

Key Advances in the Management of Colorectal Cancer – The Role of Molecular Residual Disease (MRD) Assessment

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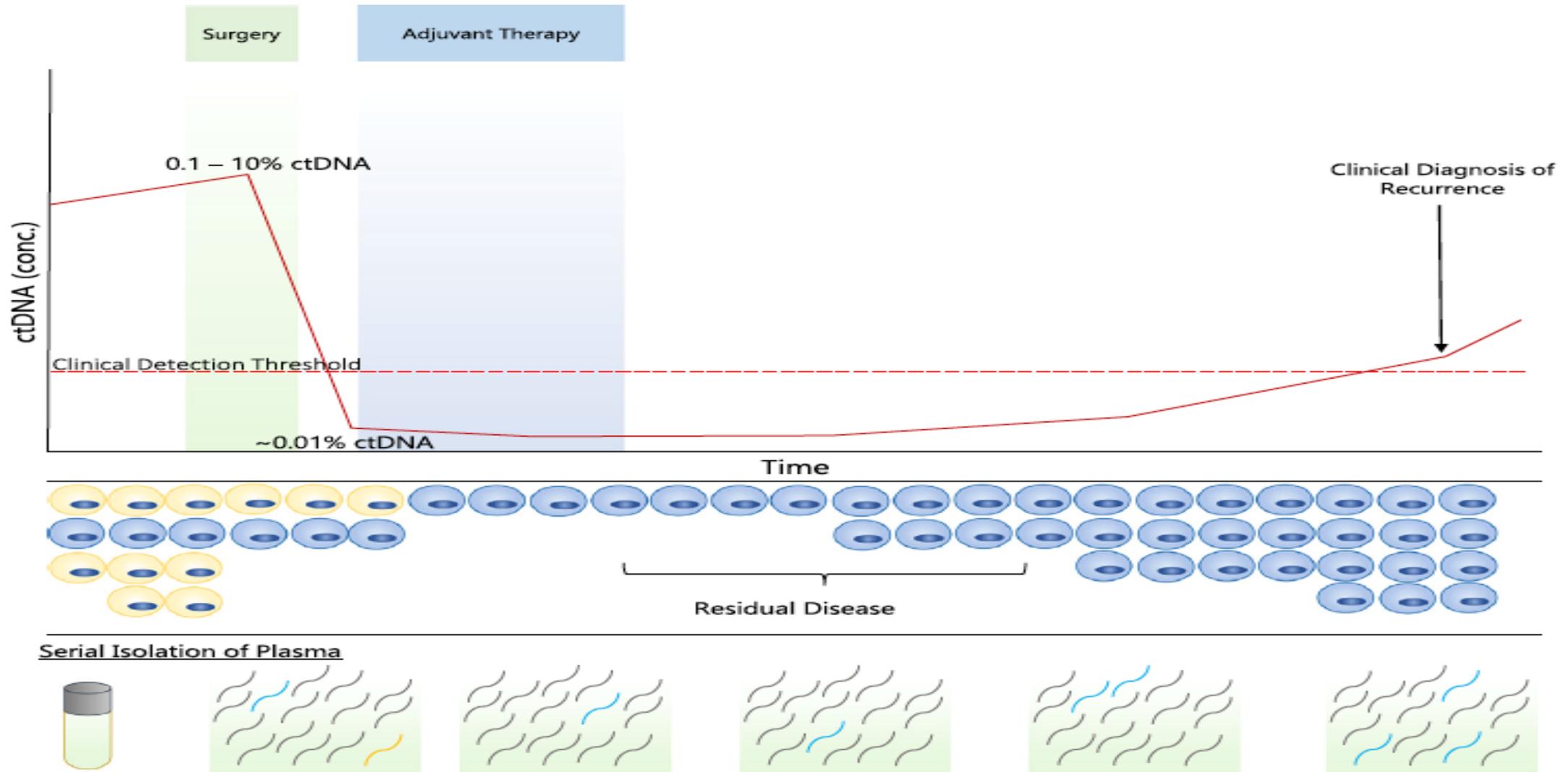
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Professor, Mayo Clinic College of Medicine and Science

Mayo Clinic in Arizona



Minimal Residual Disease (MRD)



False positives are most common when CEA is under 10

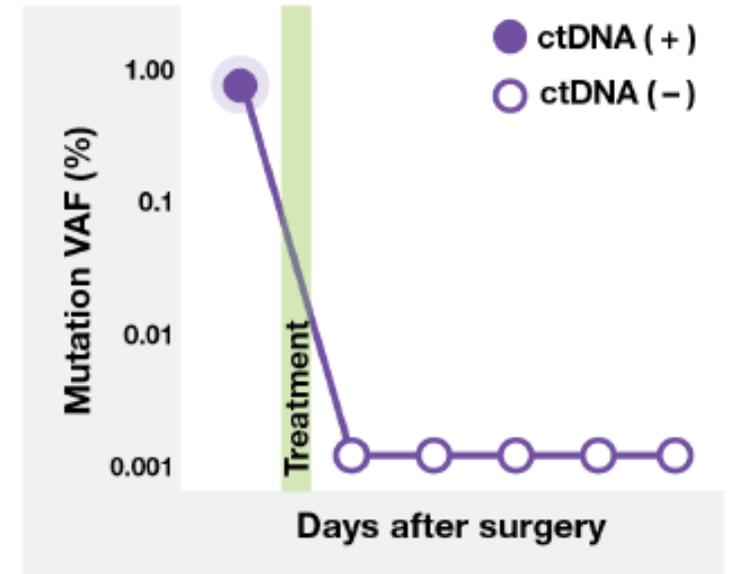
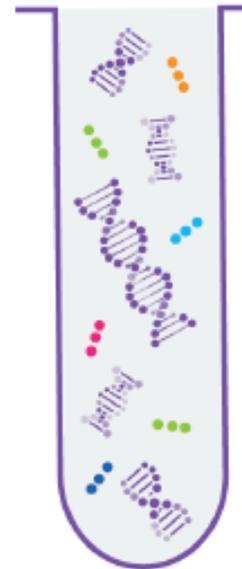
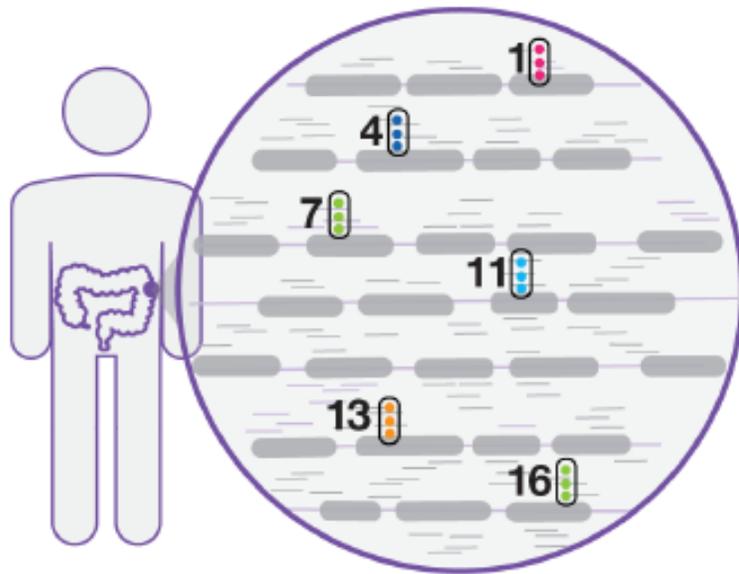
Peak CEA Level	Nonrecurrence With ≥ 2 Elevated Postoperative CEA Levels	Recurrence	Noncolorectal Malignancy	False-Positive Rates
≥ 5.1 ng/mL	247	335	35	 40%
≥ 10.1 ng/mL	23	256	16	8%
≥ 15.1 ng/mL	5	221	15	2%
≥ 20.1 ng/mL	3	200	13	1%
≥ 25.1 ng/mL	2	177	8	1%
≥ 30.1 ng/mL	1	153	7	0.6%
≥ 35.1 ng/mL	0	145	7	0%

“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

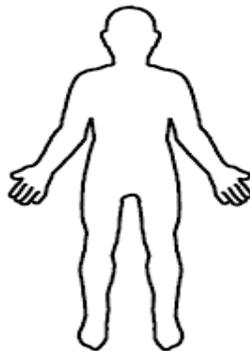
Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)



Can ctDNA identify who will recur after surgery?

Stage III CRC:

All patients get adjuvant chemo
>50% cured by surgery alone



Curative Intent
Surgery

Negative



ctDNA

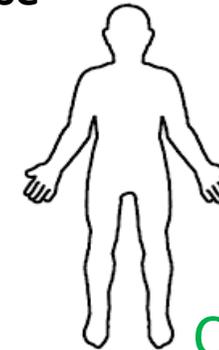
Positive

Stage II CRC:

SOC is NO adjuvant chemo
15%-20% recurrence risk

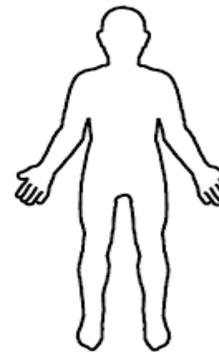
Minimal Residual Disease

None



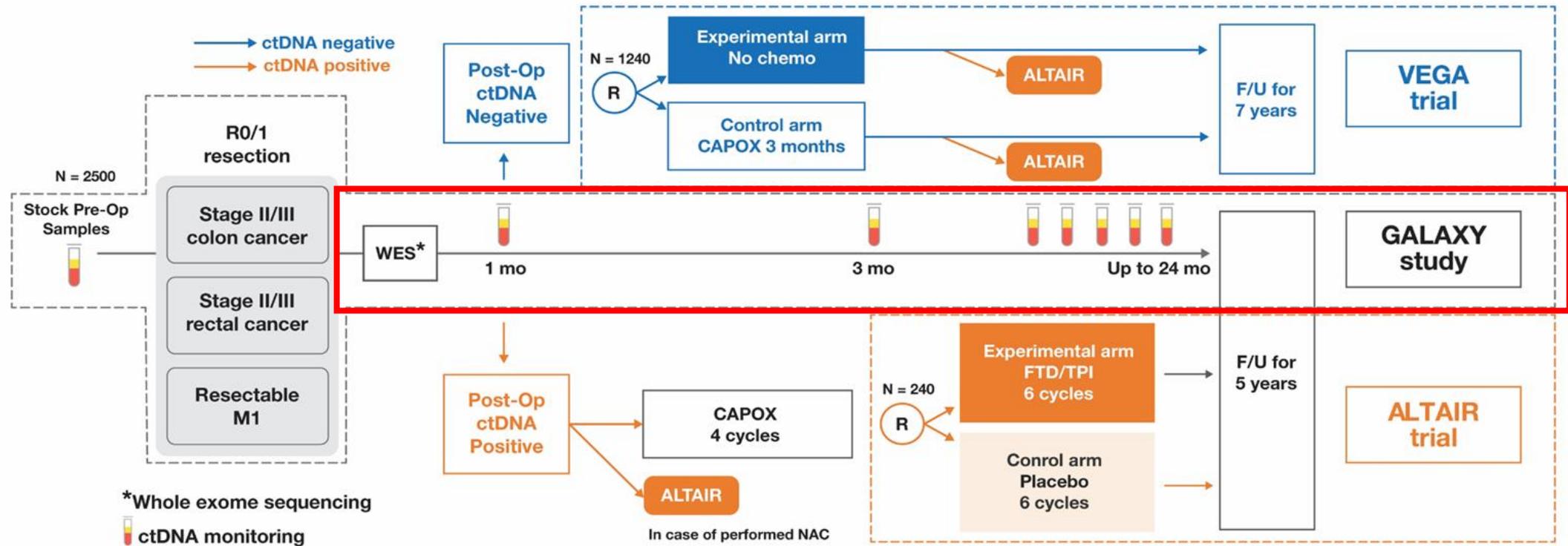
Cured

Present



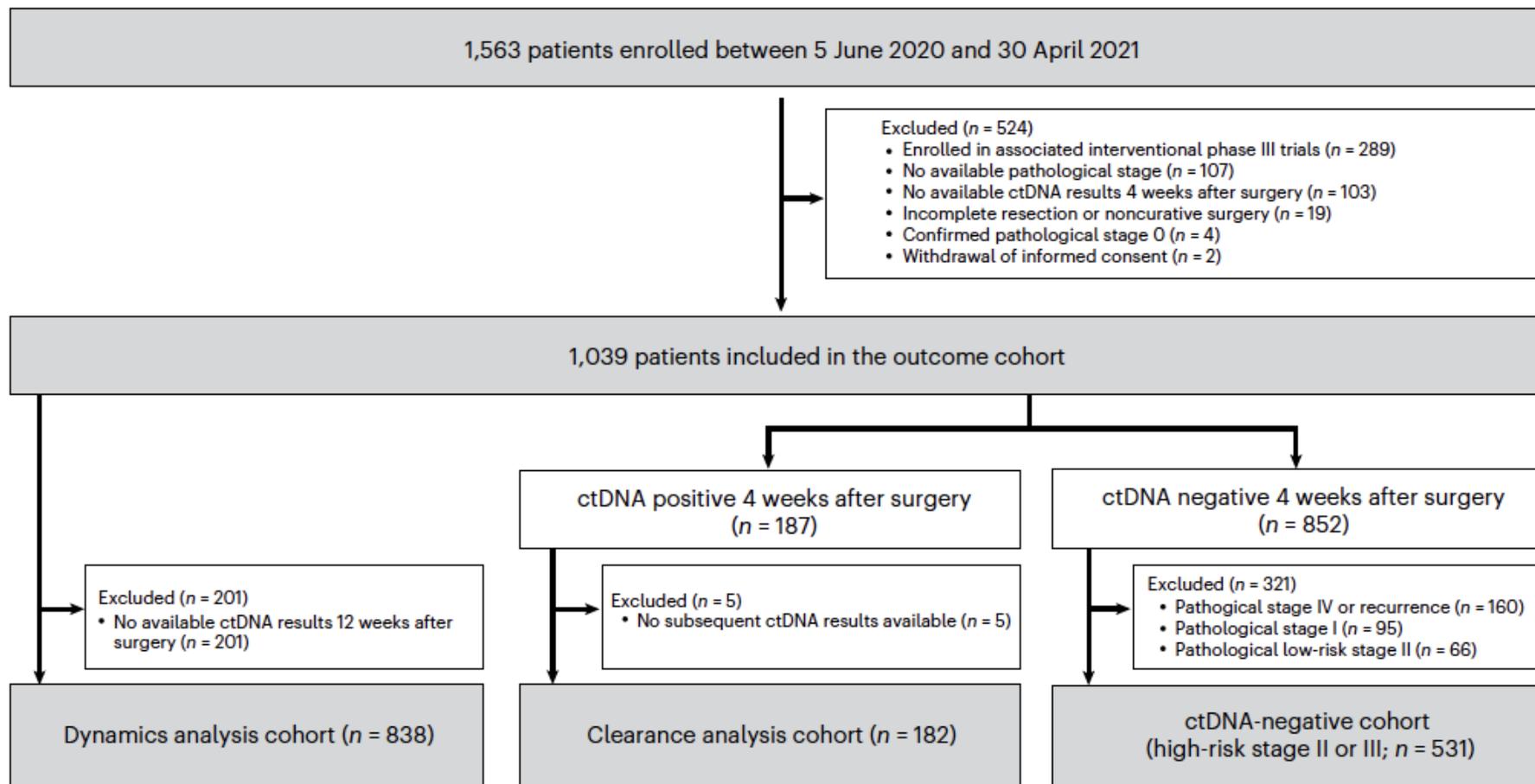
Not Cured

Circulate-Japan Study: Flowchart

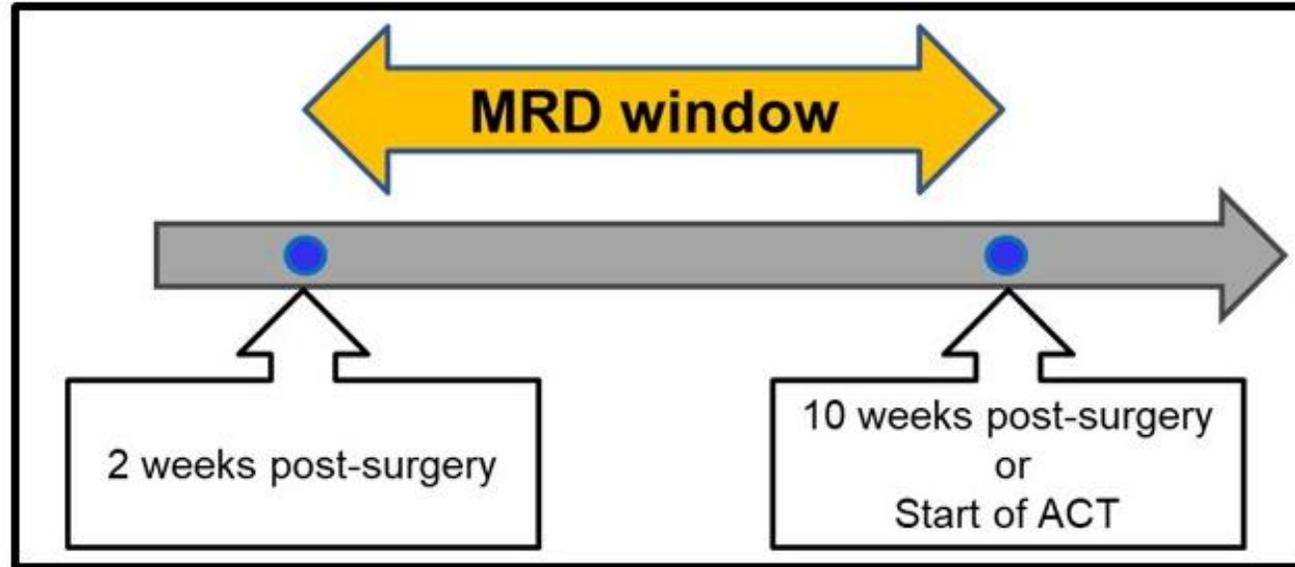


- Detect MRD
- Measure treatment responsiveness in resectable CRC
- The blood samples will be collected before surgery and at 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- Computed tomography (CT) will be performed every 6 months after surgery for 7 years

Study Design and Population



GALAXY: MRD Window

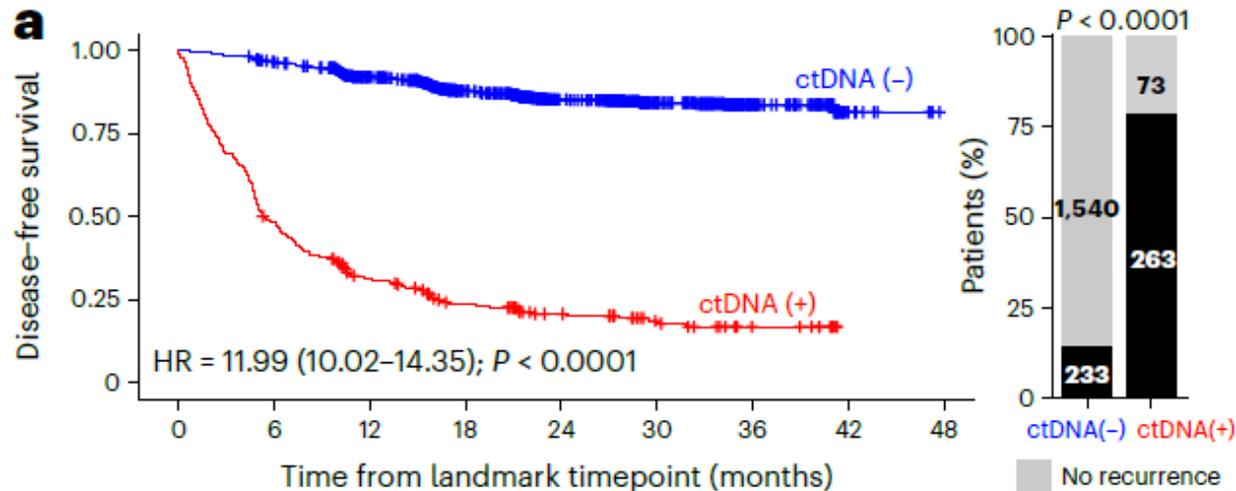


ACT: adjuvant chemotherapy

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

MRD status after surgery is strongly prognostic

Disease-free survival

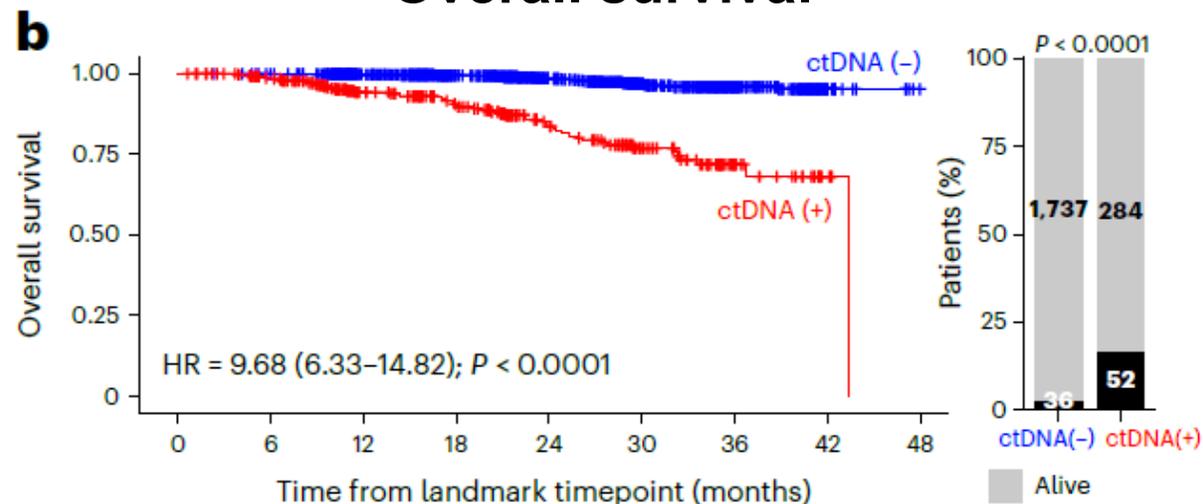


Number at risk

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

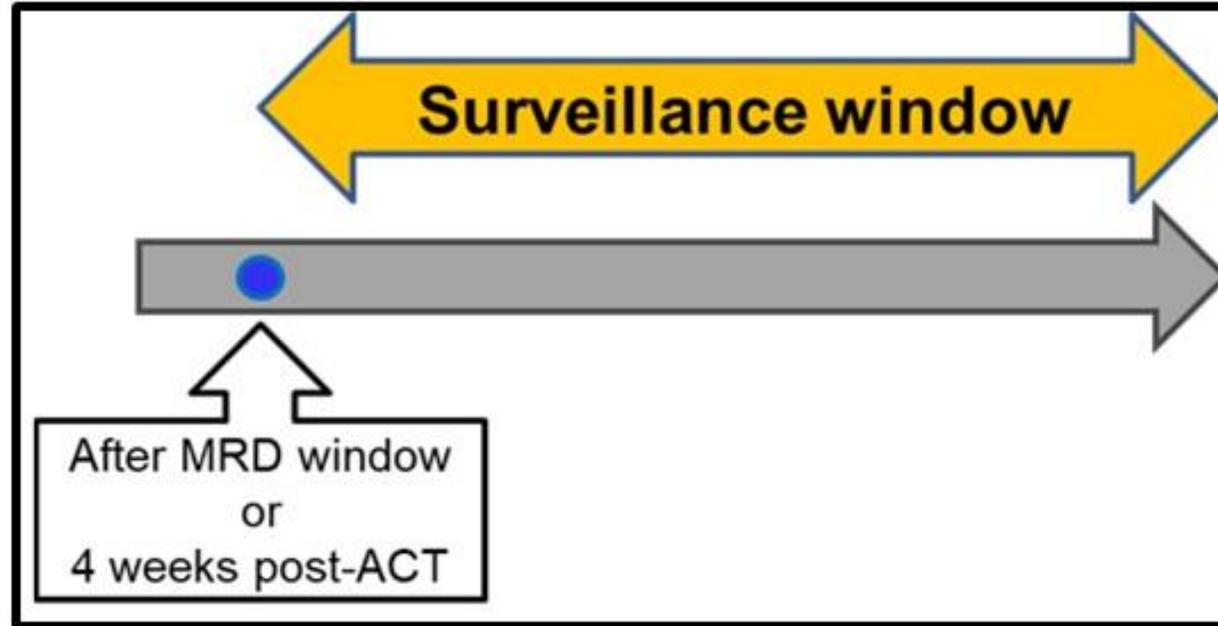


Number at risk

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)

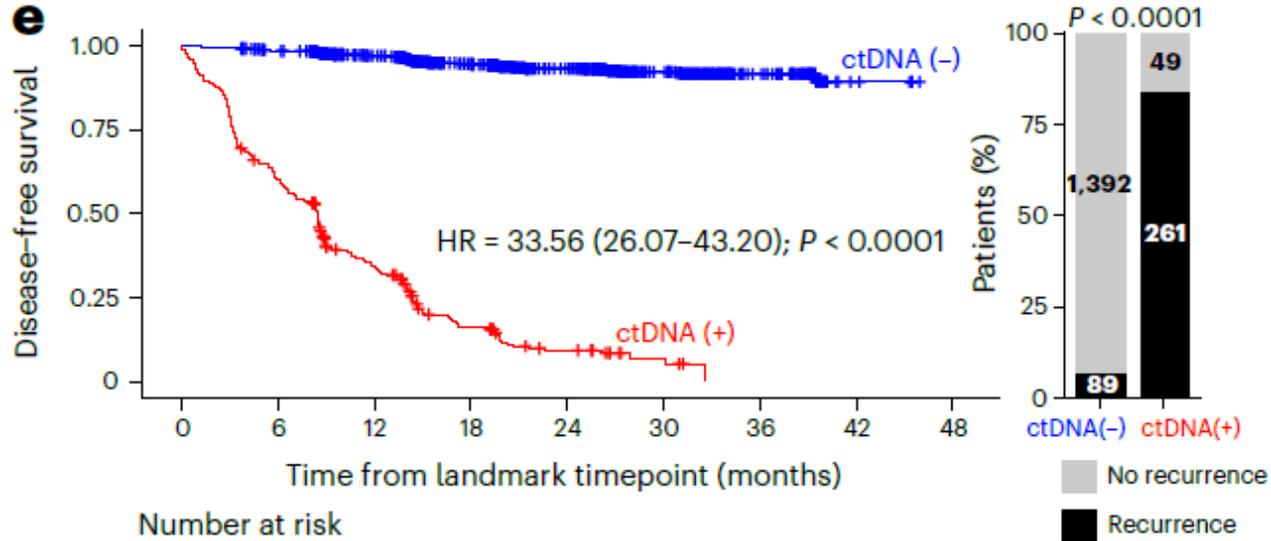
GALAXY: Surveillance window



- *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)*

ctDNA-positive in the surveillance window predicts poor prognosis

Disease-free survival

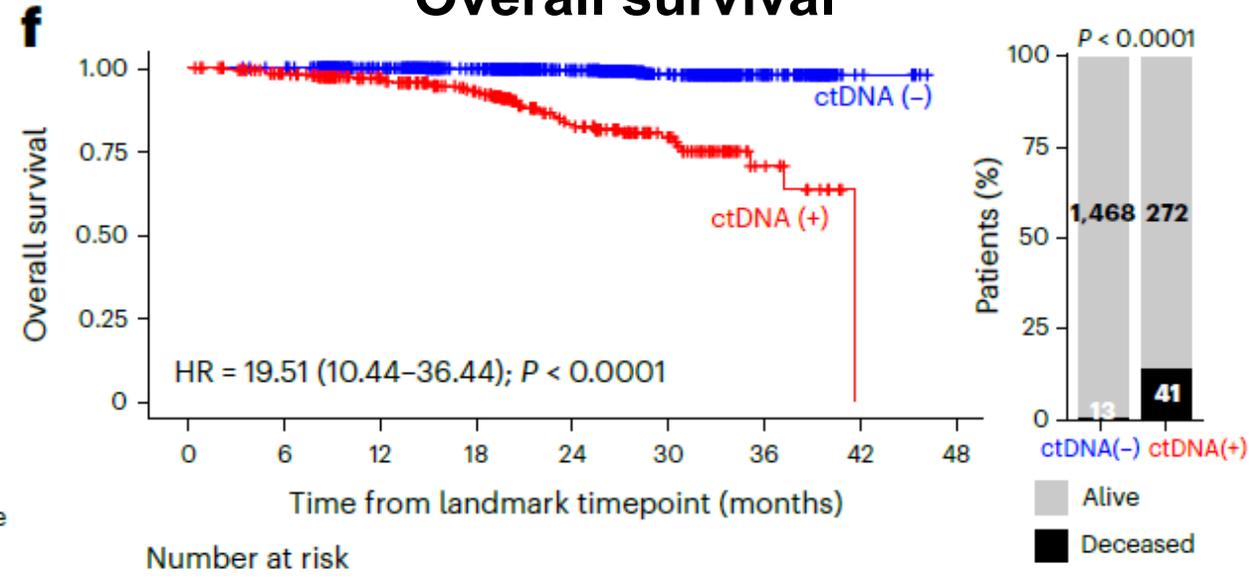


Number at risk

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

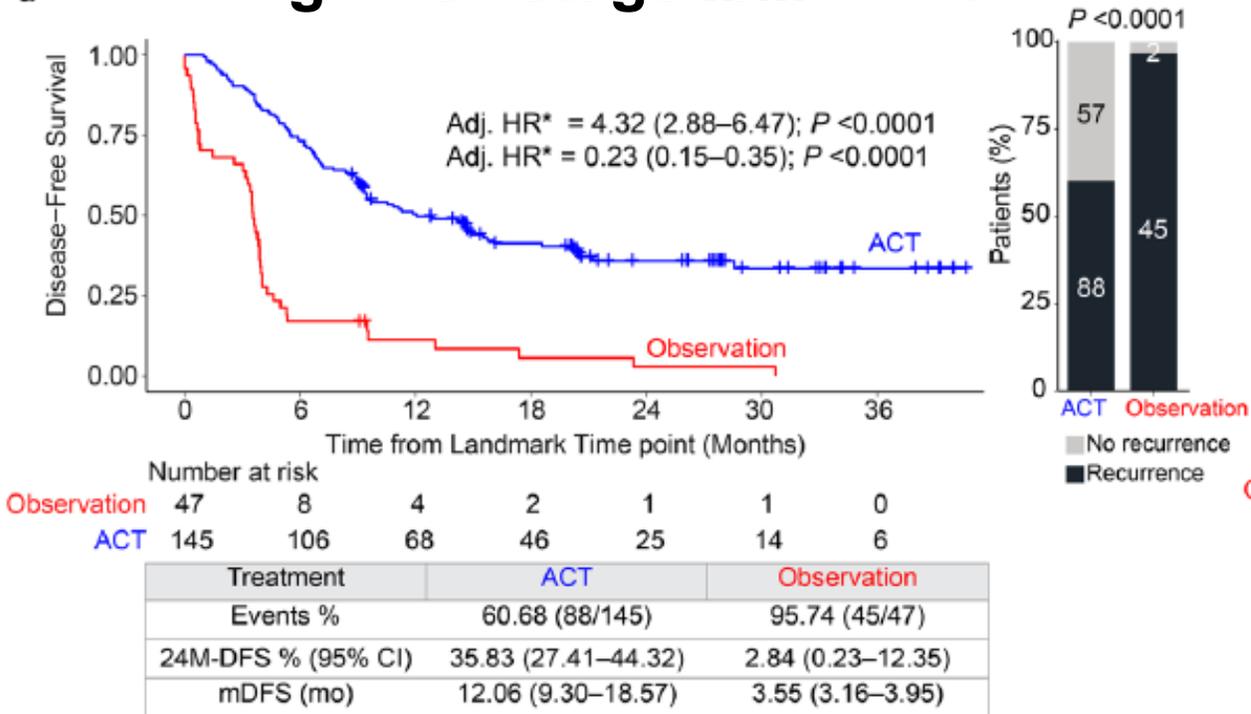
ctDNA (-)	1,481	1,478	1,275	1,063	686	384	123	6	0
ctDNA (+)	313	287	222	175	102	60	14	0	0

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)

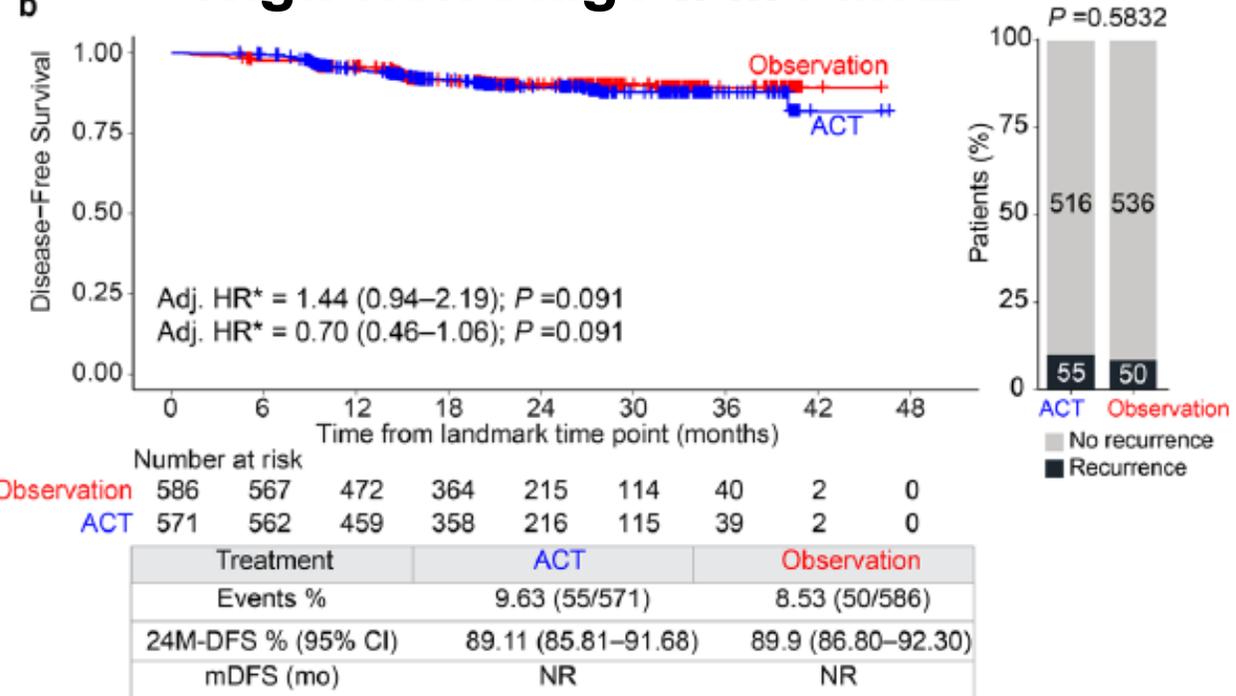
ctDNA positivity preceded radiological recurrence by a median of 5.9 months (range, 0-33.1)

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

a High-risk stage II/III: MRD+

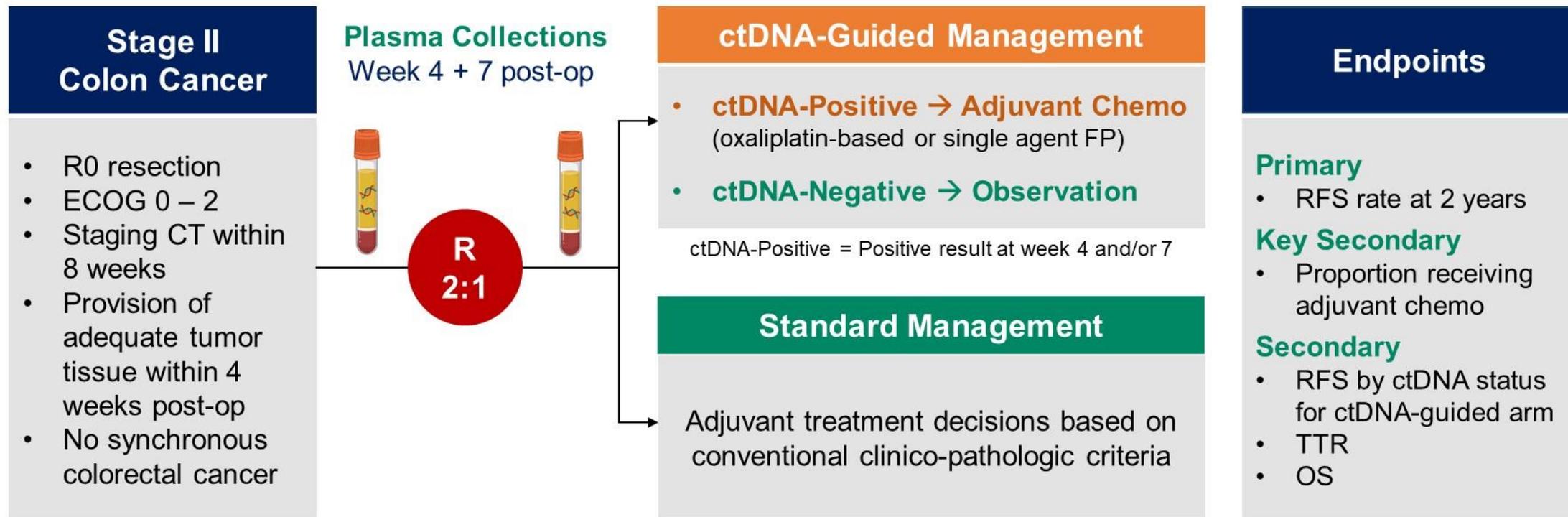


b High-risk stage II/III : MRD-



DYNAMIC Study Design

ACTRN12615000381583



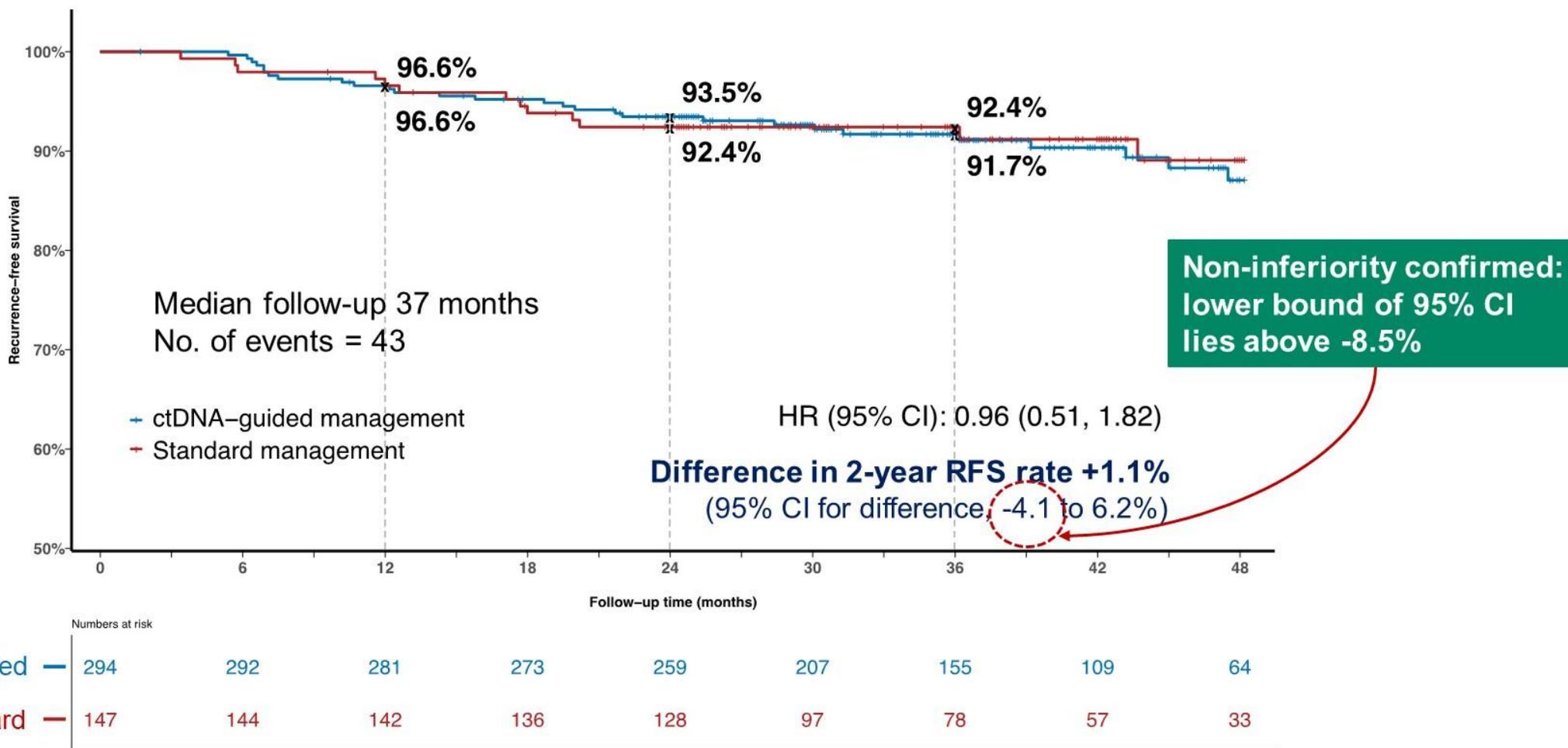
Stratification Factors

- 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

Recurrence-Free Survival



Adjuvant Treatment Delivery

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%)	<.0001
Single agent fluoropyrimidine	17/45 (38%)	37/41 (90%)	
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

MRD post ASCO GI 2025

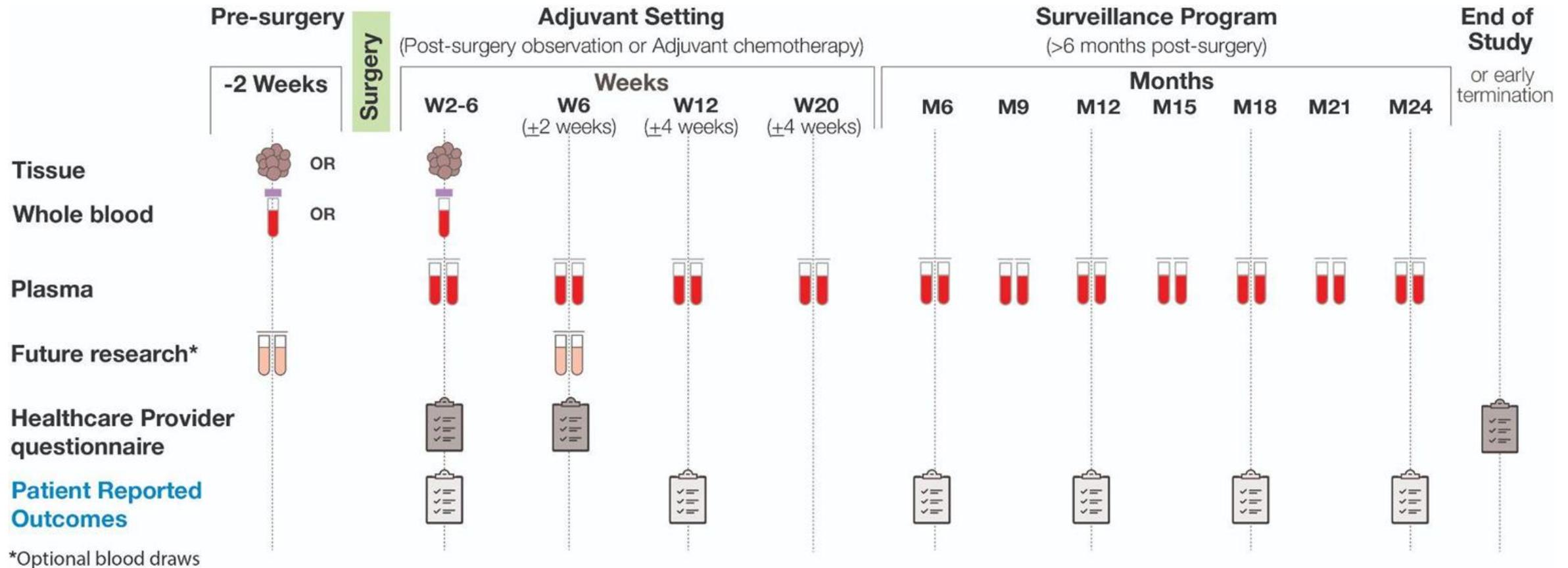
- Do US oncologists (BESPOKE) find MRD assessment helpful for guiding adjuvant chemotherapy in patients with resected colon cancer?
- MRD assessment (CALGB 80702) and “adjuvant” celecoxib in patients with resected stage III colon cancer following surgery?
- Do patients with cMRD+ disease following definitive therapy for colon cancer be offered TAS-102 effectively?

MRD post ASCO GI 2025

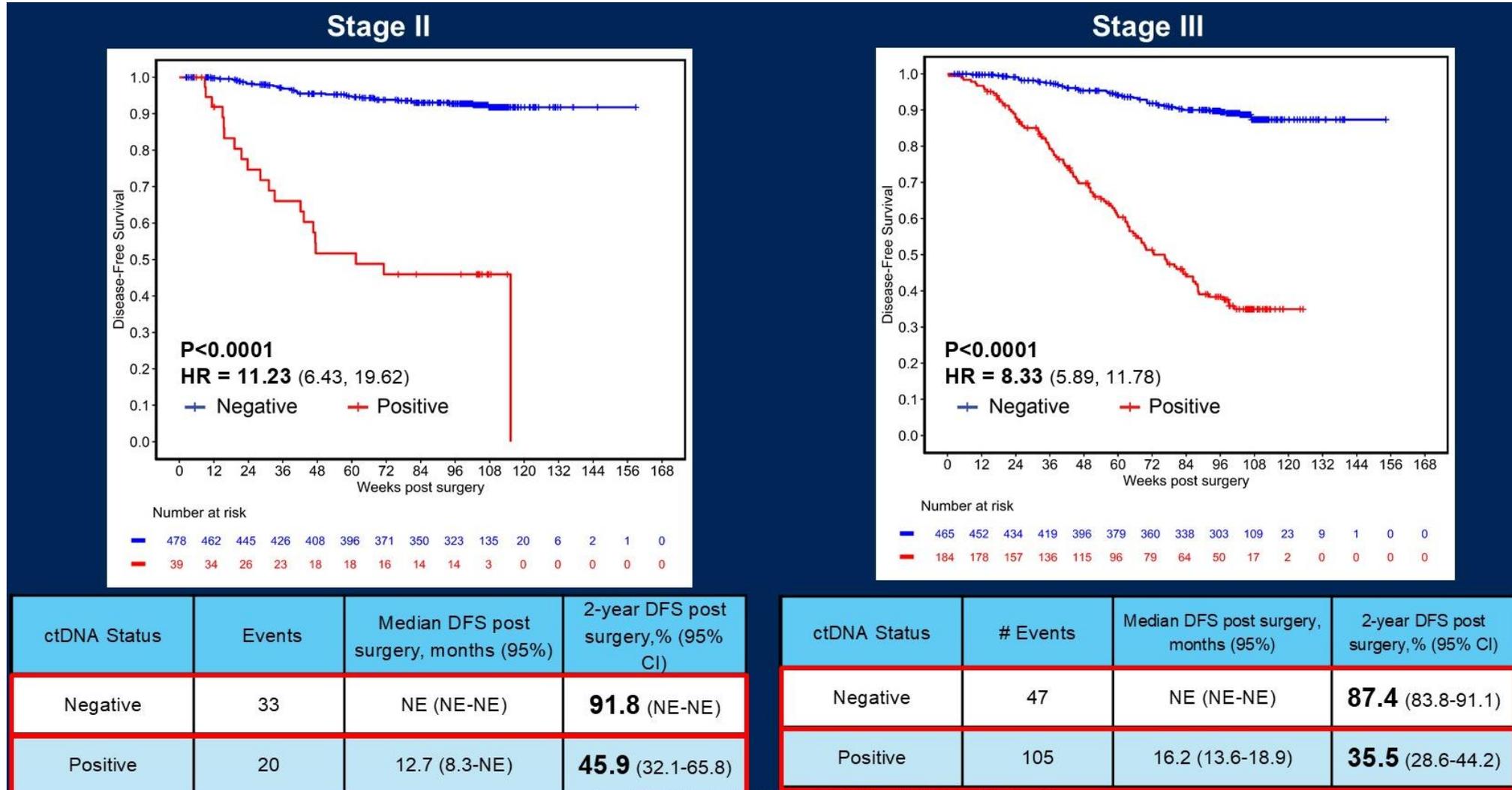
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BESPOKE CRC study design

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

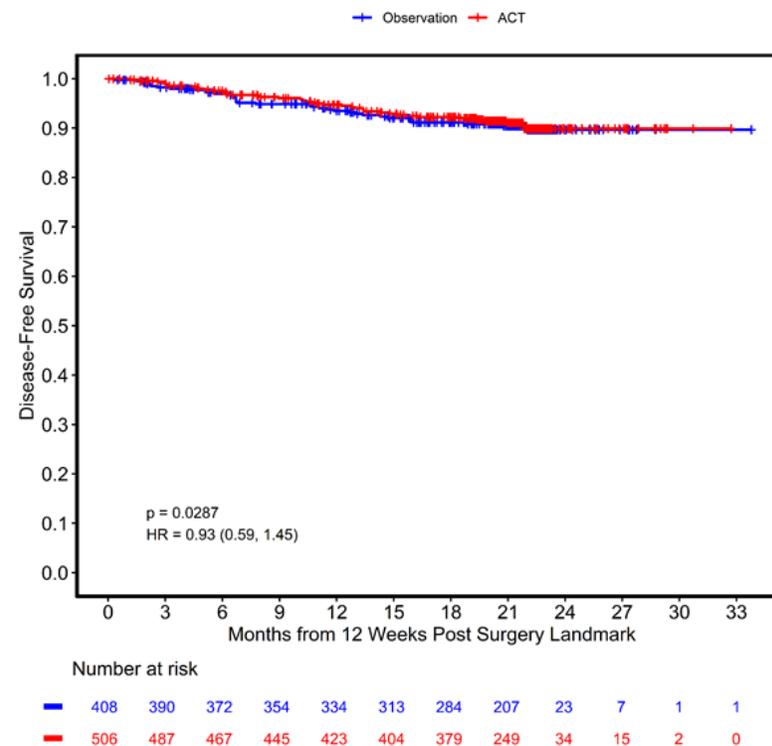
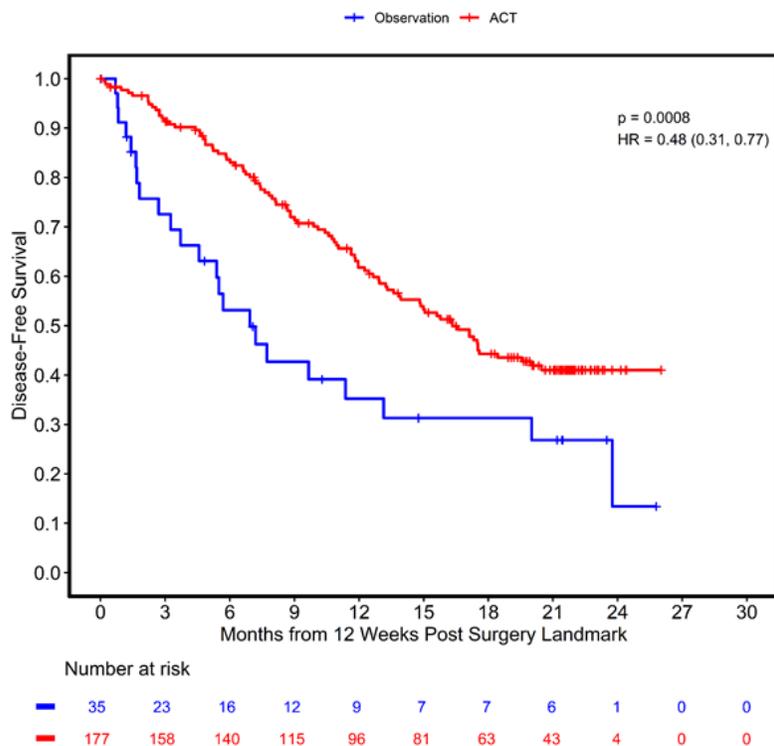


Post-operative ctDNA positivity predicts inferior DFS



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

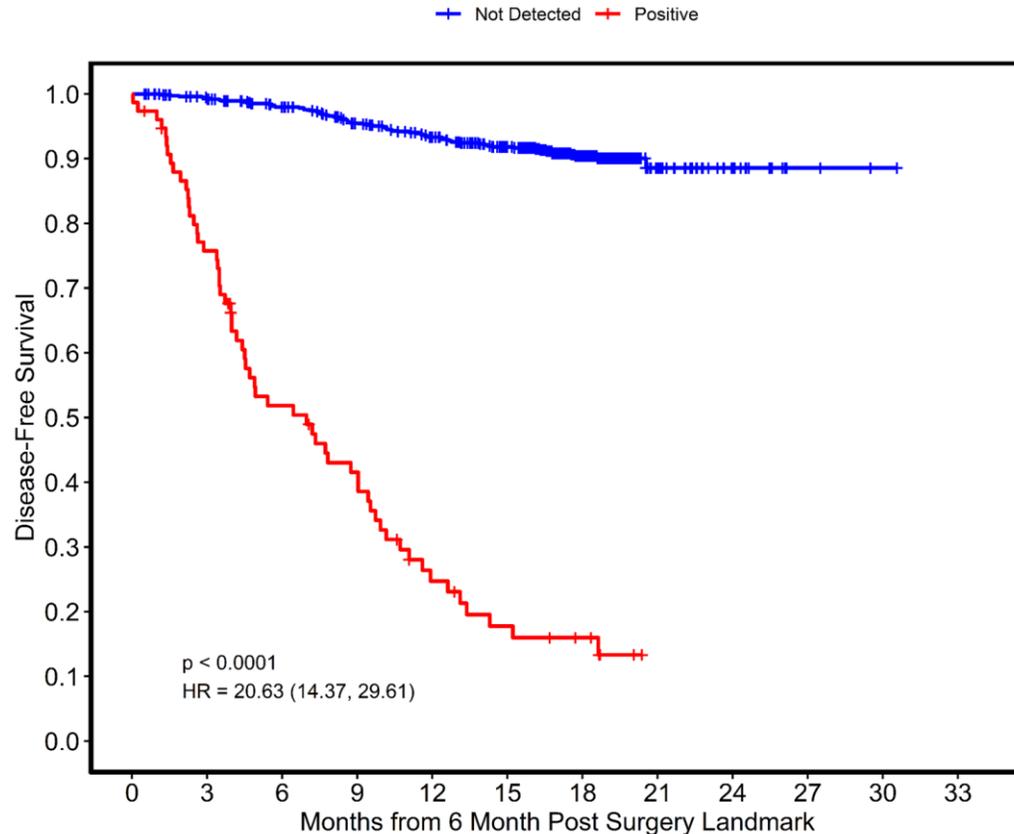
ctDNA-based MRD testing is predictive of the benefit of ACT



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

First surveillance Signatera timepoint positivity predicts inferior DFS



Number at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33
Not Detected (Blue)	767	746	716	675	640	589	375	47	15	3	1	0
Positive (Red)	76	56	36	28	15	10	7	0	0	0	0	0

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

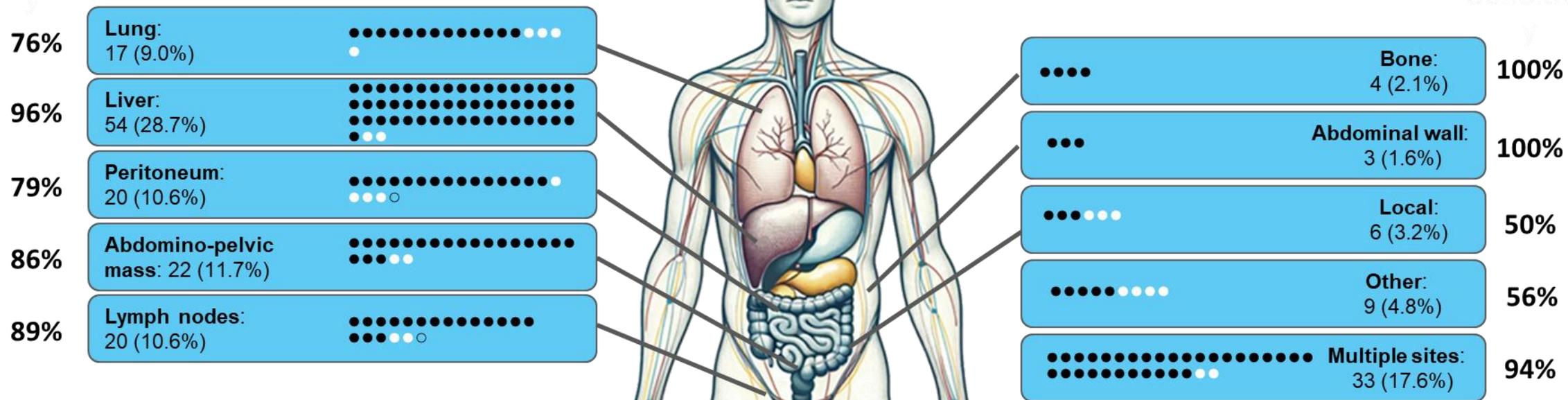
MRD test sensitivity is impacted by site of recurrence

Recurrence sites

(N=188)

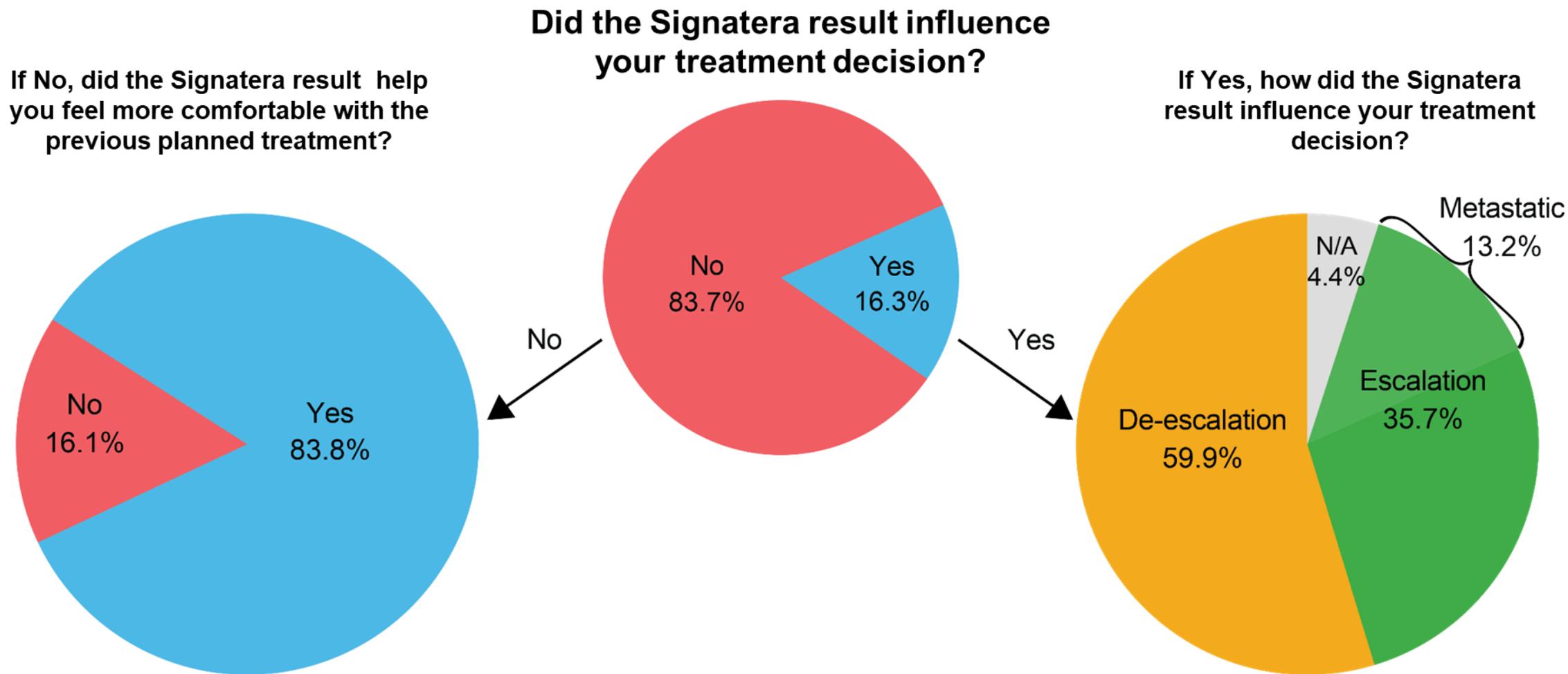
Sensitivity

Sensitivity



- ctDNA+ within 24w before recurrence
- ctDNA- within 24w before recurrence
- ctDNA not available within 24w before recurrence

Impact of Signatera MRD test on adjuvant treatment decision



MRD post ASCO GI 2025

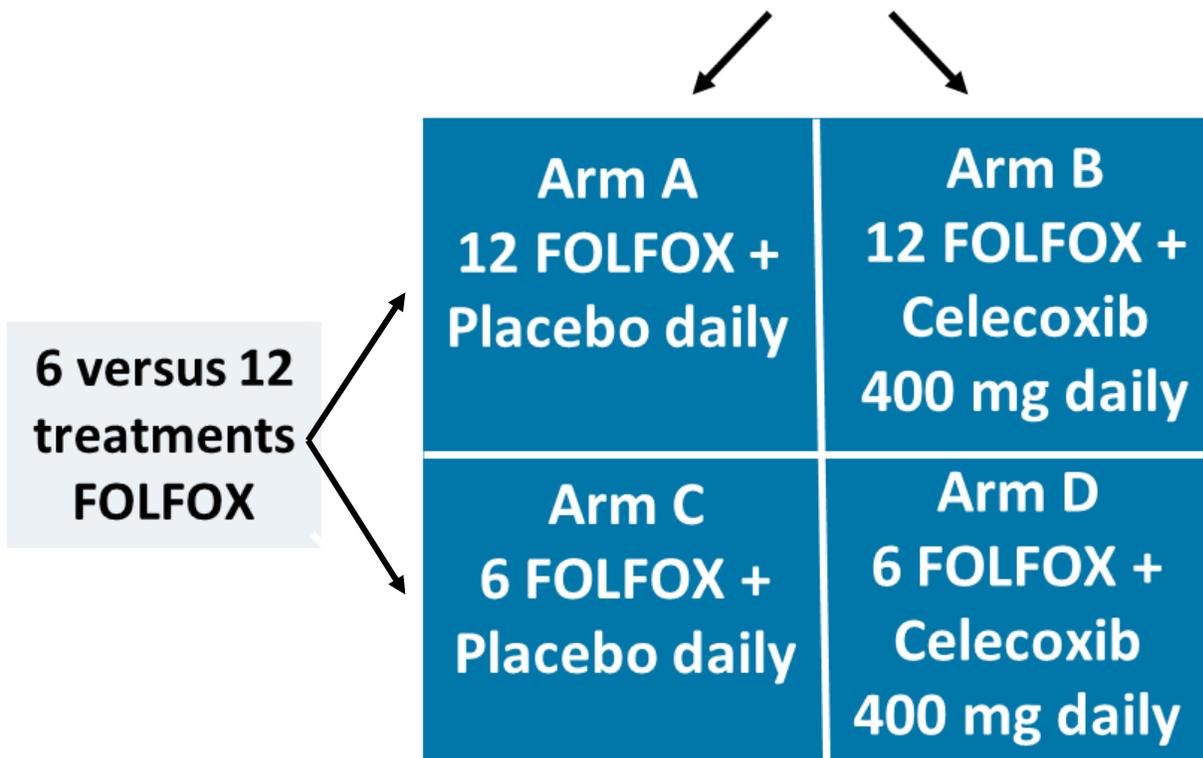
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- Do patients with cMRD+ disease following definitive therapy for colon cancer be offered TAS-102 effectively?

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 versus Placebo

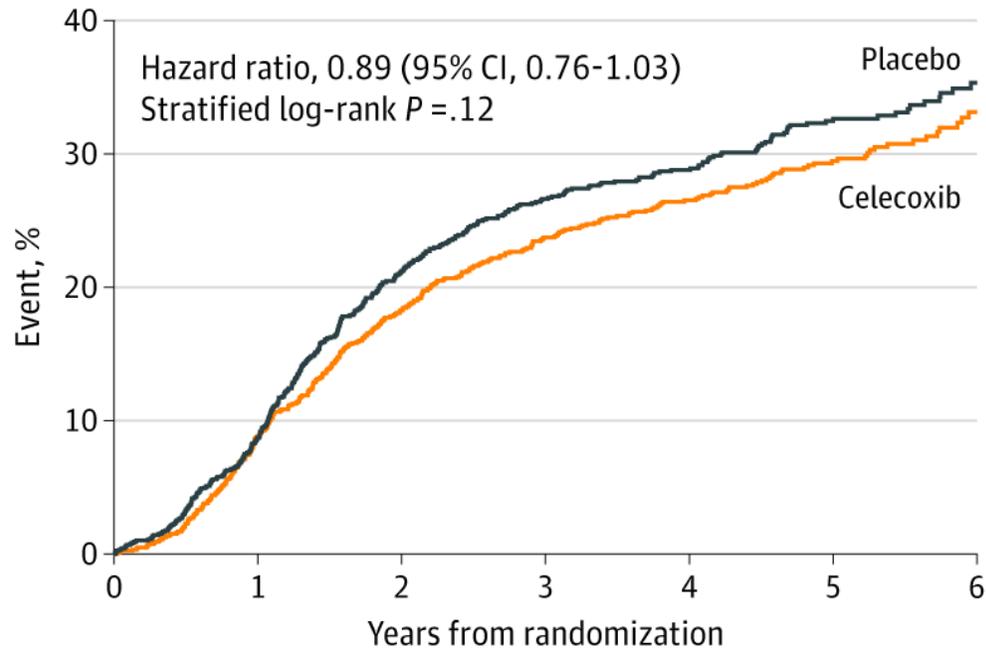


Celecoxib/placebo continued for a total of 3 years from the day study drug was initiated

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

CALGB/SWOG 80702: Survival according to adjuvant celecoxib

A Disease-free survival

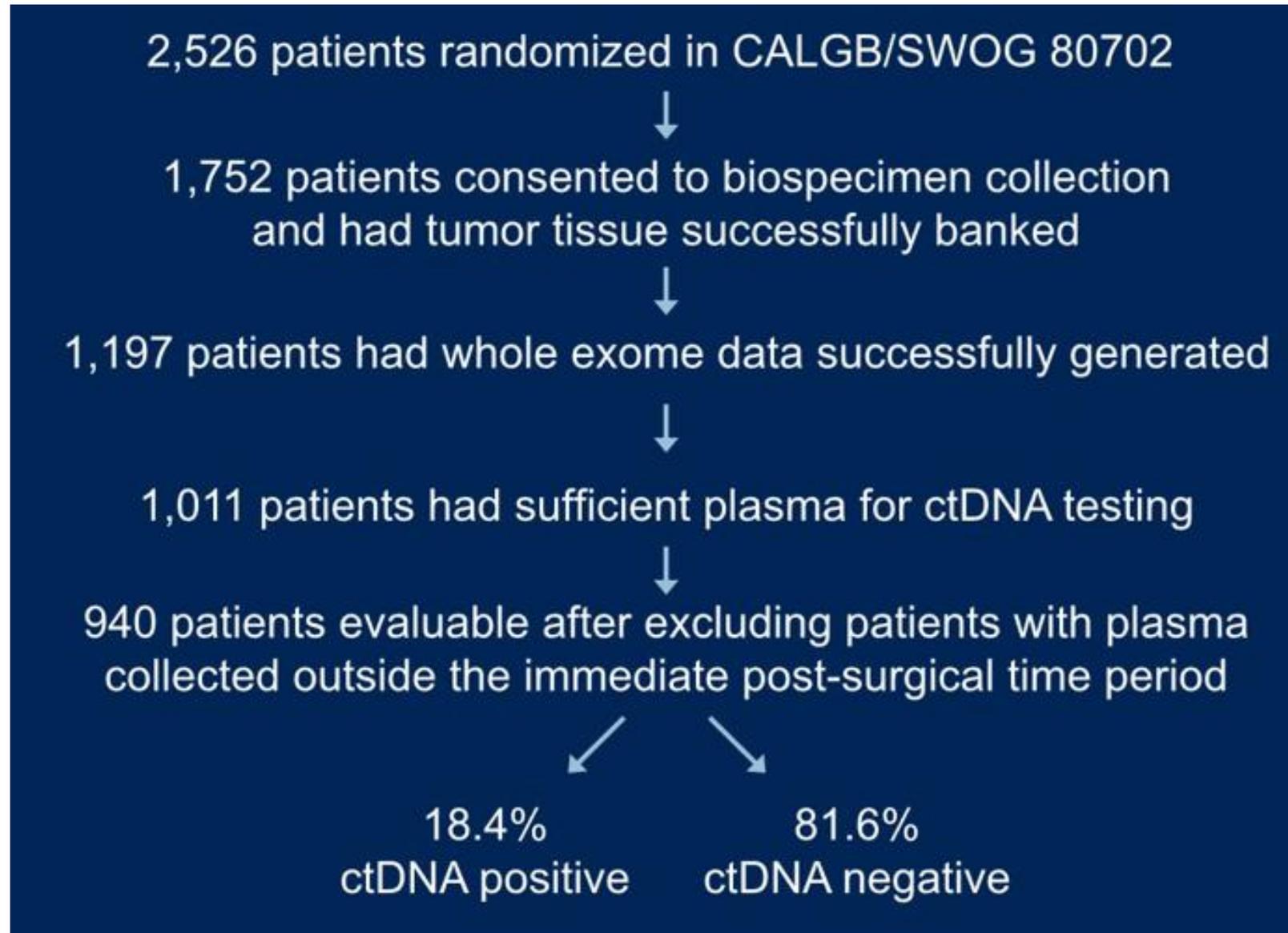


No. at risk

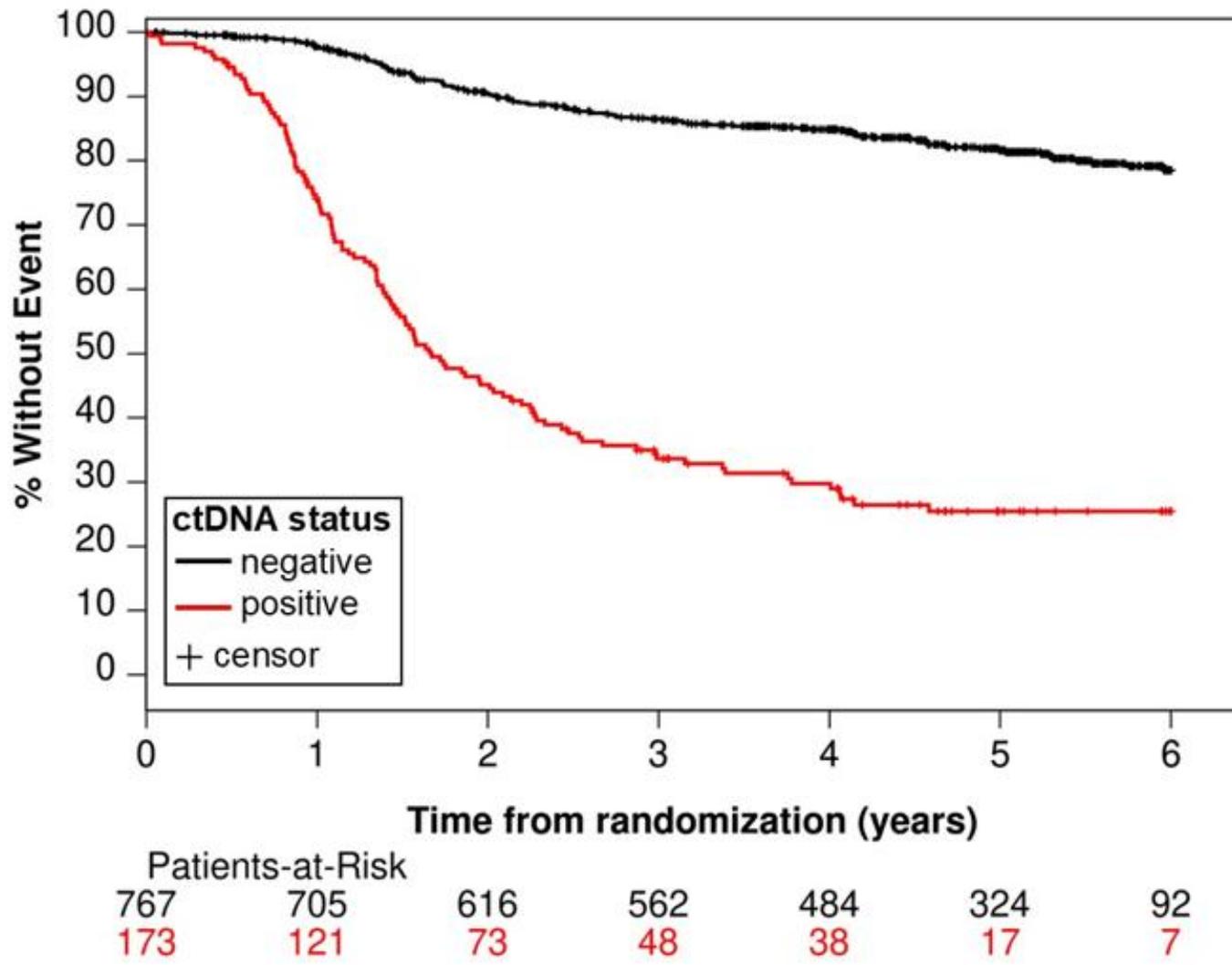
Celecoxib	1263	1049	893	769	653	414	123
Placebo	1261	1042	847	742	629	400	116

- 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

Study composition for Signatera ctDNA analysis



Disease-free survival by ctDNA status

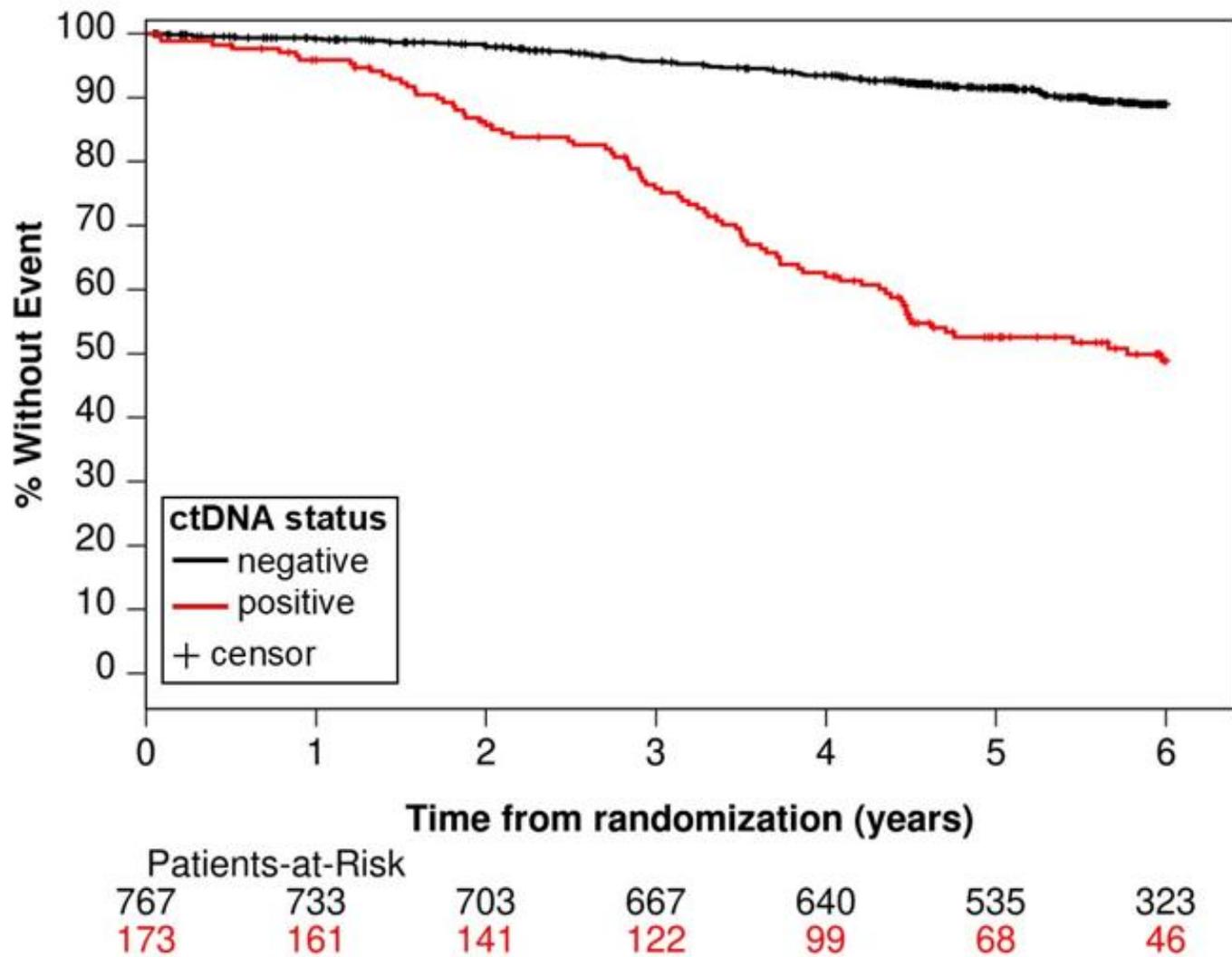


ctDNA Status	Events / Total	Hazard Ratio (95% CI) ¹	3 Year Survival Estimate (95% CI) ²
Negative	131/767	Reference	86.5 (84.0-89.1%)
Positive	118/173	7.14 (5.54-9.21)	33.7 (27.1-41.8%)

Logrank P-value: <0.0001³

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

Overall survival by ctDNA status

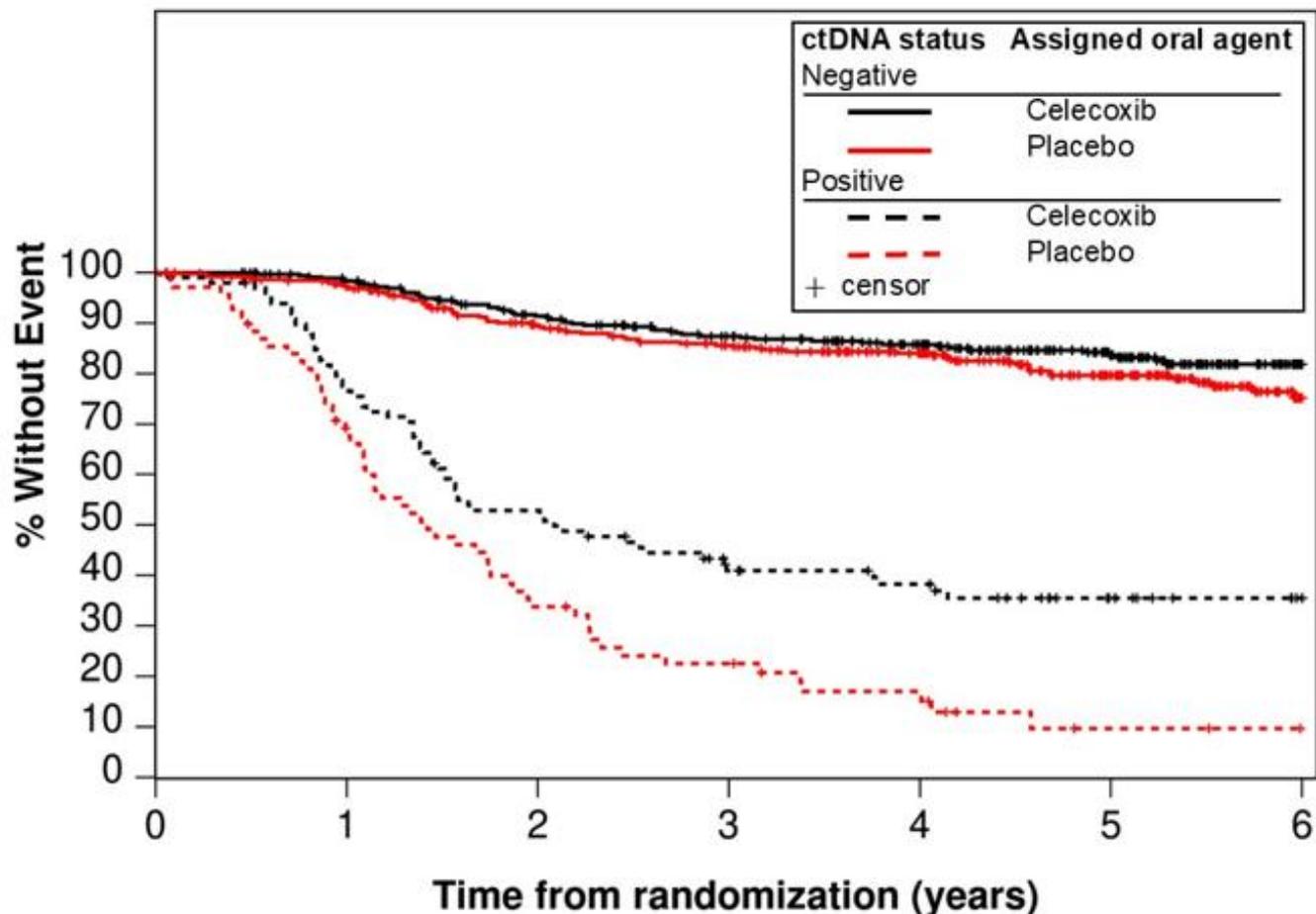


ctDNA Status	Events / Total	Hazard Ratio (95% CI) ¹	5 Year Survival Estimate (95% CI) ²
Negative	77/767	Reference	91.5 (89.5-93.6%)
Positive	85/173	6.72 (4.91-9.18)	52.6 (45.3-61.0%)

Logrank P-value: <0.0001³

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

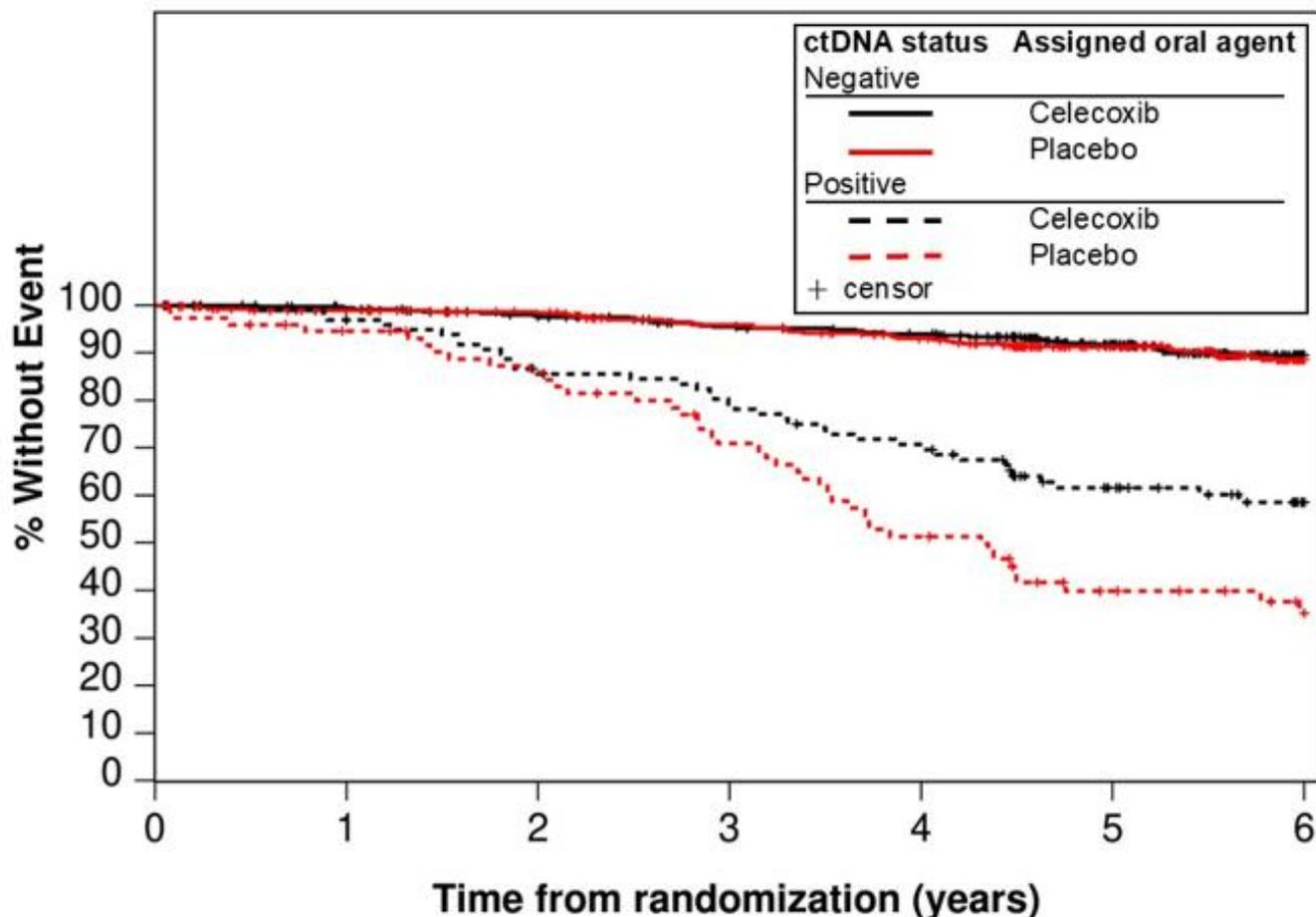
Disease-free survival by ctDNA status and celecoxib use



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

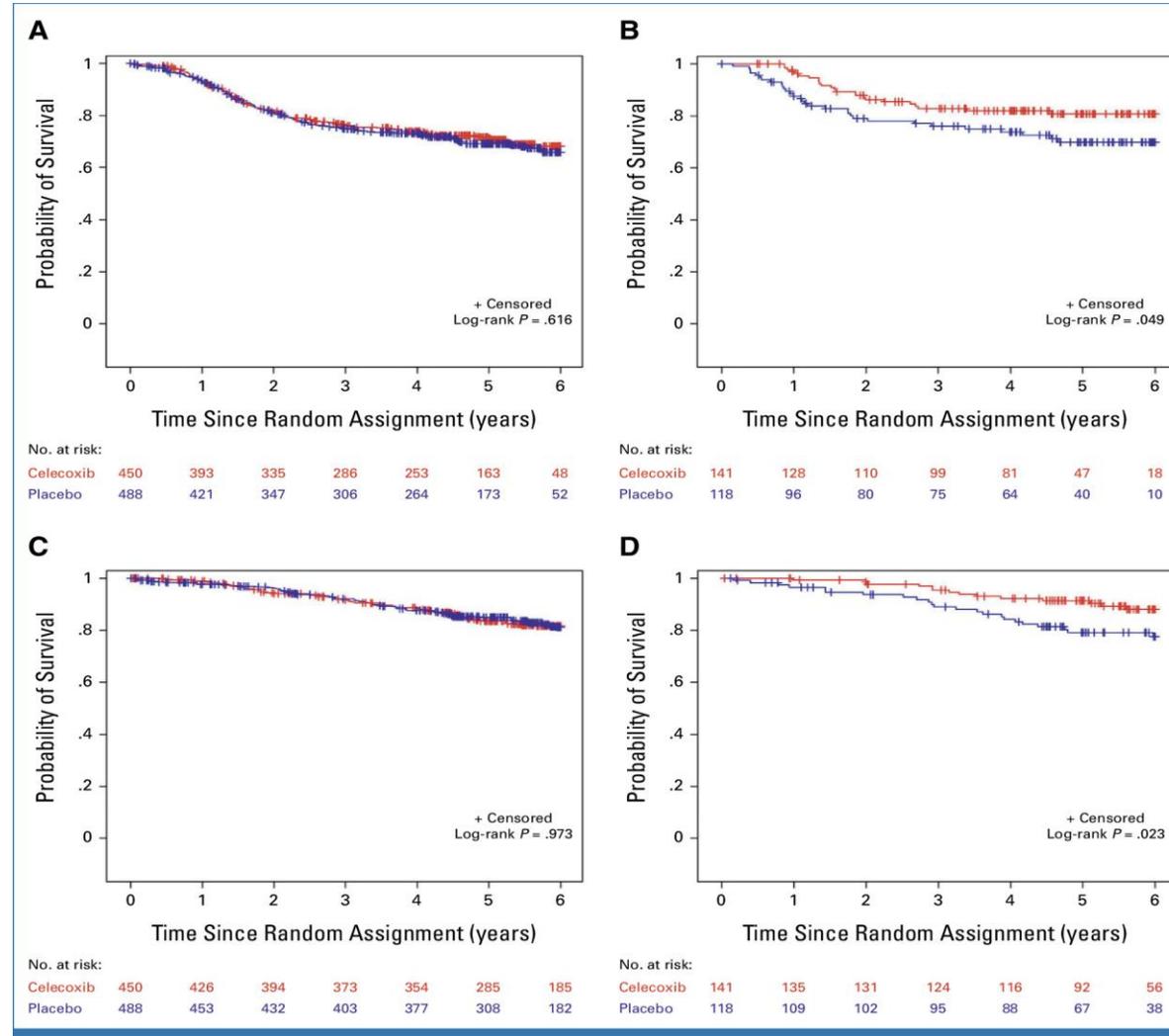
Overall survival by ctDNA status and celecoxib use



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

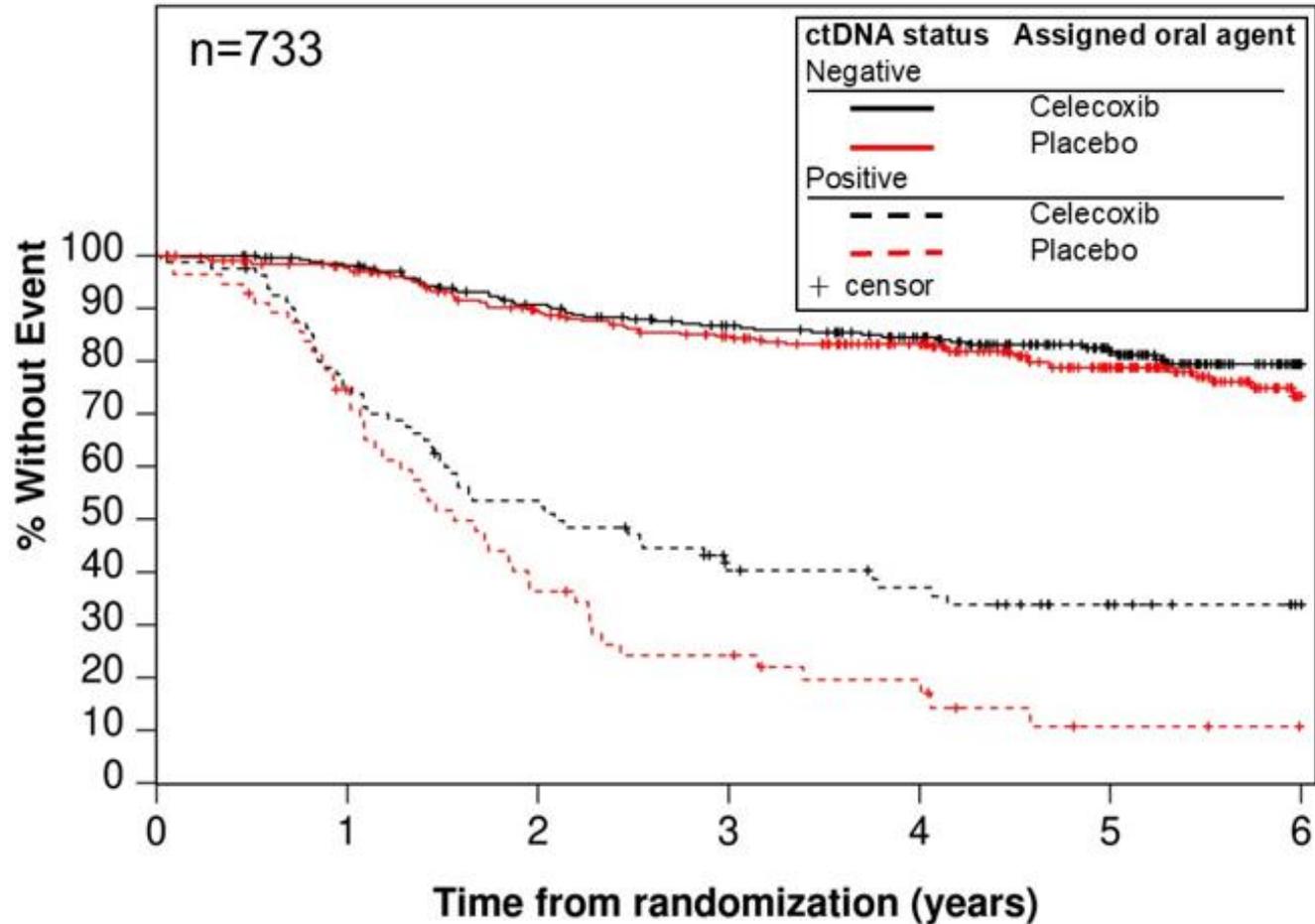
¹ Unadjusted Cox model, ² Kaplan-Meier method, ³ Likelihood-ratio test, ⁴ Log-rank test

Improved Survival With Adjuvant Cyclooxygenase 2 Inhibition in *PIK3CA*-Activated Stage III Colon Cancer: CALGB/SWOG 80702 (Alliance)



PIK3CA. MT

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				
Celecoxib	49/278	0.81 (0.56-1.18)	86.7 (82.7-91.0%)	0.2777 ⁴
Placebo	63/318	Reference	84.8 (80.7-89.0%)	
Positive				
Celecoxib	51/81	0.61 (0.41-0.92)	40.3 (30.7-52.9%)	0.0166 ⁴
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

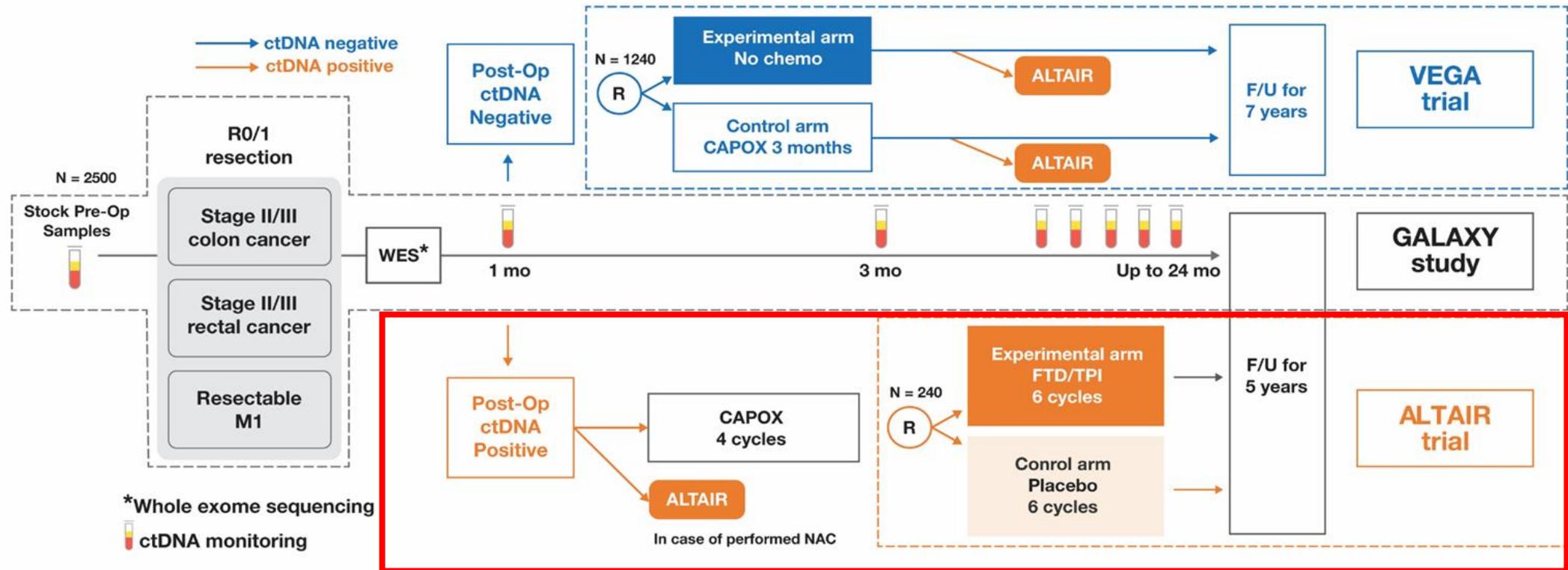
CALGB/SWOG 80702: Conclusions

- MRD status after surgery and prior to starting adjuvant therapy was highly prognostic of DFS and OS
- MRD status also appeared relatively predictive of benefit of adjuvant celecoxib
- Significant limitations:
 - Post hoc analysis with a subset of patients included
 - ctDNA status not used prospectively to select patients for adjuvant celecoxib
- Studies on the predictive value of ctDNA for 3 versus 6 months of adjuvant FOLFOX are underway

MRD post ASCO GI 2025

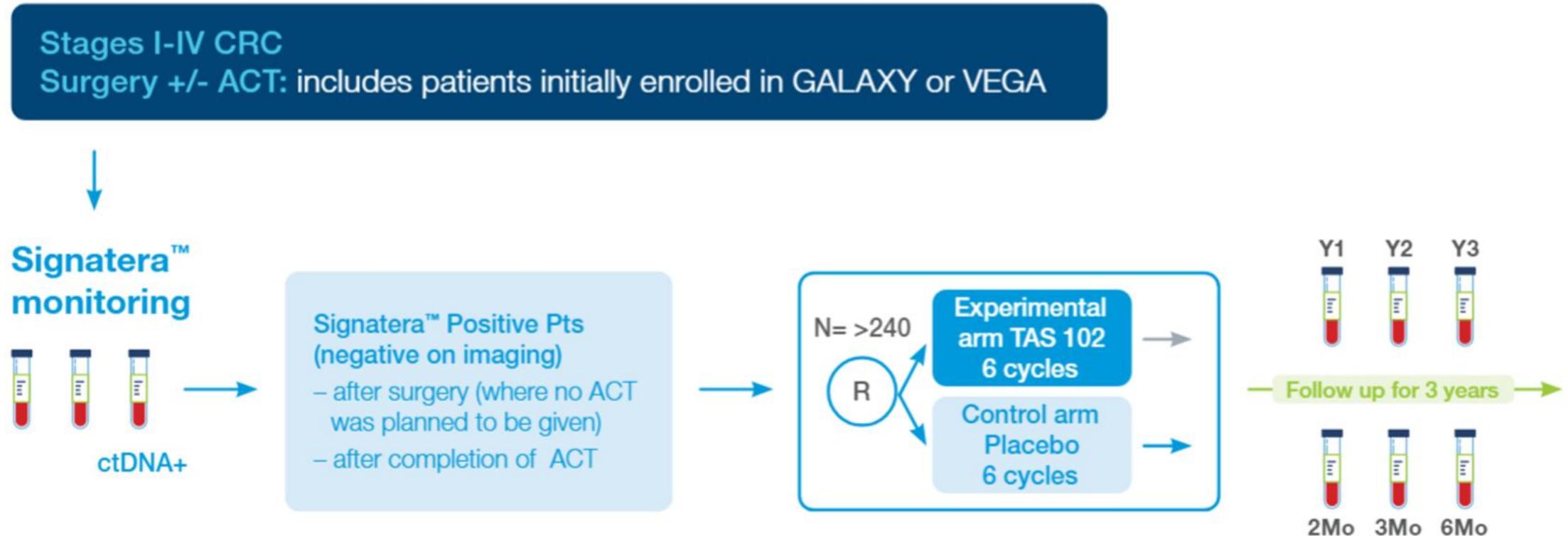
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Circulate-Japan Study: Flowchart



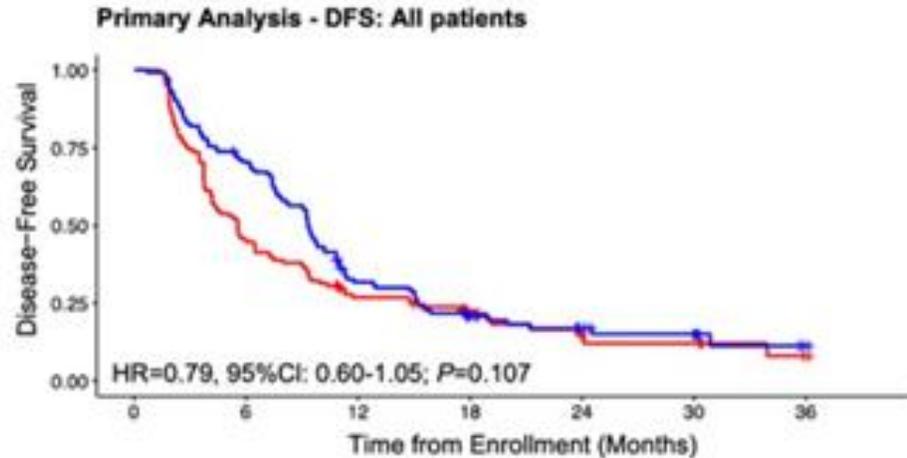
- Detect MRD
- Measure treatment responsiveness in resectable CRC
- The blood samples will be collected before surgery and at 4, 12, 24, 36, 48, 72, and 96 weeks after surgery
- Computed tomography (CT) will be performed every 6 months after surgery for 7 years

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

ALTAIR: Results



Number at risk

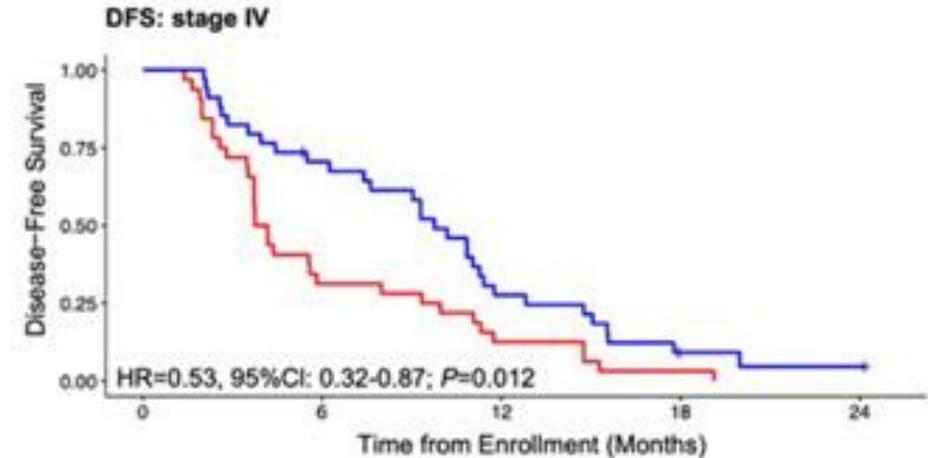
FTD/TPI

Placebo

122	85	35	19	11	6	1
121	55	28	16	6	5	1

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)



Number at risk

FTD/TPI

Placebo

34	23	9	2	1
32	10	4	1	0

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 (2.36-21.9)	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

ALTAIR: Results

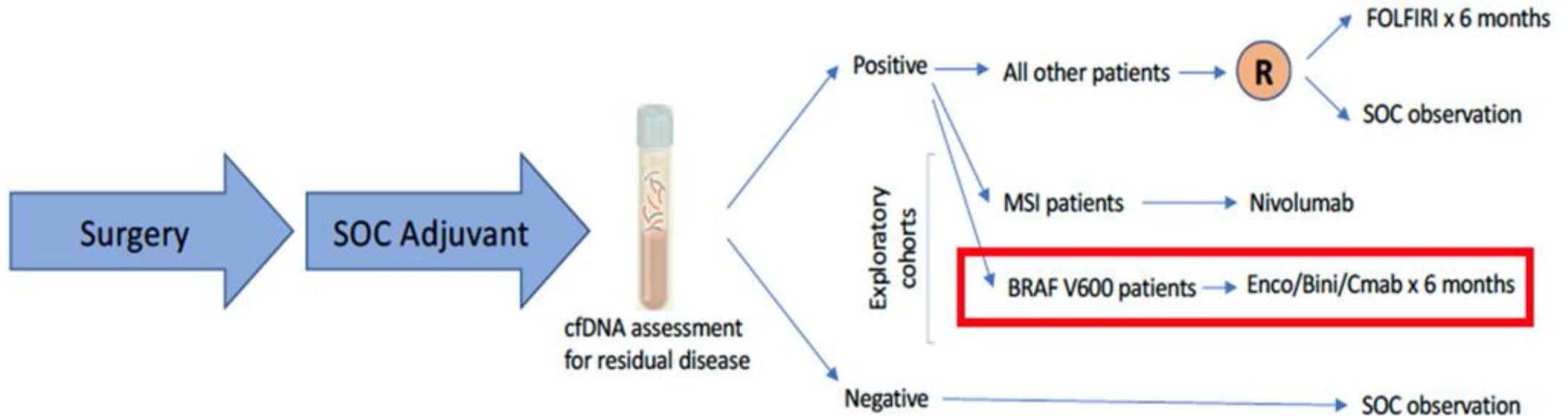
		Primary population	Stage IV	Non-Stage IV
Number		243	66	177
Mean Baseline MTM/ml		0.40	0.68	0.32
Median DFS (months)	FTD/TPI	9.30	9.76	9.26
	Placebo	5.55	3.96	6.05
		HR, 0.79 P = 0.107	HR, 0.53 P = 0.012	HR, 0.86 P = 0.378

	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 investigational 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

MRD post ASCO GI 2025

- Do US oncologists (BESPOKE) find MRD assessment helpful for guiding adjuvant chemotherapy in patients with resected colon cancer? **Yes, for prognostic implications and possible as a predictive test**
- MRD assessment (CALGB 80702) and “adjuvant” celecoxib in patients with resected stage III colon cancer following surgery? **Further studies needed to validate although discussion on a case-by-case basis TBD with patients**
- Do patients with cMRD+ disease following definitive therapy for colon cancer be offered TAS-102 effectively? **No – implications relate to TAS 102 only**

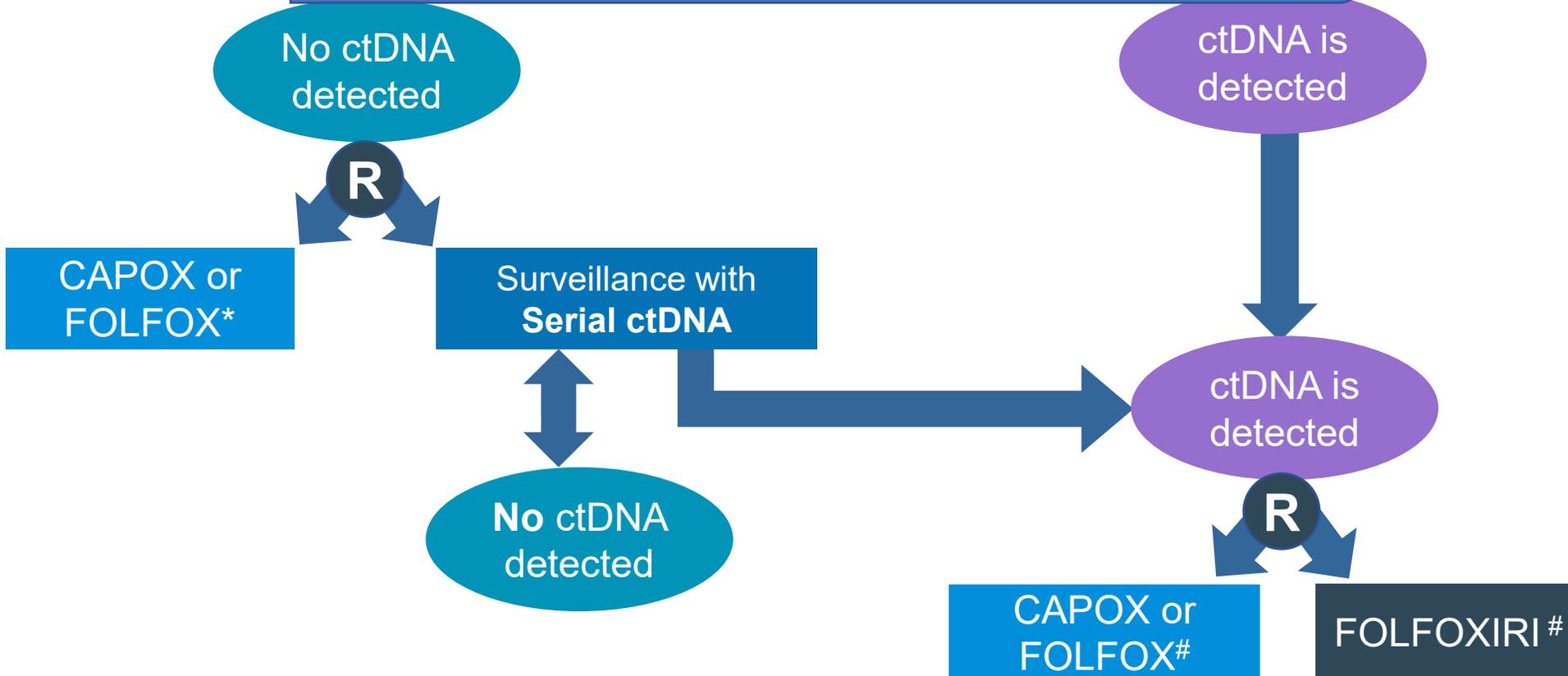
SU2C CRC DT: Early Intervention in Stage 3 CRC



Summary

- Multiple liquid biopsy methods have been developed for cfDNA analysis
- cfDNA detection and quantification methods have the potential to transform clinical practice with MRD assessment
 - Tumor-informed vs. tumor-naïve platforms (liquid only)
 - Residual disease detection at earlier timepoints than standard clinical and/or imaging surveillance
- Will this allow for improved patient selection for:
 - Adjuvant chemotherapy (ACT) ?
 - ACT duration ?
 - Intensity of radiologic surveillance? and, ultimately,
 - Outcome for patients with colorectal cancer (CRC)? Does clearing cfDNA by chemotherapy equate to cure ?
 - Predictive value when selecting for molecular targets? (MSI, BRAF , HER2..)
 - Celecoxib?
- Randomized Clinical Trials (RCT) remain key for answering pending questions

T1-3, N1 Stage III Colon Adenocarcinoma
 Circulating tumor DNA (ctDNA) results within 6-8 weeks of surgery



Pls:

Arvind Dasari (MDACC)
 Christopher Lieu (UCCC)

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

CASE Discussion



Case



- 54 y/o patient with perforated R side CRC. Stage IIIA.
- Treated with surgery and 6 months mFOLFOX6.
- Decision was made to monitor with CtDNA.
- Negative at the start and completion of adjuvant therapy.
- 6 months later CtDNA positive.
- CT-PET and dedicated high resolution liver scan are negative. Surgeon declined to do diagnostic laparoscopy.

Next step ?(Patient and I decided to repeat imaging and circulating DNA in 3 months)



Case



56 year-old woman with rectal cancer

- 2017 neoadjuvant chemoradiation with Xeloda
- 8/2017 s/p LAR, low-grade adenocarcinoma, 3 separate tumor deposits present, negative surgical margins negative, ypT3pN1c, stage III–B, MSS
- Received 4-6 months of FOLFOX.
- 4/2019 R lower lobe recurrence treated with RLL lobectomy with 1.2 cm lesions.

No further therapy given – Signatera surveillance monitoring for recurrence
How frequently should we obtain it?

THANK YOU