The Role of ctDNA-MRD Assessment in the Management of Colon Cancer

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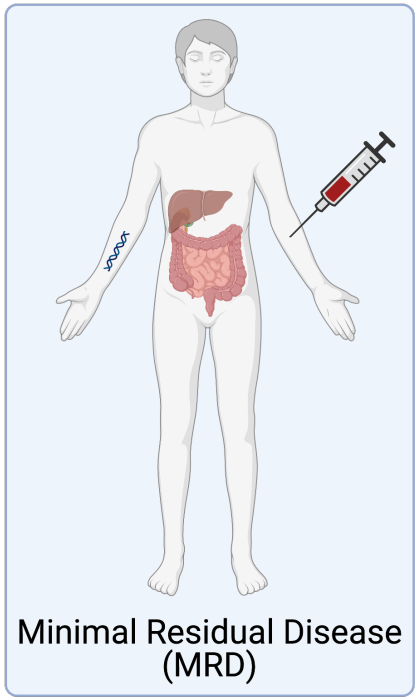
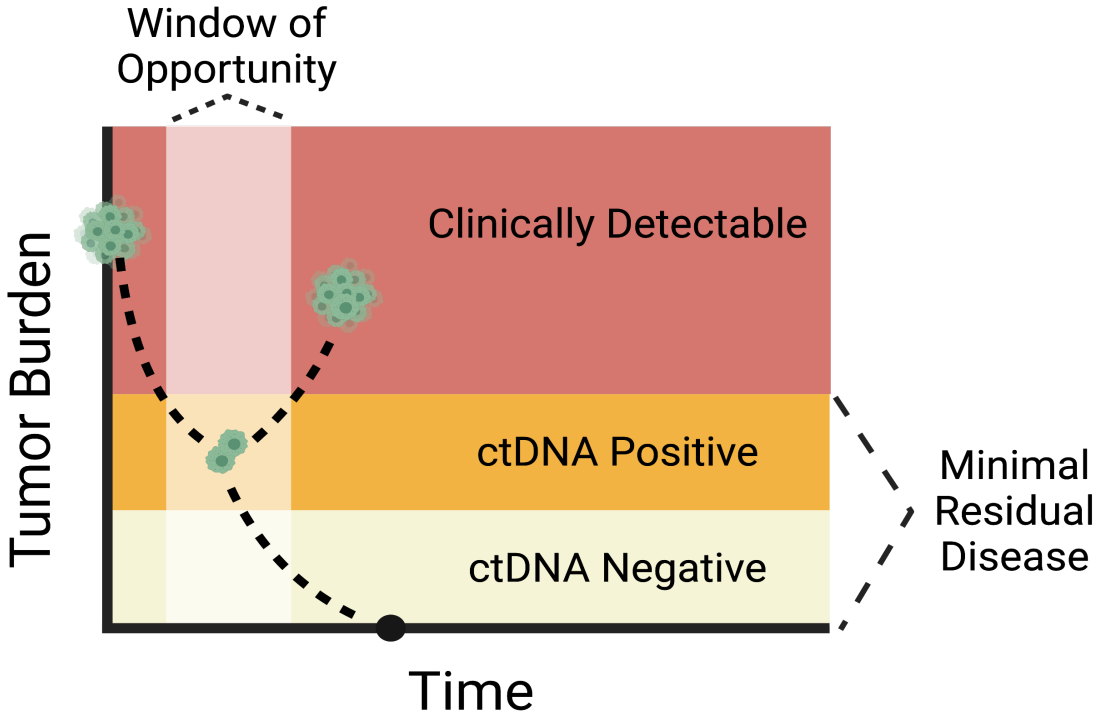
Overview

- MRD: Testing options and assays
- MRD as a prognostic tool
- MRD to guide adjuvant chemotherapy
- Clinical trials evaluating clinical utility
- Major studies on the horizon

Defining Molecular Residual Disease (MRD)





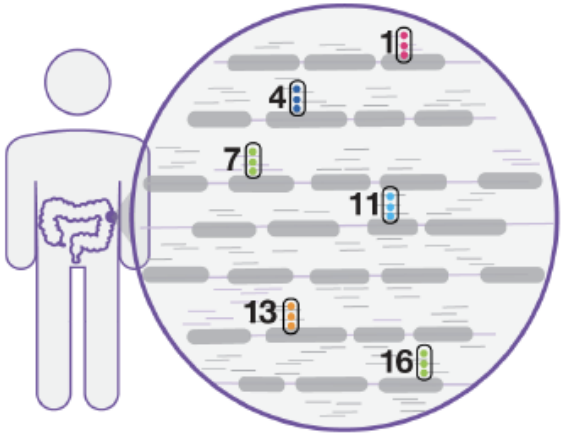
Question: My patient wants MRD testing. Which test should I order?

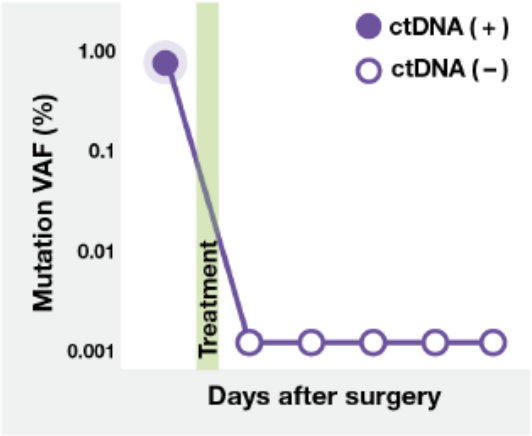
Option 1: “Tumor informed” MRD

Sequencing of tumor tissue, to identify unique signature of tumor mutations

Custom design and manufacture of personalized mPCR assay for each patient, targeting the top 16 clonal mutations found in tumor

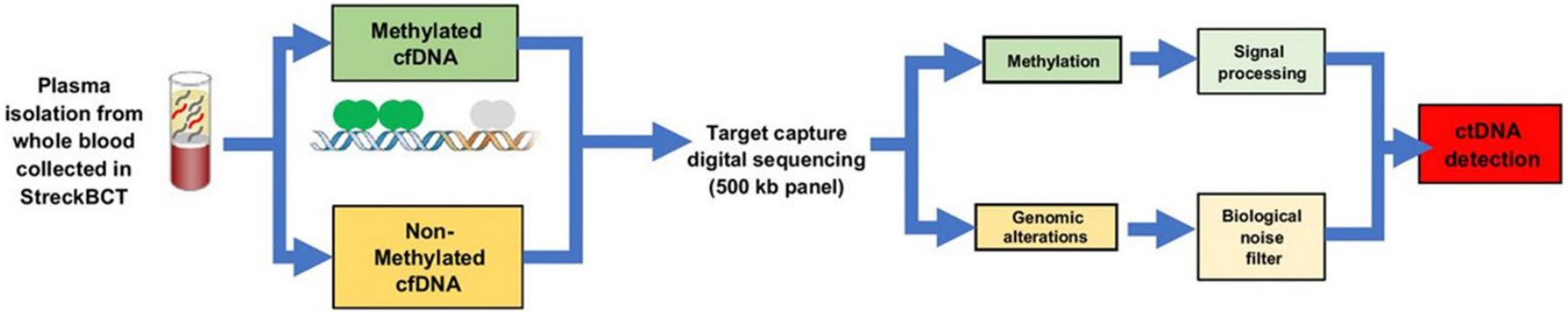
Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)





Option 2: “Tumor naïve” MRD

Example: Guardant Lunar Assay (Version 1.0)



Parikh et al., Clin Cancer Res. 2021; Presented at ASCO GI 2024

ctDNA (MRD) detection assays in the clinic

Tumor-informed assays

Assay	Development Company / Academia	Tumor Tissue Analysis	Number of target gene mutations
Signatera	Natera	Whole exome	16
RaDaR	NeoGenomics	Whole exome	48
Invitae PCM	Invitae	Whole exome	50
Oncodetect	Exact Sciences	Whole exome	up to 200
Signatera	Natera	Whole genome	64
NEXT Personal	Peronalis	Whole genome	up to 1,800
MAESTRO	Broad Institute	Whole genome	1000
Precise MRD	Myriad Genetics	Whole genome	100-1000

Tumor-naïve assays

Assay	Development Company / Academia	Analysis population
Guardant Reveal	Guardant Health	DNA methylation
xM	Tempus	DNA methylation/genetic alteration
-	GRAIL	DNA methylation
Bladder EpiCheck	Nucleix	DNA methylation (urine)

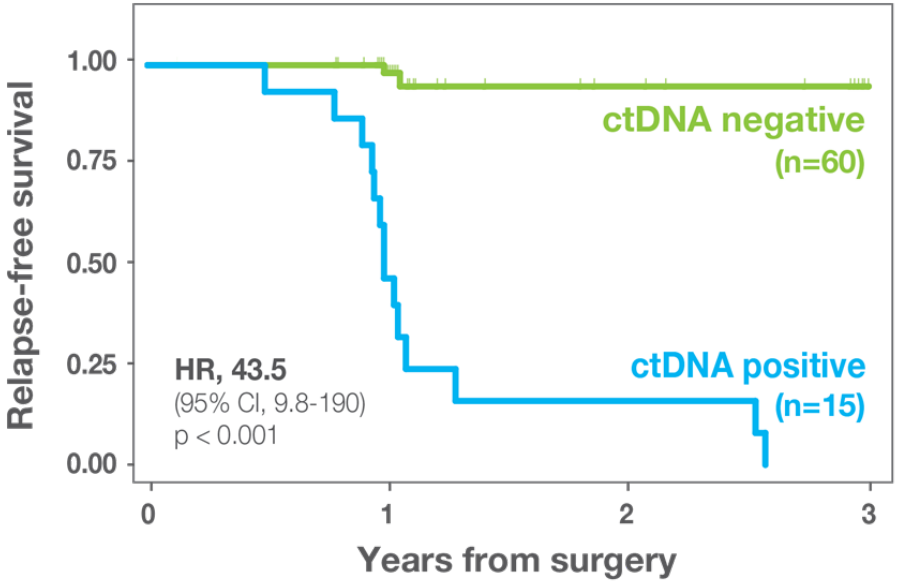
Slide credit: Takayuki Yoshino (slide modified/ updated)

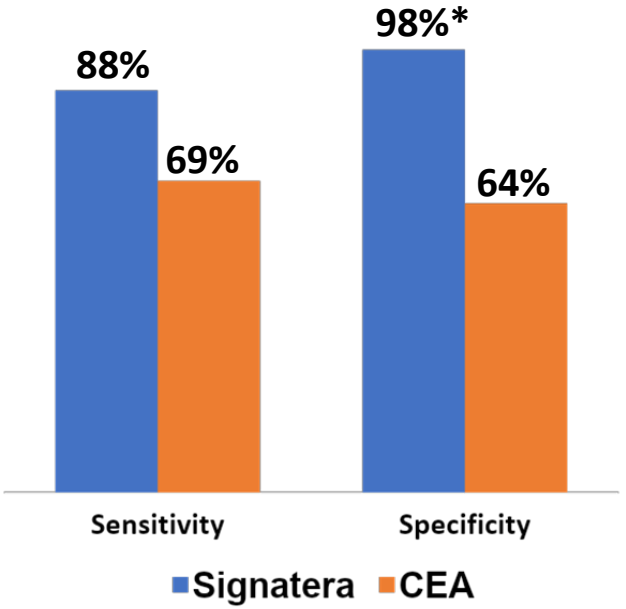
Question: My patient wants MRD testing. Which test should I order?

- There are no head-to-head comparisons between assays
- Tumor informed assays likely offer greater sensitivity
- Increased number of target gene mutations increases sensitivity, but clinical value is not well defined (impact on cost, tissue requirements, and specificity)
- Blood-only tests also have advantages (speed & convenience)

Question: My patient has a positive MRD test.
What is the impact on prognosis?
What should I do if CT scan is negative?

Signatera (tumor informed) MRD assay: Initial validation for stage I-III colon ca

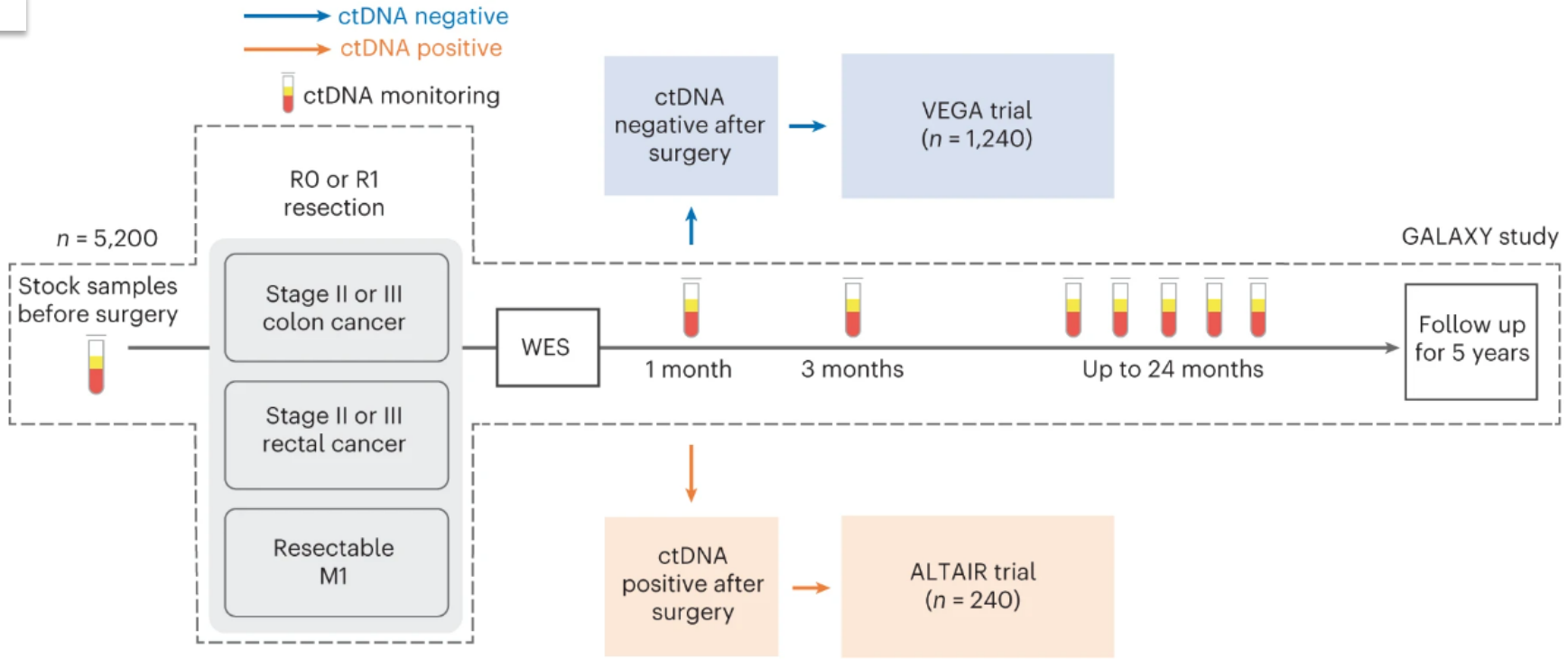




*Patient-level specificity 98%. Test-level specificity 99.7%.[2]

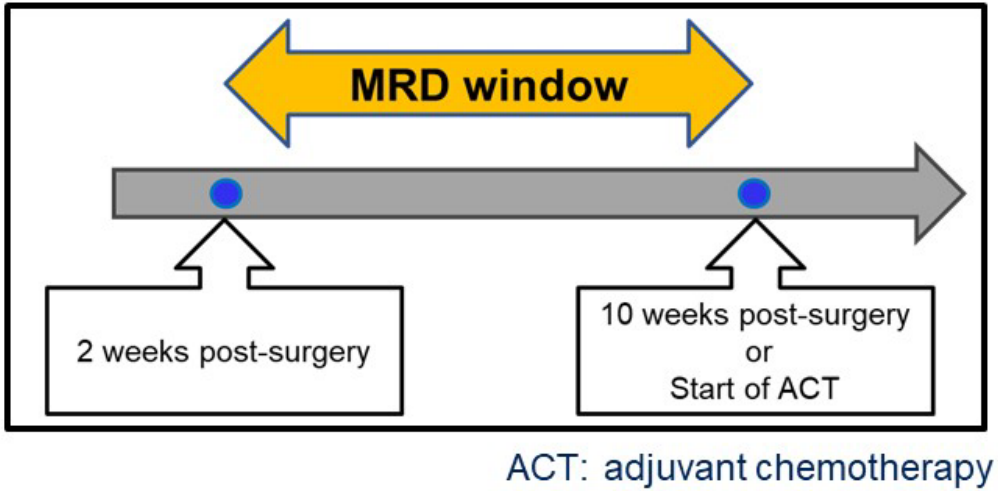
Reinert et al., JAMA Oncol. 2019;5(8):1124-1131.

Clinical validation of tumor informed MRD testing: GALAXY Study Design



Kotani et. al., *Nature Medicine* (2023) 29, 127–134.

GALAXY: MRD Window



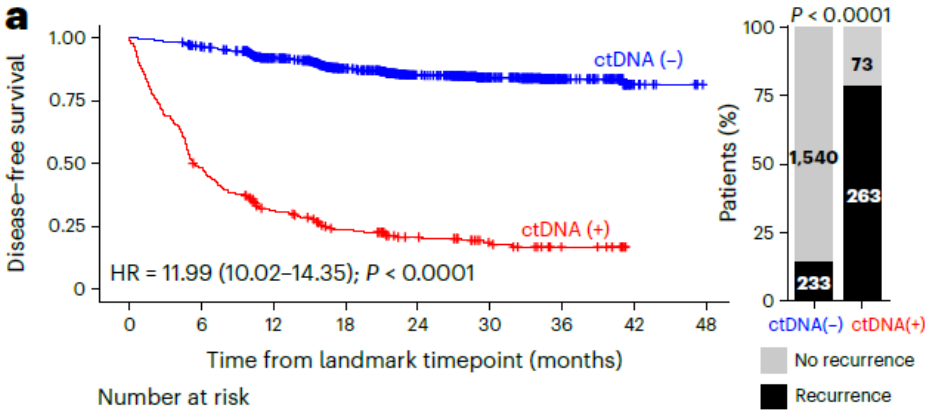
ACT: adjuvant chemotherapy

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

Yukami et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 6). Presented at ASCO GI 2024

MRD status after surgery is strongly prognostic

Disease-free survival

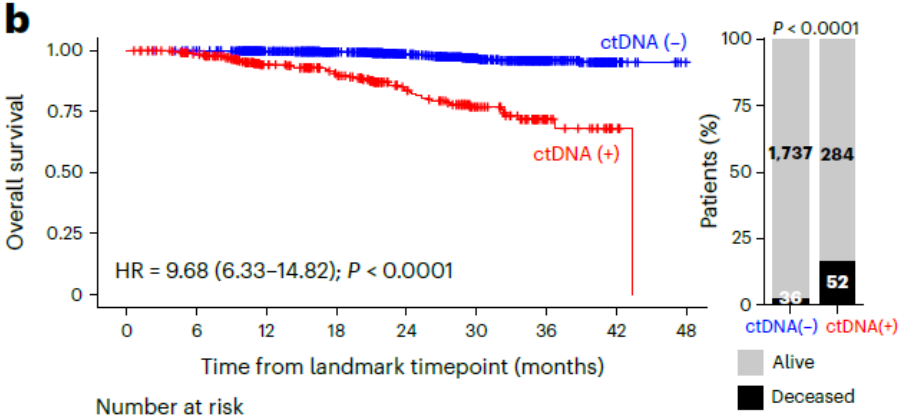


Number at risk

ctDNA (–)	1,773	1,701	1,379	1,057	625	353	131	11	0
ctDNA (+)	336	161	95	60	36	21	10	0	0

ctDNA status	Negative	Positive
Events %	13.14 (233/1773)	78.27 (263/336)
24M-DFS % (95% CI)	85.10 (83.20–86.9)	20.57 (16.14–25.37)
30M-DFS % (95% CI)	84.10 (82.0–86.0)	18.50 (14.0–23.40)
36M-DFS % (95% CI)	83.50 (81.20–85.60)	16.70 (12.10–21.90)
mDFS (mo)	NR	5.34 (4.83–6.70)

Overall survival



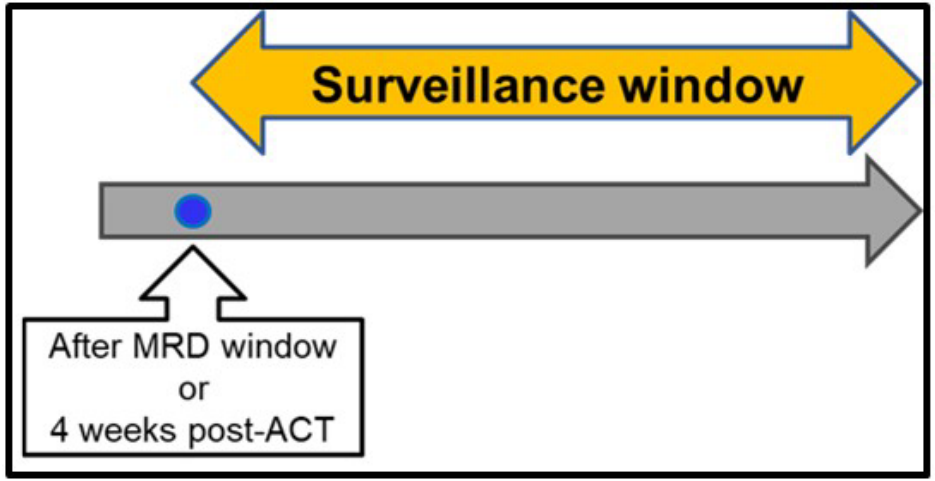
Number at risk

ctDNA (–)	1,773	1,765	1,511	1,252	825	497	185	19	1
ctDNA (+)	336	309	228	189	119	73	24	4	0

ctDNA status	Negative	Positive
Events %	2.03 (36/1773)	15.48 (52/336)
24M-OS % (95% CI)	98.50 (97.70–99.10)	83.65 (77.84–88.06)
30M-OS % (95% CI)	96.80 (95.40–97.80)	76.90 (69.80–82.50)
36M-OS % (95% CI)	96.0 (94.30–97.20)	71.80 (63.40–78.60)
mOS (mo)	NR	43.40 (NR–NR)

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

GALAXY: Surveillance window

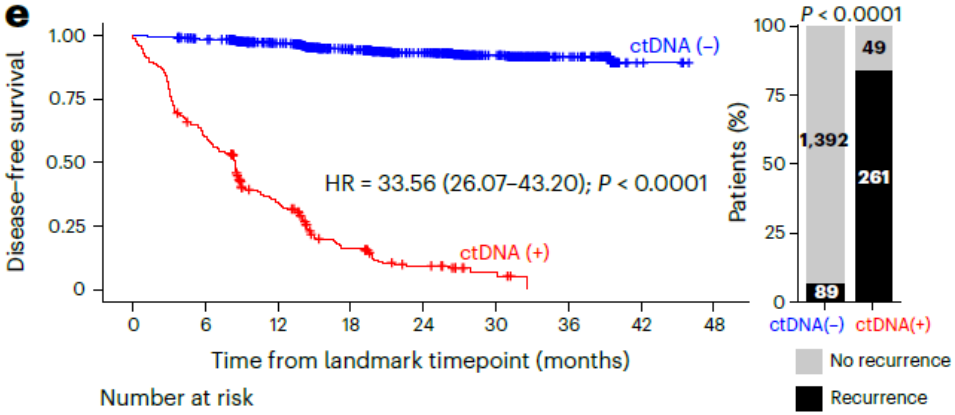


- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

Yukami et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 6). Presented at ASCO GI 2024

ctDNA-positive in the surveillance window predicts poor prognosis

Disease-free survival

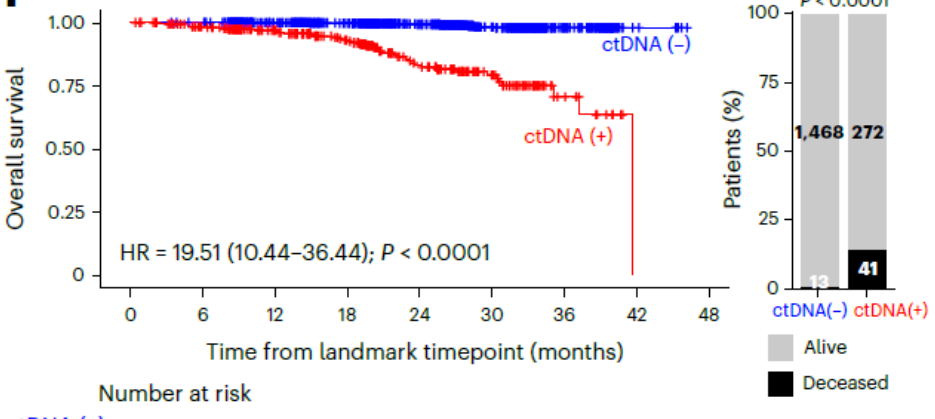


Number at risk

ctDNA (–)	1,481	1,445	1,222	948	565	311	113	5	0
ctDNA (+)	310	185	93	35	14	4	0	0	0

ctDNA status	Negative	Positive
Events %	6.01 (89/1481)	84.19 (261/310)
24M-DFS % (95% CI)	93.20 (91.50–94.50)	8.93 (5.56–13.27)
30M-DFS % (95% CI)	92.20 (90.20–93.70)	6.49 (3.14–11.50)
36M-DFS % (95% CI)	91.50 (89.40–93.30)	NR
mDFS (mo)	NR	8.47 (7.09–8.74)

Overall survival



Number at risk

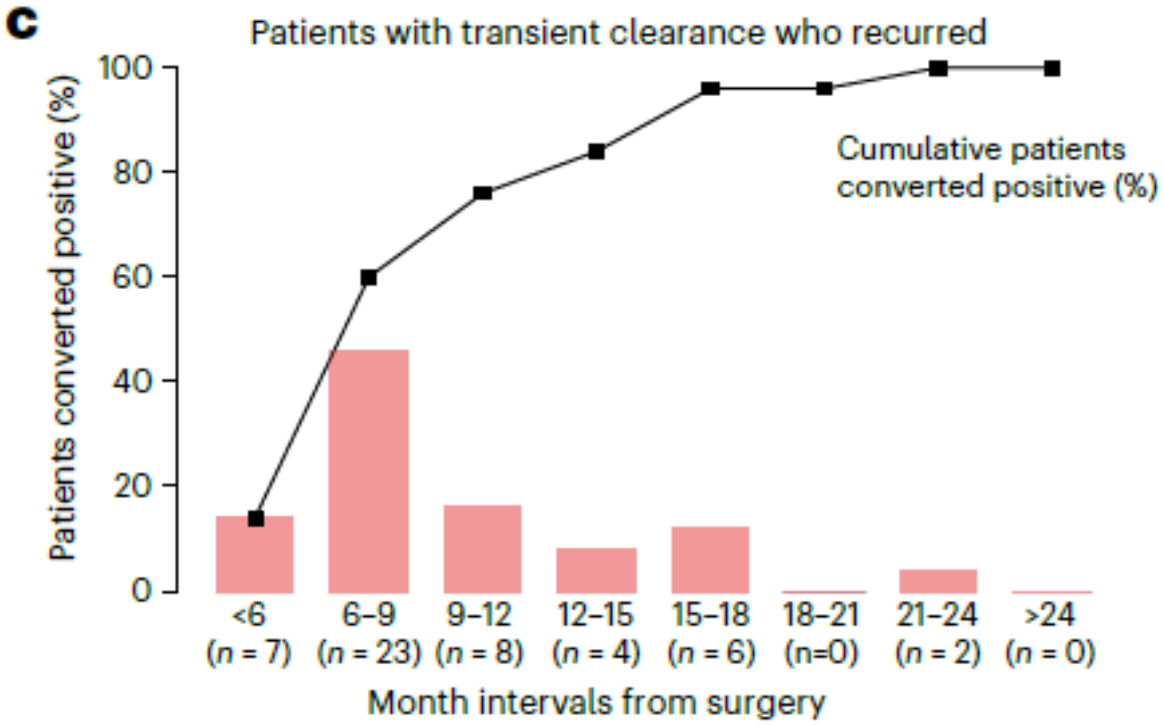
ctDNA (–)	1,481	1,478	1,275	1,063	686	384	123	6	0
ctDNA (+)	313	287	222	175	102	60	14	0	0

ctDNA status	Negative	Positive
Events %	0.88 (13/1481)	13.10 (41/313)
24M-OS % (95% CI)	99.30 (98.40–99.70)	83.20 (76.50–88.10)
30M-OS % (95% CI)	98.20 (96.70–99.0)	79.20 (71.50–85.0)
36M-OS % (95% CI)	97.90 (96.30–98.90)	70.50 (57.70–80.10)
mOS (mo)	NR	41.80 (37.30–NR)

ctDNA positivity preceded radiological recurrence by a median of 5.9 months (range, 0–33.1)

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

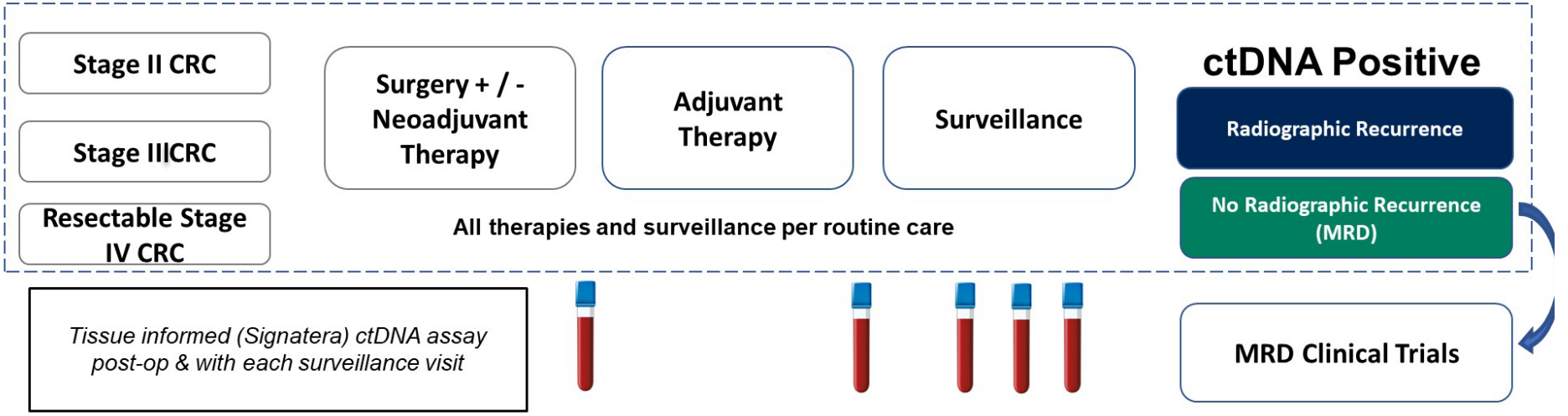
ctDNA dynamics of transient clearance with recurrence



- Among patients with transient clearance, 60% became ctDNA+ within 9 months from surgery, and almost all turned positive by 18 months
- True spontaneous clearance rate with no clinical recurrence= 1.9% (2/105)

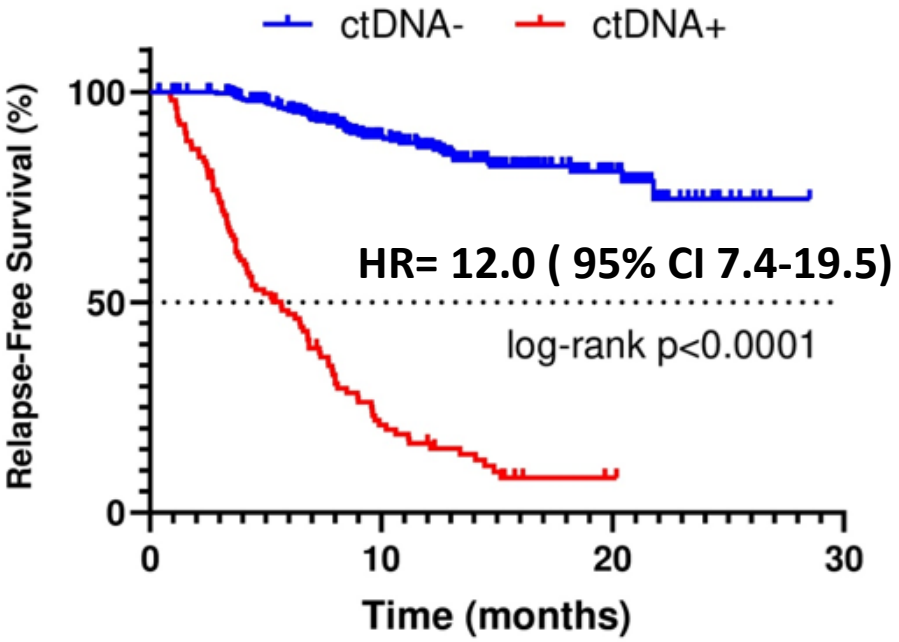
Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

INTERCEPT Study Design



Dasari et. al., J Clin Oncol 41, 2023 (suppl 16; abstr 3522). Presented at ASCO 2023

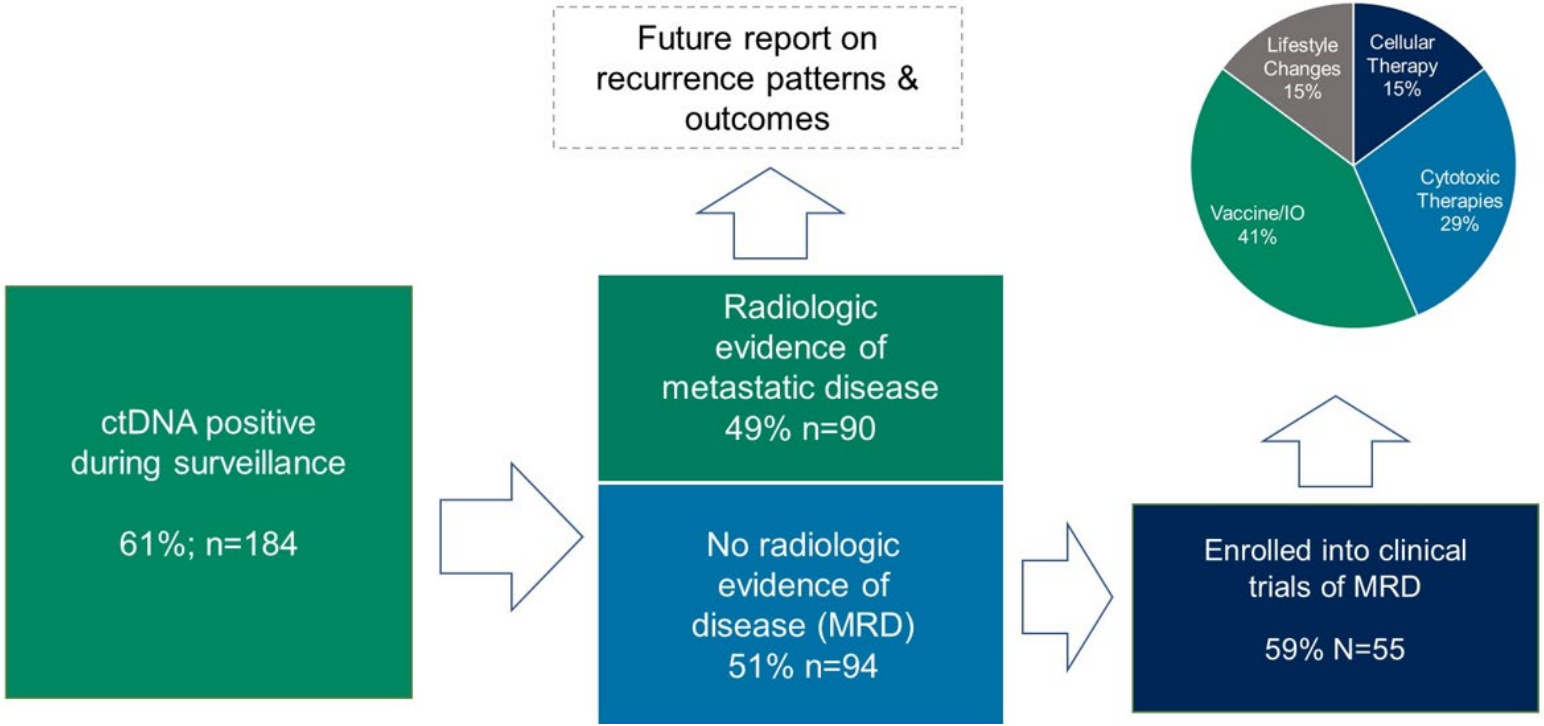
INTERCEPT: Post-op ctDNA+ associated with inferior RFS (n=1,140)



12m-DFS	ctDNA detected post-op	No detectable ctDNA post-op
Stage II	16.7% (95 CI: 51.7 – 0.8)	94.9% (95% CI: 98.4 – 84.5)
Stage III	34.9% (95% CI: 56.6 – 14.2)	93.3% (95% CI: 96.8 – 86.2)
Stage IV	12.4% (95% CI: 21.0 – 6.1)	74.1% (95% CI: 81.9 – 63.8)

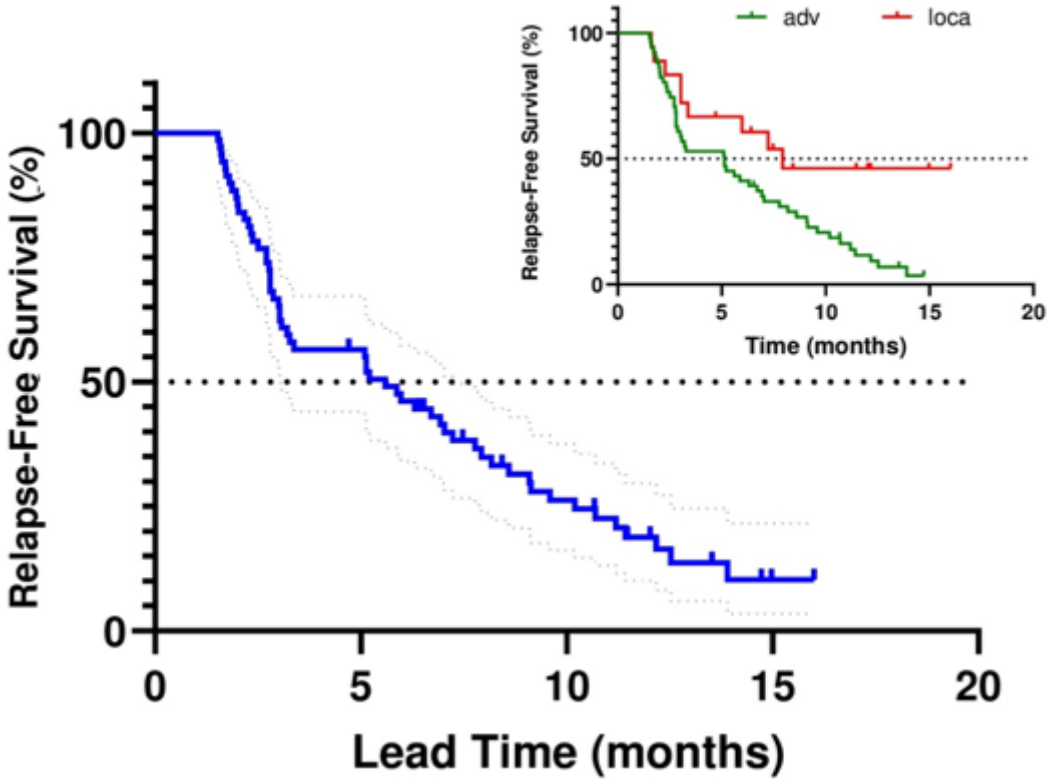
Maddalena et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 27). Presented at ASCO 2023

Half of all ctDNA+ patients during surveillance had radiologic evidence of disease



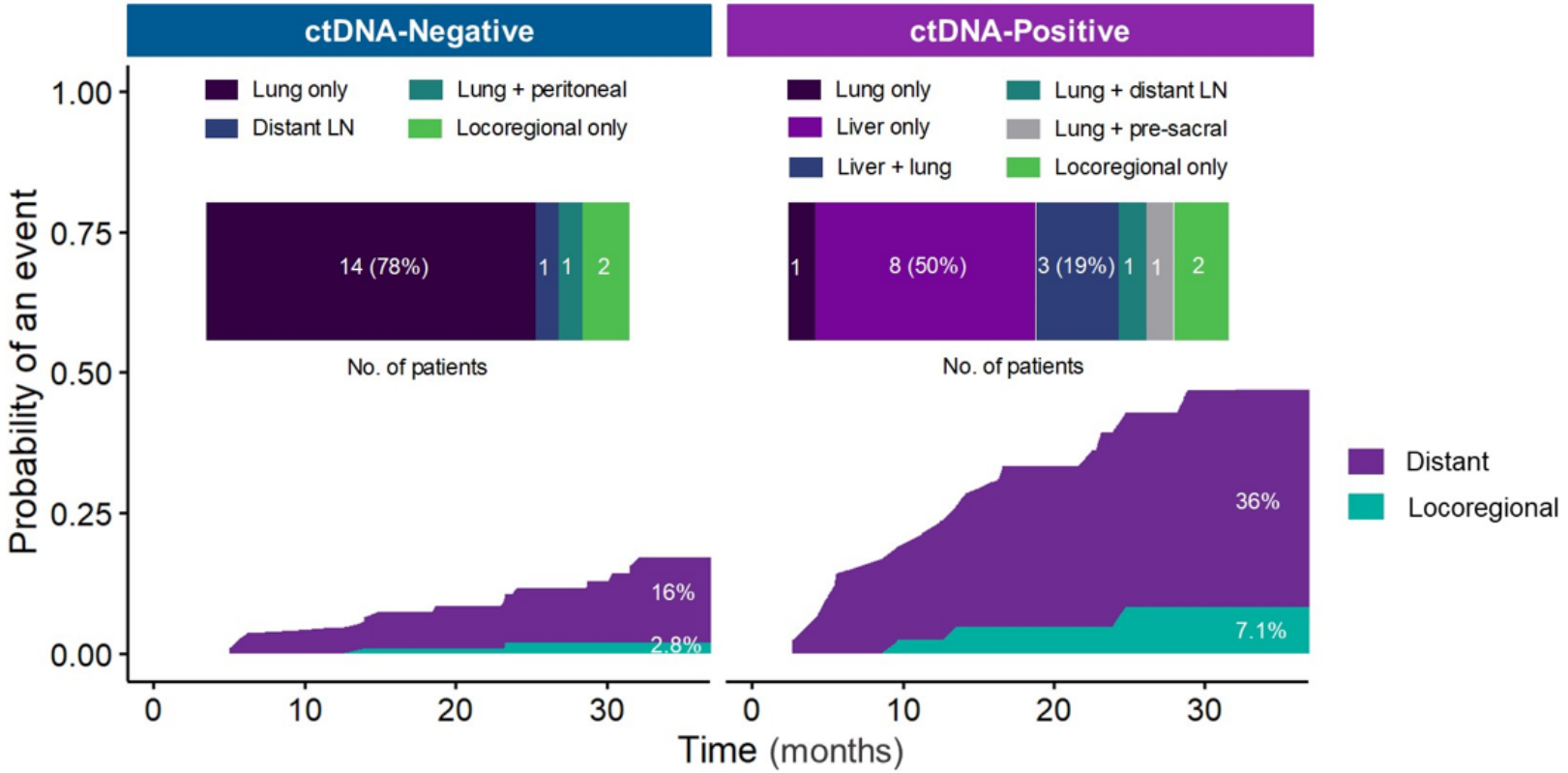
Dasari et. al., J Clin Oncol 41, 2023 (suppl 16; abstr 3522). Presented at ASCO 2023

INTERCEPT: Lead-time for confirmed recurrence



Maddalena et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 27). Presented at ASCO 2023

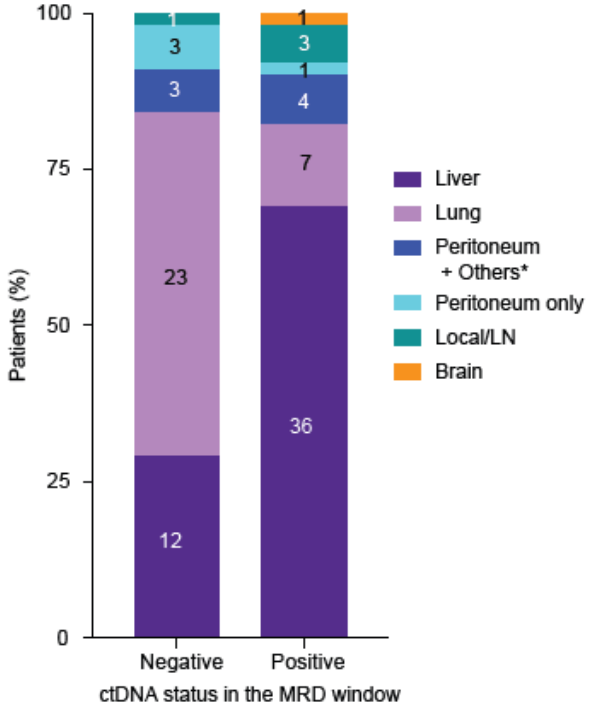
DYNAMIC-Rectal: Sites of Relapse by Post-Op ctDNA Status



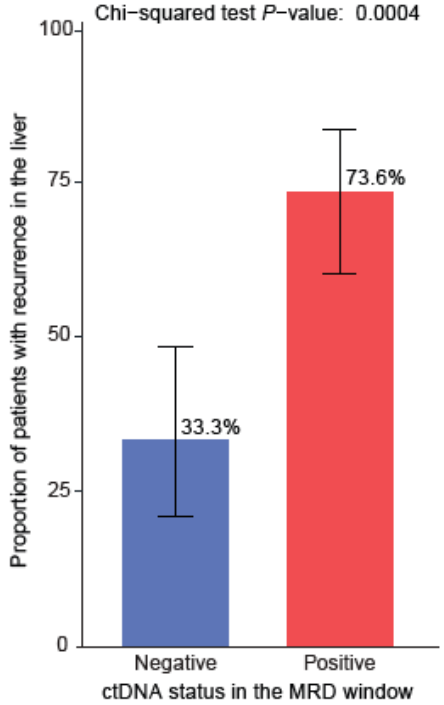
Tie et al., Presented at 2024 ASCO GI Annual Meeting

GALAXY: A positive result indicates high likelihood of liver mets

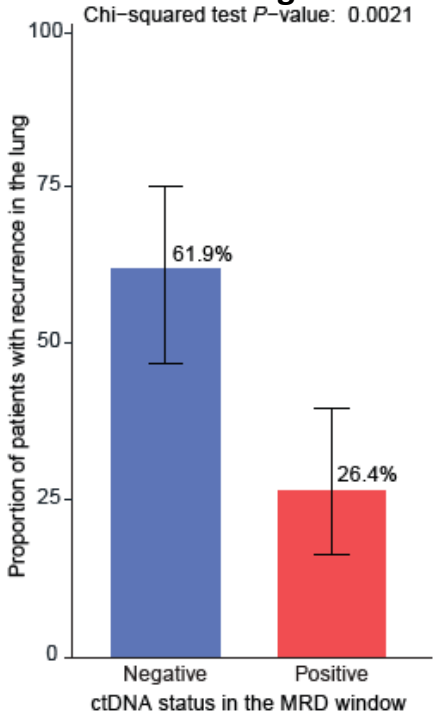
Site of recurrence and ctDNA status in the MRD window



Patients with recurrence in the liver



Patients with recurrence in the lung



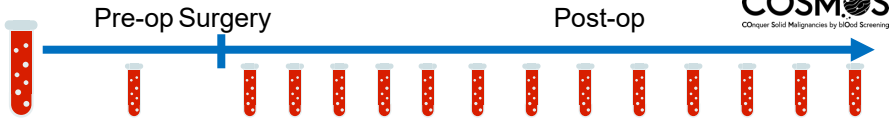
Kataoka et. al., Annals of Oncology 2024 (35) 11 1015-1025. Presented at 2024 ESMO Annual Congress

COSMOS-CRC-01 Trial

Study evaluating perioperative MRD using Guardant REVEAL for colorectal cancer

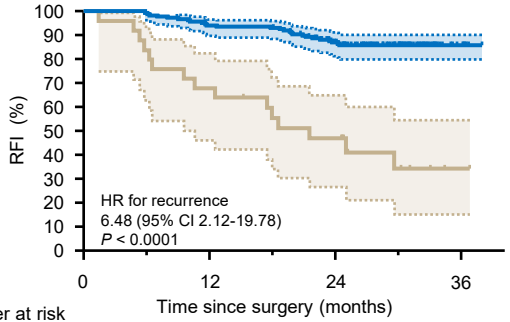
COSMOS

COnquer **S**olid **M**alignancies by bl**O**od **S**creening



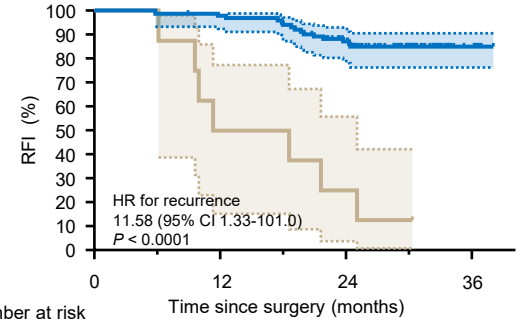
Nakamura Y, et al. JSMO 2022.

MRD assessment by Guardant REVEAL



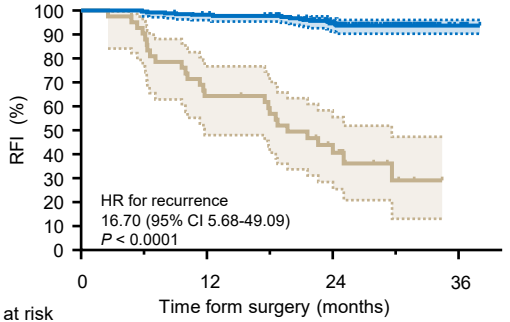
Number at risk				
Not detected	191	178	149	10
Detected	25	17	11	1

Postoperative MRD positive vs. negative



Number at risk				
Not detected	104	101	82	7
Detected	8	4	2	0

MRD positive vs. negative after adjuvant therapy



Number at risk				
Never detected	291	283	249	14
Ever detected	42	27	14	0

MRD positive vs. negative during post-operative surveillance

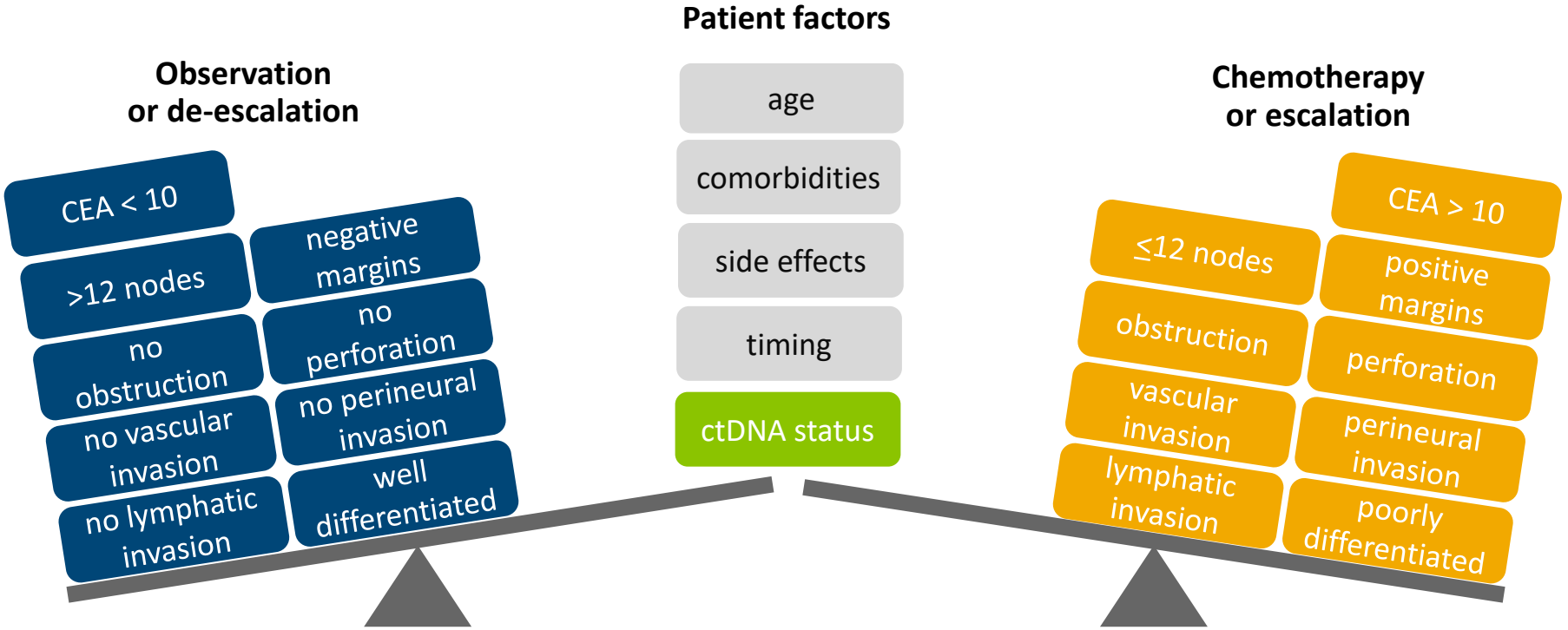
Slide credit: Takayuki Yoshino; Nakamura Y, Tsukada Y, Matsuhashi N, et al. Clin Cancer Res 2024

Question: My patient has a positive MRD test. What is the impact on prognosis? What should I do if CT scan is negative?

- Spontaneous clearance from a positive result is rare (<5%)
- There is currently no evidence-based strategy to manage a MRD+ result
- If MRD+ and CT scan is NED, median time to recurrence is 5-6 months
- For CRC, the leading site of recurrence is liver
- My approach for MRD+ result and CT scan NED:
  1. Repeat ctDNA test within 2-4 weeks
  2. Liver MRI (preferred)
  3. If liver MRI negative, consider PET-CT
  4. If disease is oligometastatic consider locally directed options

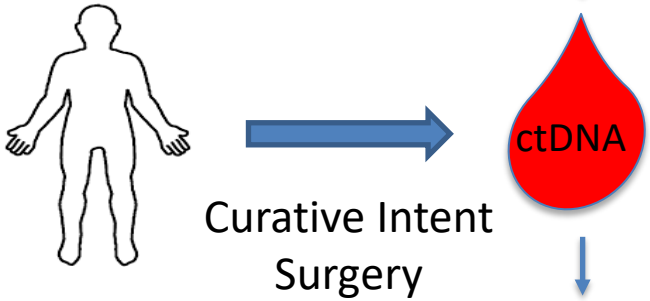
Question: My patient has resected non-metastatic colon cancer (MSS). What is the role for MRD testing?

Factors that influence adjuvant chemotherapy: T3N0 colon cancer

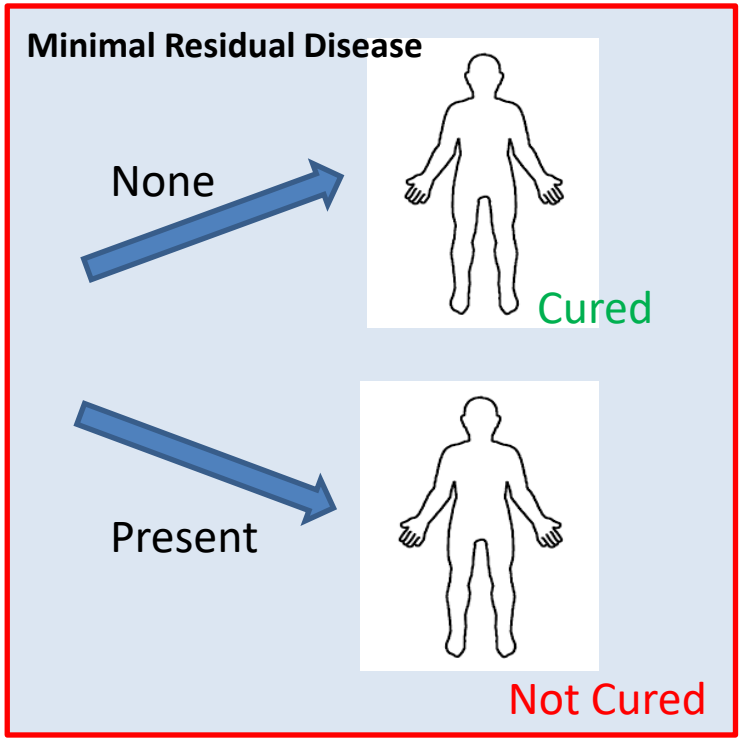


Can ctDNA identify who will recur after surgery?

Stage III colon cancer:
All patients get adjuvant chemo
>50% cured by surgery alone

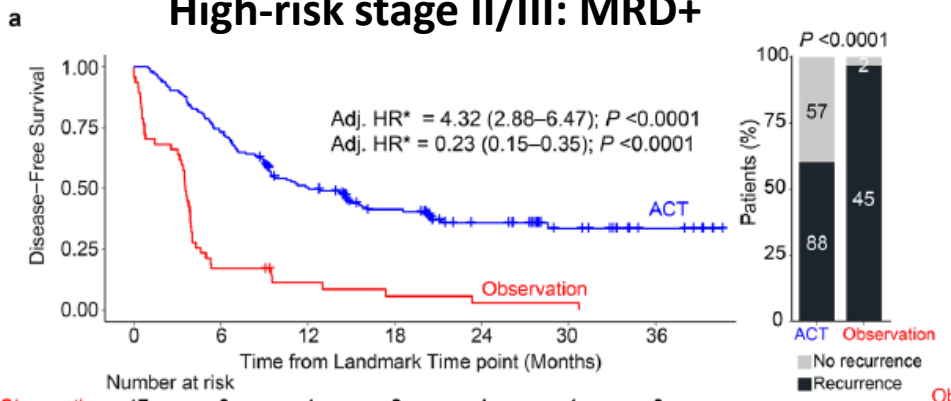


Stage II colon cancer:
SOC is NO adjuvant chemo
15%-20% recurrence risk



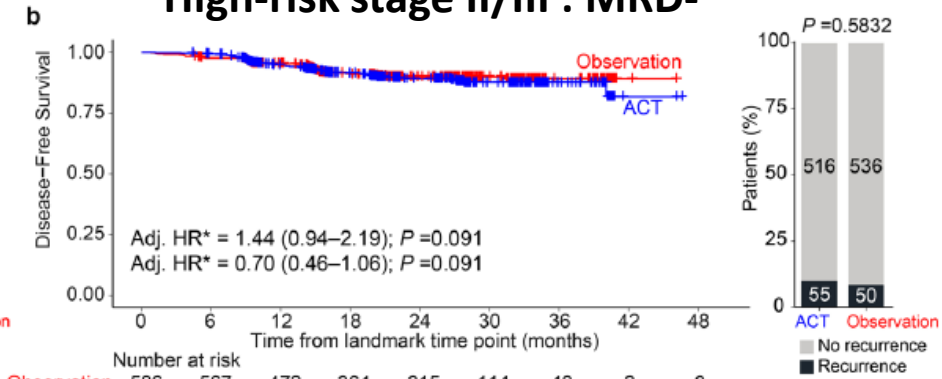
GALAXY: Adjuvant chemotherapy for high-risk stage II/III disease

High-risk stage II/III: MRD+



Treatment	ACT	Observation
Events %	60.68 (88/145)	95.74 (45/47)
24M-DFS % (95% CI)	35.83 (27.41–44.32)	2.84 (0.23–12.35)
mDFS (mo)	12.06 (9.30–18.57)	3.55 (3.16–3.95)

High-risk stage II/III : MRD-

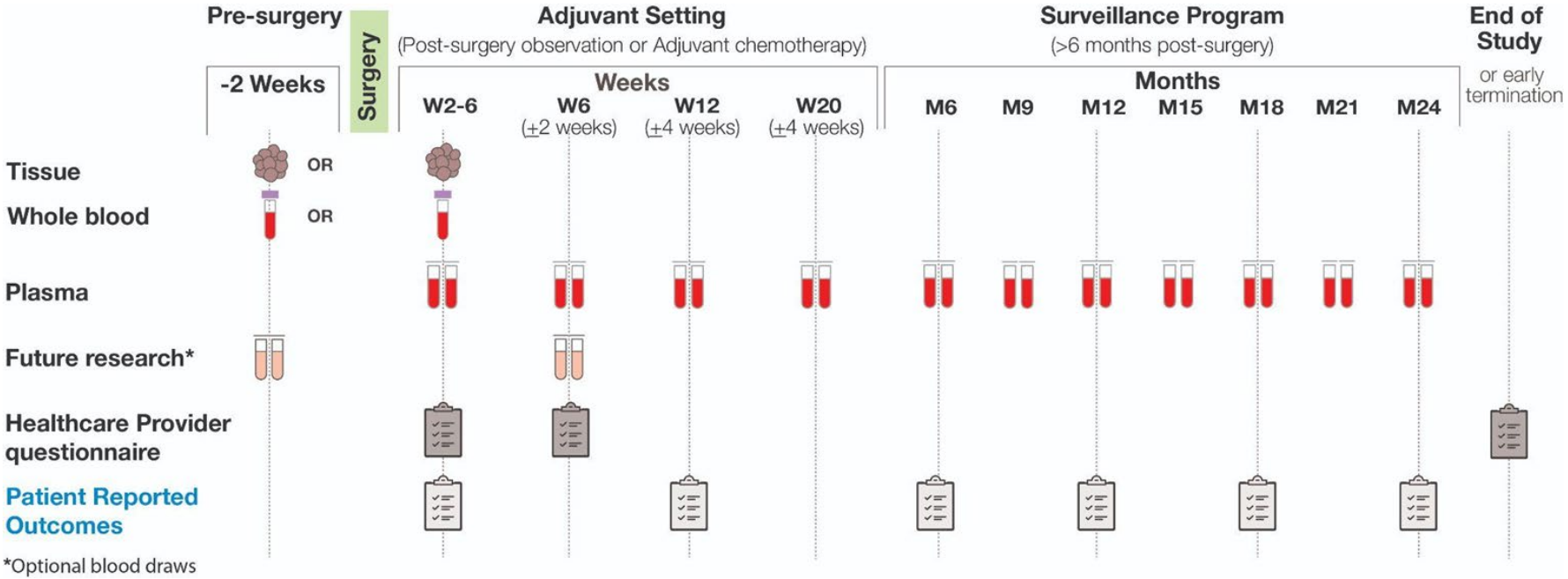


Treatment	ACT	Observation
Events %	9.63 (55/571)	8.53 (50/586)
24M-DFS % (95% CI)	89.11 (85.81–91.68)	89.9 (86.80–92.30)
mDFS (mo)	NR	NR

Nakamura et. al., Nature Medicine (2024) 30, 3272–3283

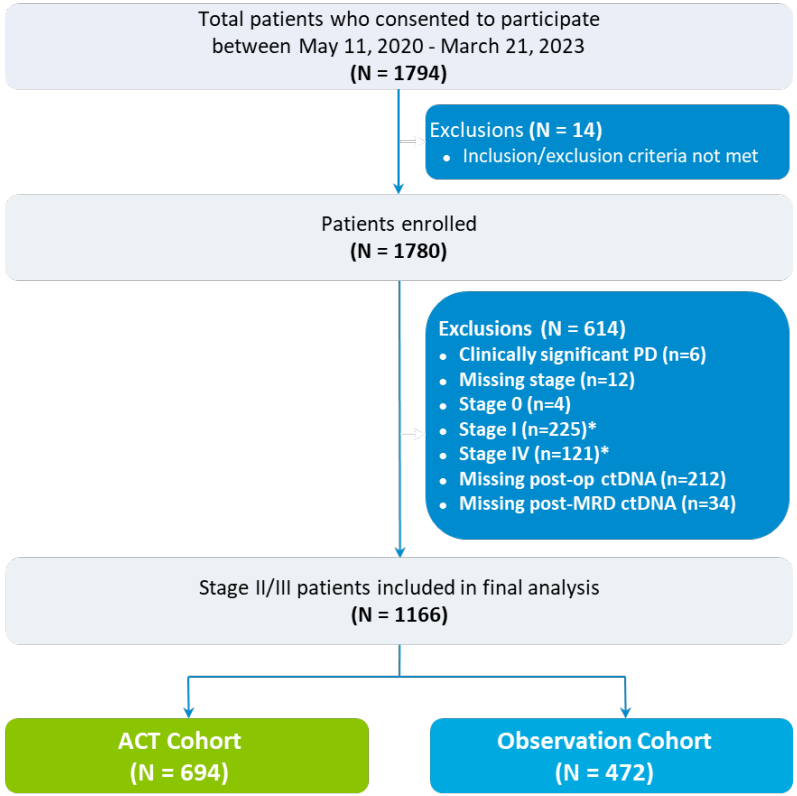
BESPOKE CRC study design

BESPOKE CRC (NCT04264702) is a multicenter (133 US sites), prospective, observational study evaluating the ability of a tumor-informed, personalized ctDNA assay to inform ACT treatment decisions in patients with stage II/III CRC.[1]



Kasi et. al., J Clin Oncol 42, 2024 (suppl 3; abstr 9). Presented at ASCO GI 2025

BESPOKE Consort Diagram



MRD window:
2-6 weeks post-surgery, before the start of adjuvant chemotherapy (ACT)

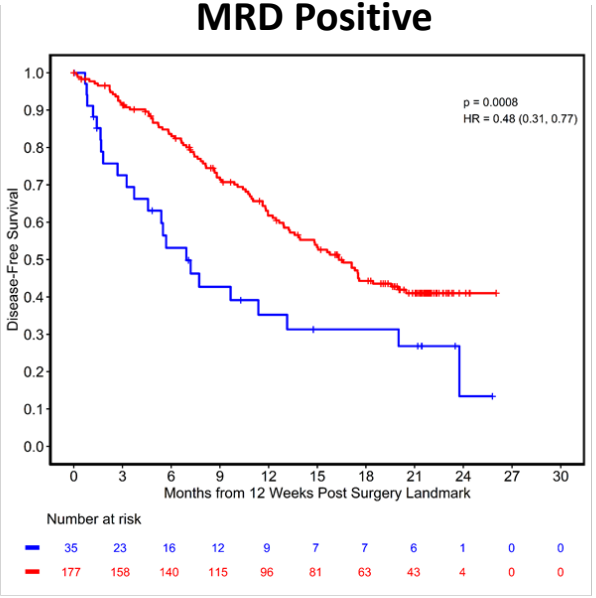
Surveillance window:
>6 months post-surgery

*Stage I and IV patients to be included in future analyses

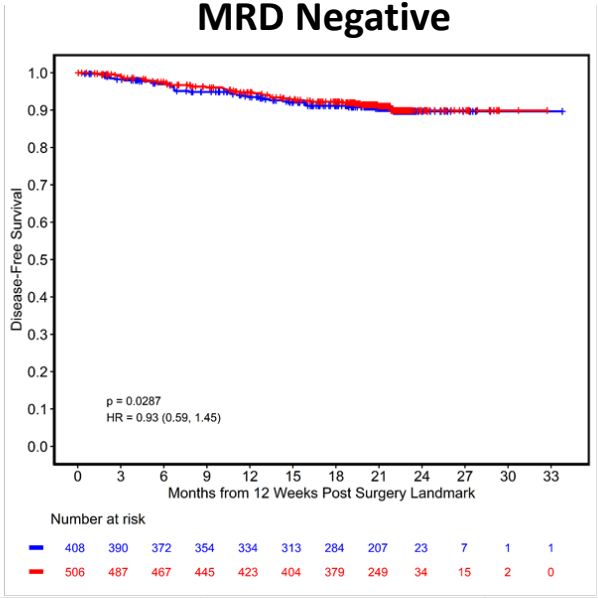
Shah et. al., J Clin Oncol 43, 2025 (suppl 4; abstr 15). Presented at ASCO GI 2025

ctDNA-based MRD testing is predictive of the benefit of ACT

MRD Positive



MRD Negative



Adjuvant strategy	ACT	Observation
Numbers of events (%)	96/177 (54.24)	29/35 (82.86)
2-year DFS post surgery, % (95% CI)	40.3 (33.3 - 48.9)	24.7 (13.2 - 46.3)
Median DFS post surgery, months (95%)	17.7 (14.6 - 21.4)	7.1 (4.6 - 21.4)

Adjuvant strategy	ACT	Observation
Numbers of events (%)	43/506 (8.50)	37/408 (9.07)
2-year DFS post surgery, % (95% CI)	89.7 (86.7- 92.9)	89.5 (86.2- 92.9)
Median DFS post surgery, months (95%)	Not reached	Not reached

Shah et. al., J Clin Oncol 43, 2025 (suppl 4; abstr 15). Presented at ASCO GI 2025

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

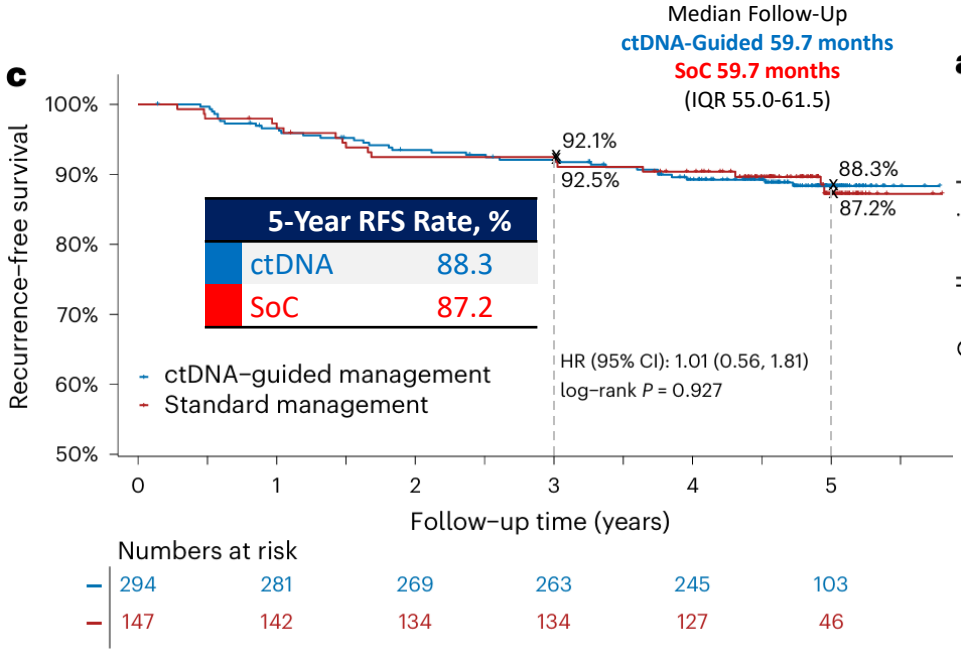
Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.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

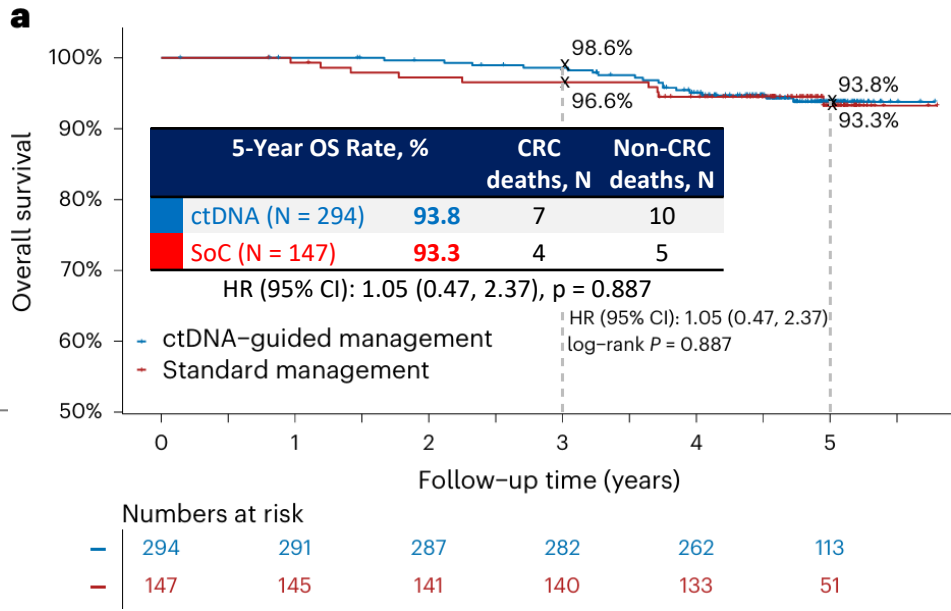
DYNAMIC: Updated 5-year RFS and Overall survival

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.**

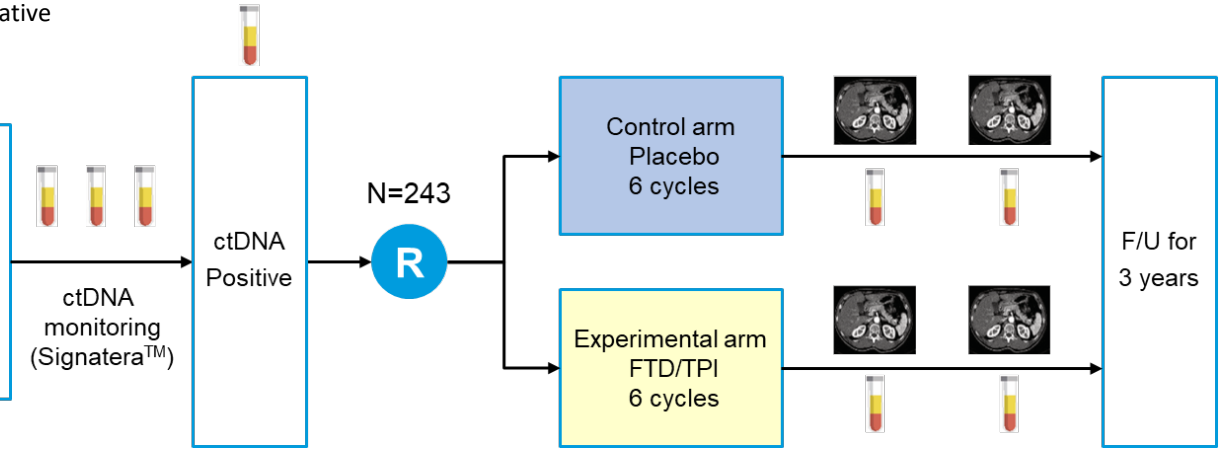
Tie J, et al. Nature Medicine 2025

ALTAIR: Study Schema

Monitoring by ctDNA and CT imaging:
ctDNA:2,4,6,8,10,12,15,18,24 months after randomization
CT:2,4,6,8,10,12,15,18,24,30,36 months after randomization

Stratification factors for DFS analysis:
Stage (≤ Stage II / Stage III / M1), ctDNA status at 1 month postoperatively (negative or unmeasurable)

Inclusion criteria:
- Colorectal adenocarcinoma
- After curative resection
- Prior standard perioperative therapy
- Age ≥ 20
- Informed consent

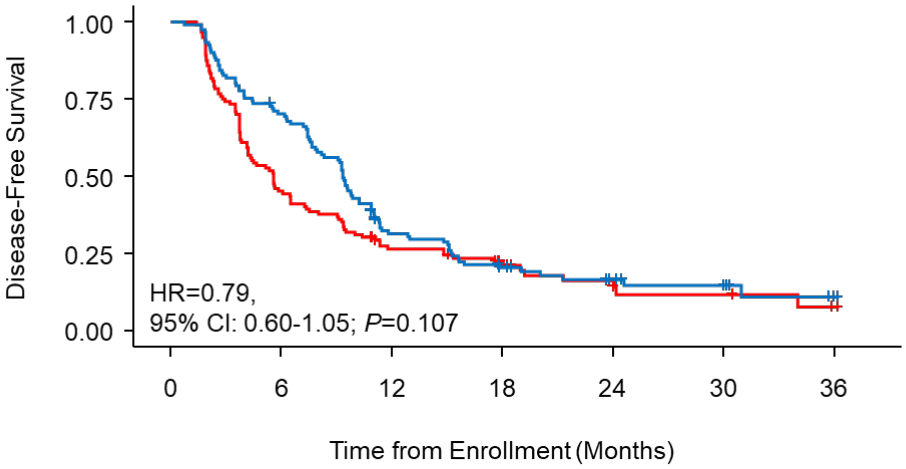


ctDNA-guided treatment escalation arm of the CIRCULATE-Japan adaptive trial platform, evaluating the utility of Signatera in patients with clinical stage II-IV resectable CRC

Bando et. al., J Clin Oncol 43, 2025 (suppl 4; LBA22). Presented at ASCO GI 2025

ALTAIR: Results

Primary Analysis - DFS: All patients



Number at risk

FTD/TPI	122	85	35	19	11	6	1
Placebo	121	55	28	16	6	5	1

DFS analysis stratified by Stage (Stage II or Lower, Stage III or M1) and ctDNA status 1mo post-surgery (Positive vs Negative/Unmeasured)

Treatment status	FTD/TPI	Placebo
Events %	81.15 (99/122)	81.82 (99/121)
6M-DFS %	70.5 (61.5-77.7)	45.5 (36.42-54)
12M-DFS %	31.8 (23.6–40.2)	26.8 (19.16-35)
18M-DFS %	20.8 (13.9–28.7)	21.5 (14.43-29.6)
24M-DFS %	16.9 (10.4–24.8)	14.5 (7.85-23.1)
mDFS (mo)	9.30 (7.92–10.84)	5.55 (4.17-7.33)

Abbreviations: CI, Confidence interval; ctDNA, circulating tumor DNA; DFS, disease-free survival; HR, Hazard ratio; MTM, mean tumor molecules.

Bando et. al., J Clin Oncol 43, 2025 (suppl 4; LBA22). Presented at ASCO GI 2025

2025 ASCO ANNUAL MEETING

ctDNA-Guided Adjuvant Chemotherapy Escalation in Stage III Colon Cancer

Primary Analysis of the ctDNA-Positive Cohort from the Randomized AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

Jeanne Tie

Peter MacCallum Cancer Centre and Walter & Eliza Hall Institute of Medical Research, Melbourne, Australia

On behalf of the AGITG DYNAMIC-III Investigators

Yuxuan Wang, Jonathan Loree, Joshua Cohen, David Espinosa, Rachel Wong, Timothy Price, Niall Tebbutt, Margaret Lee, Matthew Burge, Sam Harris, Belinda Lee, James Lynam, Chris O'Callaghan, Daniel Breadner, Chetan Bettegowda, Nickolas Papadopoulos, Kenneth Kinzler, Bert Vogelstein, Peter Gibbs

DYNAMIC-III Study Design Randomized Phase II/III (ACTRN12617001566325)

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

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

Standard Management

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

Stratified by clinical risk (low vs high) and sites

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

1. Cohen, J.D. *et al. Nat Biotechnol* **39**, 1220–1227 (2021)

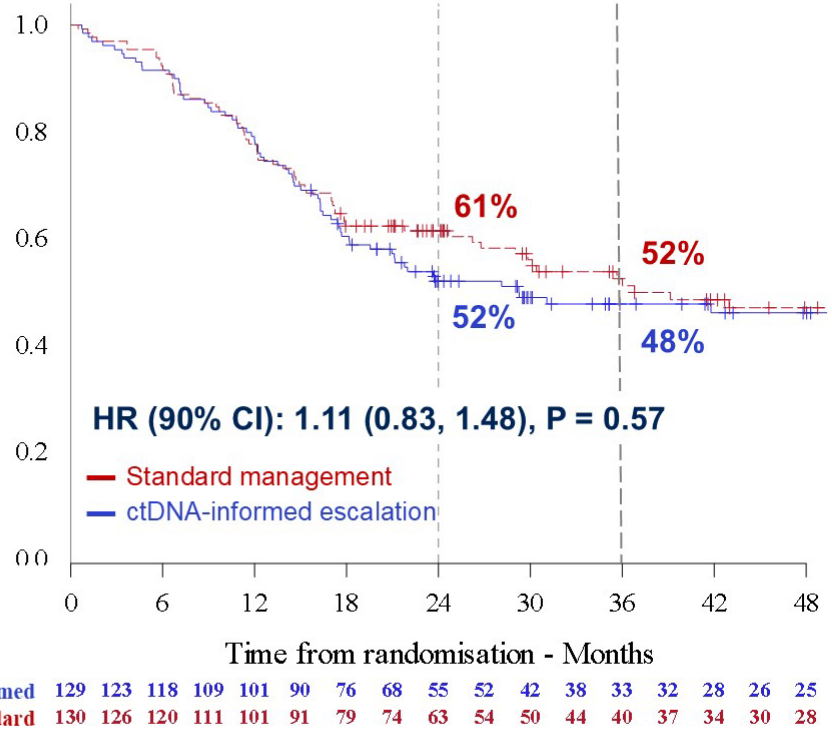
Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ASCO Annual Meeting

Treatment Exposure: ITT Population

Treatment Information		ctDNA-Informed Escalation N = 129, N (%)	Standard Management N = 130, N (%)
Commenced protocol treatment escalation		115 (89)	--
Chemotherapy received	No Chemotherapy	4 (3)	4 (3)
	Single agent FP	3 (2)	14 (11)
	3M Oxaliplatin doublet	1 (1)	59 (45)
	6M Oxaliplatin doublet	56 (44)	53 (41)
	≥ 3M FOLFOXIRI	65 (50)	0 (0)
Time from surgery to commencing chemotherapy, median (IQR), days		59 (52-68)	53 (49-61)
Treatment duration, median (IQR), days		150 (126-161)	147 (76-161)
Completed planned treatment		95 (74)	86 (68)

Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ASCO Annual Meeting

Recurrence-Free Survival



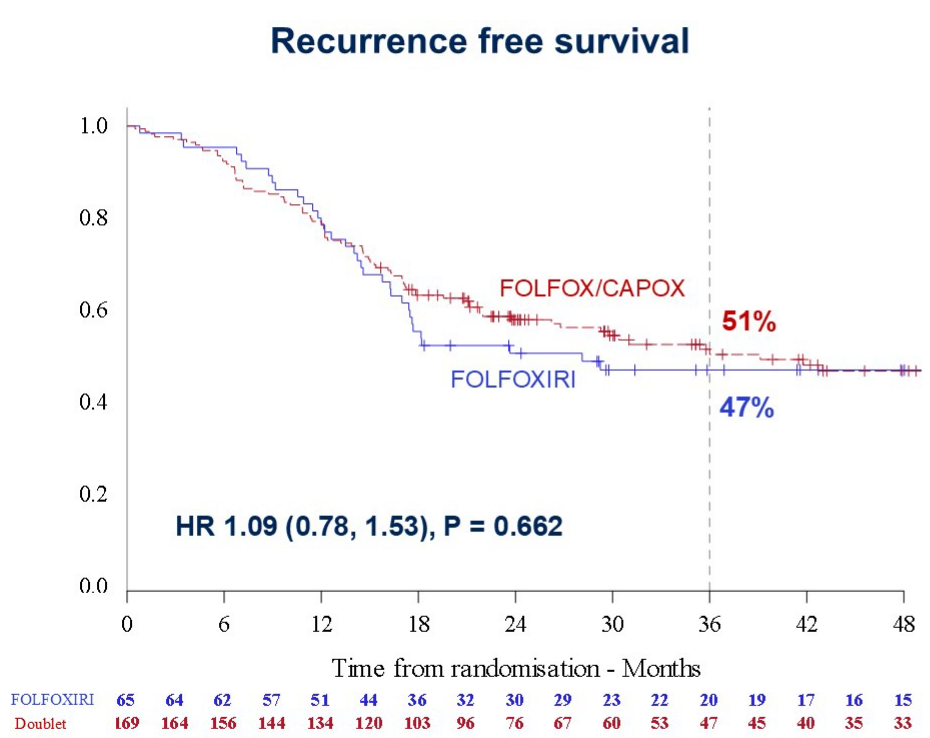
	Total	Events	Median RFS (mths)	2-year RFS (90% CI)	3-year RFS (90% CI)
ctDNA	129	66	29.24	52% (44, 59)	48% (40, 55)
SoC	130	62	36.80	61% (54, 68)	52% (44, 60)

Median follow-up 42.2 months (0.78 - 63.0)

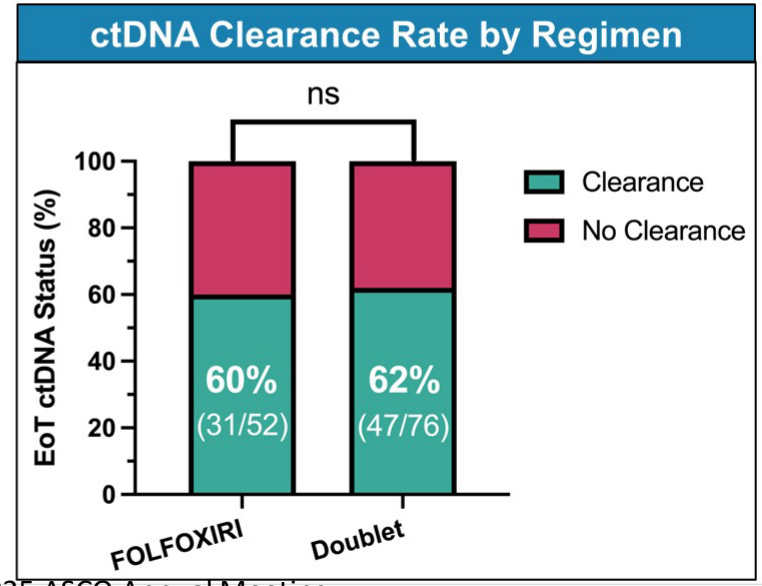
Data cut-off: 14 Nov 2024

Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ASCO Annual Meeting

Post-Hoc Analysis: FOLFOXIRI vs FOLFOX/CAPOX



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



Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ASCO Annual Meeting

BERLIN 2025 ESMO congress

ctDNA-Guided Adjuvant Chemotherapy De-Escalation in Stage III Colon Cancer

Primary Analysis of the ctDNA-Negative Cohort from the Randomised AGITG DYNAMIC-III Trial (Intergroup Study of AGITG and CCTG)

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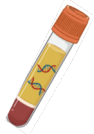
50 YEARS ESMO

DYNAMIC-III Study Design Randomised Phase II/III (ACTRN12617001566325)

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	Secondary
3-year recurrence-free survival (RFS)	treatment adherence, safety

Jeanne Tie

Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ESMO Congress

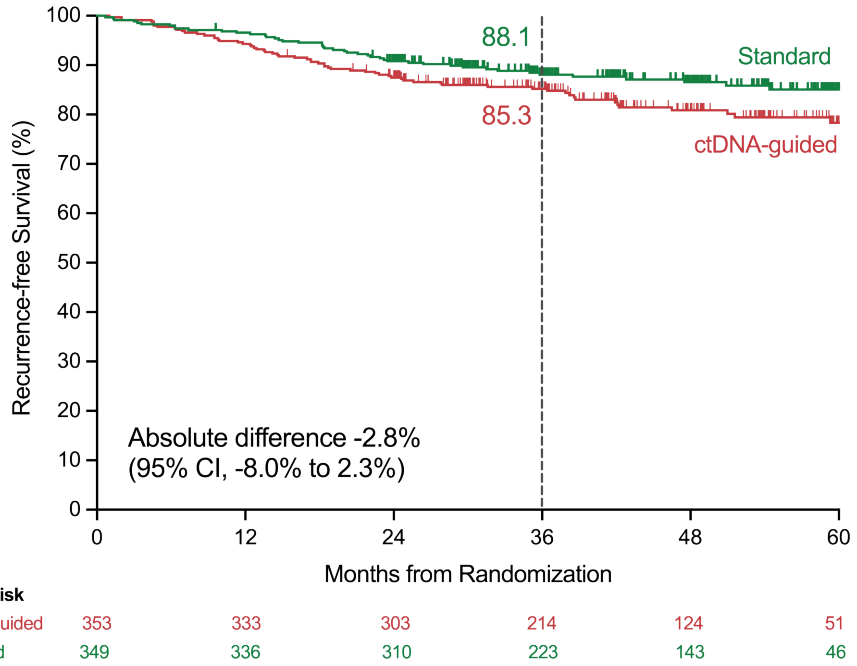
1. Cohen, J.D. et al. Nat Biotechnol 39, 1220–1227 (2021)

Treatment Delivery and Adherence: ctDNA-Negative

Treatment Information		ctDNA-Informed De-Escalation N = 353, N (%)	Standard Management N = 349, N (%)
Commenced per protocol treatment		319 (90.4)	347 (99.4)
Chemotherapy received	No Chemotherapy	26 (7.4)	8 (2.3)
	3M Single agent FP	119 (33.7)	1 (0.3)
	6M Single agent FP	85 (24.1)	31 (8.9)
	3M Oxaliplatin doublet	117 (33.1)	166 (47.6)
	6M Oxaliplatin doublet	6 (1.7)	143 (41.0)
Time from surgery to commencing chemotherapy, median (IQR), days		56 (51, 63)	53 (48, 59)
Treatment duration, mean (SD), days		101 (43.4)	118 (48)
Completed planned treatment cycles		294 (89.9)	282 (82.7)

Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ESMO Congress

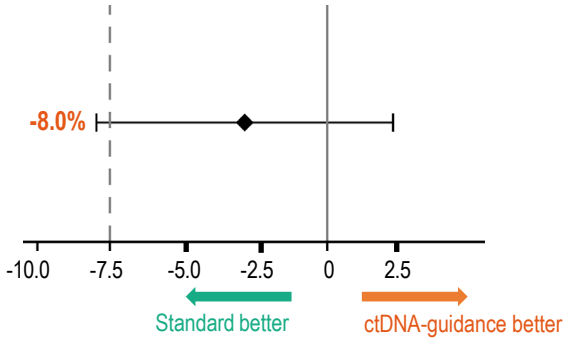
Recurrence-Free Survival



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)



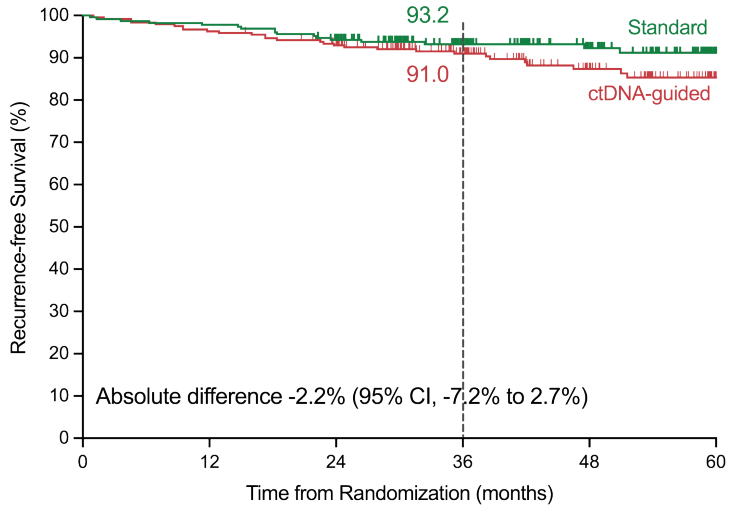
Database lock July 29, 2025

Tie et al., Nat Med 2025 Oct 20; Presented at 2025 ESMO Congress

Jeanne Tie

RFS by Clinical Risk

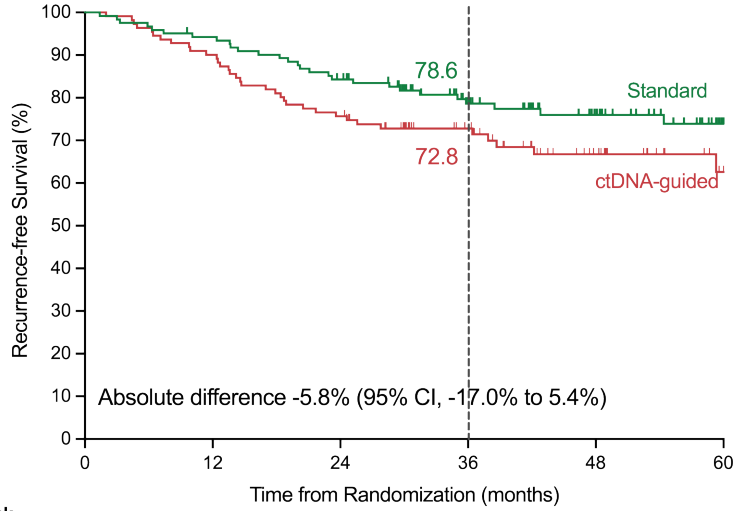
Clinical Low Risk (T1-3N1)



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., Nat Med 2025 Oct 20; Presented at 2025 ESMO Congress

Jeanne Tie

ASCO Gastrointestinal Cancers Symposium

Prognostic and predictive role of circulating tumor DNA (ctDNA) in stage III colon cancer treated with celecoxib: Findings from CALGB (Alliance)/SWOG 80702

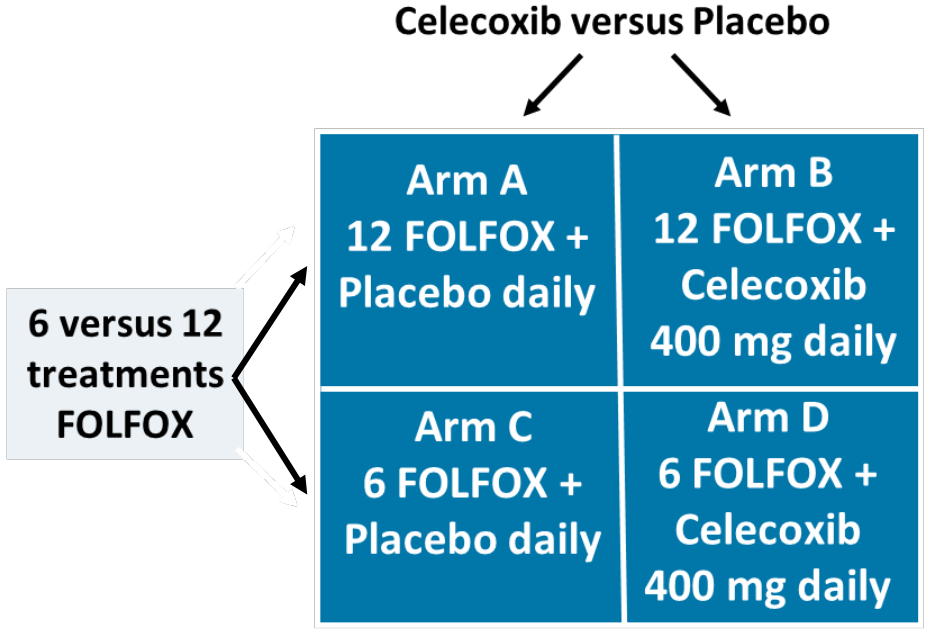
Jonathan A. Nowak, Qian Shi, Tyler Twombly, Levi Pederson, Chao Ma, Juha P. Väyrynen, Melissa Zhao, Yasutoshi Takashima, Ardaman Shergill, Pankaj Kumar, Felix Couture, Philip Kuebler, Smitha Krishnamurthi, Benjamin Tan, Eileen M. O'Reilly, Anthony F. Shields, Shuji Ogino, Alexey Aleshin, and Jeffrey A. Meyerhardt

PRESENTED BY: Jonathan A. Nowak, MD, PhD

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*

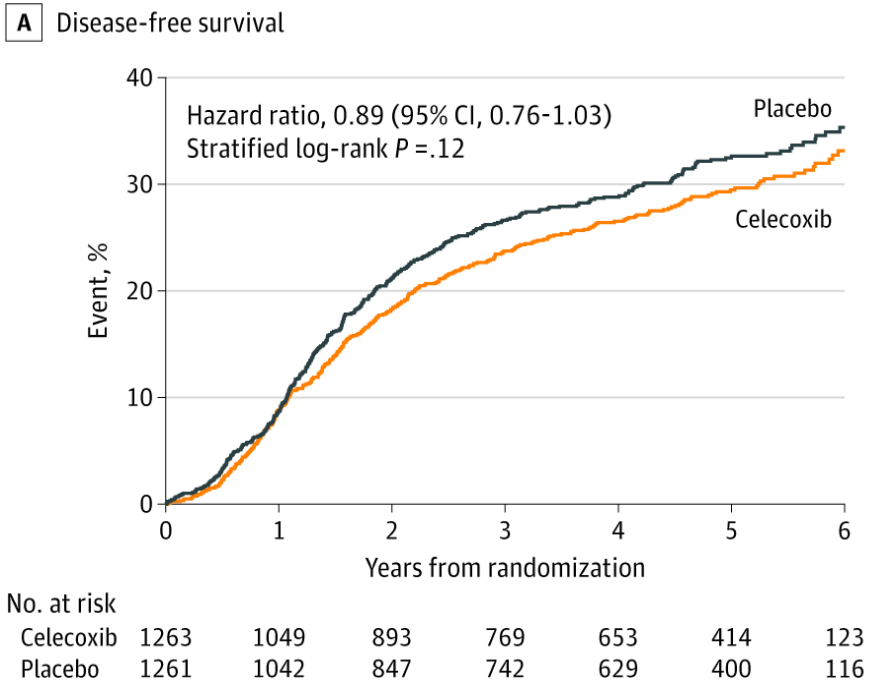


Celecoxib/placebo continued for a total of 3 years from the day study drug was initiated

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

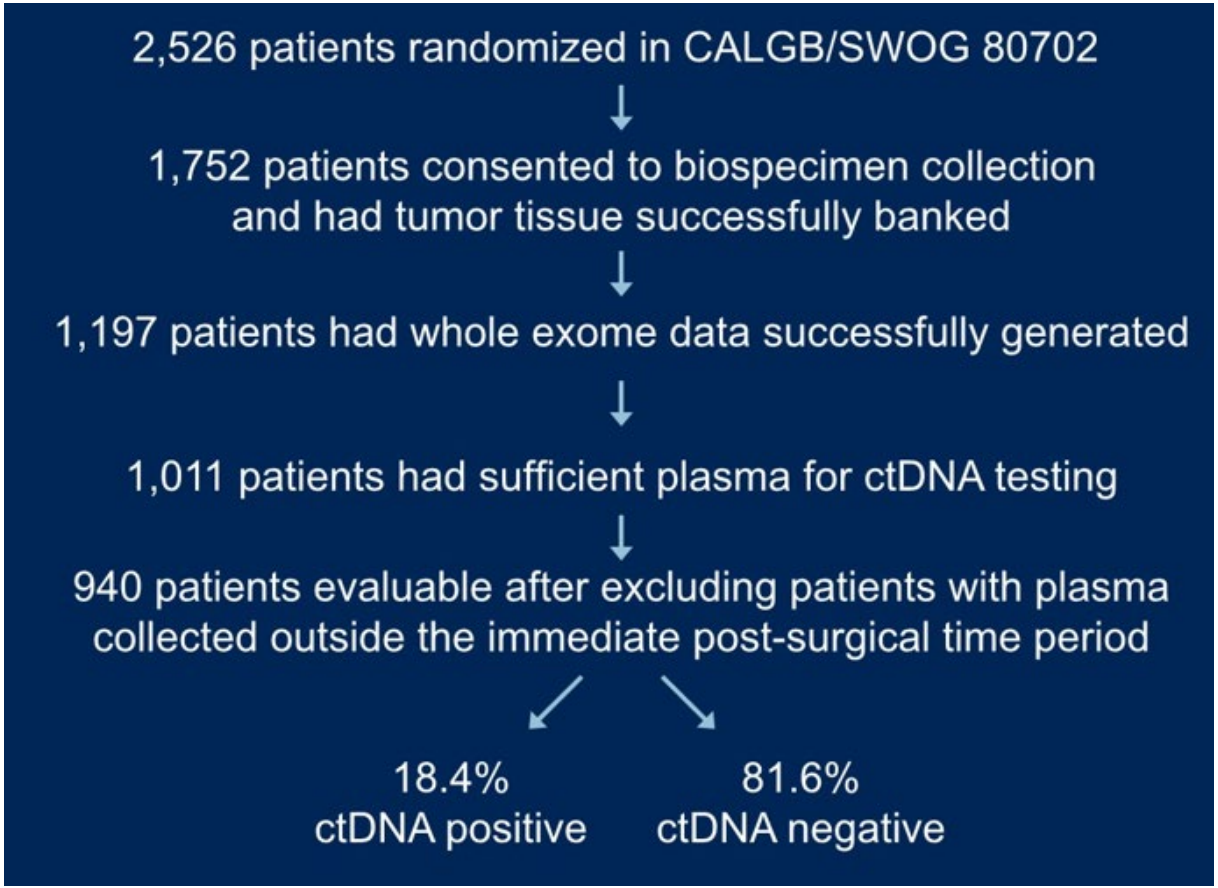
CALGB/SWOG 80702: Survival according to adjuvant celecoxib



- 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

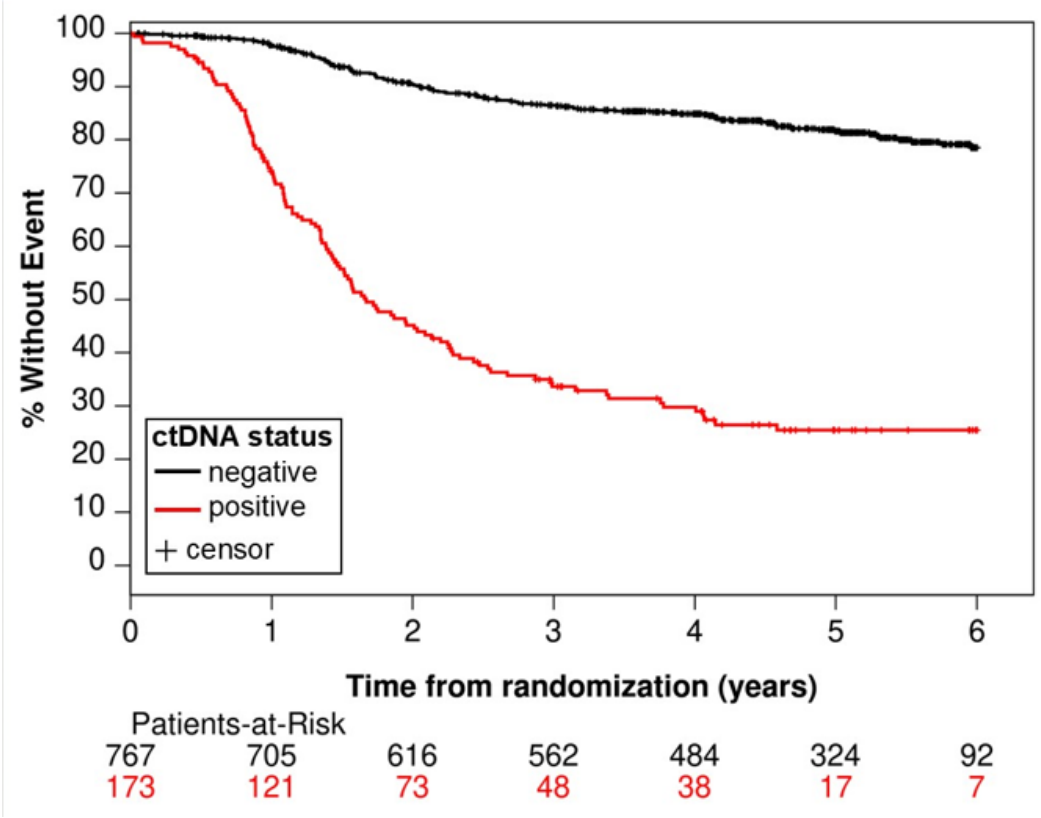
Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

Study composition for Signatera ctDNA analysis



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

Disease-free survival by ctDNA status

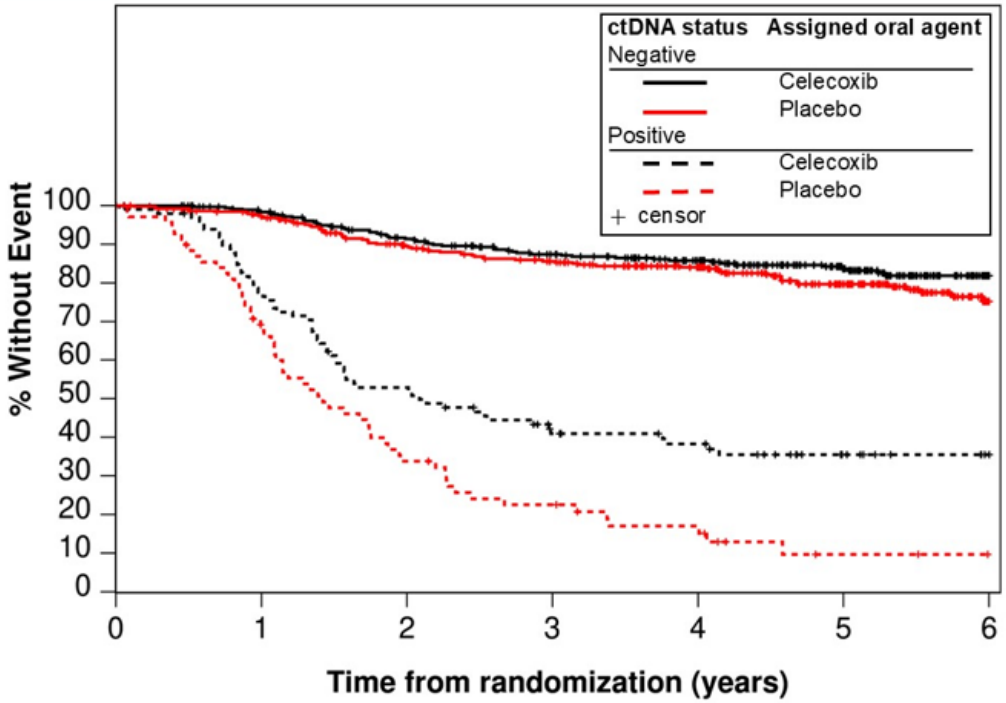


ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]
Negative	131/767	Reference	86.5 (84.0-89.1%)
Positive	118/173	7.14 (5.54-9.21)	33.7 (27.1-41.8%)
Logrank P-value: <0.0001[3]			

[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

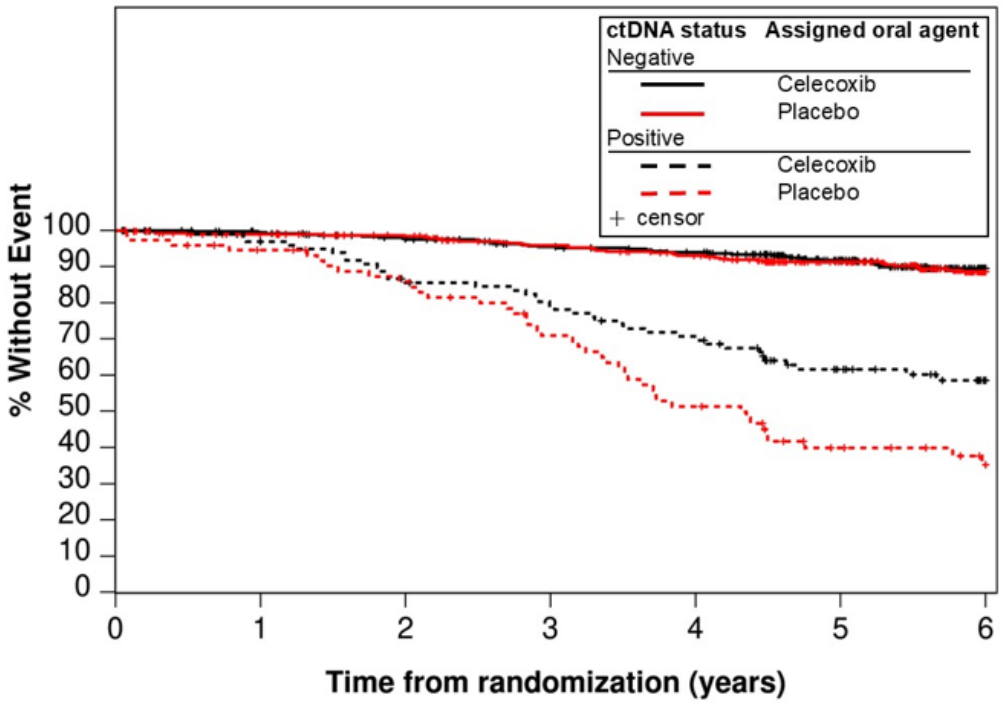


Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)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

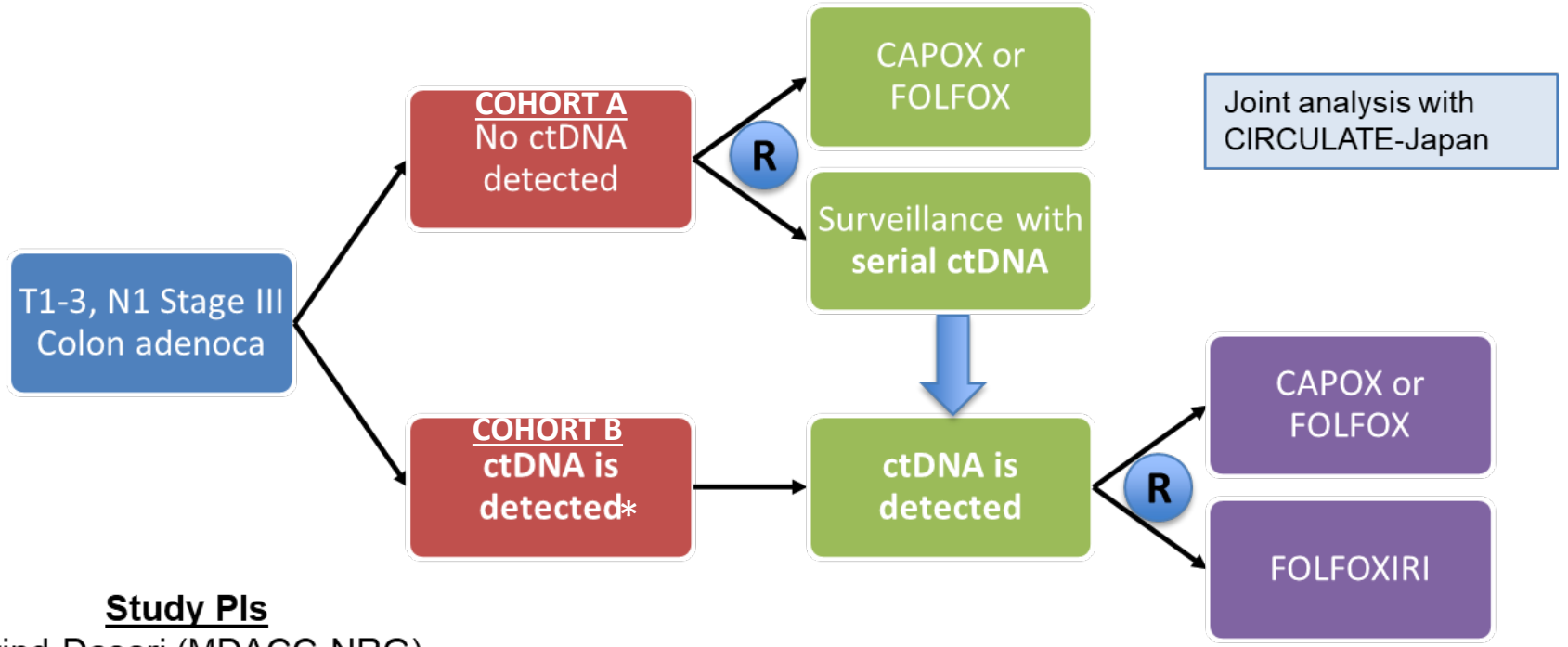
[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

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

Question: My patient has resected non-metastatic colon cancer (MSS). What is the role for MRD testing?

- MRD testing has demonstrated clinical utility for patients with stage II (T3N0, MSS) colon cancer
- Aspirin/ celecoxib can be considered for patients with MRD+ stage III 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
- But… key studies are ongoing

CIRCULATE-US (NRG-GI008)



Study PIs

Arvind Dasari (MDACC-NRG)

Christopher Lieu (UCCC-SWOG)

* Stage III (T1-3, N1/N1c) or ctDNA+ stage II or IIIC post-R0 resection

MRD testing to guide patient management- Final thoughts

- MRD testing is a validated prognostic tool
- Tumor informed assays have established clinical validity and in select circumstances clinical utility
- Blood-only tests are a reasonable alternative if tissue is limited or there is time urgency
- If MRD+ following definitive treatment-- Intensified surveillance/ imaging (MRI liver and/or PET) advised
- For stage II colon ca, MRD could be considered a “tie-breaker” for adjuvant chemotherapy
- Prospective trials are ongoing to explore the clinical utility of escalation and de-escalation strategies

49-year-old woman referred for ongoing rectal cancer management

· Diagnosed September 2024 after screening colonoscopy revealed rectal mass
· Biopsy: well-to-moderately differentiated adenocarcinoma, margin positive
    - loss of MLH1/PMS2
- Staging MRI: T3BN2, no distant metastasis
- Treated with neoadjuvant dostarlimab (Oct 2024 – Feb 2025)
- Achieved complete clinical and radiographic response on follow-up imaging
- No surgery performed
- Currently asymptomatic, normal bowel function, no evidence of recurrence

Role of ctDNA in rectal cancer management?