Are we ready to decide on adjuvant therapy in Colon Cancer based of ctDNA

Mike Cusnir MD

Division Chief Hematology and Oncology

Miami Beach, Florida

Mount Sinai
MEDICAL CENTER

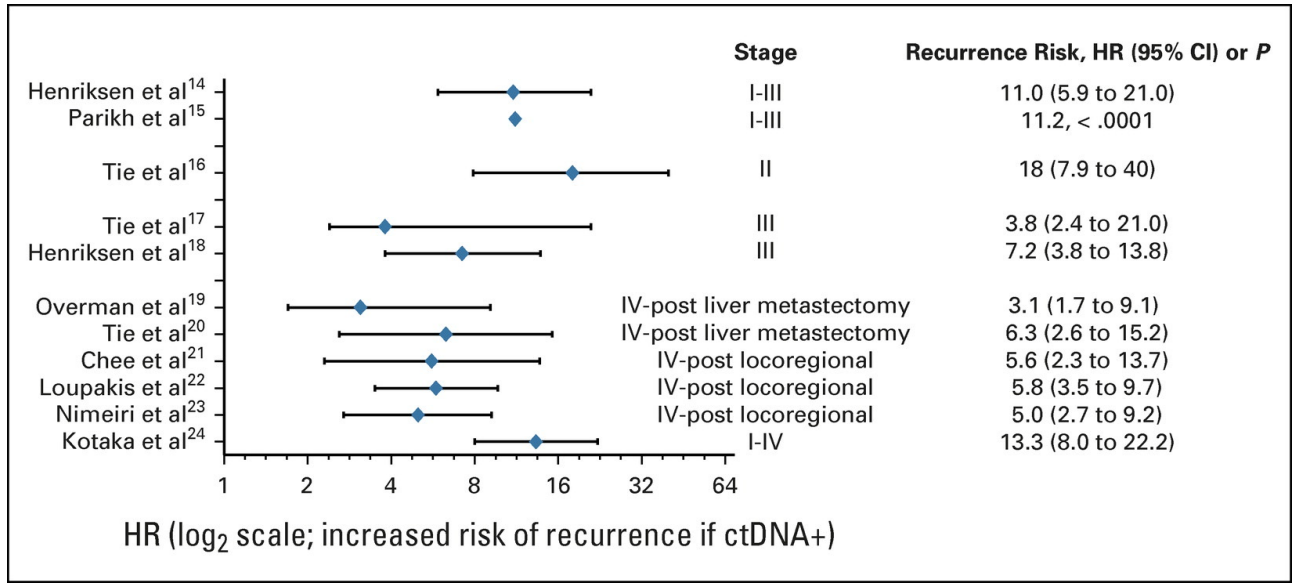


TABLE 2. Ability of Adjuvant Infusional Fluorouracil, Leucovorin, and Oxaliplatin Chemotherapy to Convert ctDNA-Positive Status to ctDNA-Negative in the Postoperative Setting After Curative-Intent Surgery in Patients With Curatively Resected Colorectal Cancer

Study	Stage	Ability of Adjuvant Therapy to Convert ctDNA-Positive to ctDNA-Negative (% of ctDNA clearance postoperatively)
Reinert et al[25]	I-III	3/10 (30)
Parikh et al[15]	I-III	1/6 (16.7)
Tie et al[16]	II	3/6 (50)
Tie et al[17]	III	5/20 (25)
Henriksen et al[18]	III	4/20 (20)
Tie et al[20]	IV	3/11 (27.3)
Kotaka et al[24]	I-IV	65/96 (67.7)

Abbreviation: ctDNA, circulating tumor DNA.

Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Overall (N=441)
Male sex — no. (%)	81 (55)	154 (52)	235 (53)
Median age (range) — yr	62 (28–84)	65 (30–94)	64 (28–94)
Age group — no. (%)			
≤70 yr	113 (77)	207 (70)	320 (73)
>70 yr	34 (23)	87 (30)	121 (27)
ECOG performance-status score — no./total no. (%)†			
0	124/147 (84)	226/293 (77)	350/440 (80)
1	20/147 (14)	65/293 (22)	85/440 (19)
2	3/147 (2)	2/293 (1)	5/440 (1)
Type of center — no. (%)			
Metropolitan	121 (82)	240 (82)	361 (82)
Regional	26 (18)	54 (18)	80 (18)
Primary tumor site — no. (%)‡			
Left side	78 (53)	126 (43)	204 (46)
Right side	69 (47)	168 (57)	237 (54)
Tumor stage — no. (%)			
T3	127 (86)	250 (85)	377 (85)
T4	20 (14)	44 (15)	64 (15)
Poor tumor differentiation — no. (%)	17 (12)	43 (15)	60 (14)
Lymph node yield <12 — no. (%)	7 (5)	13 (4)	20 (5)
Tumor perforation — no. (%)	7 (5)	7 (2)	14 (3)
Bowel obstruction — no./total no. (%)†	18/147 (12)	26/291 (9)	44/438 (10)
Lymphovascular invasion — no. (%)	38 (26)	82 (28)	120 (27)
Deficient mismatch repair — no. (%)	27 (18)	59 (20)	86 (20)
Clinical risk group — no./total no. (%)§			
High	60/147 (41)	116/293 (40)	176/440 (40)
Low	87/147 (59)	177/293 (60)	264/440 (60)
Median time from surgery to randomization (IQR) — days	33 (28–41)	32 (28–39)	32 (28–39.5)

* The abbreviation ctDNA denotes circulating tumor DNA, and IQR interquartile range.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers reflecting greater disability.
‡ A tumor on the left side was defined as a tumor arising in the area from the splenic flexure to the rectum; a tumor on the right side was defined as a tumor arising in the area from the cecum to the transverse colon.
§ Clinical high risk was defined as the presence of tumors with proficient mismatch repair along with any clinicopathological risk feature, including T4 extension, poor tumor differentiation, a lymph node yield of less than 12, lymphovascular invasion, tumor perforation, or bowel obstruction. Clinical low risk was defined as the presence of a tumor with deficient mismatch repair or a tumor with proficient mismatch repair and none of the above risk features. One case could not be classified because of missing information on bowel obstruction.

J Tie et al. N Engl J Med 2022;386:2261-2272.

The NEW ENGLAND JOURNAL of MEDICINE

Treatment Delivery and Adherence.*

Table 2. Treatment Delivery and Adherence.*

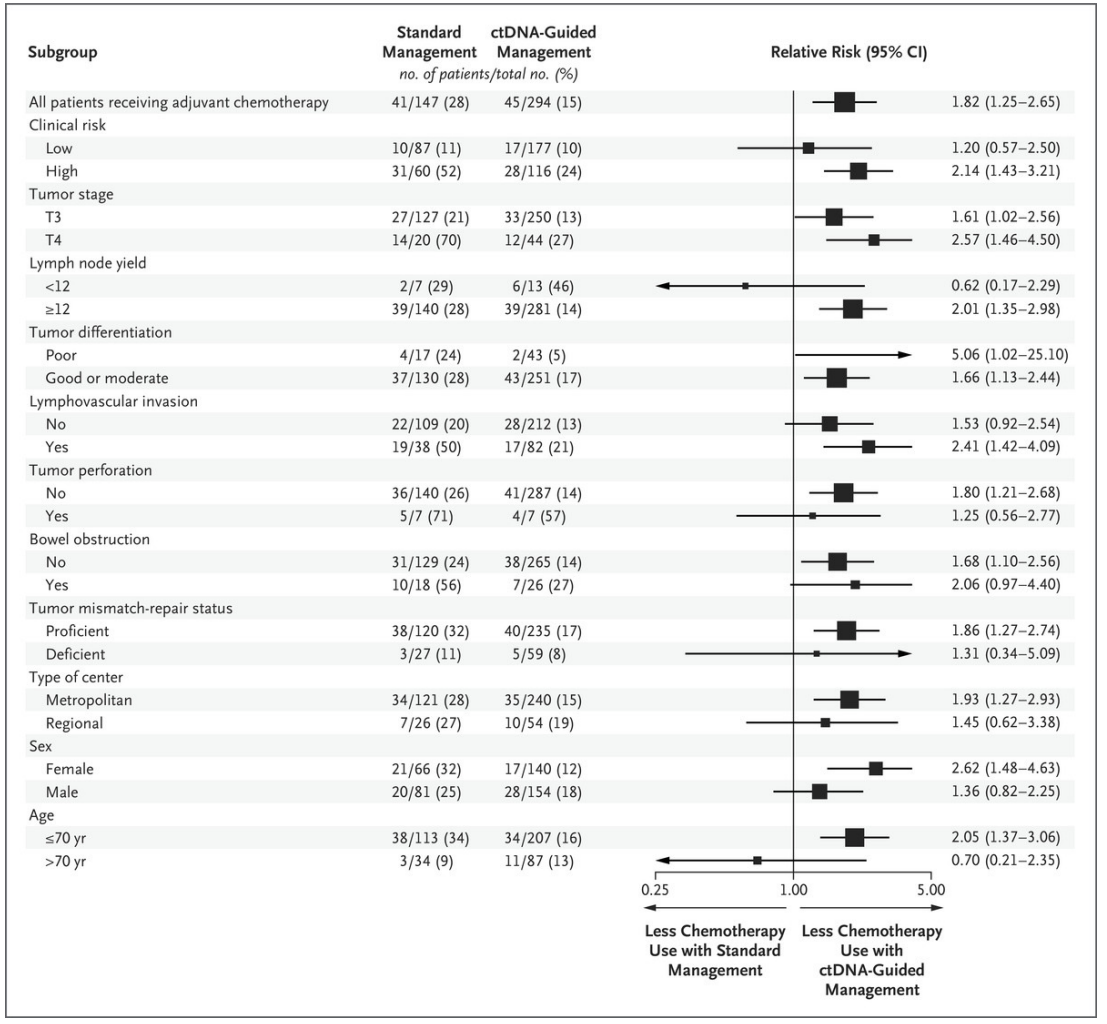
Treatment Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Relative Risk (95% CI)
Adjuvant chemotherapy received — no. (%)			
No	106 (72)	249 (85)	
Yes	41 (28)	45 (15)	1.82 (1.25–2.65)
Chemotherapy regimen received — no./total no. (%)			
Oxaliplatin-based doublet	4/41 (10)	28/45 (62)	
Single-agent fluoropyrimidine	37/41 (90)	17/45 (38)	2.39 (1.62–3.52)
Median time from surgery to start of chemotherapy (IQR) — days	53 (49–61)	83 (76–89)	
Median treatment duration (IQR) — wk	24 (21–24)	24 (19–24)	
Reason for stopping chemotherapy — no./total no. (%)			
Completion of planned treatment	32/41 (78)	38/45 (84)	
Disease relapse	1/41 (2)	0/45 (0)	
Patient request	1/41 (2)	1/45 (2)	
Toxic effects	7/41 (17)	6/45 (13)	
Percentage of full dose delivered			
Mean	77±26	74±24	
Median (IQR)	84 (64–100)	78 (56–100)	

* Plus–minus values are means ±SD. CI denotes confidence interval.

J Tie et al. N Engl J Med 2022;386:2261-2272.

The NEW ENGLAND JOURNAL of MEDICINE

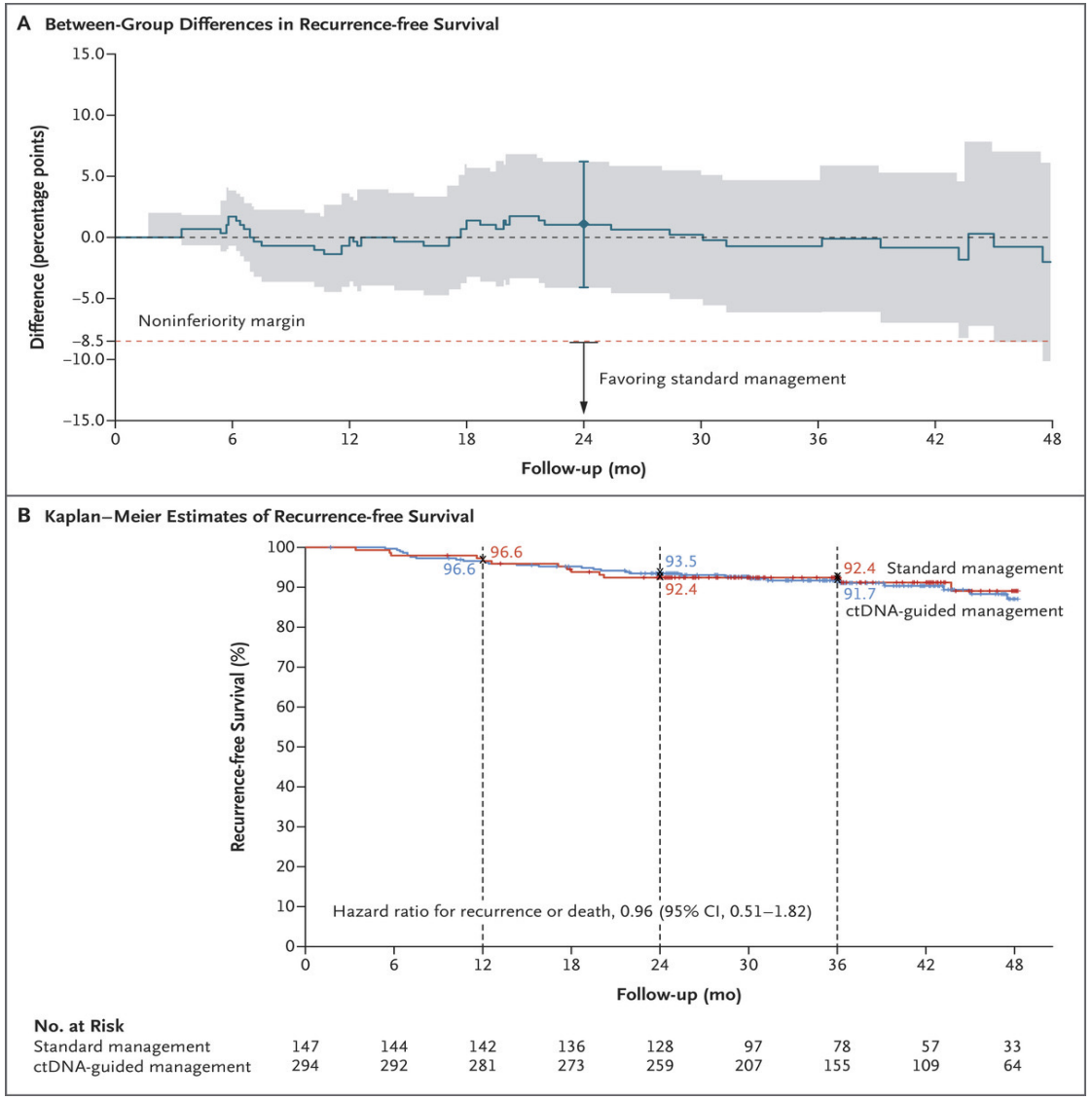
Receipt of Adjuvant Chemotherapy in the Intention-to-Treat Population According to Subgroup.



J Tie et al. N Engl J Med 2022;386:2261-2272.

The NEW ENGLAND JOURNAL of MEDICINE

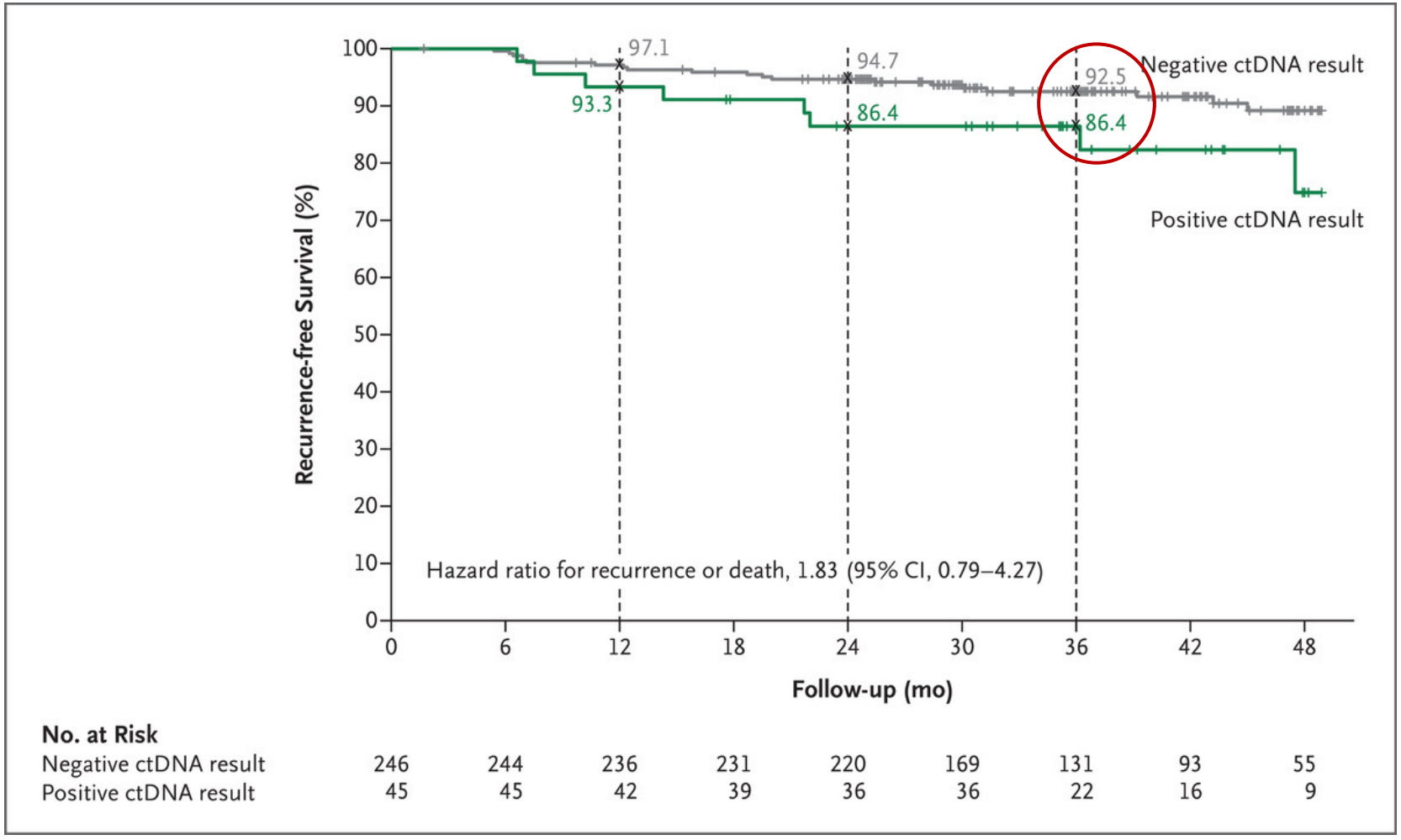
Outcomes with ctDNA-Guided as Compared with Standard Management in the Intention-to-Treat Population.



J Tie et al. N Engl J Med 2022;386:2261-2272.

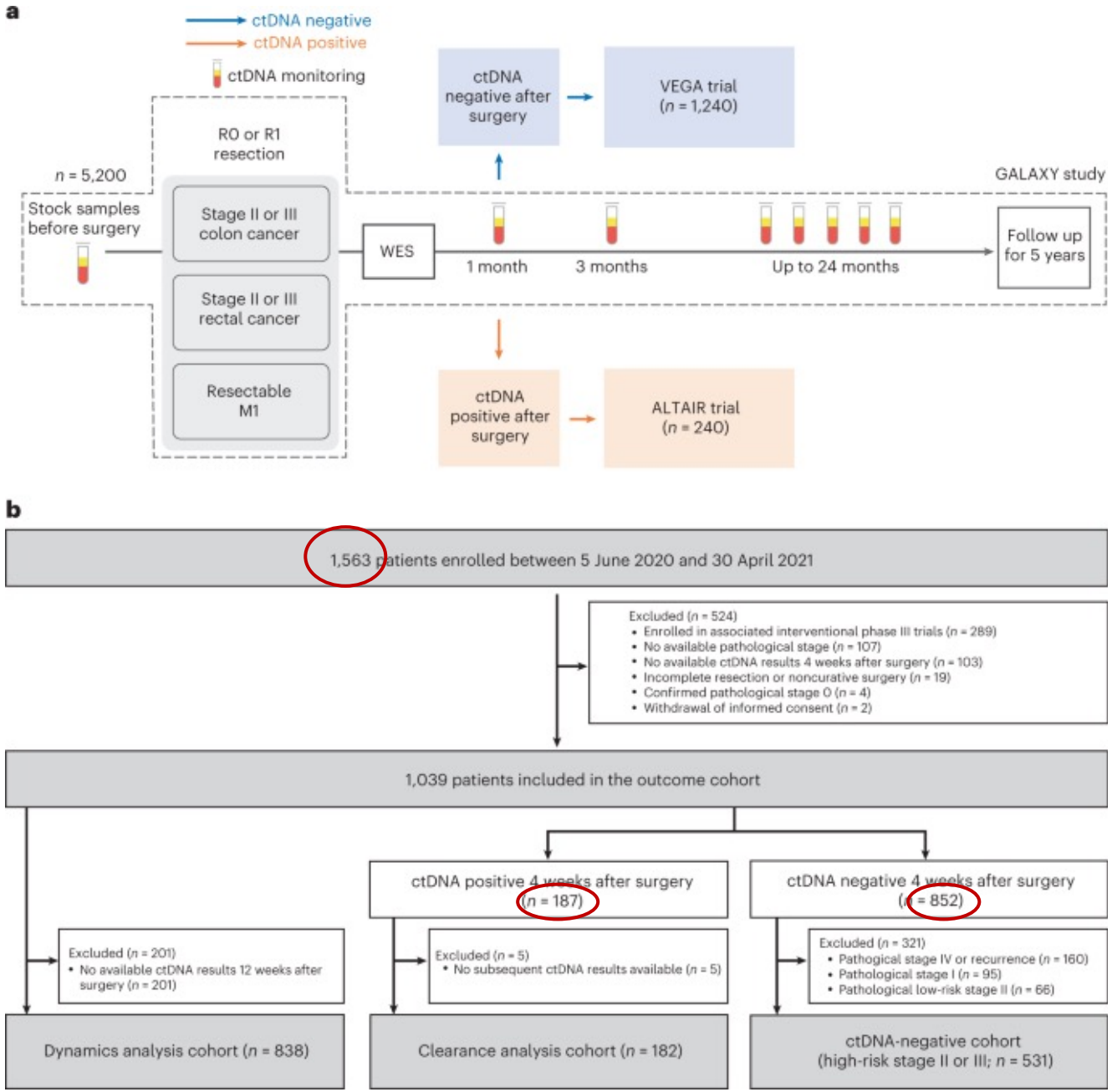
The NEW ENGLAND JOURNAL of MEDICINE

Recurrence-free Survival in the ctDNA-Guided Group According to ctDNA Status.

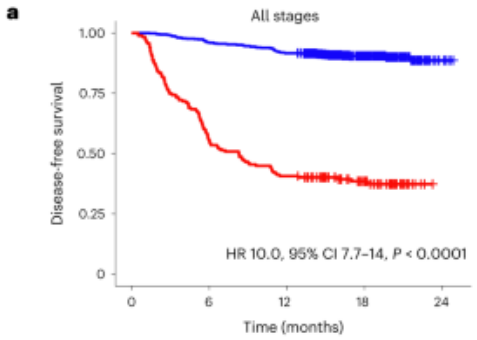


J Tie et al. N Engl J Med 2022;386:2261-2272.

The NEW ENGLAND JOURNAL of MEDICINE



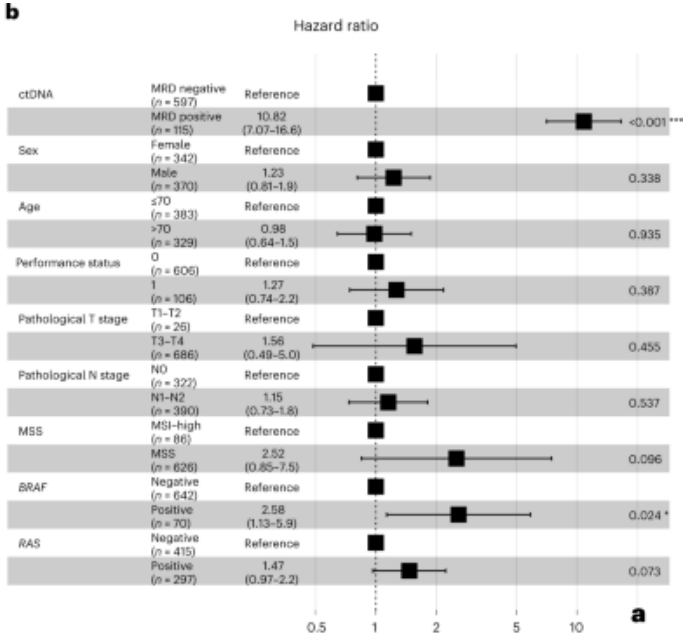
Nature Medicine **volume 29**, pages127–134 (2023)



Number at risk

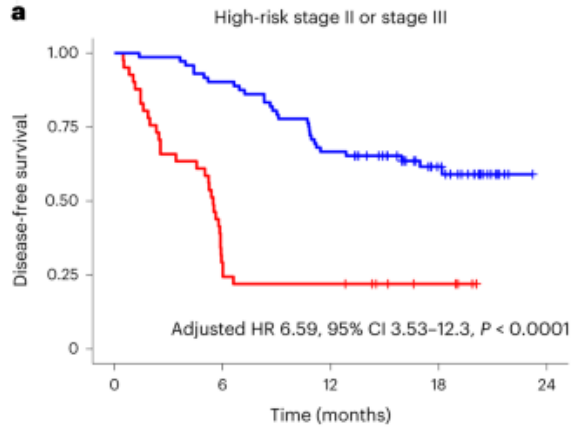
ctDNA negative	852	819	781	347	5
ctDNA positive	187	104	76	37	0

ctDNA	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
ctDNA negative	81 out of 852	96.1% (94.6–97.2)	91.7% (89.6–93.3)	90.5% (88.3–92.3)
ctDNA positive	115 out of 187	55.6% (48.2–62.64)	40.6% (33.6–47.6)	38.4% (31.4–45.5)



c

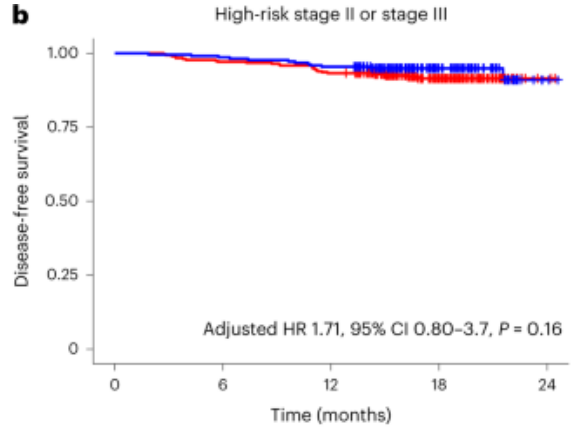
Biomarker Status	ctDNA positive	ctDNA negative
CEA positive	28 (23 relapsed, 82.1%)	67 (8 relapsed, 12%)
CEA negative	83 (58 relapsed, 70%)	626 (46 relapsed, 7.3%)



Number at risk

Observation	41	12	9	4	0
ACT	72	65	48	26	0

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	32 out of 41	29.3% (16.4–43.4)	22.0% (10.9–35.5)	22.0% (10.9–35.5)
ACT	28 out of 72	90.3% (80.7–95.2)	66.7% (54.5–76.3)	61.6% (49.0–71.9)

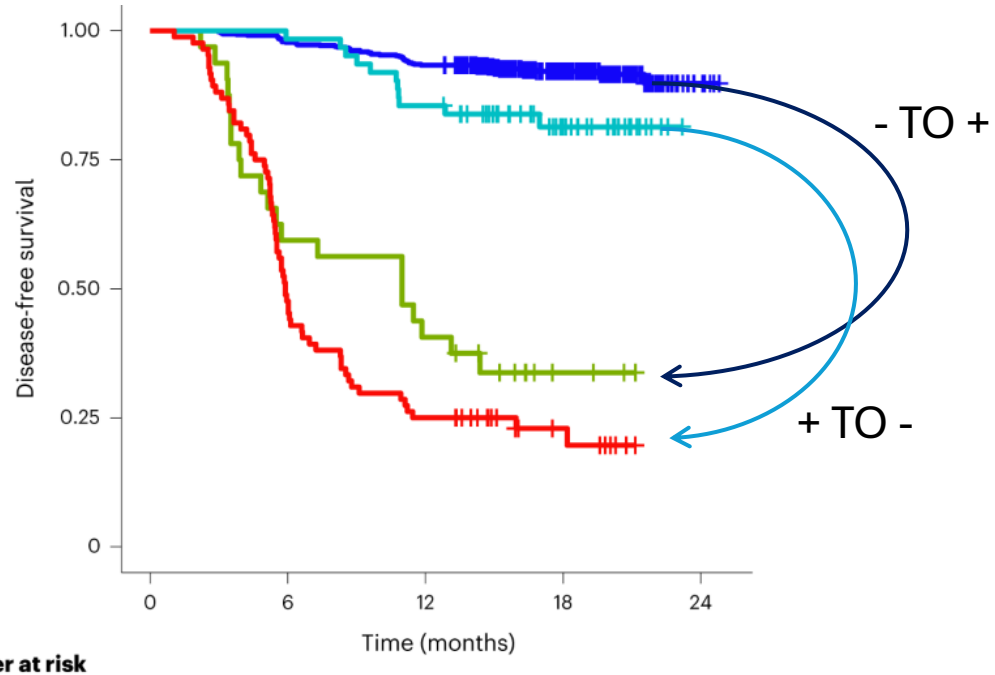


Number at risk

Observation	312	303	291	131	2
ACT	219	216	209	87	2

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	25 out of 312	97.1% (94.5–98.5)	93.3% (89.9–95.6)	91.5% (87.6–94.2)
ACT	12 out of 219	98.6% (95.8–99.6)	95.4% (91.7–97.5)	94.9% (91.0–97.2)

Nature Medicine **volume 29**, pages127–134 (2023)



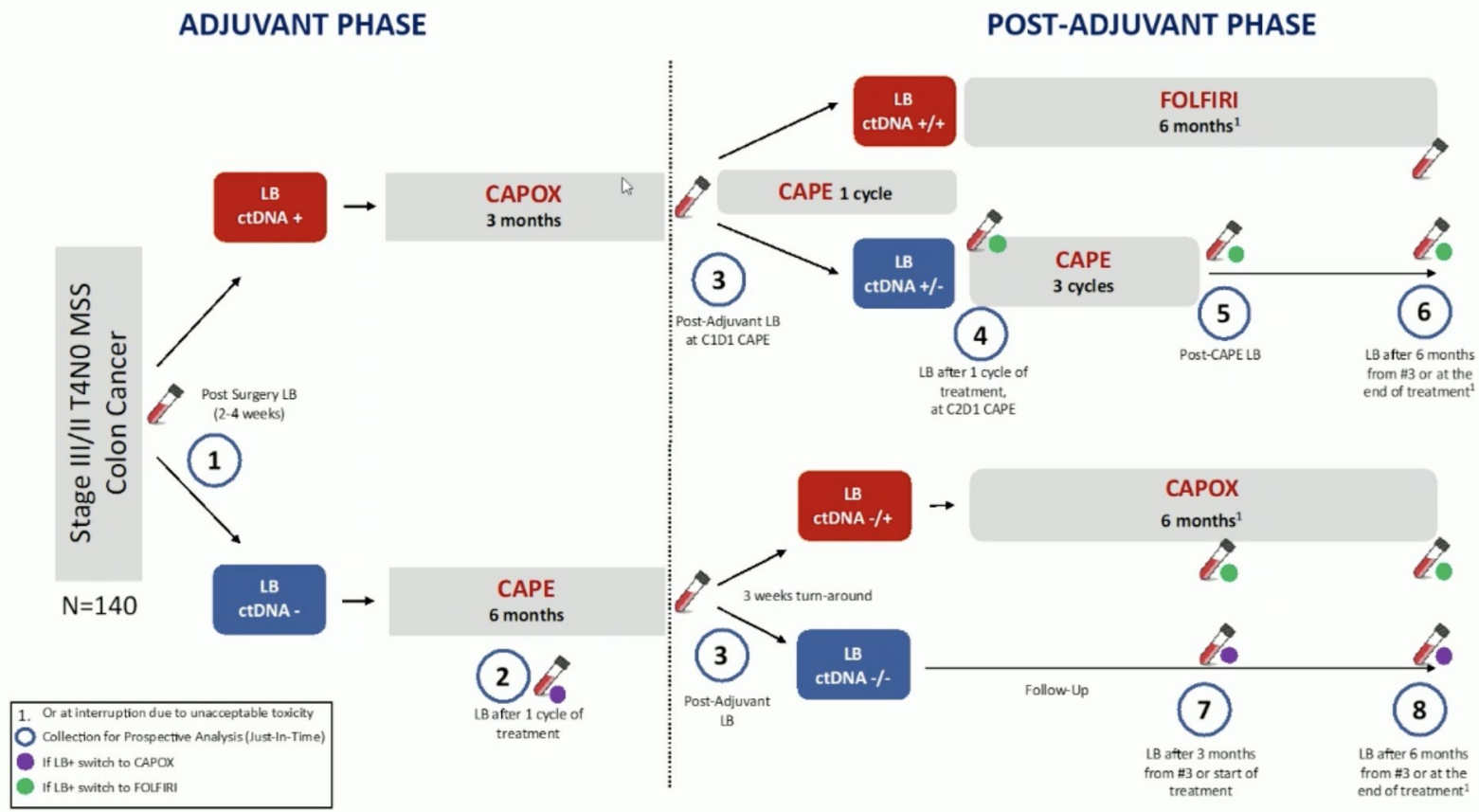
Number at risk					
Persistently negative	660	645	616	271	5
Converted positive	32	19	13	3	0
Converted negative	62	61	53	28	0
Persistently positive	84	40	21	7	0

Dynamics	Persistently negative	Converted positive	Converted negative	Persistently positive
Number of events	52 out of 660	21 out of 32	11 out of 62	65 out of 84
18M-DFS	92.1% (91.1–95.0)	33.8% (18.1–50.2)	81.4% (68.6–89.3)	22.9% (14.3–32.7)
HR	Reference	14.0	2.3	21.0
95% CI	Not applicable	8.5–24.0	1.2–4.4	14.0–31.0
P	Not applicable	<0.001	0.012	<0.001

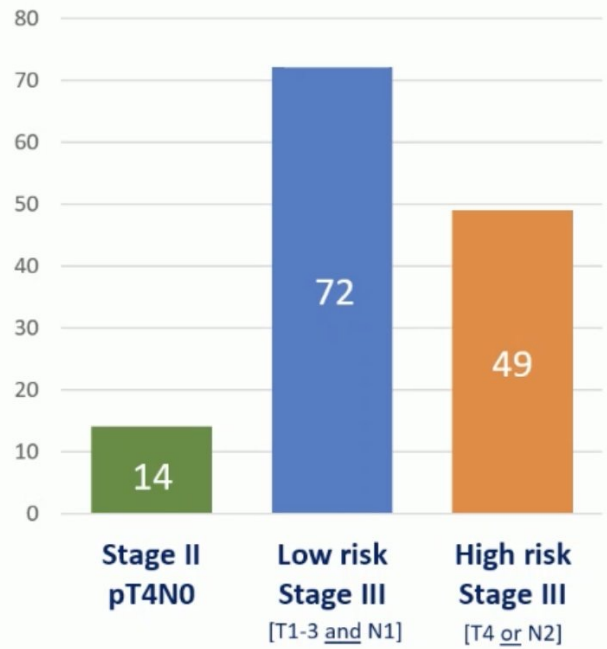
PEGASUS

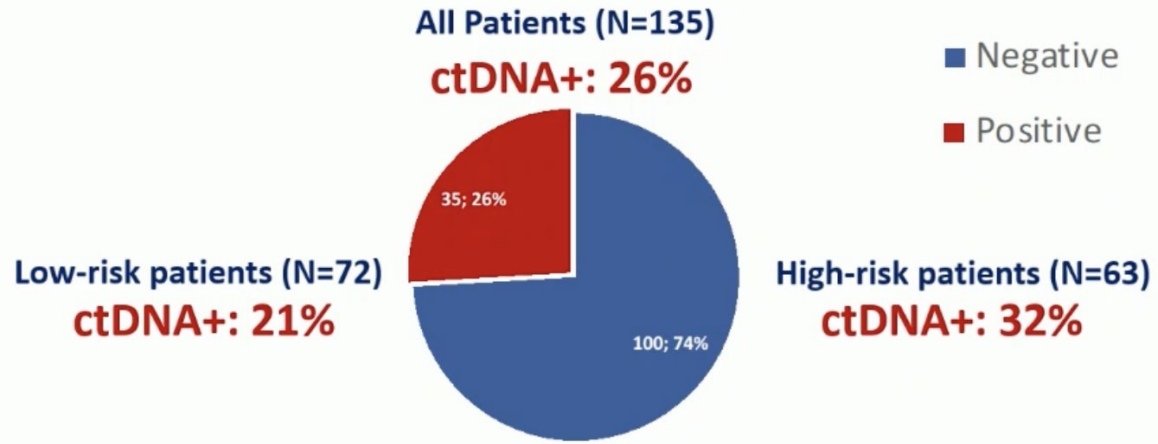
- Post-surgical liquid biopsy-guided treatment of stage III and high-risk stage II colon cancer patients #ESMO23
- ✅PEGASUS phs-II, 135 pts
- 👉Post-OP ctDNA: 35/135 pts (26)
- 👉ctDNA+ w/ increased risk of relapse, HR 4.37
- 👉Seroconversion in 40% of LB+
- 👉Promising benefit for LB guided treatment

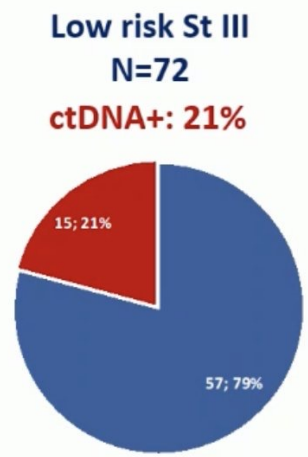
Study Design

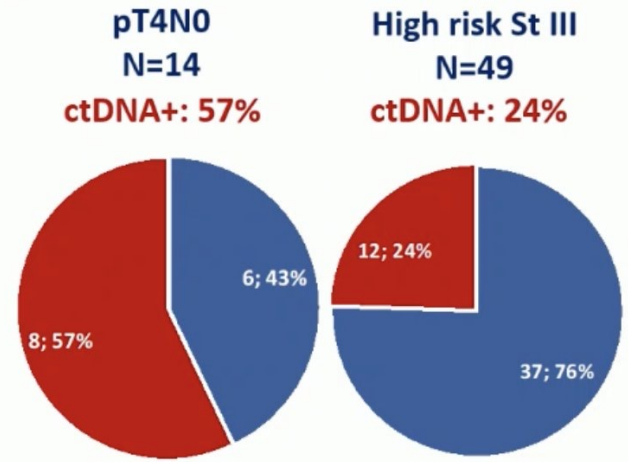


Stage and MRD detection rate









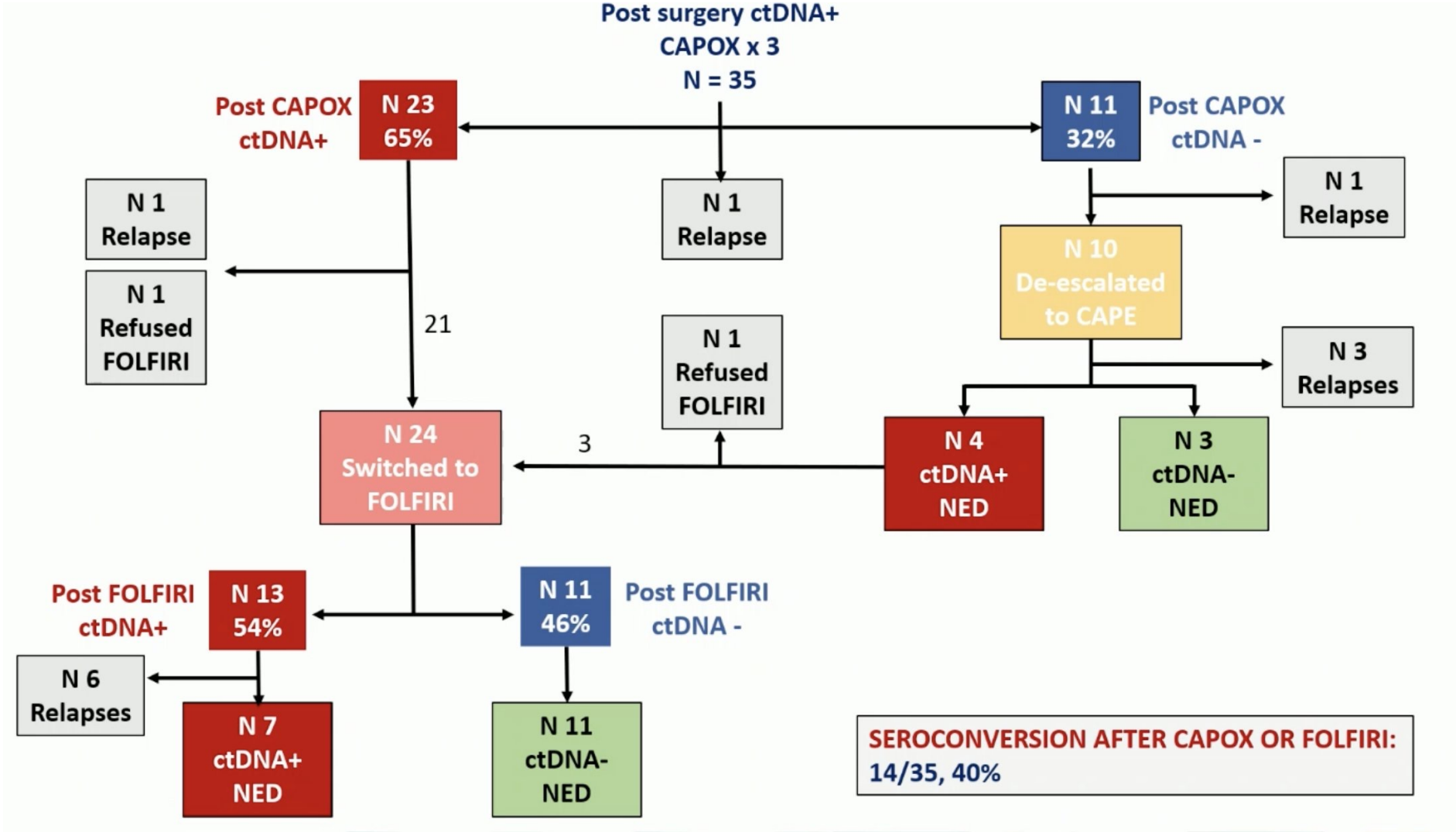
Univariate and multivariate analysis of Time To Relapse

Univariate Analysis

	DF	P value	Contrast	P value	Hazard Ratio	95%CI range
Clinical risk class	2	0.4631	Risk Class Stage III HR vs. Stage II HR	0.4262	1.85	0.41 – 8.49
			Risk Class Stage III LR vs. Stage II HR	0.8911	1.11	0.24 – 5.08
ctDNA status	1	**0.0016**	ctDNA Status ctDNA pos vs. ctDNA neg	**0.0016**	3.86	1.67 – 8.94

Multivariate Analysis

	DF	P value	Contrast	P value	Hazard Ratio	95%CI range
Clinical risk class	2	0.2189	Risk Class Stage III HR vs. Stage II HR	0.1141	3.51	0.74 – 16.62
			Risk Class Stage III LR vs. Stage II HR	0.3539	2.08	0.44 – 9.82
ctDNA status	1	**0.0005**	ctDNA Status ctDNA pos vs. ctDNA neg	**0.0005**	4.58	1.94 – 10.82


Post surgery ctDNA+
CAPOX x 3
N = 35
Post CAPOX ctDNA+
N 23 65%
N 11 32%
Post CAPOX ctDNA -
N 1 Relapse
N 1 Relapse
N 1 Relapse
N 1 Refused FOLFIRI
21
N 10 De-escalated to CAPE
N 1 Refused FOLFIRI
N 3 Relapses
N 24 Switched to FOLFIRI
3
N 4 ctDNA+ NED
N 3 ctDNA- NED
Post FOLFIRI ctDNA+
N 13 54%
N 11 46%
Post FOLFIRI ctDNA -
N 6 Relapses
N 7 ctDNA+ NED
N 11 ctDNA- NED
SEROCONVERSION AFTER CAPOX OR FOLFIRI: 14/35, 40%

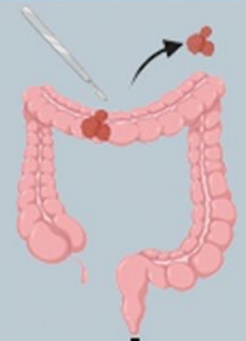
NCT 04068103

RECRUITING

Circulating Tumor DNA Testing in Predicting Treatment for Patients With Stage IIA Colon Cancer After Surgery

Principal Investigator: Van K. Morris, MD – NRG Oncology

Phase II/III



Resected Low-Risk Stage IIA Colon Adenocarcinoma Suitable for Surveillance

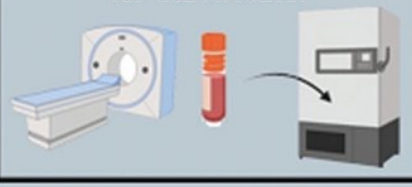
1,408 Adults

Liquid Biopsy

ARM 1

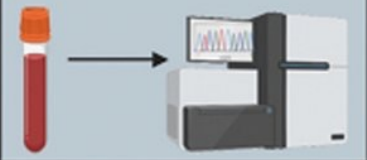
Active surveillance

Blood stored and tested for ctDNA later



ARM 2

Blood tested for ctDNA at baseline



ctDNA detected

ctDNA not detected

Group 1

Combination chemotherapy

Group 2

Active surveillance

OUTCOMES

PRIMARY

Clearance of ctDNA in ctDNA positive patients in Arms 1and 2 after 6 months (Phase II)

Recurrence-free survival in ctDNA positive patients in Arms 1and 2 for up to 3 years (Phase III)

SECONDARY

Recurrence-free survival for all included in study

Overall survival

Compliance with chemotherapy and/or active surveillance

Incidence of ctDNA in blood after resection

Morris et al. *Ann Surg Oncol.*
Ongoing Clinical Trials in Surgical Oncology Series

ANNALS OF SURGICAL ONCOLOGY

NO

- Prognostic but not Predictive
- Numbers are extremely low
- Not ready for prime time