., NEJM 2025 DOI: 10.1056/NEJMoa2501912
Presented at ASCO 2025

Question: What is the optimal management of chemotherapy refractory metastatic colorectal cancer?

- In the chemotherapy refractory setting, several therapies have demonstrated a survival benefit
  - TAS-102 + bev validated in the 3rd line
  - Fruquintinib validated in the 3rd line (FRESCO) and 4th line (FRESCO-2)
  - Regorafenib should be given using the ReDOS dosing regimen
  - More options possible in the future