Post ASCO-GI Update on ctDNA in Management of Colon cancer

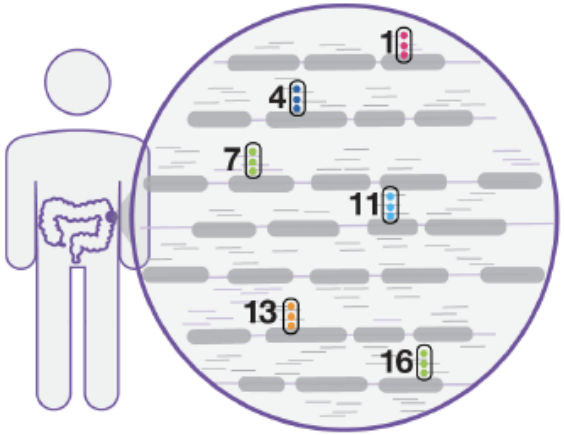
John Strickler, MD
Professor of Medicine
Duke University
February 13, 2025

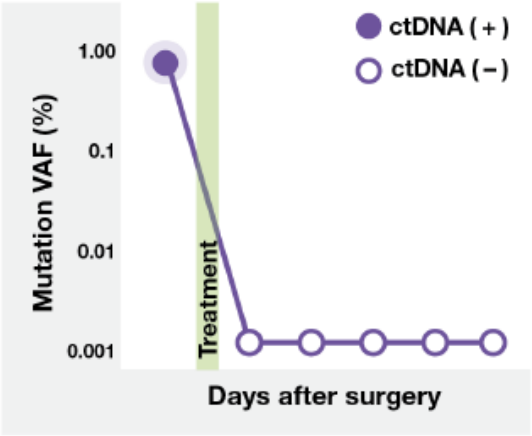
“Tumor informed” mutation detection

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

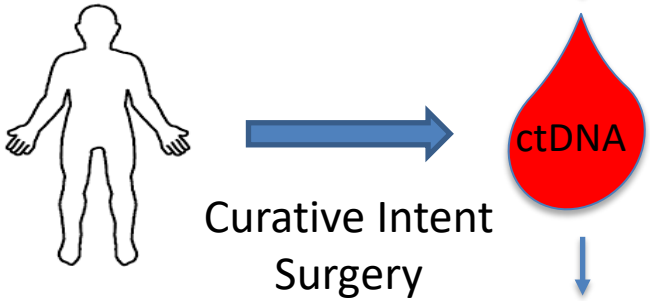
Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)



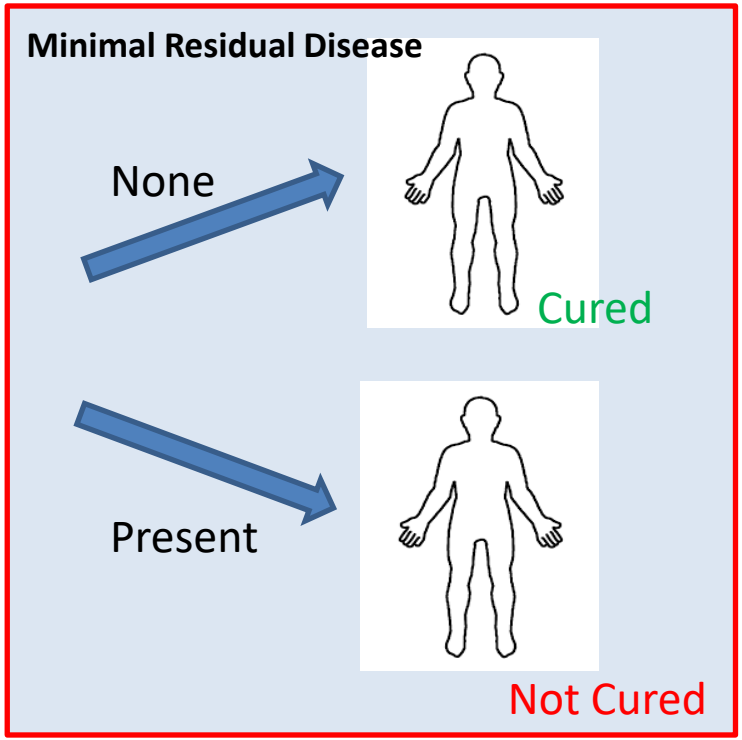


Can ctDNA identify who will recur after surgery?

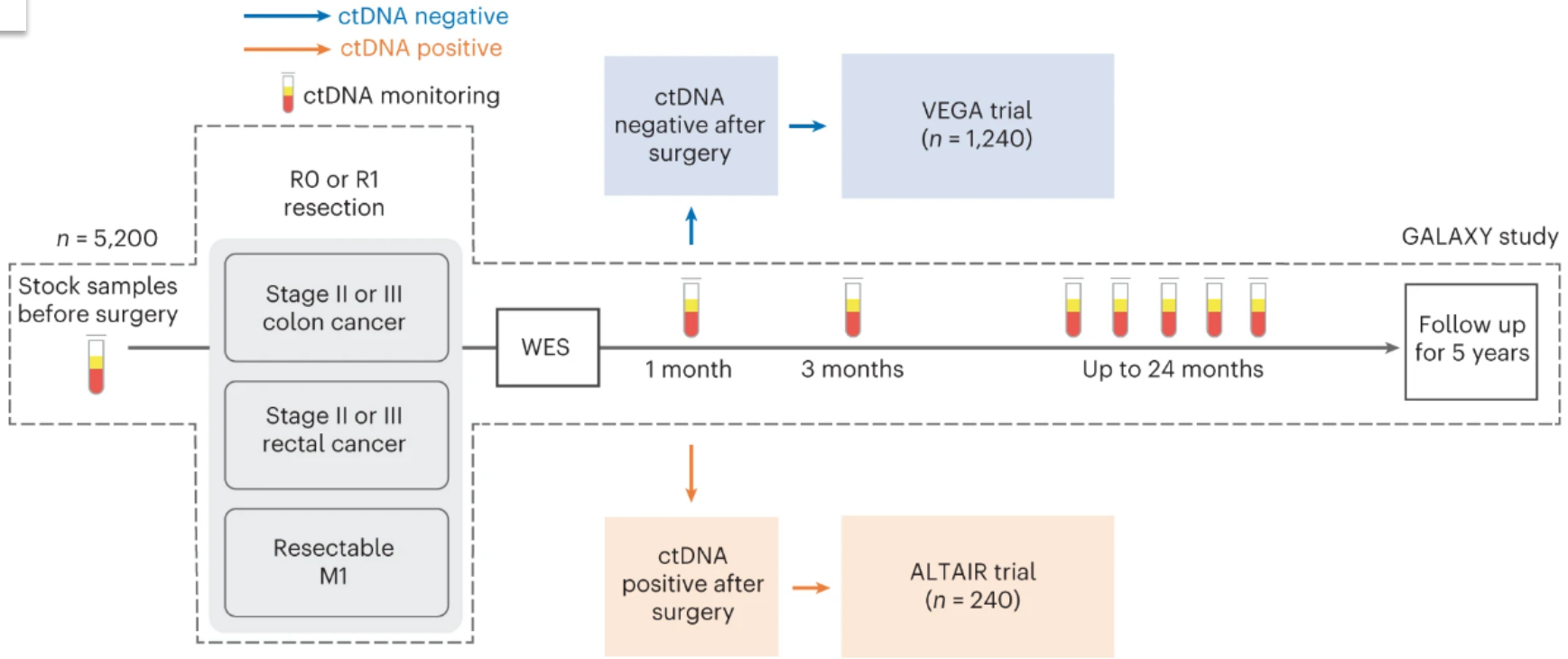
Stage III CRC:
All patients get adjuvant chemo
>50% cured by surgery alone



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

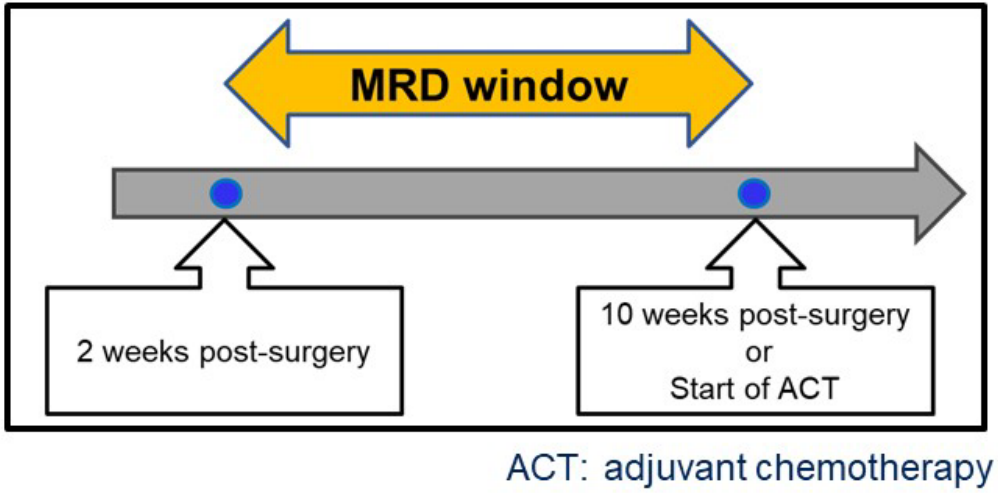


Clinical validation of tumor informed MRD testing: GALAXY Study Design



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

GALAXY: MRD Window

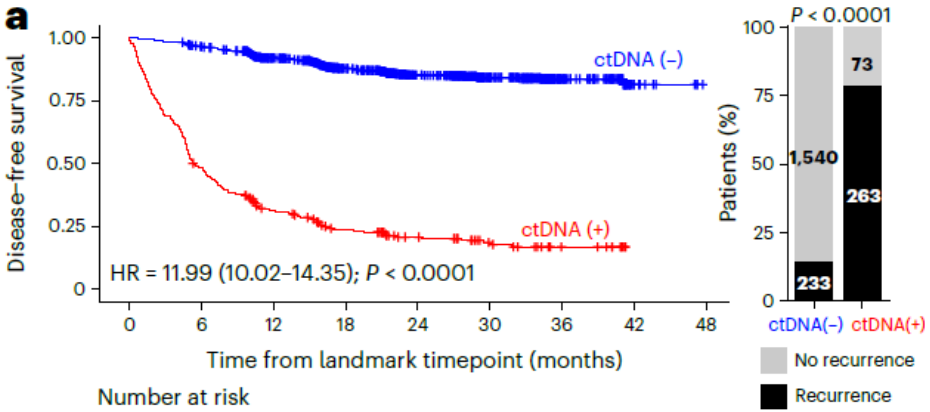


MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

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

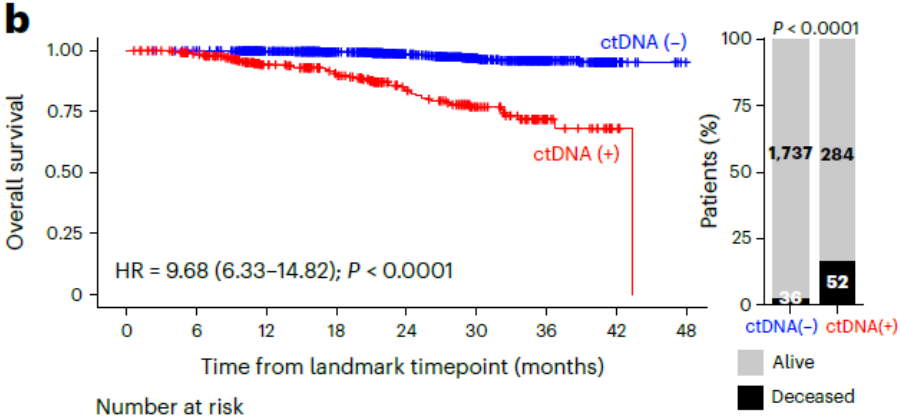


Number at risk

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



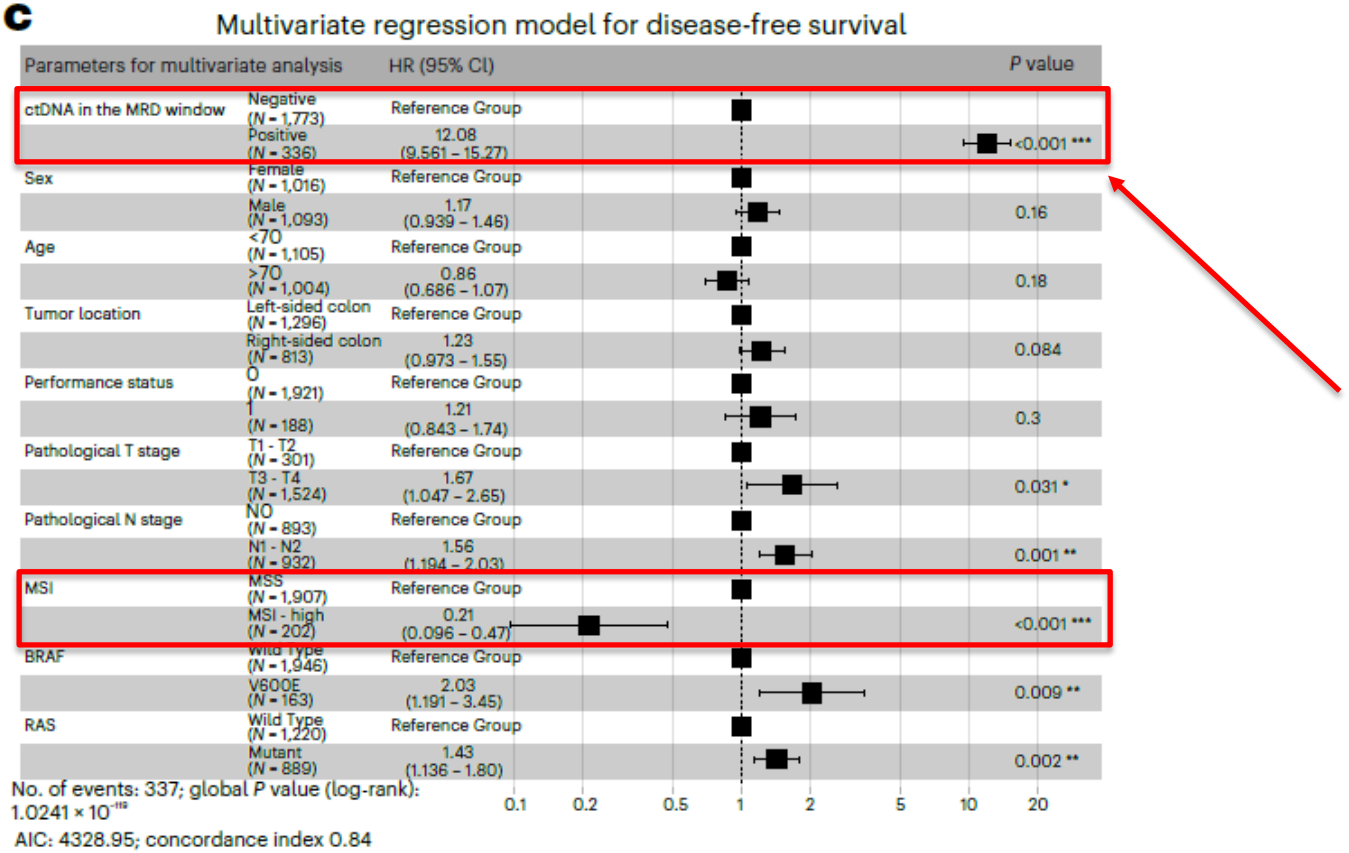
Number at risk

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)

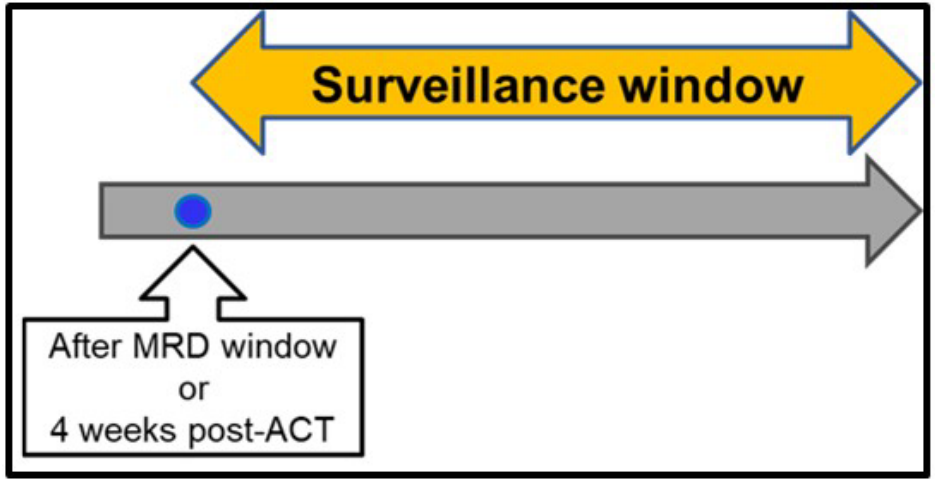
Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

MRD status after surgery is strongly prognostic



Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

GALAXY: Surveillance window

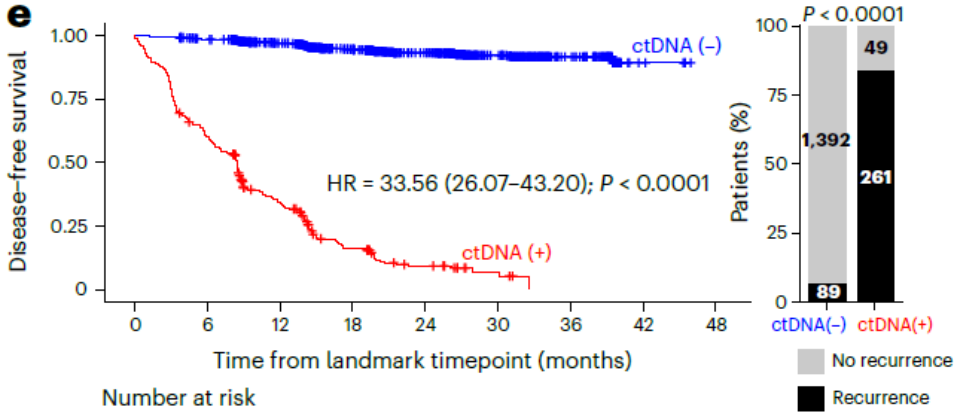


- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

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

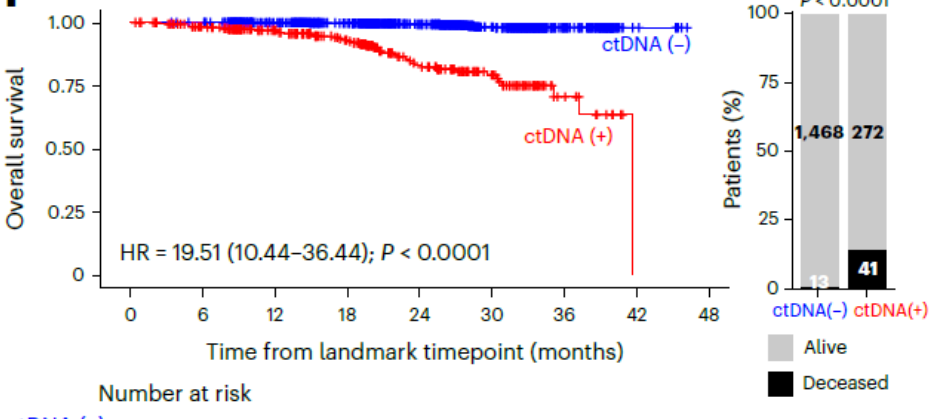


Number at risk

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

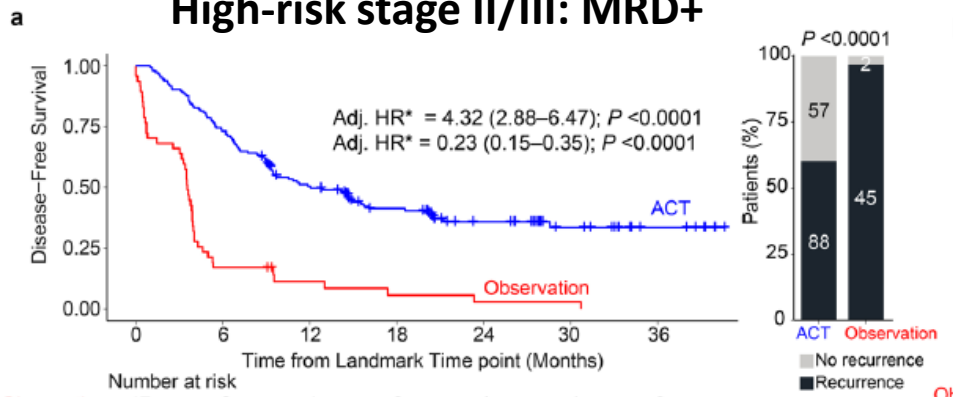
ctDNA status	Negative	Positive
Events %	0.88 (13/1481)	13.10 (41/313)
24M-OS % (95% CI)	99.30 (98.40–99.70)	83.20 (76.50–88.10)
30M-OS % (95% CI)	98.20 (96.70–99.0)	79.20 (71.50–85.0)
36M-OS % (95% CI)	97.90 (96.30–98.90)	70.50 (57.70–80.10)
mOS (mo)	NR	41.80 (37.30–NR)

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

Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

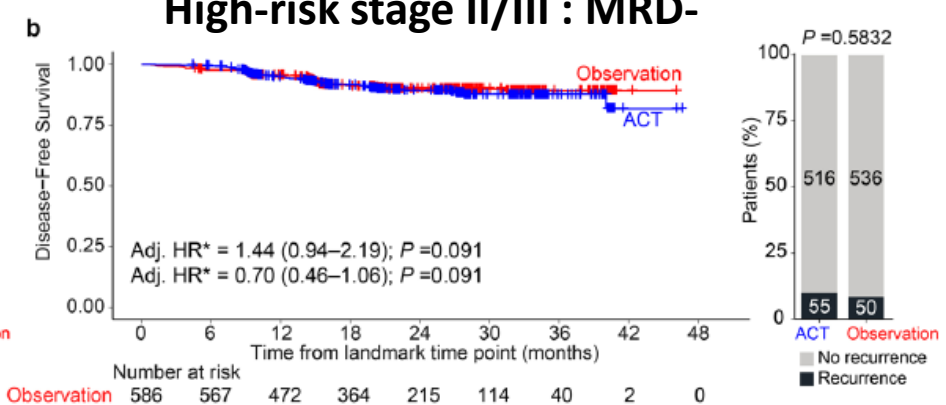
Adjuvant chemotherapy for high-risk stage II/III disease: MRD status impacts benefit

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-

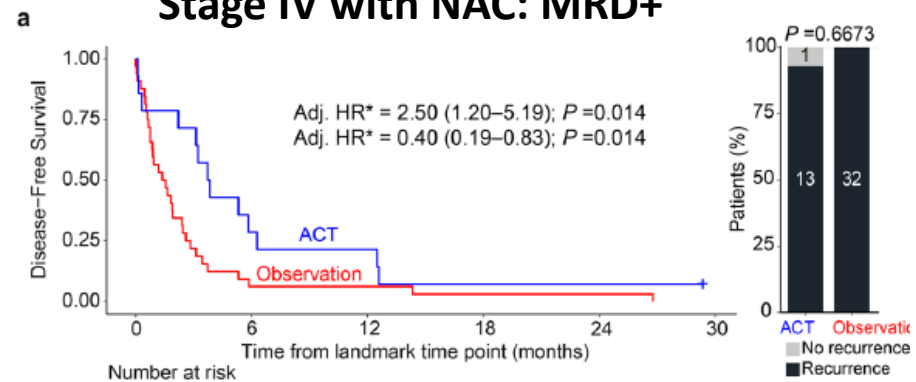


Treatment	ACT	Observation
Events %	9.63 (55/571)	8.53 (50/586)
24M-DFS % (95% CI)	89.11 (85.81–91.68)	89.9 (86.80–92.30)
mDFS (mo)	NR	NR

Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

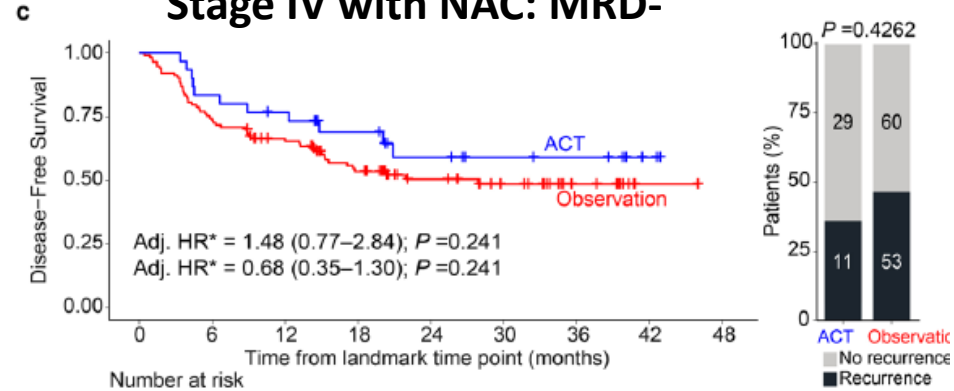
Adjuvant chemotherapy for stage IV: MRD status impacts benefit (all received neoadjuvant chemotherapy)

Stage IV with NAC: MRD+



ctDNA status	ACT	Observation
Events %	92.86 (13/14)	100 (32/32)
3M-DFS % (95% CI)	71.43 (40.63–88.20)	21.88 (9.65–37.20)
6M-DFS % (95% CI)	28.57 (8.83–52.40)	6.25 (1.11–18.10)
24M-DFS % (95% CI)	7.14 (0.45–27.50)	3.12 (0.24–13.70)
mDFS (mo)	3.78 (3.13–12.59)	1.46 (0.86–2.44)

Stage IV with NAC: MRD-

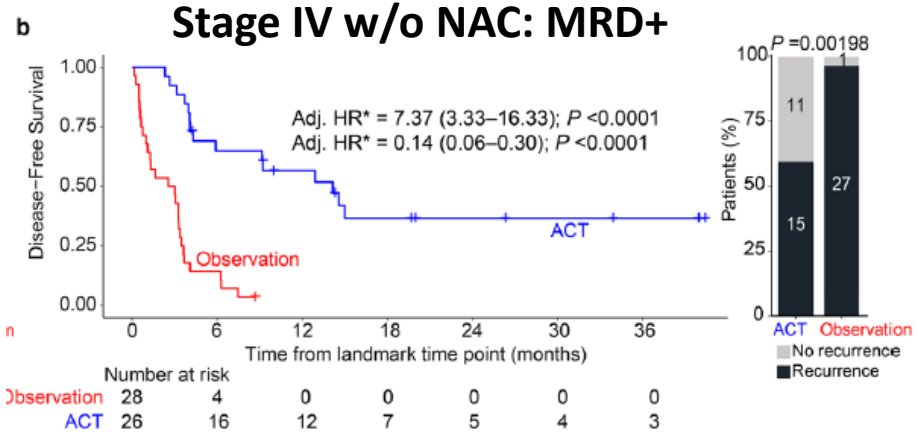


ctDNA status	ACT	Observation
Events %	36.67 (11/30)	46.90 (53/113)
24M-DFS % (95% CI)	58.90 (37.30–75.30)	50.40 (40.0–59.80)
36M-DFS % (95% CI)	58.90 (37.30–75.30)	48.40 (37.90–58.20)
mDFS (mo)	NR (20.10–NR)	27.90 (15.30–NR)

Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

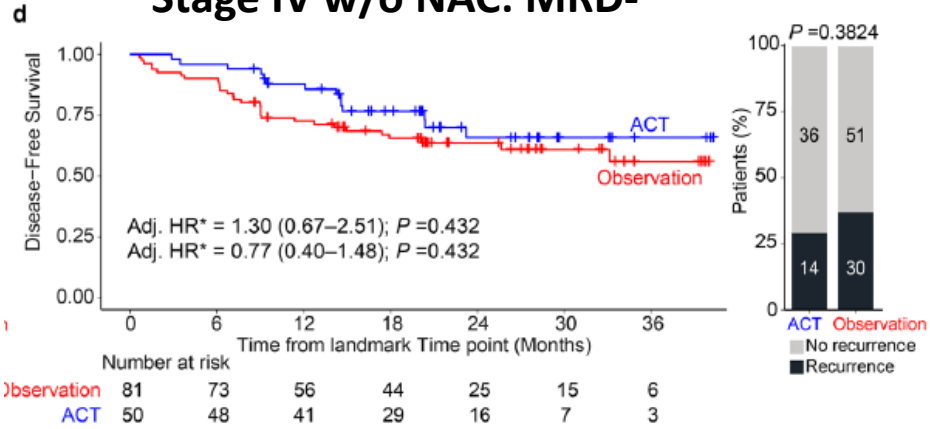
Adjuvant chemotherapy for stage IV: MRD status impacts benefit (NO neoadjuvant chemotherapy)

Stage IV w/o NAC: MRD+



ctDNA status	ACT	Observation
Events %	57.69 (15/26)	96.43 (27/28)
3M-DFS % (95% CI)	92.30 (72.60–98.0)	50 (30.60–66.60)
6M-DFS % (95% CI)	65.0 (43.4–80.0)	14.3 (4.50–29.50)
24M-DFS % (95% CI)	36.70 (17.6–56)	NR
mDFS (mo)	14.20 (5.92–NR)	2.8 (1.12–3.52)

Stage IV w/o NAC: MRD-



ctDNA status	ACT	Observation
Events %	28.0 (14/50)	37.04 (30/81)
24M-DFS % (95% CI)	65.80 (47.90–78.70)	64.60 (51.60–73.40)
36M-DFS % (95% CI)	65.80 (47.90–78.70)	55.90 (40.50–68.70)
mDFS (mo)	NR	NR (33.10–NR)

Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

MRD questions answered at ASCO GI 2025

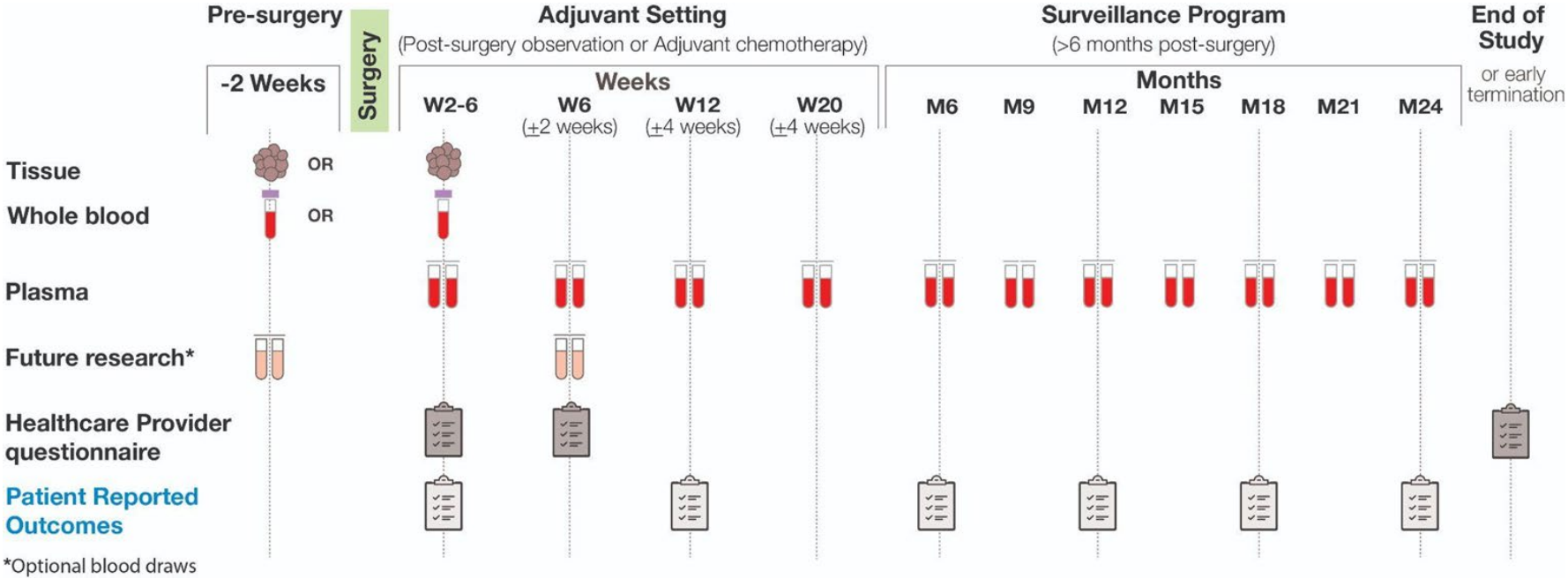
- Do US oncologists find ctDNA helpful for guiding adjuvant chemotherapy in patients with resected colon cancer?
- Can “adjuvant” celecoxib improve DFS and OS in patients with resected stage III colon cancer with ctDNA positivity following surgery?
- Should patients with ctDNA positivity after completing definitive therapy for colon cancer be offered TAS-102?

MRD questions answered at ASCO GI 2025

- Do US oncologists find ctDNA helpful for guiding adjuvant chemotherapy in patients with resected colon cancer?
- Can “adjuvant” celecoxib improve DFS and OS in patients with resected stage III colon cancer with ctDNA positivity following surgery?
- Should patients with ctDNA positivity after completing definitive therapy for colon cancer be offered TAS-102?

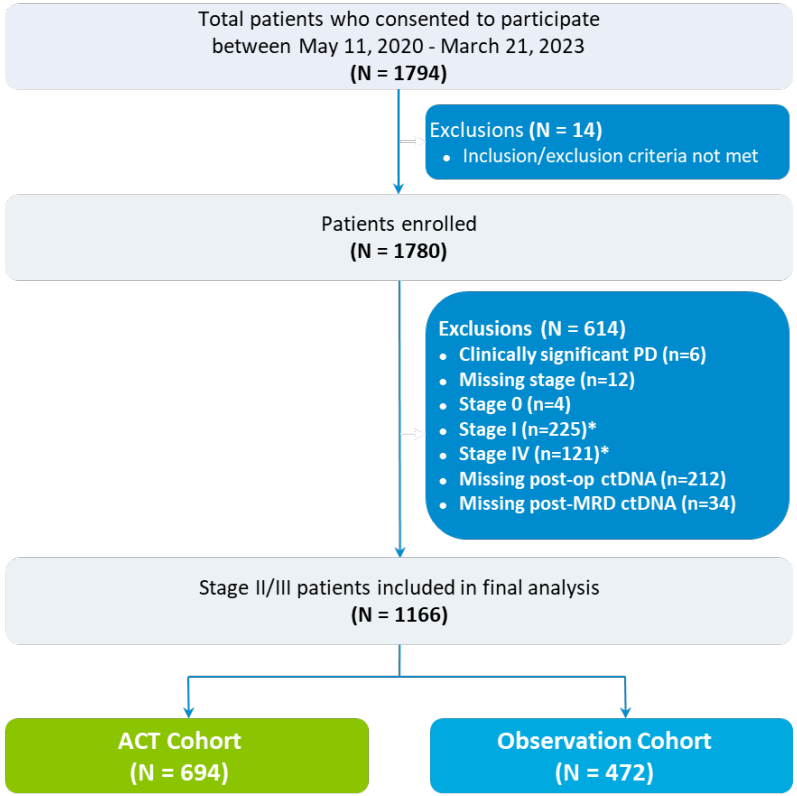
BESPOKE CRC study design

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)

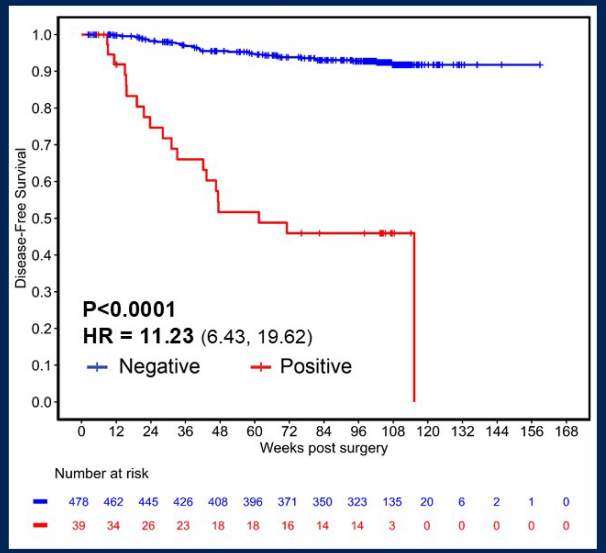
Surveillance window:
>6 months post-surgery

*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

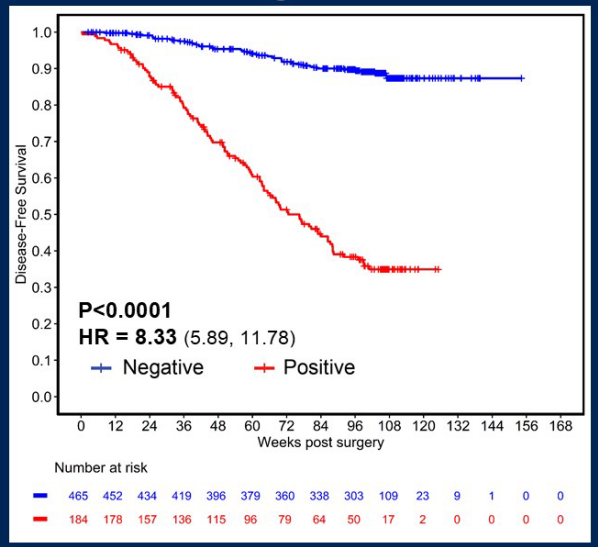
Post-operative ctDNA positivity predicts inferior DFS

Stage II



ctDNA Status	Events	Median DFS post surgery, months (95%)	2-year DFS post surgery,% (95% CI)
Negative	33	NE (NE-NE)	**91.8** (NE-NE)
Positive	20	12.7 (8.3-NE)	**45.9** (32.1-65.8)

Stage III

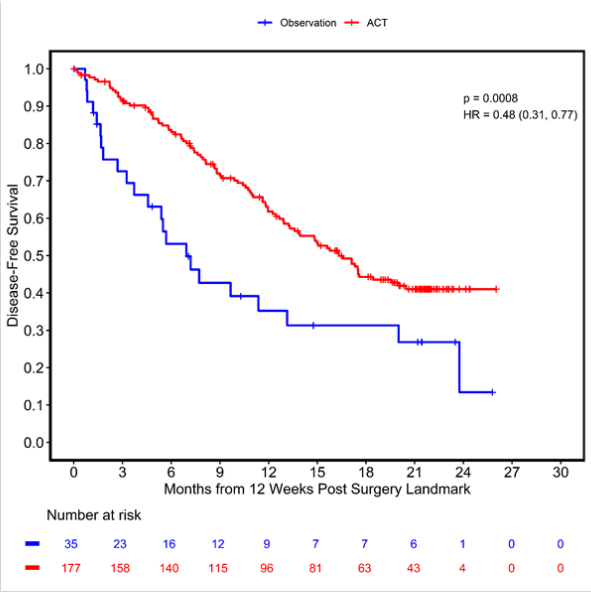


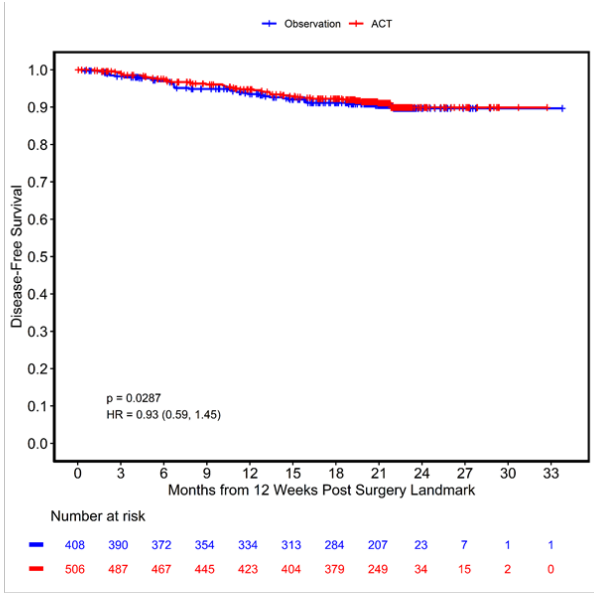
ctDNA Status	# Events	Median DFS post surgery, months (95%)	2-year DFS post surgery,% (95% CI)
Negative	47	NE (NE-NE)	**87.4** (83.8-91.1)
Positive	105	16.2 (13.6-18.9)	**35.5** (28.6-44.2)

Landmark DFS Analysis at 6 weeks (42 Days). NE: Not Estimable

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



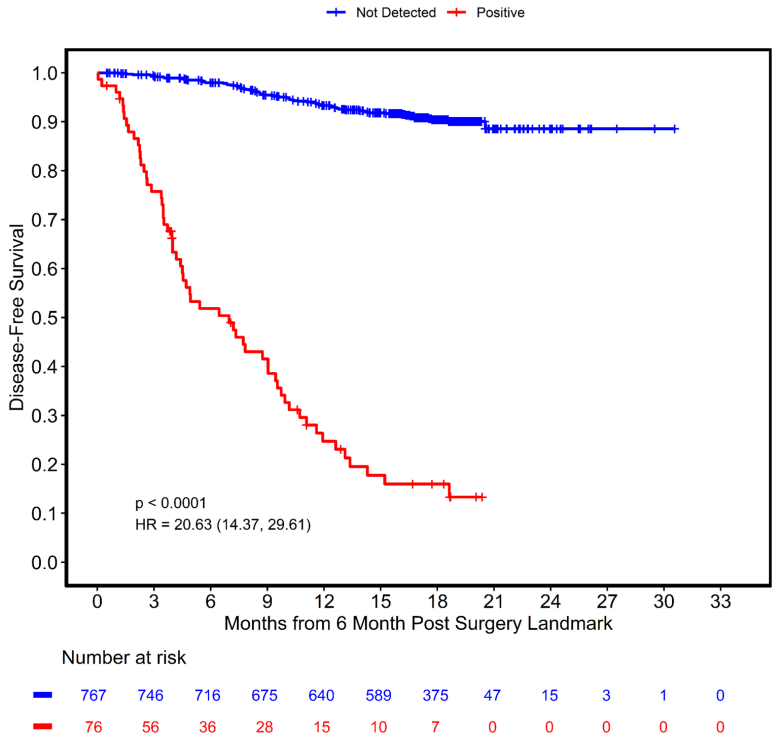


Adjuvant strategy	ACT	Observation
Numbers of events (%)	96/177 (54.24)	29/35 (82.86)
2-year DFS post surgery, % (95% CI)	40.3 (33.3 - 48.9)	24.7 (13.2 - 46.3)
Median DFS post surgery, months (95%)	17.7 (14.6 - 21.4)	7.1 (4.6 - 21.4)

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

First surveillance Signatera timepoint positivity predicts inferior DFS

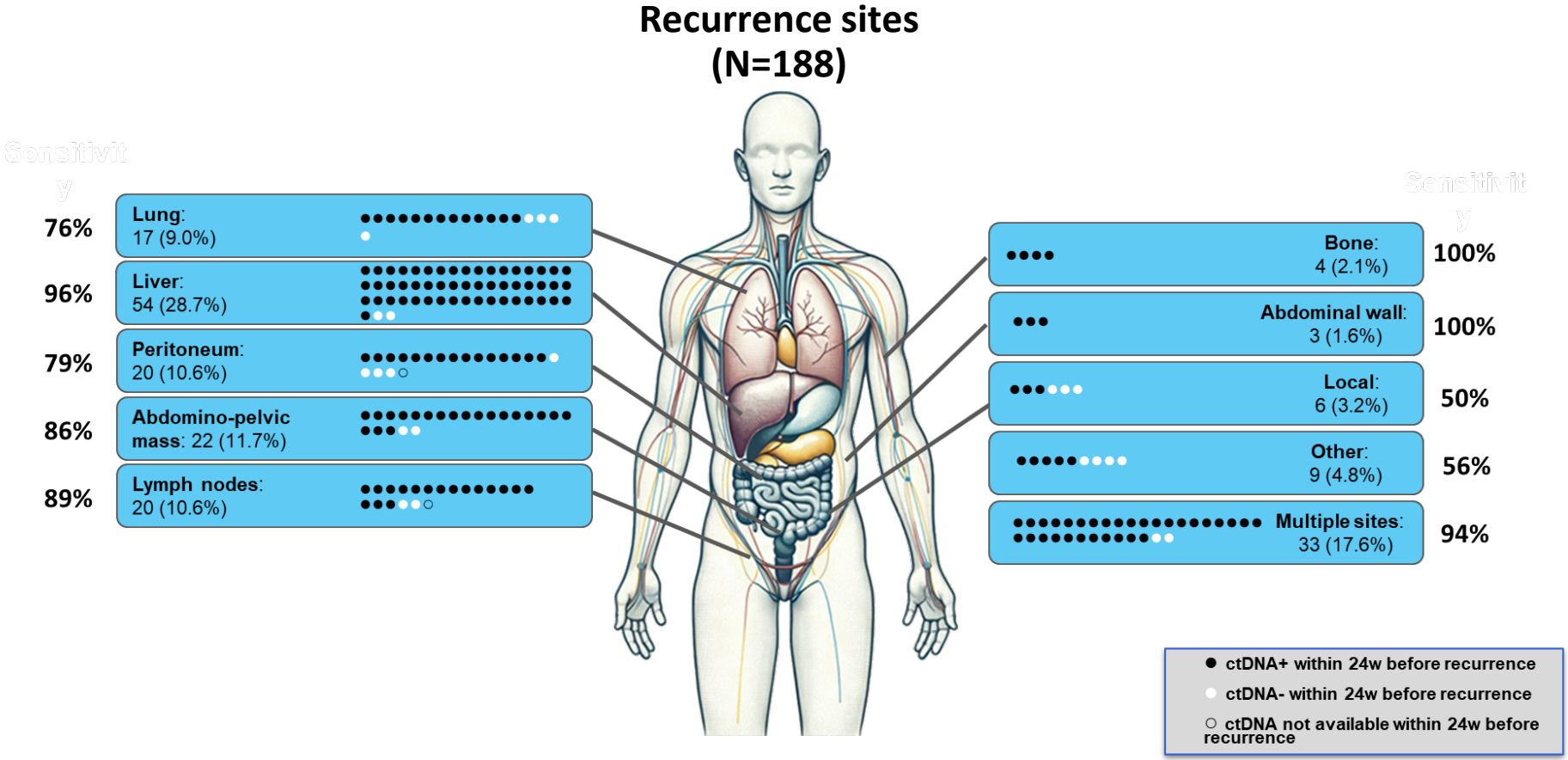


Time-dependent of DFS during Surveillance stratified by Signatera Status

Stage	Parameter Estimate	Hazard Ratio	Confidence Interval		p-value
Stage II/III	**3.3**	**26.4**	**21.6**	**32.4**	**<0.0001**

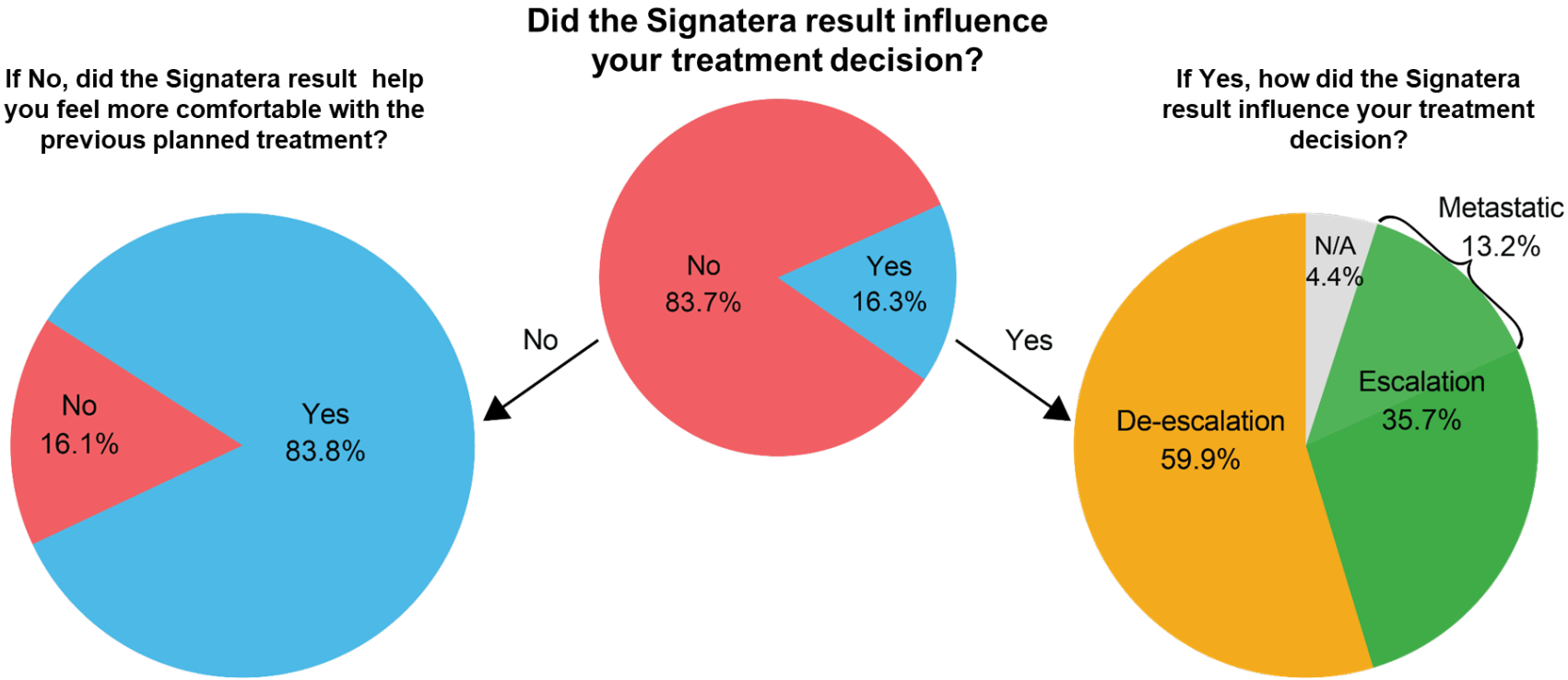
Shah et. al., J Clin Oncol 43, 2025 (suppl 4; abstr 15). Presented at ASCO GI 2025

MRD test sensitivity is impacted by site of recurrence



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

Impact of Signatera MRD test on adjuvant treatment decision



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

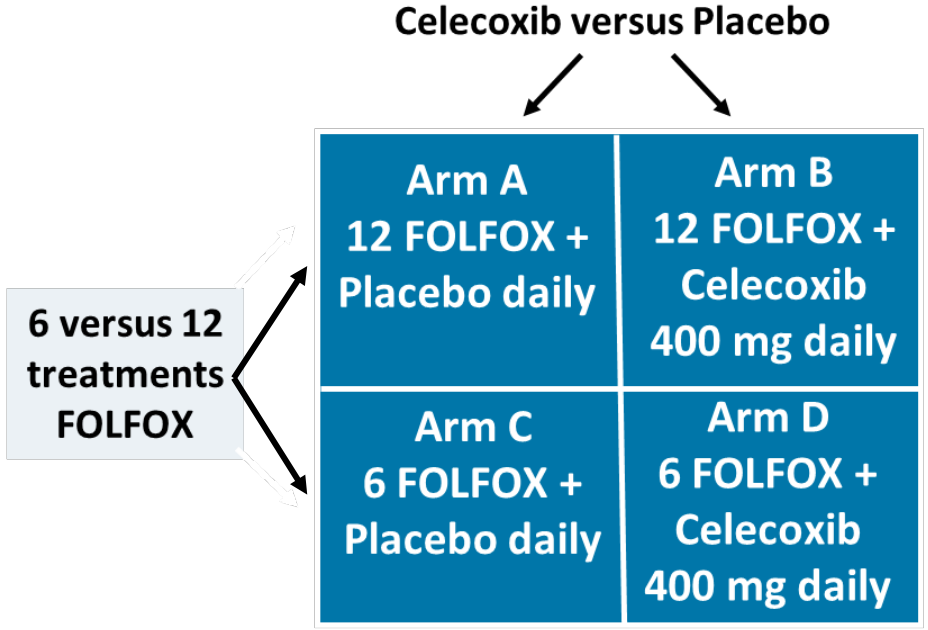
MRD questions answered at ASCO GI 2025

- Do US oncologists find ctDNA helpful for guiding adjuvant chemotherapy in patients with resected colon cancer?
- Can “adjuvant” celecoxib improve DFS and OS in patients with resected stage III colon cancer with ctDNA positivity following surgery?
- Should patients with ctDNA positivity after completing definitive therapy for colon cancer be offered TAS-102?

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*

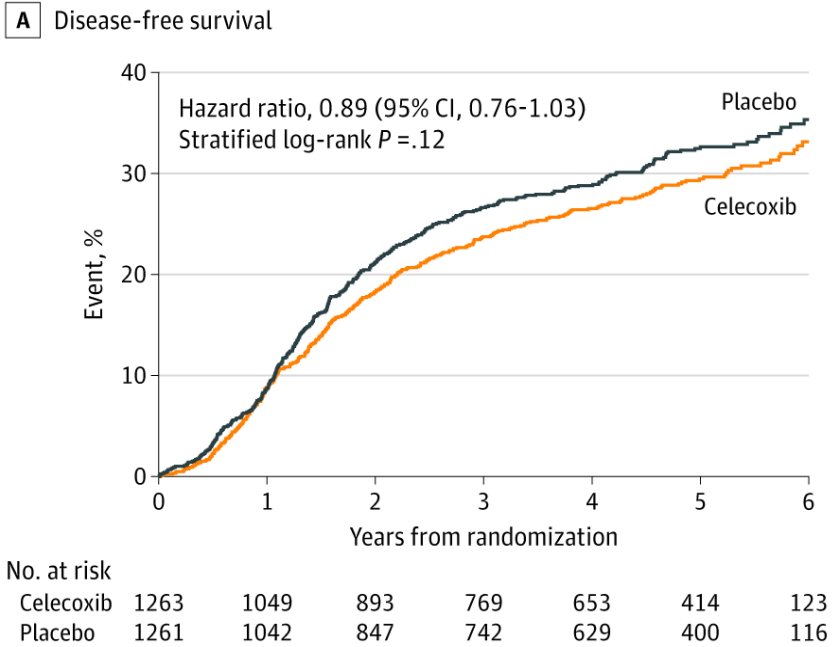


Celecoxib/placebo continued for a total of 3 years from the day study drug was initiated

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

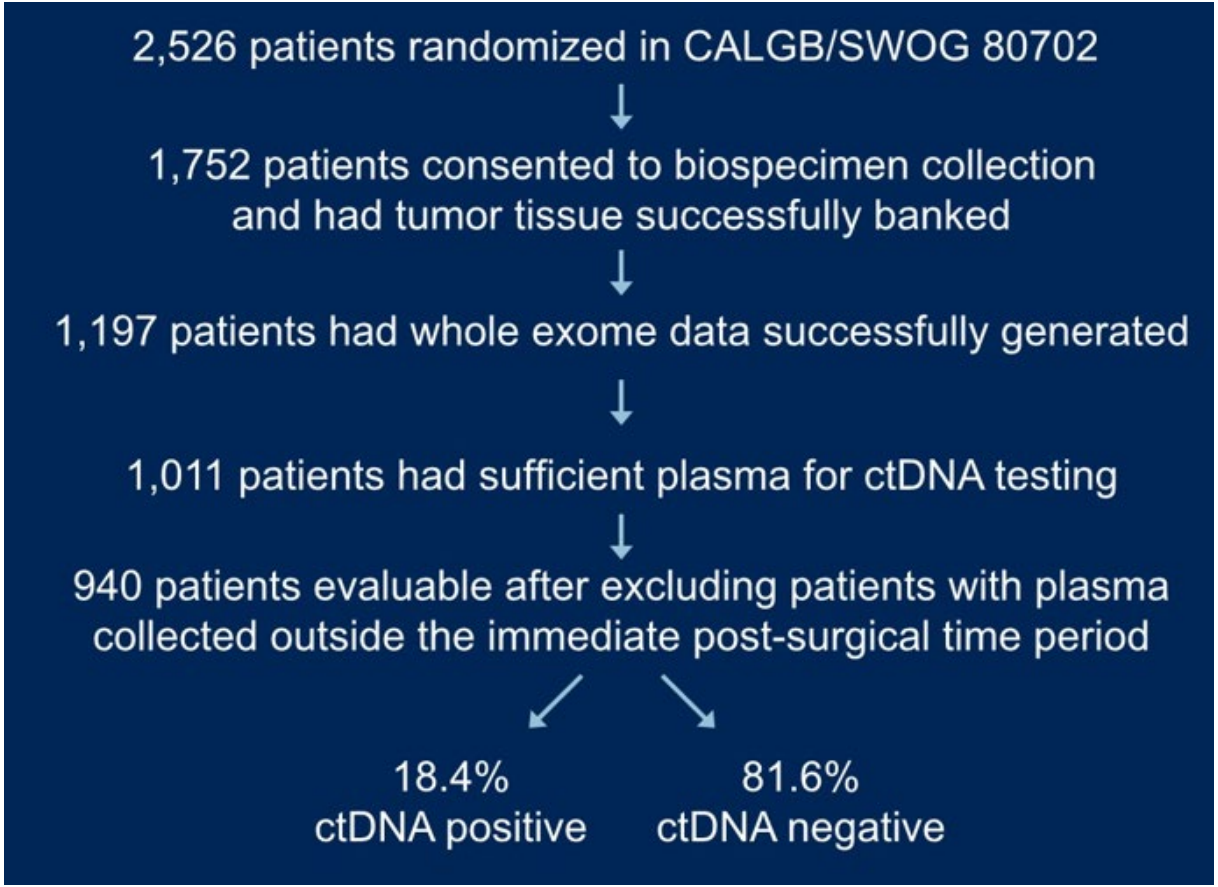
CALGB/SWOG 80702: Survival according to adjuvant celecoxib



- 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

CALGB/SWOG 80702: Baseline characteristics

	ctDNA negative (N=767)	ctDNA positive (N=173)	Total (N=940)	P-value
Tumor Location, n (%)				
Left	353 (46.4%)	81 (46.8%)	434 (46.5%)	0.990
Right/Transverse	402 (52.9%)	91 (52.6%)	493 (52.8%)	
Multiple	5 (0.7%)	1 (0.6%)	6 (0.6%)	
KRAS, mutant (%)	287 (37.4%)	77 (44.5%)	364 (38.7%)	0.084
MSI, unstable (%)	83 (10.8%)	14 (8.1%)	97 (10.3%)	0.287
FOLFOX duration, n (%)				0.498
3 months	386 (50.3%)	92 (53.2%)	478 (50.9%)	
6 months	381 (49.7%)	81 (46.8%)	462 (49.1%)	
Assigned oral agent, n (%)				0.048
Celecoxib	375 (48.9%)	99 (57.2%)	474 (50.4%)	
Placebo	392 (51.1%)	74 (42.8%)	466 (49.6%)	
Days from surgery to ctDNA blood draw, mean (SD)	44.2 (10.76)	45.3 (10.55)	44.4 (10.72)	0.202

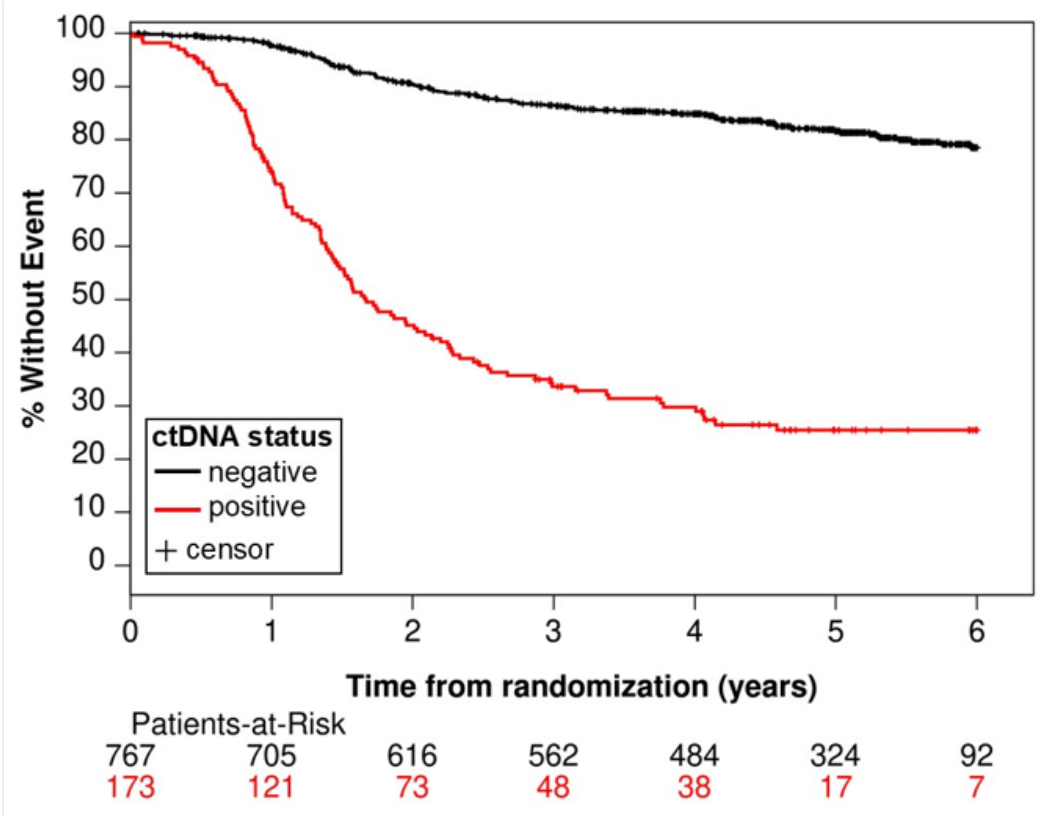
Nowak et. al., J Clin Oncol 43, 2025 (suppl 4; LBA14). Presented at ASCO GI 2025

CALGB/SWOG 80702: Baseline characteristics

	ctDNA negative (N=767)	ctDNA positive (N=173)	Total (N=940)	P-value
Age, mean (SD)	60.7 (11.16)	61.2 (10.27)	60.8 (11.00)	0.674
Sex, n (%)				0.003
Male	402 (52.4%)	112 (64.7%)	514 (54.7%)	
Female	365 (47.6%)	61 (35.3%)	426 (45.3%)	
T-stage, n (%)				0.001
T1 or T2	131 (17.1%)	17 (9.9%)	148 (15.8%)	
T3	543 (71.0%)	119 (69.2%)	662 (70.7%)	
T4	91 (11.9%)	36 (20.9%)	127 (13.6%)	
N stage, n (%)				<.0001
N1	581 (75.9%)	90 (52.3%)	671 (71.6%)	
N2	184 (24.1%)	82 (47.7%)	266 (28.4%)	
Race, n (%)				0.503
White	628 (81.9%)	146 (84.4%)	774 (82.3%)	
Black or African American	85 (11.1%)	20 (11.6%)	105 (11.2%)	
Asian	32 (4.2%)	5 (2.9%)	37 (3.9%)	
All others or not reported	22 (2.9%)	2 (1.2%)	24 (2.6%)	
Ethnicity, n (%)				0.128
Hispanic or Latino	41 (5.3%)	6 (3.5%)	47 (5.0%)	
Not Hispanic or Latino	713 (93.0%)	167 (96.5%)	880 (93.6%)	

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

Disease-free survival by ctDNA status

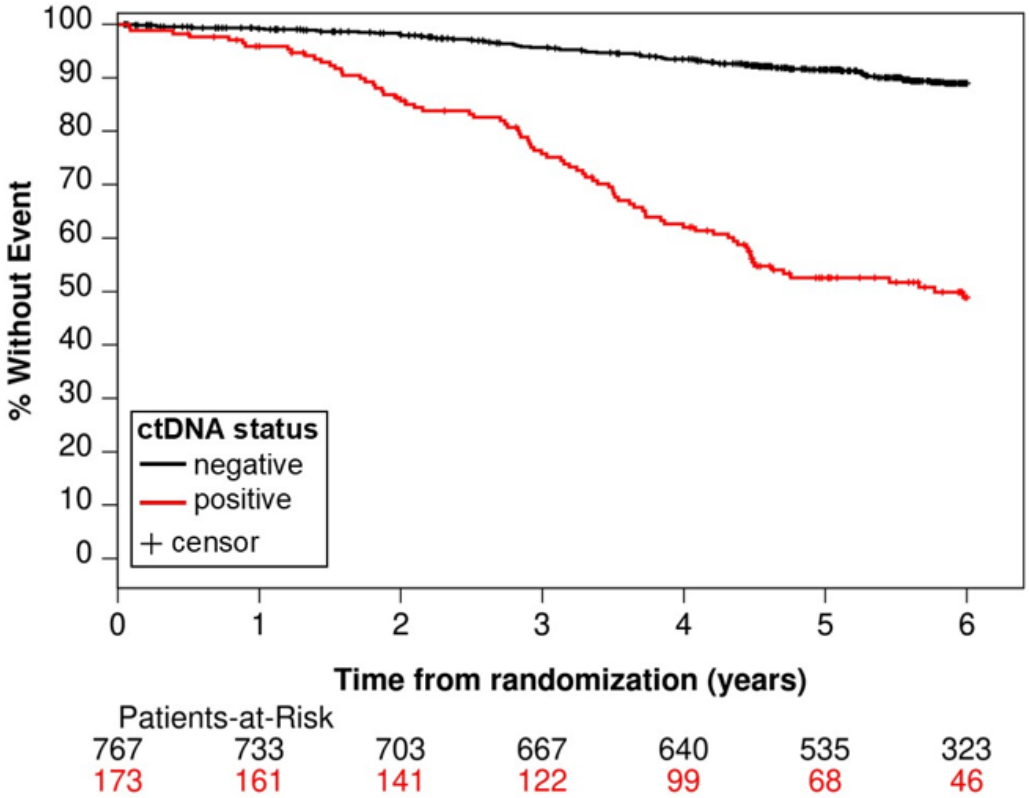


ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]
Negative	131/767	Reference	86.5 (84.0-89.1%)
Positive	118/173	7.14 (5.54-9.21)	33.7 (27.1-41.8%)
Logrank P-value: <0.0001[3]			

[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

Overall survival by ctDNA status

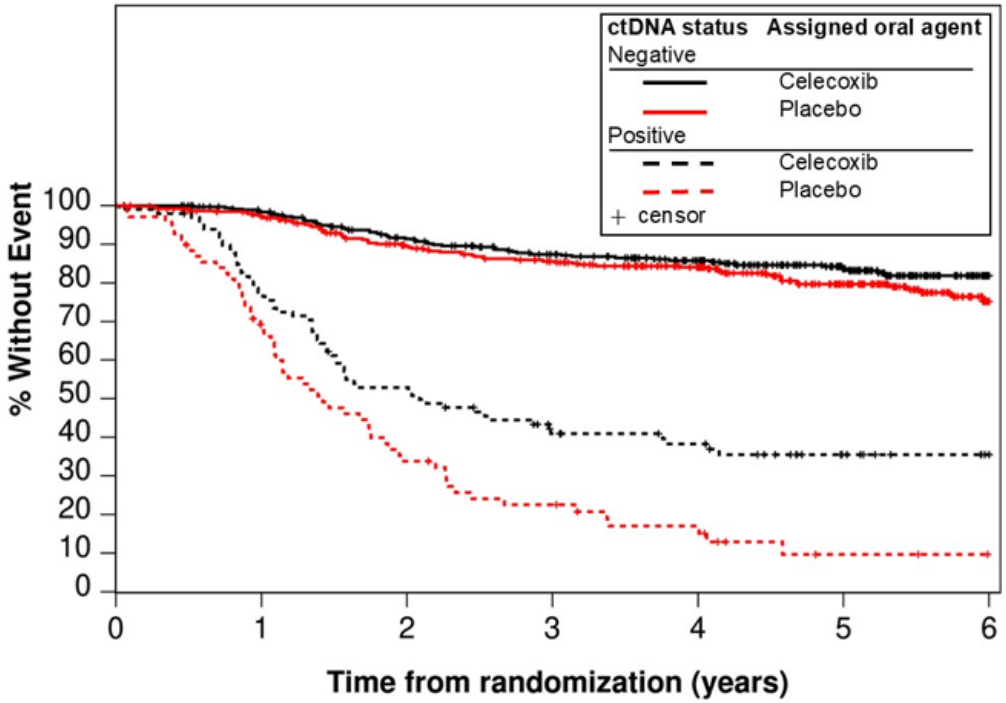


ctDNA Status	Events / Total	Hazard Ratio (95% CI)[1]	5 Year Survival Estimate (95% CI)[2]
Negative	77/767	Reference	91.5 (89.5-93.6%)
Positive	85/173	6.72 (4.91-9.18)	52.6 (45.3-61.0%)
Logrank P-value: <0.0001[3]			

[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 celcoxib use

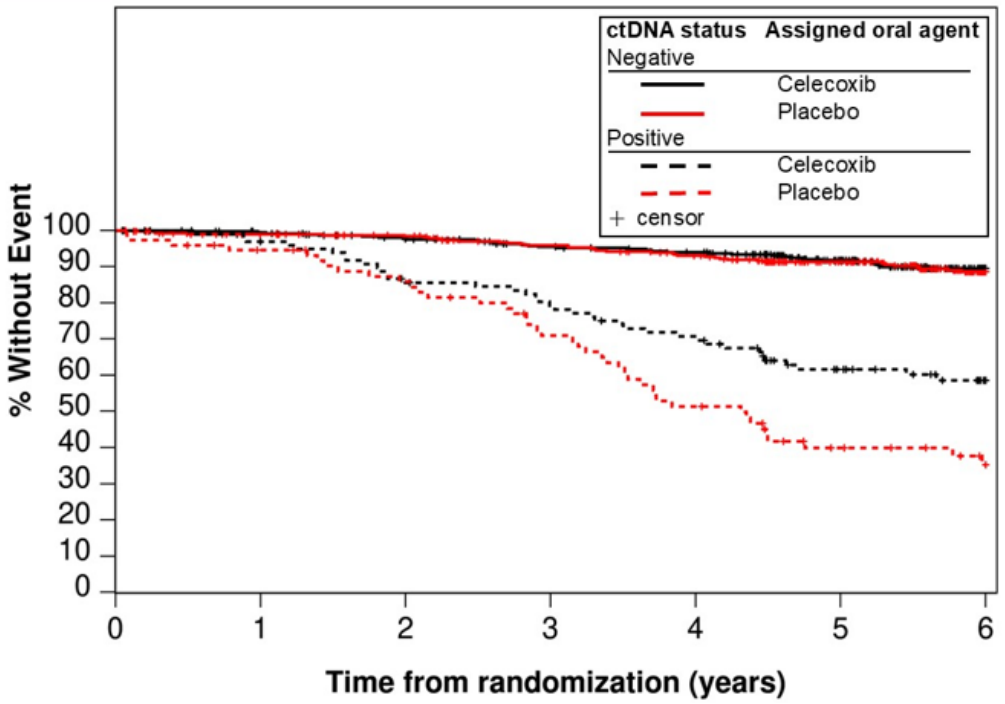


Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)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

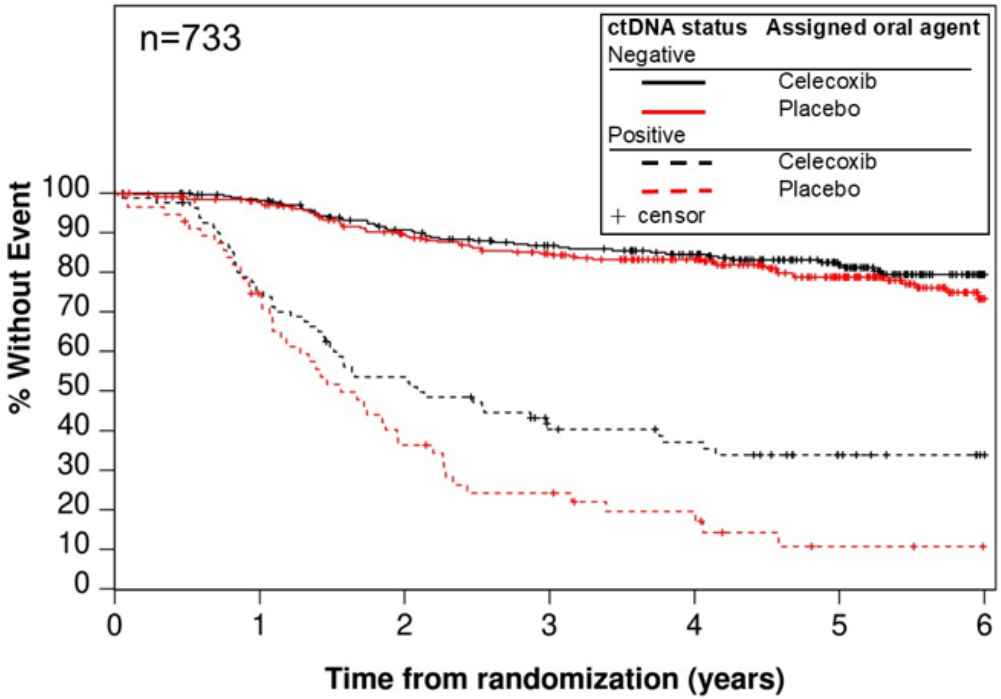
Survival by ctDNA status and celecoxib use

Endpoint	Comparison	Events / Total	Adjusted HR (95% CI)	Adjusted P-value	Adjusted Interaction P-value
Disease-free survival		247/930			0.4826
	ctDNA+: Celecoxib v Placebo (ref)		0.63 (0.43-0.92)	0.0167	
	ctDNA-: Celecoxib v Placebo (ref)		0.76 (0.53-1.08)	0.1262	
Overall survival		160/930			0.3873
	ctDNA+: Celecoxib v Placebo (ref)		0.63 (0.40-0.98)	0.0419	
	ctDNA-: Celecoxib v Placebo (ref)		0.84 (0.53-1.34)	0.4593	

Adjusted for ctDNA, age, sex, low dose aspirin usage, performance status, T stage, N stage, sidedness, days from surgery to blood draw, *KRAS*, *BRAF*, and MSI status

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

Survival by ctDNA status and celecoxib use in PIK3CA wildtype tumors



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.2777[4]
Celecoxib	49/278	0.81 (0.56-1.18)	86.7 (82.7-91.0%)	
Placebo	63/318	Reference	84.8 (80.7-89.0%)	
Positive				0.0166[4]
Celecoxib	51/81	0.61 (0.41-0.92)	40.3 (30.7-52.9%)	
Placebo	45/61	Reference	24.2 (14.9-39.3%)	
Interaction P-value: 0.2217[3]				

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

PIK3CA status as defined in Nowak JA, et al. J Clin Oncol. 42(24):2853-2859. 2024.

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

CALGB/SWOG 80702: Limitations

- Post hoc analysis
- ctDNA status not used to select patients for adjuvant celecoxib
- Only a subset of patients in CALGB/SWOG 80702 tested

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

CALGB/SWOG 80702: Conclusions

- In a subset of patients enrolled in CALGB/SWOG 80702, ctDNA status after surgery and prior to starting adjuvant therapy was highly prognostic of DFS and OS
- ctDNA status also appeared predictive of benefit of adjuvant celecoxib
- Sensitivity and subgroup analyses are ongoing
- Studies on the predictive value of ctDNA for 3 versus 6 months of adjuvant FOLFOX are underway

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

ASCO Gastrointestinal Cancers Symposium

ALASCCA
Adjuvant ASA vid kolorektalcancer

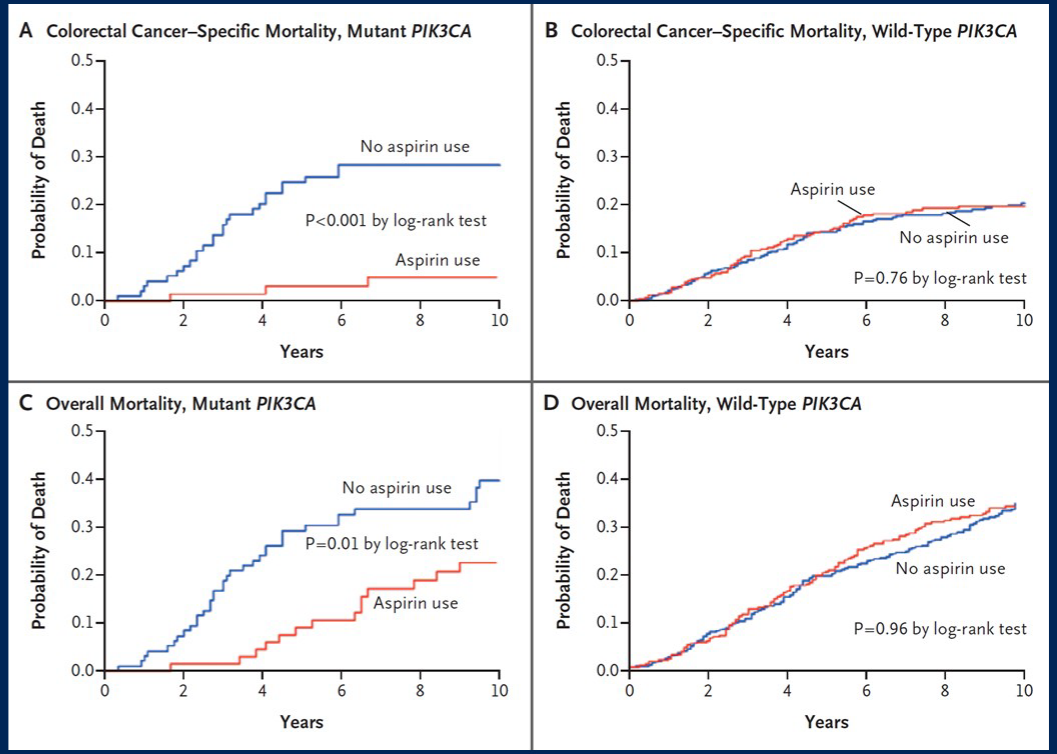
Low-Dose Aspirin Reduces Recurrence Rate in Colorectal Cancer Patients with PI3K Pathway Alterations

3-Year Results from the ALASCCA Trial

Prof. Anna Martling M.D, PhD, FACS (Hon), FASCRS (Hon)
Karolinska Institutet & Karolinska University Hospital, Stockholm, Sweden

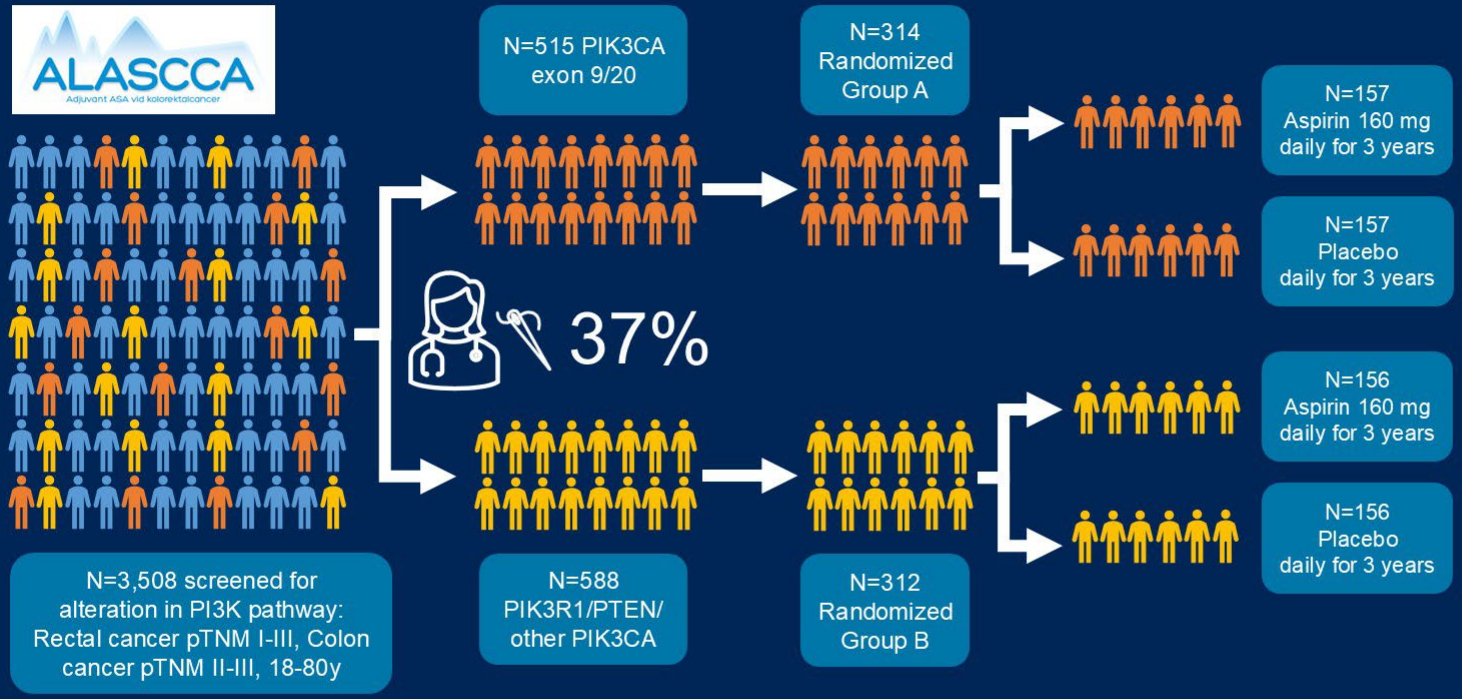
Aspirin in CRC

- Shown in RCTs to reduce incidence of colorectal adenomas
- Reduced CRC incidence & slightly reduced mortality in observational studies
- PIK3CA mutations possible predictor of treatment effect



Liao et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med. 2012 Oct 25;367(17):1596-606. doi: 10.1056/NEJMoa1207756.

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

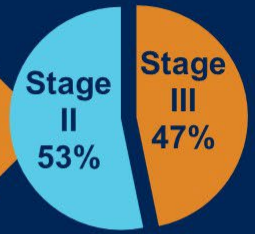
626 patients randomized

Median age 66 years (range 31-80)

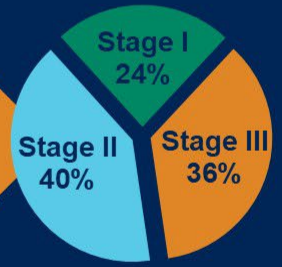
52% Females

67% Colon cancer
33% Rectal cancer

pTNM Stage in colon cancer patients



pTNM Stage in rectal cancer patients

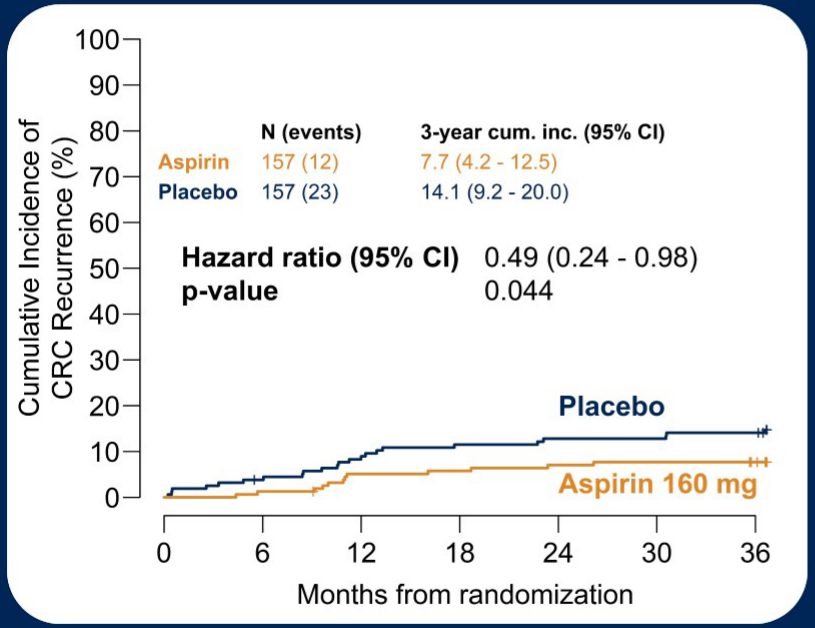


50% of rectal cancer patients given neoadjuvant therapy

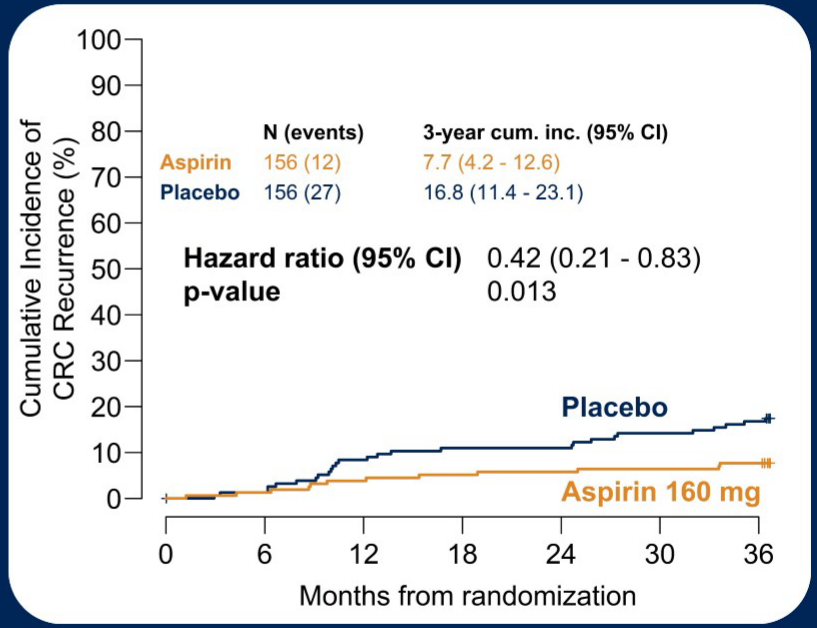
50% of colon cancer patients given adjuvant therapy

Primary Outcome: CRC Recurrence

Group A (PIK3CA Exons 9/20)

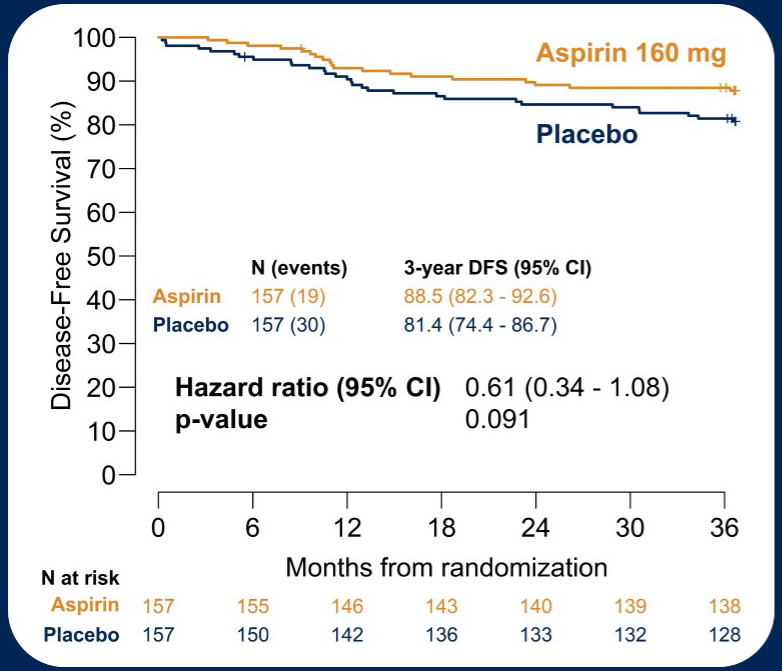


Group B (PIK3R1/PTEN/Other PIK3CA)



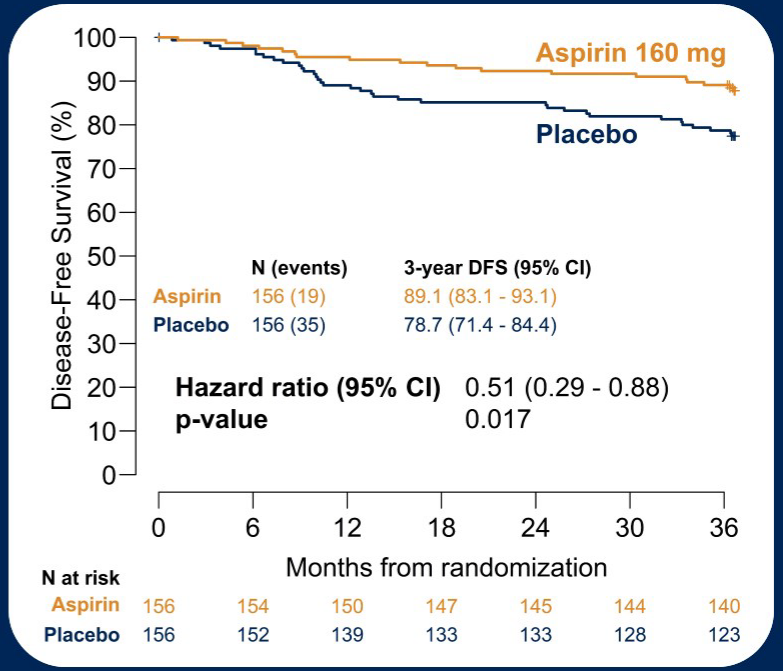
Secondary Outcome: Disease-Free Survival*

Group A (PIK3CA Exons 9/20)

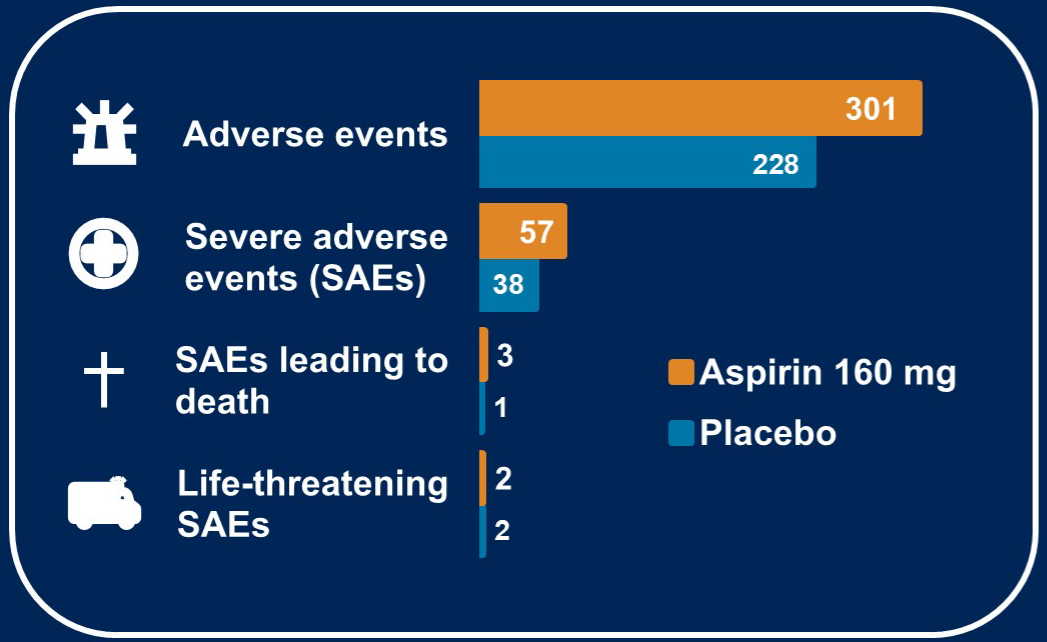


*Events: CRC local recurrence, CRC distant metastases, new other primary cancer, death of any cause

Group B (PIK3R1/PTEN/Other PIK3CA)



Safety



Most common SAEs (N):	Aspirin 160 mg	Placebo
Late post-operative Complication	15	8
Deep vein Thrombosis	9	7
Embolism	6	4
Infection	4	4
Heart disease	4	3
Inflammatory Disorder	3	4
Hemorrhage	4	0

Key Takeaway Points

Aspirin 160 mg reduced recurrence rate by 50% in CRC patients with tumors harboring mutations in the PI3K pathway

Can change clinical practice for around one third of patients with non-metastasized CRC

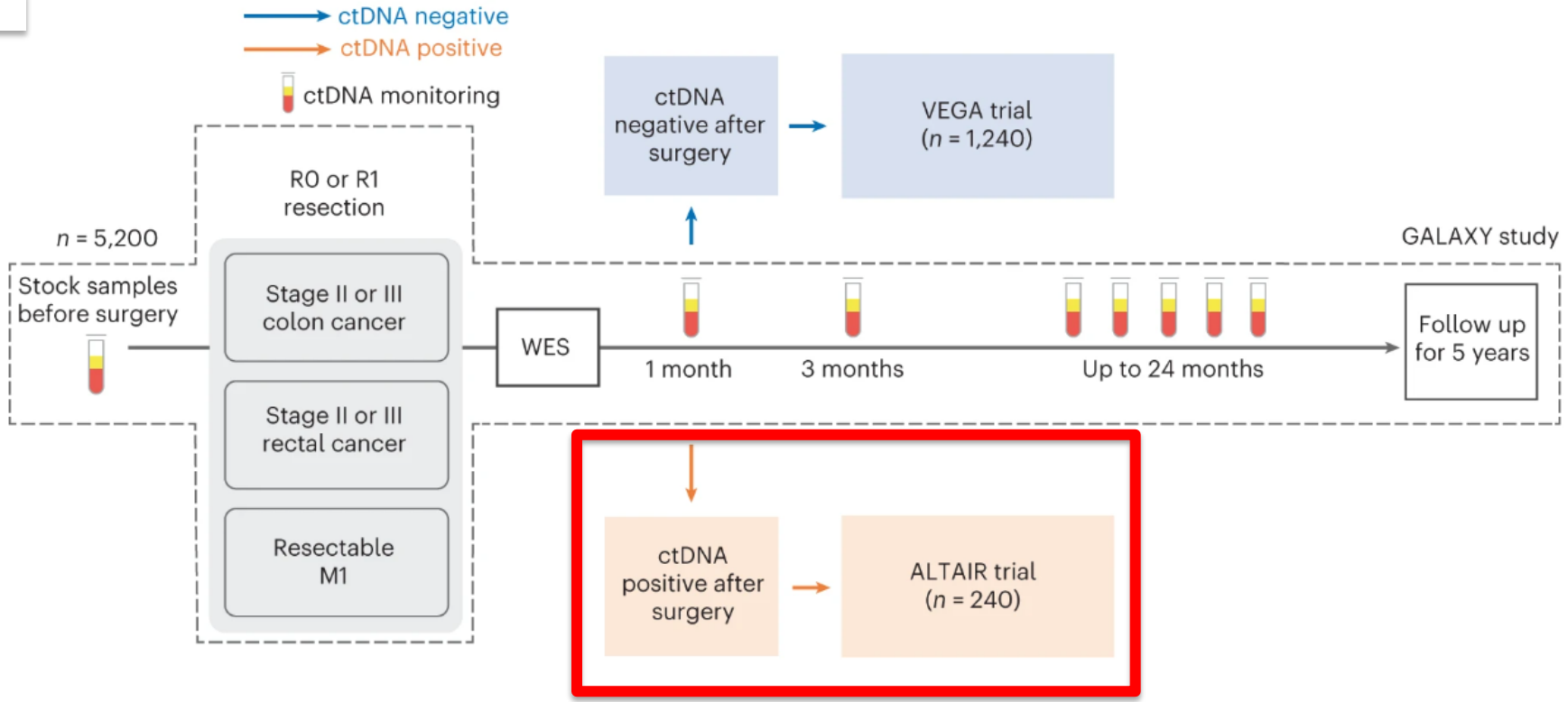
Repurposing of safe, inexpensive, globally available drug

Importance of upfront genomic testing

MRD questions answered at ASCO GI 2025

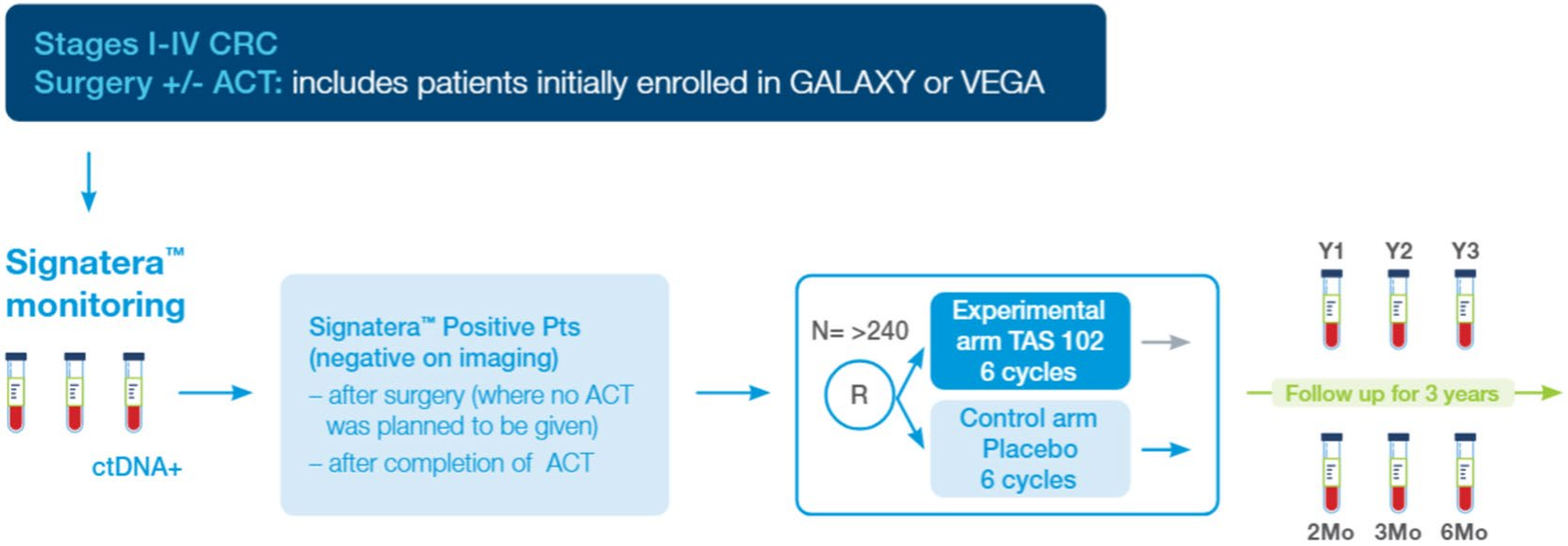
- Do US oncologists find ctDNA helpful for guiding adjuvant chemotherapy in patients with resected colon cancer?
- Can “adjuvant” celecoxib improve DFS and OS in patients with resected stage III colon cancer with ctDNA positivity following surgery?
- Should patients with ctDNA positivity after completing definitive therapy for colon cancer be offered TAS-102?

Clinical validation of tumor informed MRD testing: GALAXY Study Design



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

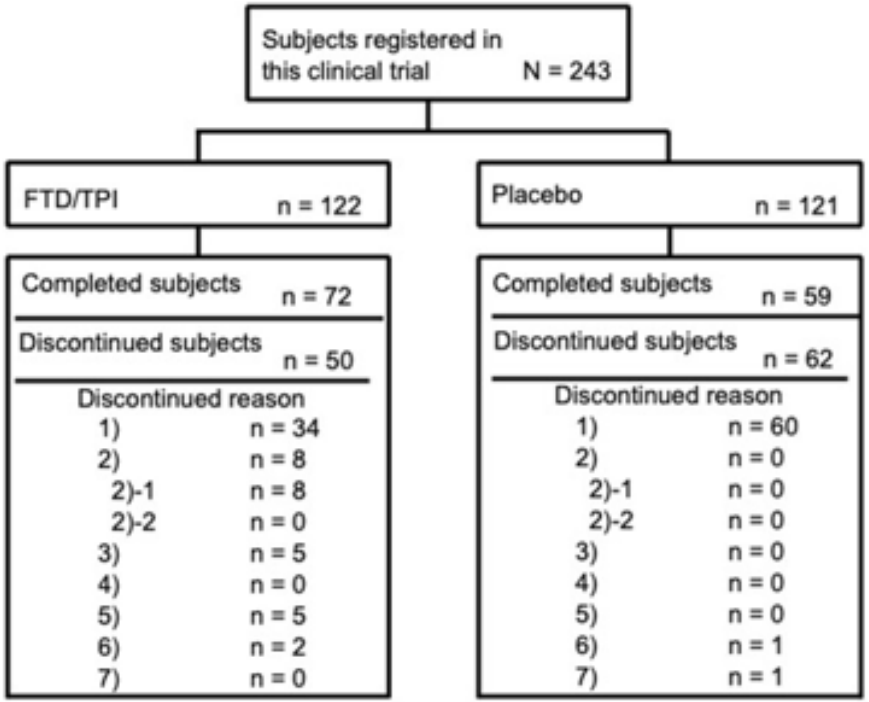
ALTAIR: Study Schema



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

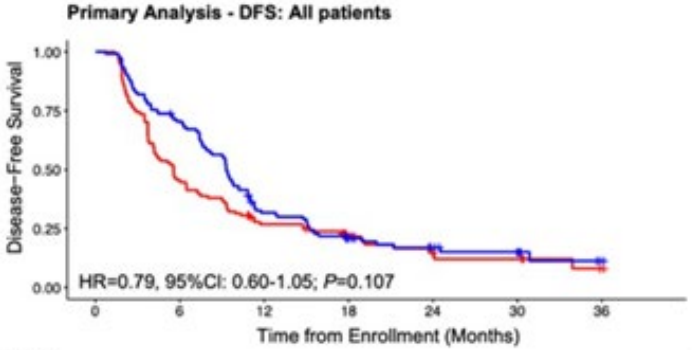
ALTAIR: Consort Diagram

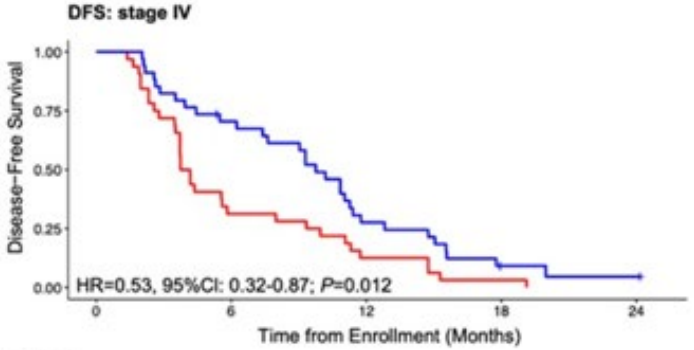


Discontinued reason is shown below.
1) Relapse of the primary disease
2) Study treatment cannot be continued due to an adverse event
2)-1 The planned start date of the next course is set as the first day, and the start of the next course is delayed more than the same day of the week 4 weeks later in accordance with [6.3. Criteria for the Modification of Study Treatment]
2)-2 After a dose reduction to 30 mg/day in accordance with [6.3. Criteria for the Modification of Study Treatment], a further dose reduction is judged to be necessary
3) The patient requested to discontinue study treatment
4) Death during study treatment
5) The subject is shown to be out of the scope of this trial
6) The investigator judges that the trial needs to be discontinued
7) Discontinuation due to reasons other than those described above 1) to 6)

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

ALTAIR: Results





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)

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 %	94.12 (31/34)	100 (32/32)
6M-DFS %	70.47 (52.05–82.9)	31.25 (16.38–47.3)
12M-DFS %	27.57 (13.79–43.3)	12.5 (3.95–26.2)
18M-DFS %	9.19 (.236–21.9)	3.12 (0.24–13.7)
24M-DFS %	4.60 (0.43–17.5)	NR
mDFS (mo)	9.76 (7.62–11.76)	3.96 (3.71–7.98)

Enrollment ctDNA timepoint MTM/mL
Stage IV patients vs non-Stage IV: 0.68 vs 0.32, *P* = 0.024

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

ALTAIR: Results

		Primary population	Stage IV	Non-Stage IV
Number		243	66	177
Mean Baseline MTM/ml		0.40	0.68	0.32
Median DFS (months)	FTD/TPI	9.30	9.76	9.26
	Placebo	5.55	3.96	6.05
		HR, 0.79 *P* = 0.107	HR, 0.53 *P* = 0.012	HR, 0.86 *P* = 0.378

	FTD/TPI (n = 122)	Placebo (n = 121)
Adverse events (N, %)		
Any grade	120 (98.4%)	69 (57%)
Grade 3 or more	89 (73.0%)	4 (3.3%)
Serious	6 (4.9%)	0
Lead to study discontinuation	8 (6.6%)	0
Lead to death	0	0
Adverse events related to investigatinal drug (n, %)		
Any grade	120 (98.4%)	40 (33.1%)
Grade 3 or more	87 (71.3%)	1 (0.8%)
Serious	1 (0.8%)	0
Lead to study discontinuation	5 (4.1%)	0
Lead to death	0	0

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

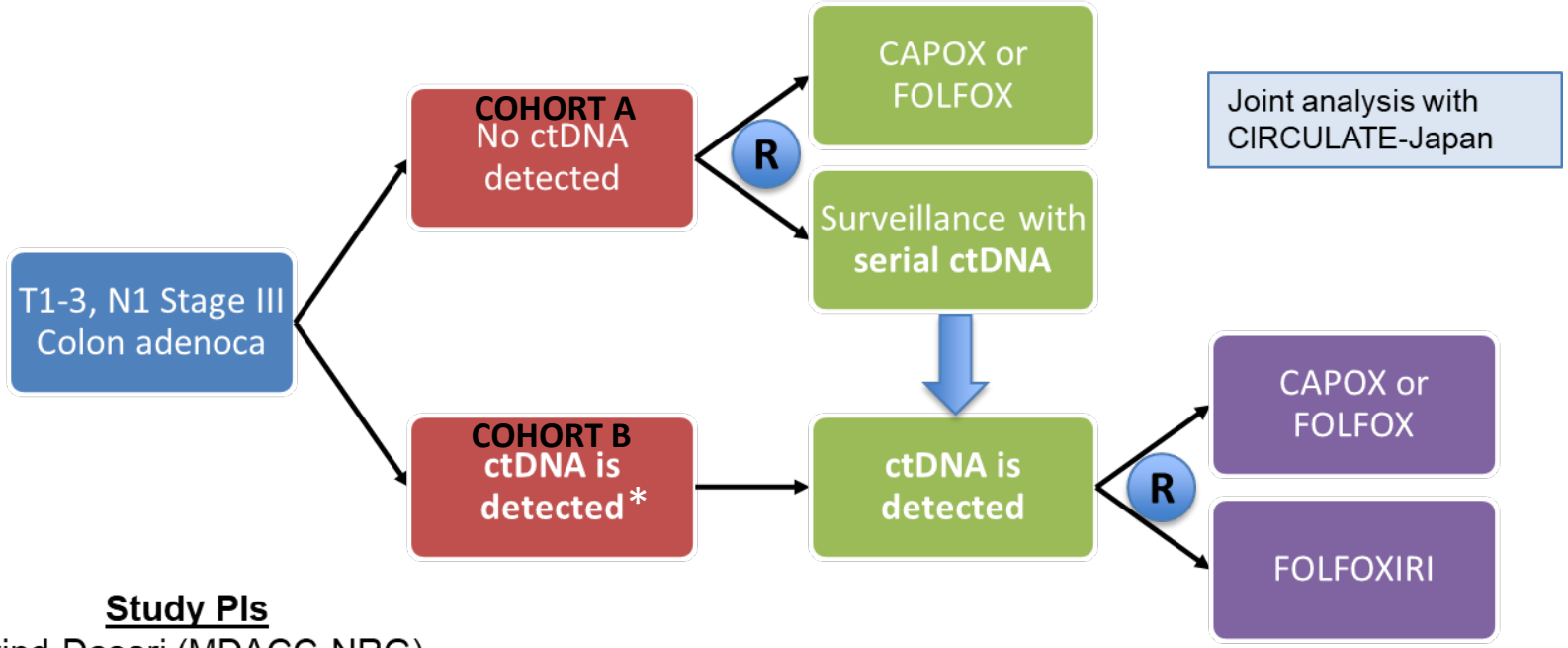
MRD questions answered at ASCO GI 2025

- Do US oncologists find ctDNA helpful for guiding adjuvant chemotherapy in patients with resected colon cancer? Yes. Most US oncologists find ctDNA helpful as a prognostic and potentially predictive tool for adjuvant chemotherapy

- Can “adjuvant” celecoxib improve DFS and OS in patients with resected stage III colon cancer with ctDNA positivity following surgery? Yes. Results are potentially practice changing.

- Should patients with ctDNA positivity after completing definitive therapy for colon cancer be offered TAS-102? No. Data does not support routine use of TAS-102 for patients with ctDNA positivity.

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

Case

- 56 y/o otherwise healthy male
- Three 1-2 cm liver Mets and colon primary
- R0 Surgical resection for T3N1 transverse colon
- poorly diff RAS/BRAF wild type
- CEA 5.6 preop
- Six cycles adjuvant modFOLFOX + bev
- Signatera negative at 4 months after completing adjuvant Rx
- Now with positive ctDNA 6.3 but negative PET and CEA 5.2

Seeking second opinion. Should chemo start now? With what agents? How to follow for response?

Case

45 y/o female with left sided colon invasive adenocarcinoma on screening colonoscopy.

- 3/13/2024 Colonoscopy - Malignant tumor in the proximal sigmoid colon.
- Left colectomy: Tubular adenoma in sigmoid and transverse colon. Sigmoid mass Invasive adenocarcinoma, moderately differentiated. All margins negative for tumor pT2N0 2.8 cm x 2cm 0 tumor invades into muscularis propria, neg margins, -LVI - PNI. Eleven lymph nodes, negative for tumor (0/11). MMR intact, HER 2 –ve
- Signatera positive 3 (1.67) weeks and 7 (3.18) weeks post-surgery.
- Adjuvant chemo CAPOX for 3 months: CT neg, ctDNA negative
- 7/19/2024 CT CAP Negative, Signatera 0.63 - PET NED, colonoscopy completed on 11/18/24 showed some inflammatory changes at site of colonic anastomosis with pathology revealing inflammatory polyp.

Case

54 y/o female with stage IIIC **adenocarcinoma of the transverse colon status post-surgery**

- 1/3/2023 right hemicolectomy **pT4bN1bM0:** Grade 2 adenocarcinoma of the transverse colon, 3.5 cm tumor size, tumor directly invades or adheres to adjacent structures (omentum), no macroscopic tumor perforation identified, LVI +, PNI - ,margins negative, 3 of 90 examined lymph nodes involved – MMRp
- 2/7/2023-7/28/23: FOLFOX +bevacizumab-awwb
- 12/26/2023 ct DNA negative
- 1/23/2024: Colonoscopy negative for recurrence
- Rising ctDNA Feb Ct DNA 0.4 - Apr ct DNA 0.2 - July ctDNA 0.33 – Aug ctDNA 0.35 – Jan 2025 ctDNA 5.47
- 1/17/2024: CT chest, abdomen and pelvis negative.
- 7/24/2024 MRI brain negative 7/26/2024 CT CAP Negative
- 10/2024 CT CAP: NED


AI-generated content