Impact of ctDNA testing on survival: Can MRD testing make a difference for metastatic CRC?

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MRD testing to guide patient management

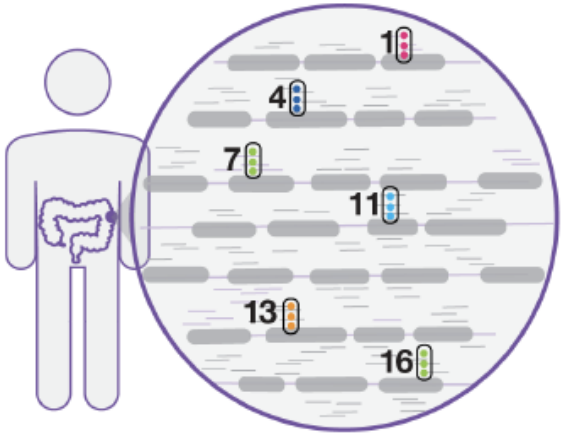
- MRD testing is a validated prognostic tool
- Tumor informed assays have the potential to change how we approach adjuvant chemotherapy decisions
- Prospective trials are ongoing to validate the clinical utility of escalation/ de-escalation strategies based on MRD test results

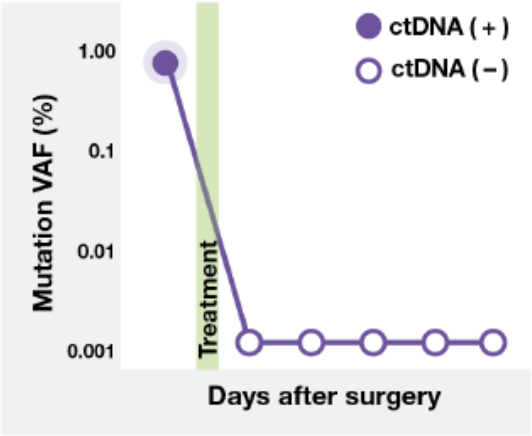
“Tumor informed” mutation detection

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

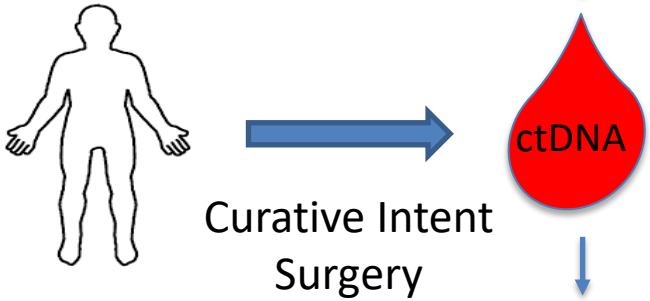
Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)



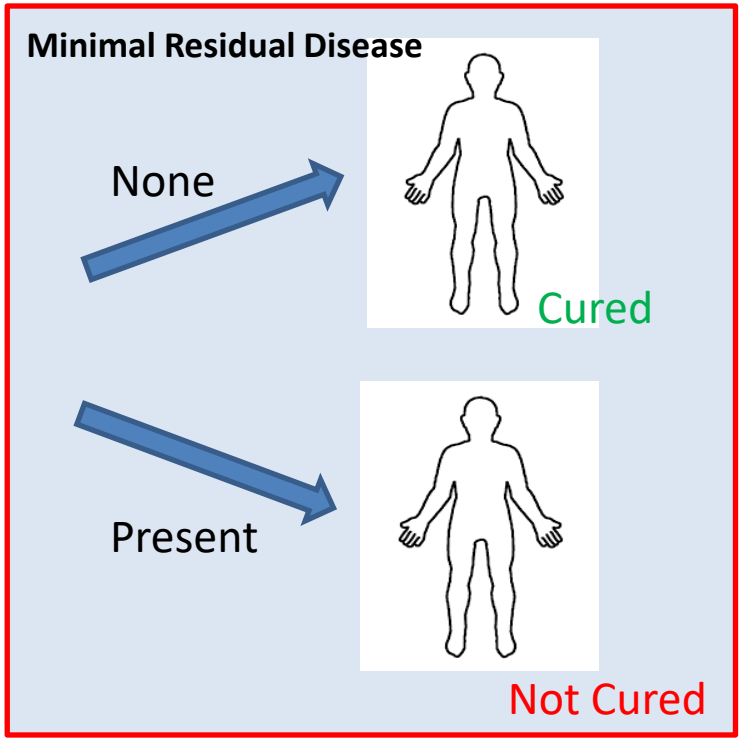


Can ctDNA identify who will recur after surgery?

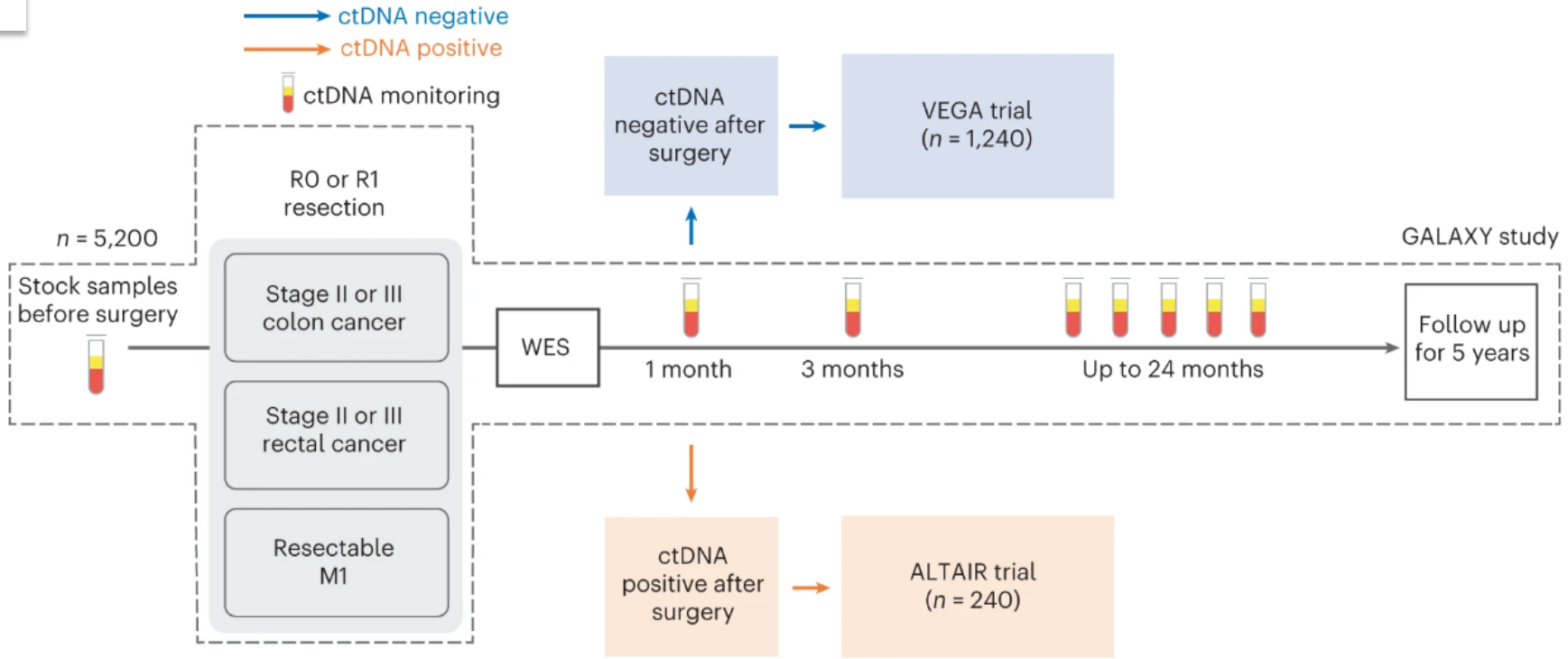
Stage III CRC:
All patients get adjuvant chemo
>50% cured by surgery alone



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

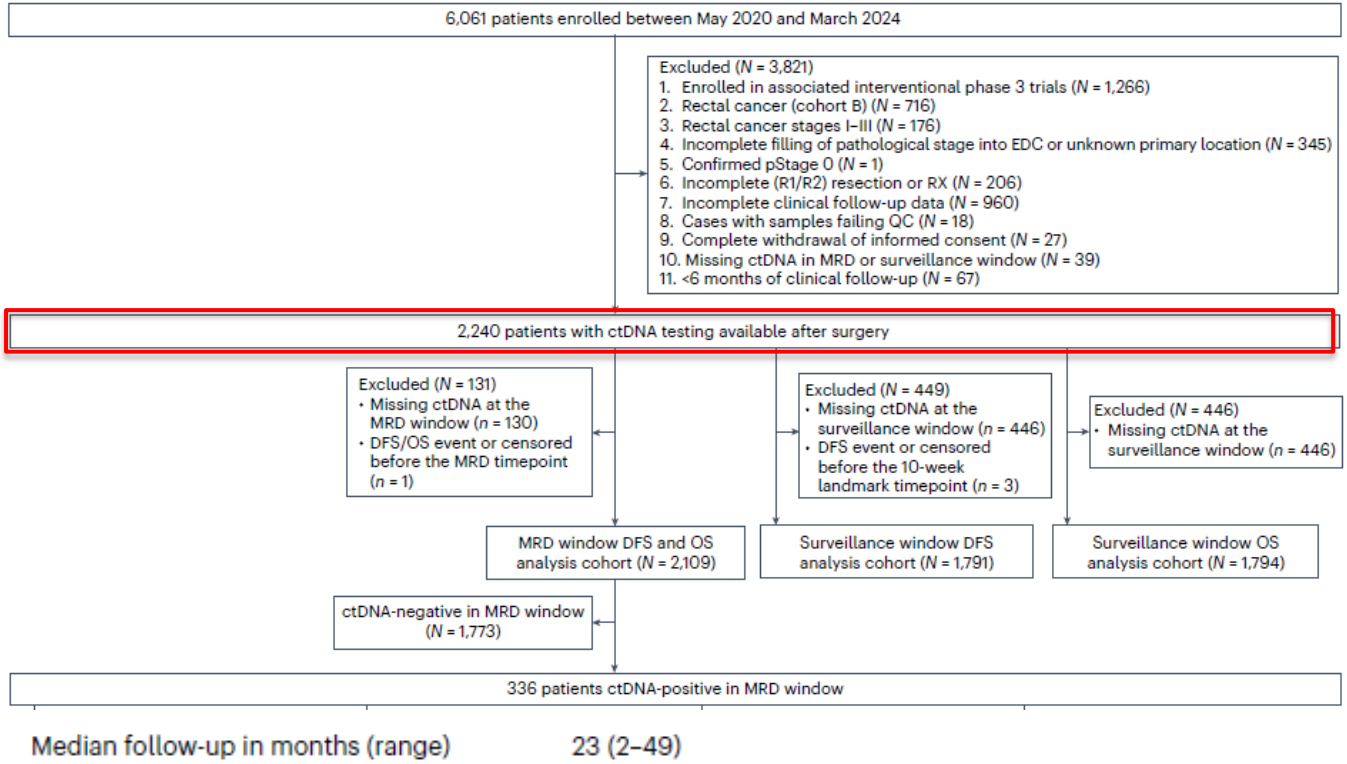


Clinical validation of tumor informed MRD testing: GALAXY Study Design



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

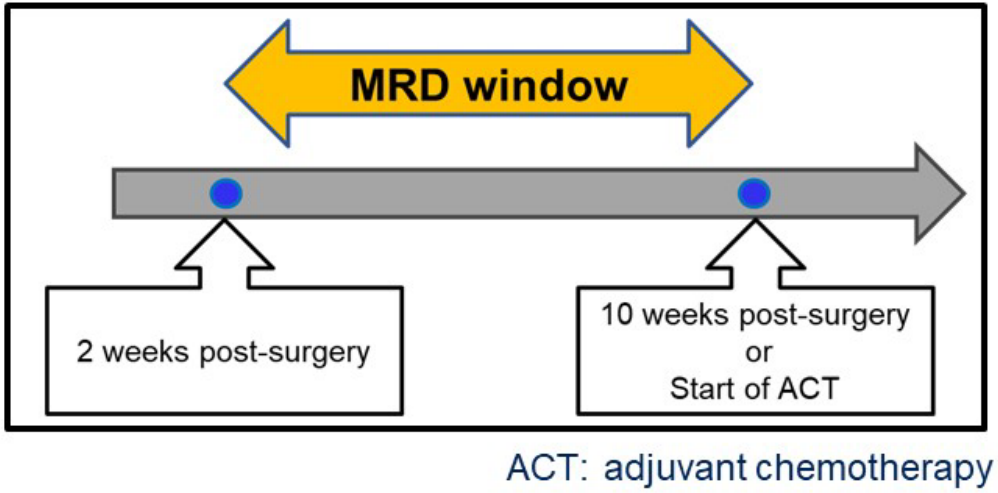
GALAXY: Patient characteristics



Characteristic	No. of patients (%)
Median age in years (range)	69 (28–95)
Sex	
Male	1,149 (51%)
Female	1,091 (49%)
Pathological stage	
I	234 (10%)
II	652 (29%)
III	936 (42%)
IV	418 (19%)
Neoadjuvant treatment	
Neoadjuvant chemotherapy	218 (10%)
None (upfront surgery)	2,022 (90%)
Adjuvant treatment	
Adjuvant chemotherapy	946 (42%)
Observation	1,294 (58%)
BRAF mutation status	
BRAF WT	2,062 (92%)
BRAF V600E	178 (8%)
RAS mutation status	
RAS WT	1,303 (58%)
RAS mut	937 (42%)
MSI status	
MSS or MSI low	2,025 (90)
MSI high	215 (10%)
Radiological recurrence	
Yes	500 (22%)
No	1,740 (78%)

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

GALAXY: MRD Window

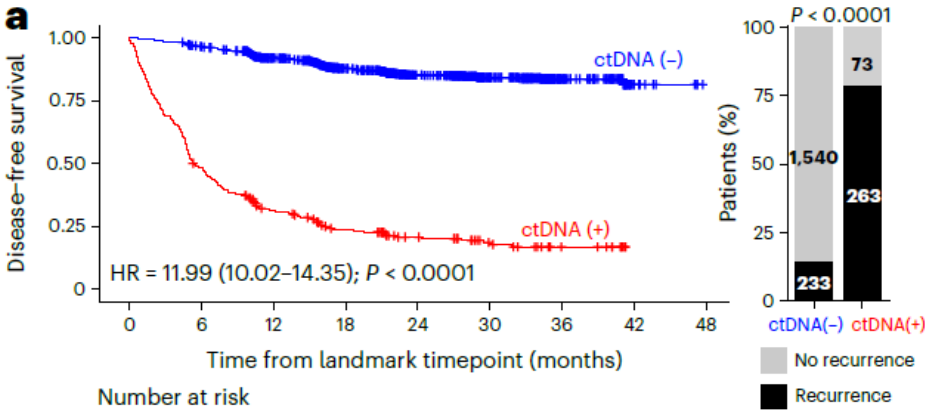


MRD window: 2-10 weeks post surgery, prior to start of any adjuvant therapy - Landmark 10 weeks post-surgery

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

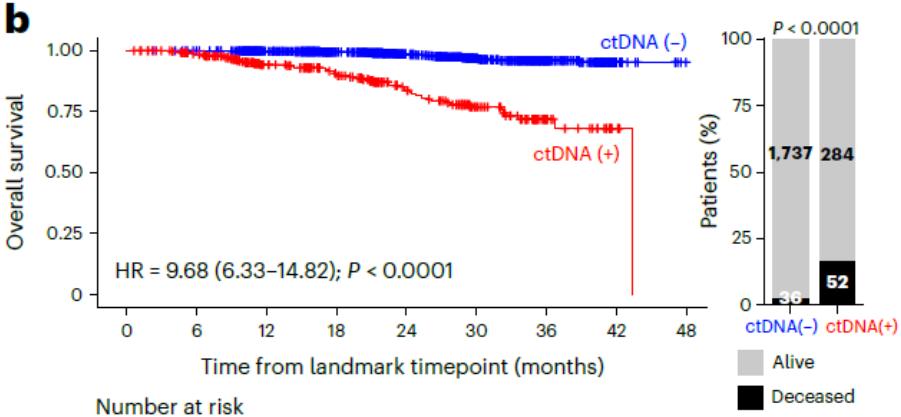


Number at risk

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



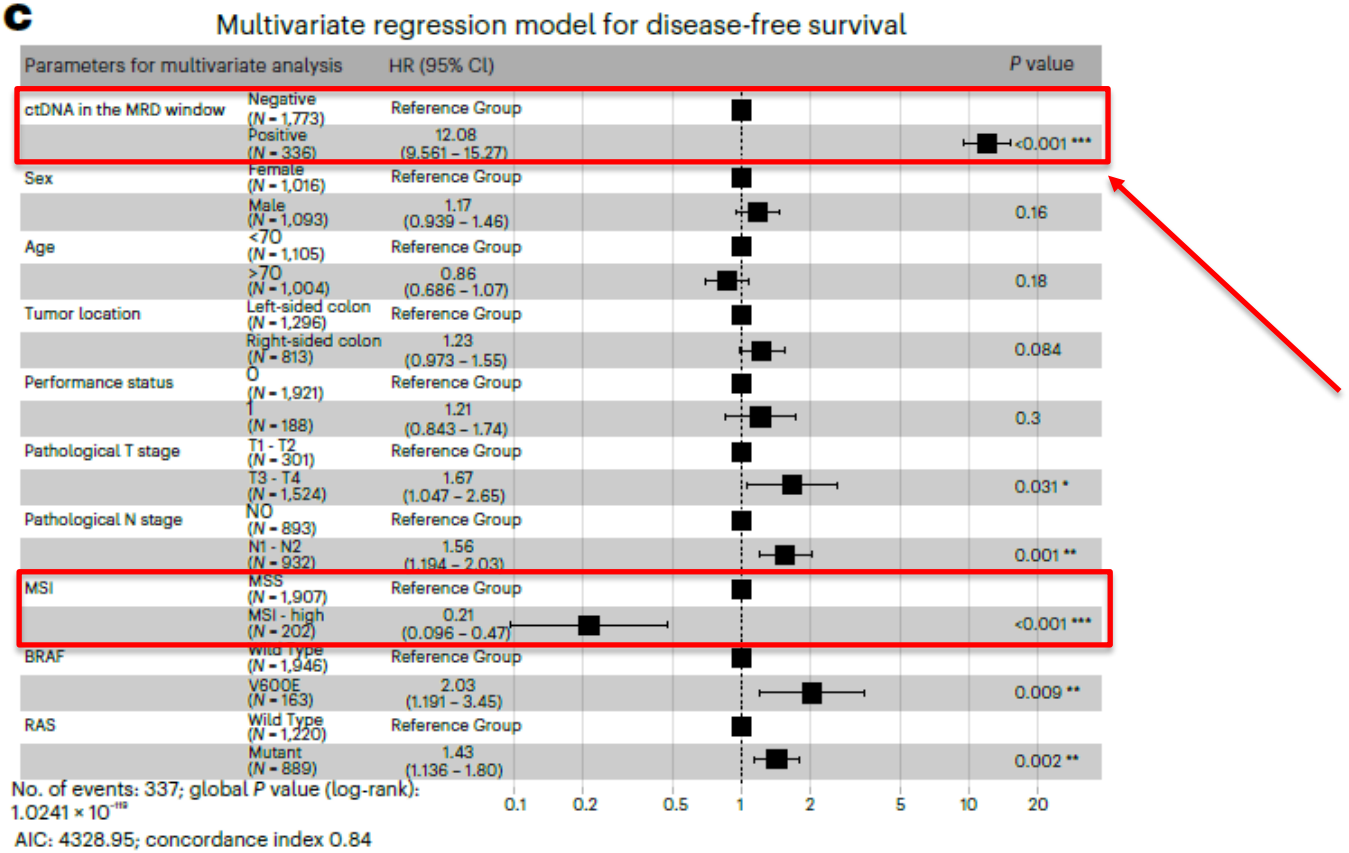
Number at risk

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)

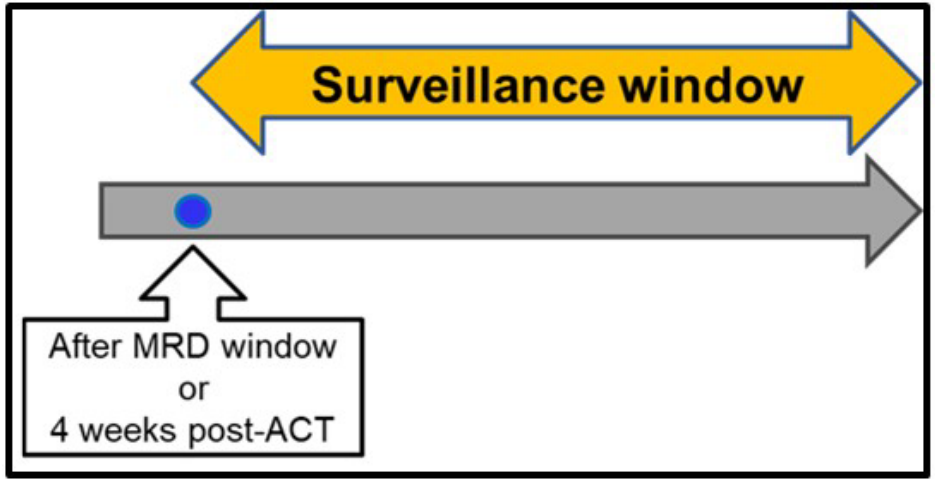
Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

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

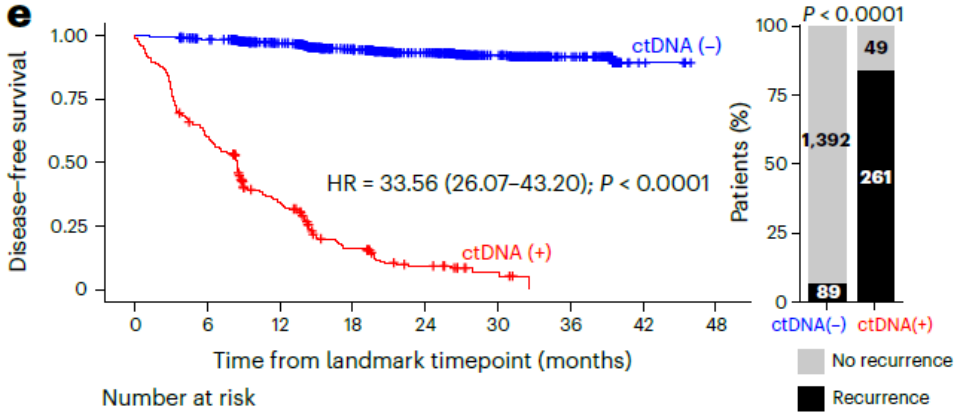


- *Surveillance window starts from 4 weeks post-ACT or at the end of MRD window if patient had no ACT, until the last follow up or relapse.*
- *Landmark 8 months post-surgery (2 months for ACT initiation + 6 months of ACT duration)*

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

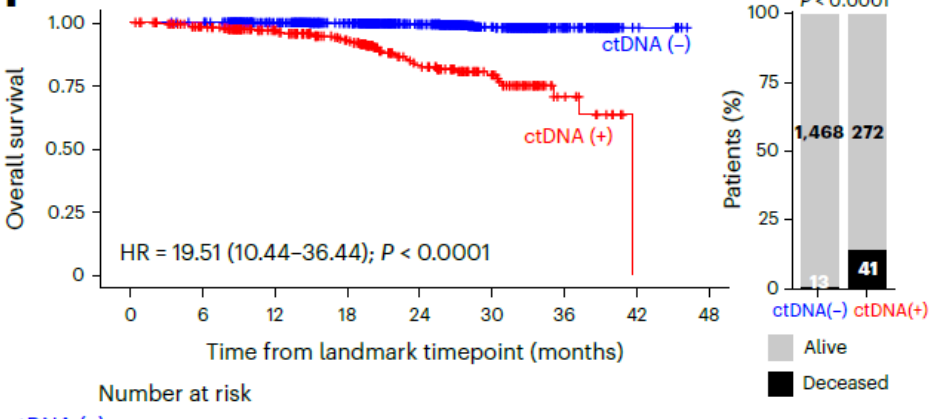


Number at risk

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

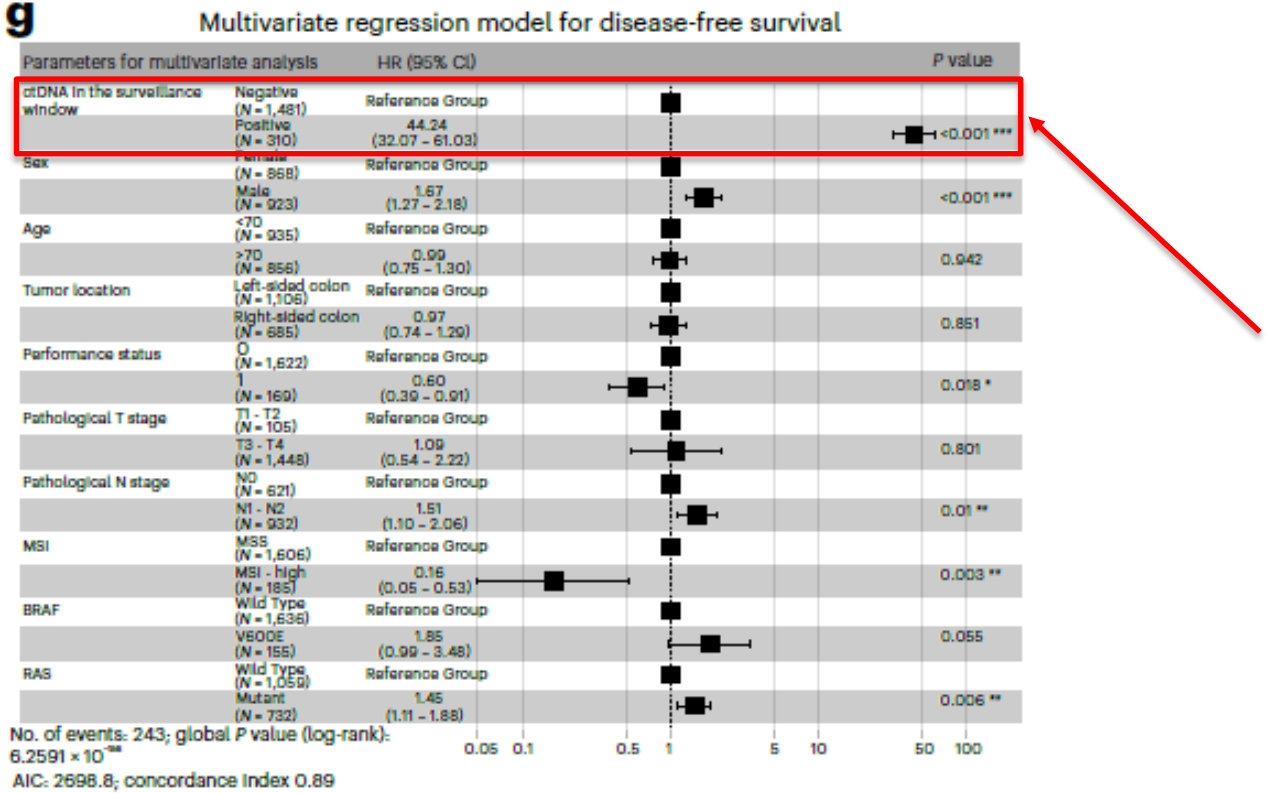
ctDNA (–)	1,481	1,478	1,275	1,063	686	384	123	6	0
ctDNA (+)	313	287	222	175	102	60	14	0	0

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)

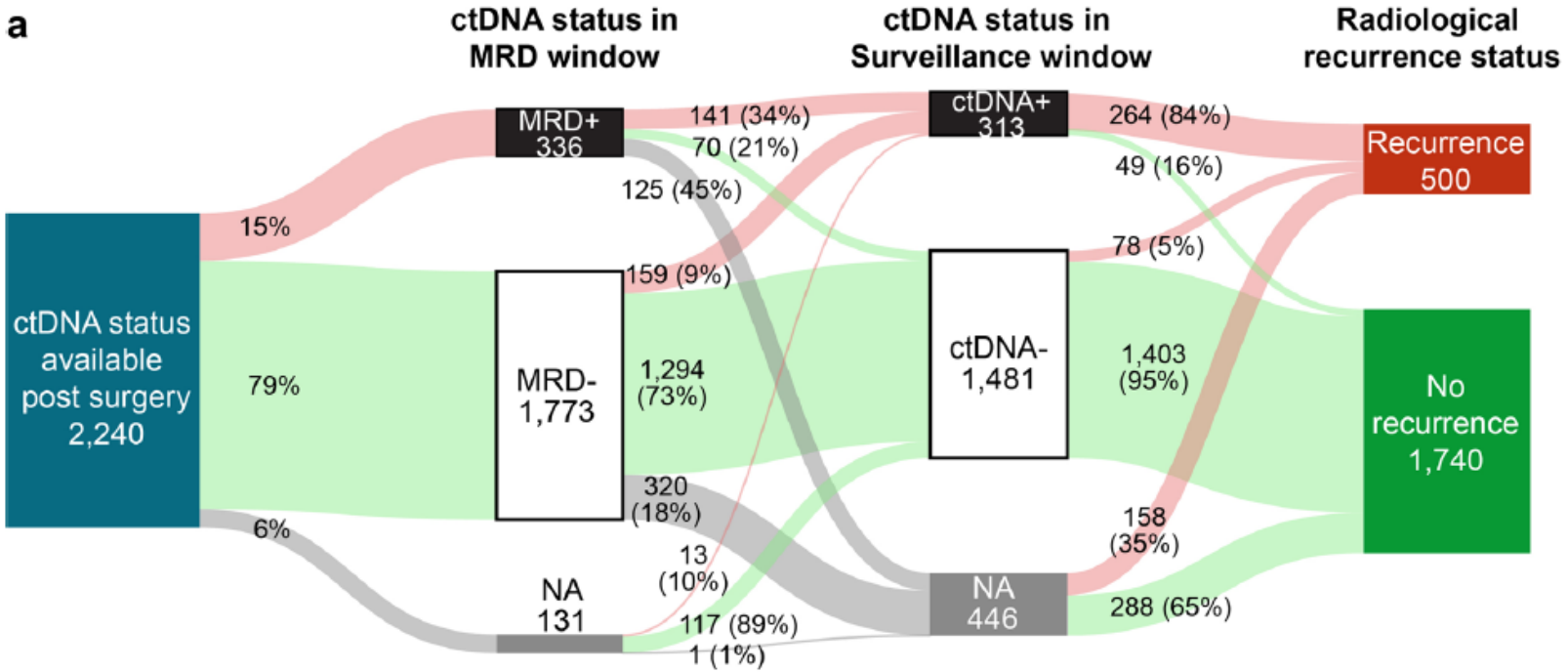
Nakamura et. al., Nature Medicine 2024 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

MRD status in the surveillance window is the strongest predictor of prognosis



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

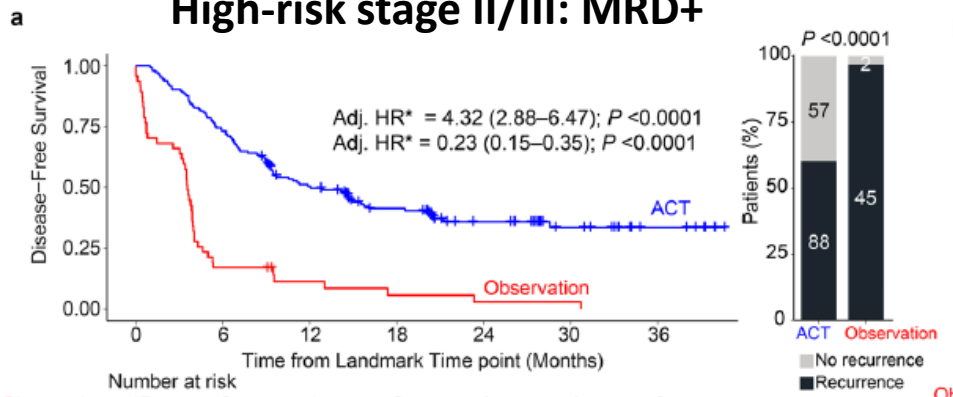
Diagram of ctDNA status in MRD and surveillance windows



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

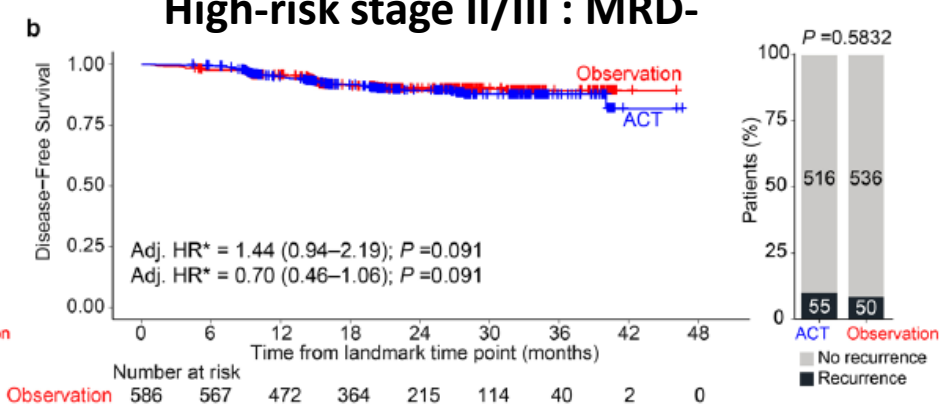
Adjuvant chemotherapy for high-risk stage II/III disease: MRD status impacts benefit

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-

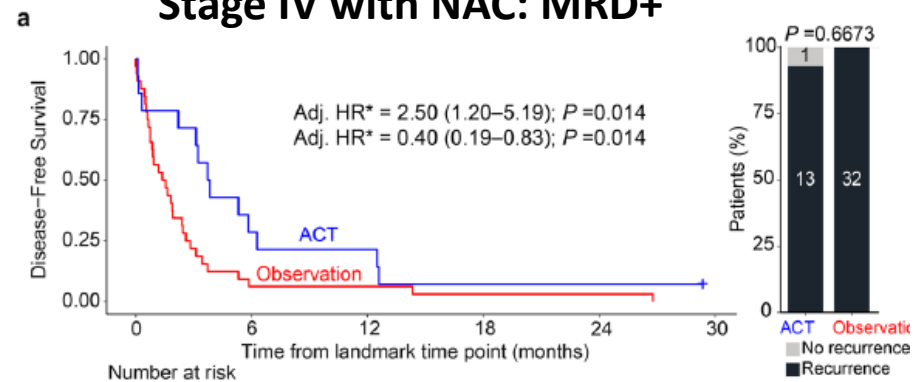


Treatment	ACT	Observation
Events %	9.63 (55/571)	8.53 (50/586)
24M-DFS % (95% CI)	89.11 (85.81–91.68)	89.9 (86.80–92.30)
mDFS (mo)	NR	NR

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

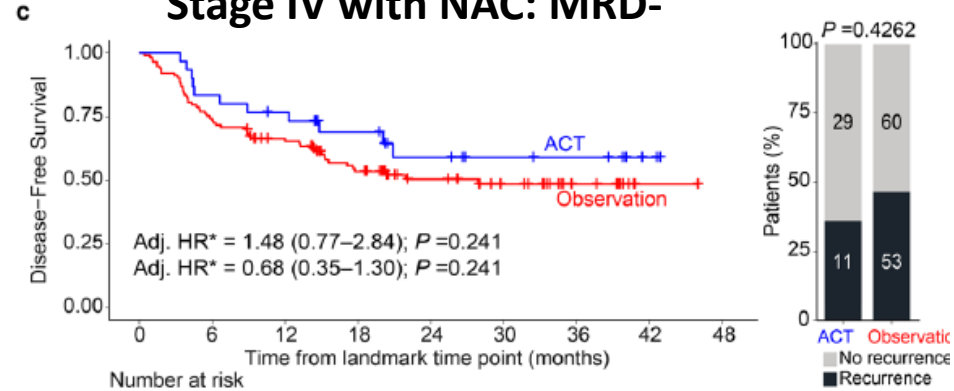
Adjuvant chemotherapy for stage IV: MRD status impacts benefit (all received neoadjuvant chemotherapy)

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-

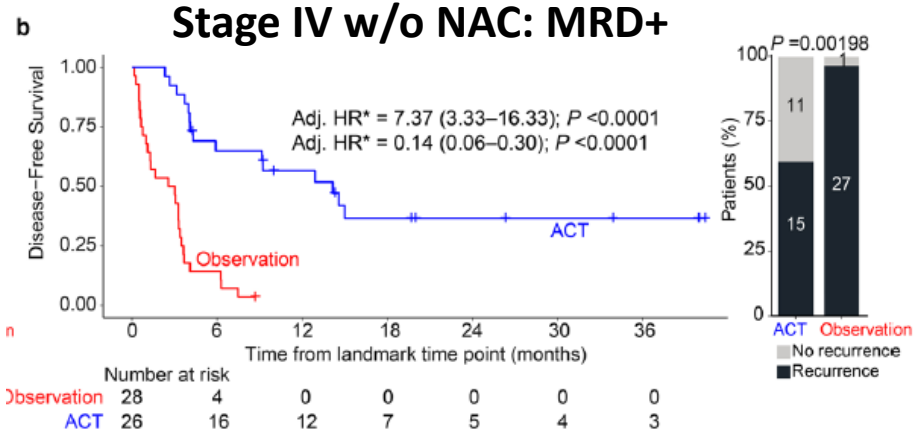


ctDNA status	ACT	Observation
Events %	36.67 (11/30)	46.90 (53/113)
24M-DFS % (95% CI)	58.90 (37.30–75.30)	50.40 (40.0–59.80)
36M-DFS % (95% CI)	58.90 (37.30–75.30)	48.40 (37.90–58.20)
mDFS (mo)	NR (20.10–NR)	27.90 (15.30–NR)

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

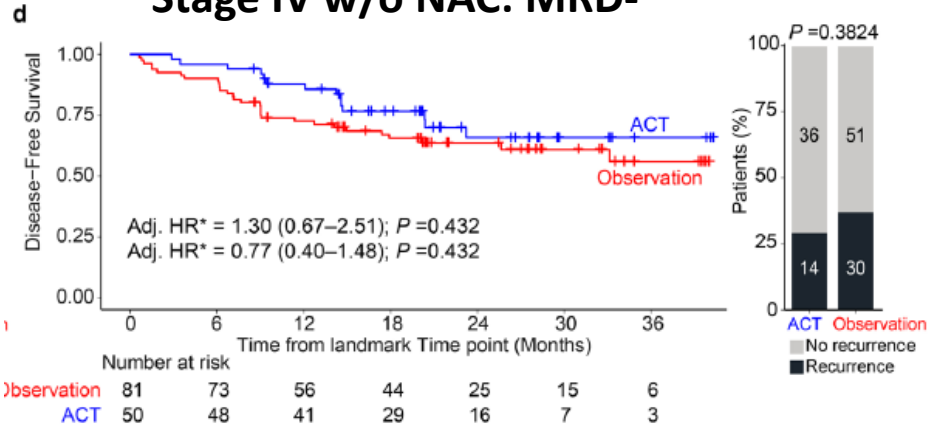
Adjuvant chemotherapy for stage IV: MRD status impacts benefit (NO neoadjuvant chemotherapy)

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)

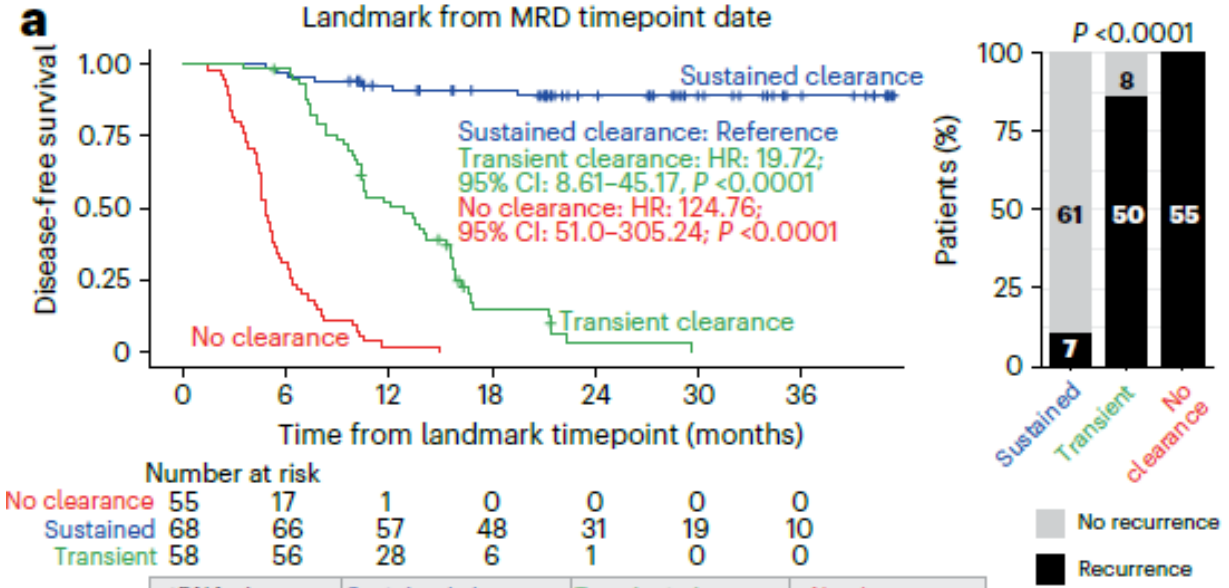
Stage IV w/o NAC: MRD-



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

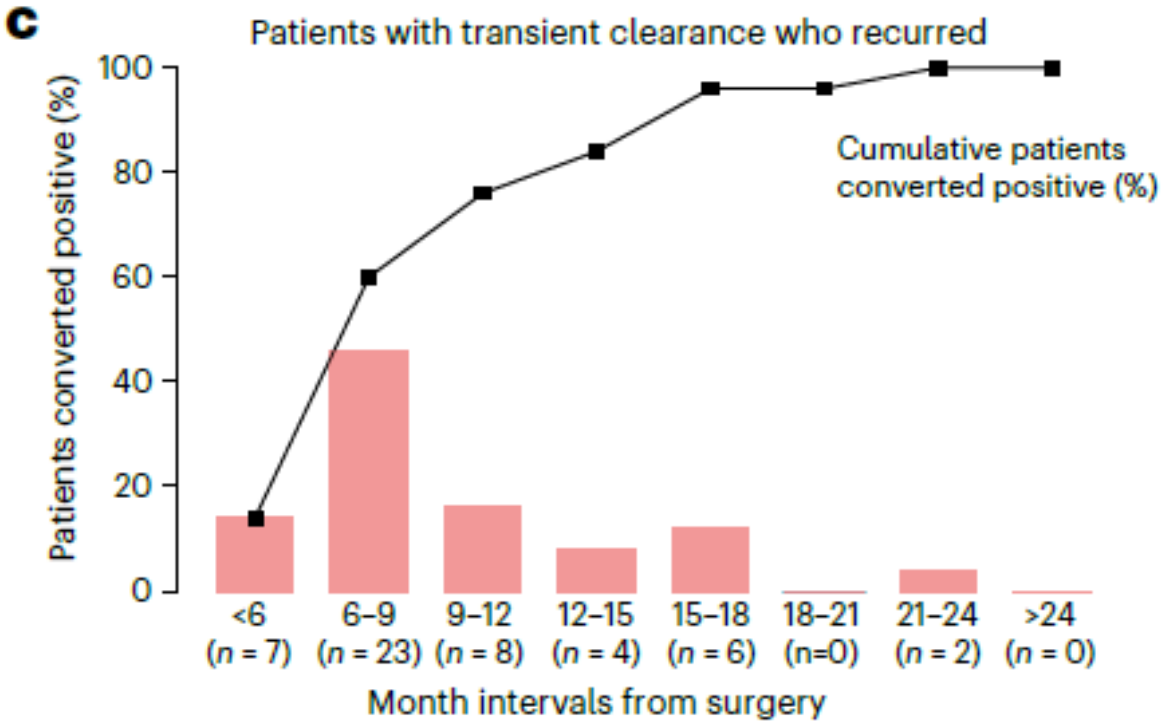
Sustained ctDNA clearance associated with superior DFS



ctDNA clearance	Sustained clearance	Transient clearance	No clearance
Events %	10.29 (7/68)	86.21 (50/58)	100 (55/55)
24M-DFS % (95% CI)	89.0 (78.30–94.60)	3.33 (0.29–13.70)	NR
mDFS (mo)	NR	12.88 (10.38–15.64)	4.83 (4.53–5.45)

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

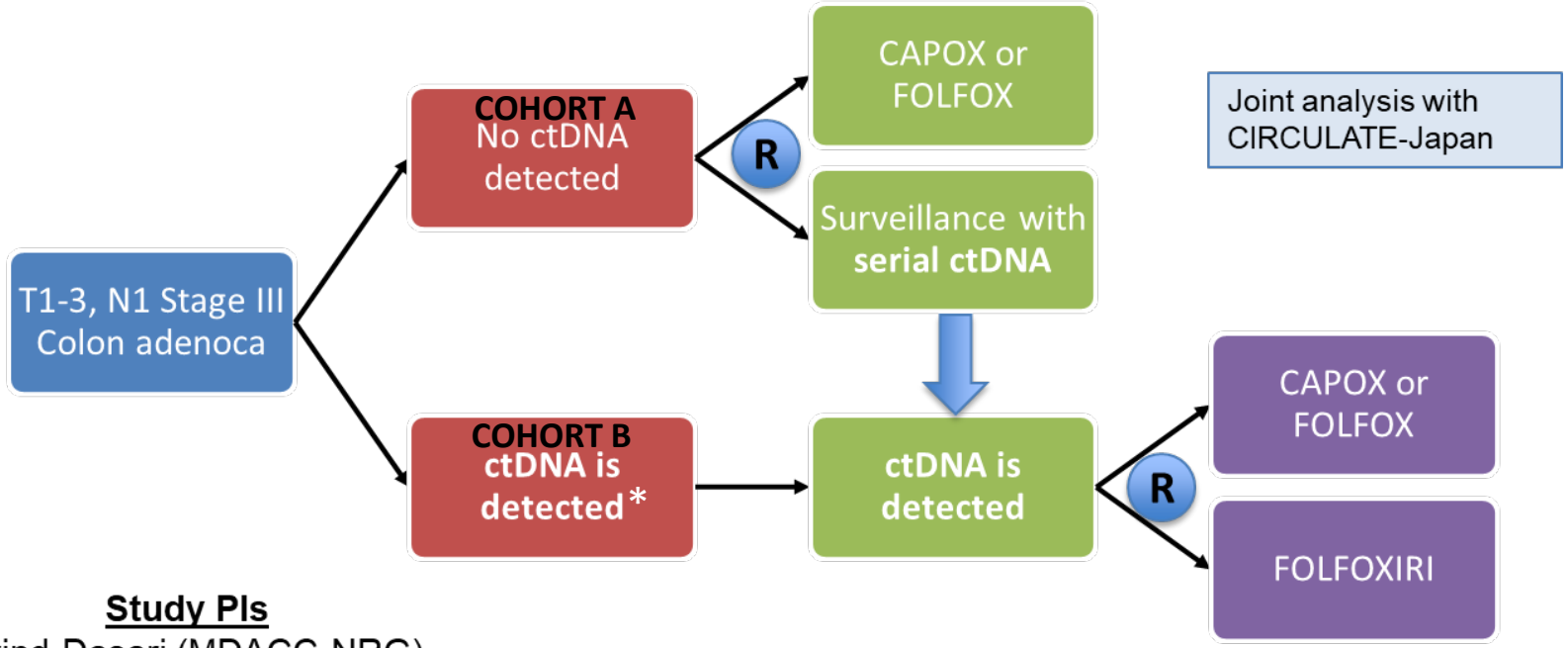
ctDNA dynamics of transient clearance with recurrence



- 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 Online ahead of print https://doi.org/10.1038/s41591-024-03254-6

CIRCULATE-US (NRG-GI008)



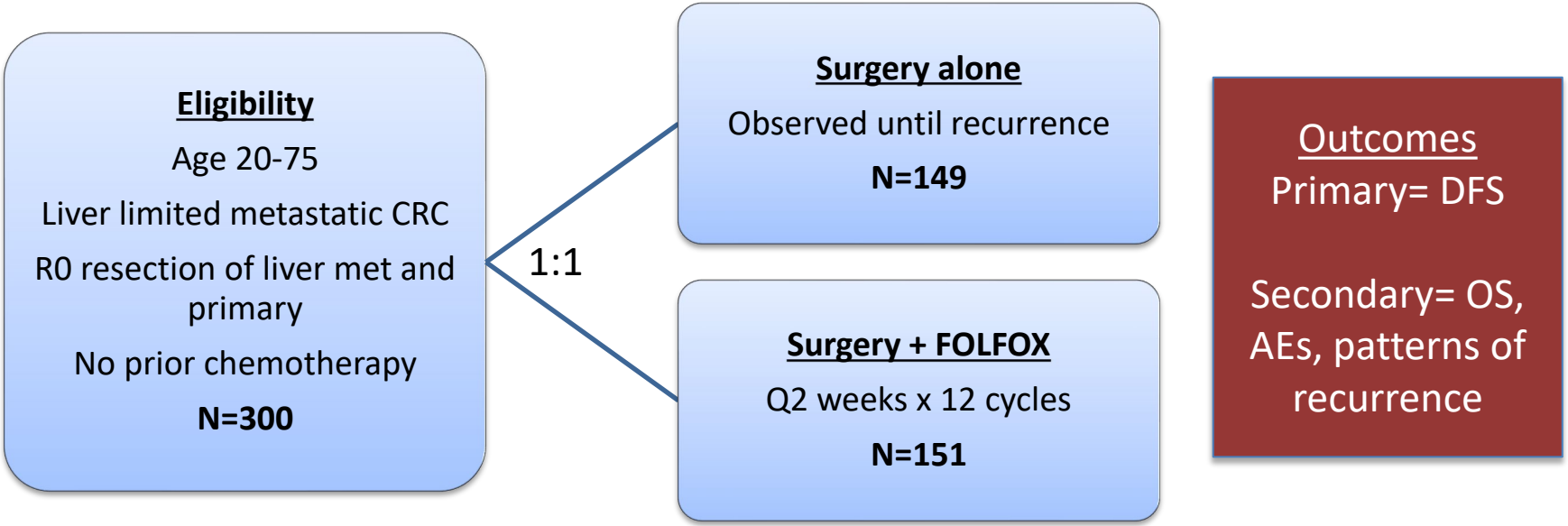
Study PIs

Arvind Dasari (MDACC-NRG)

Christopher Lieu (UCCC-SWOG)

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

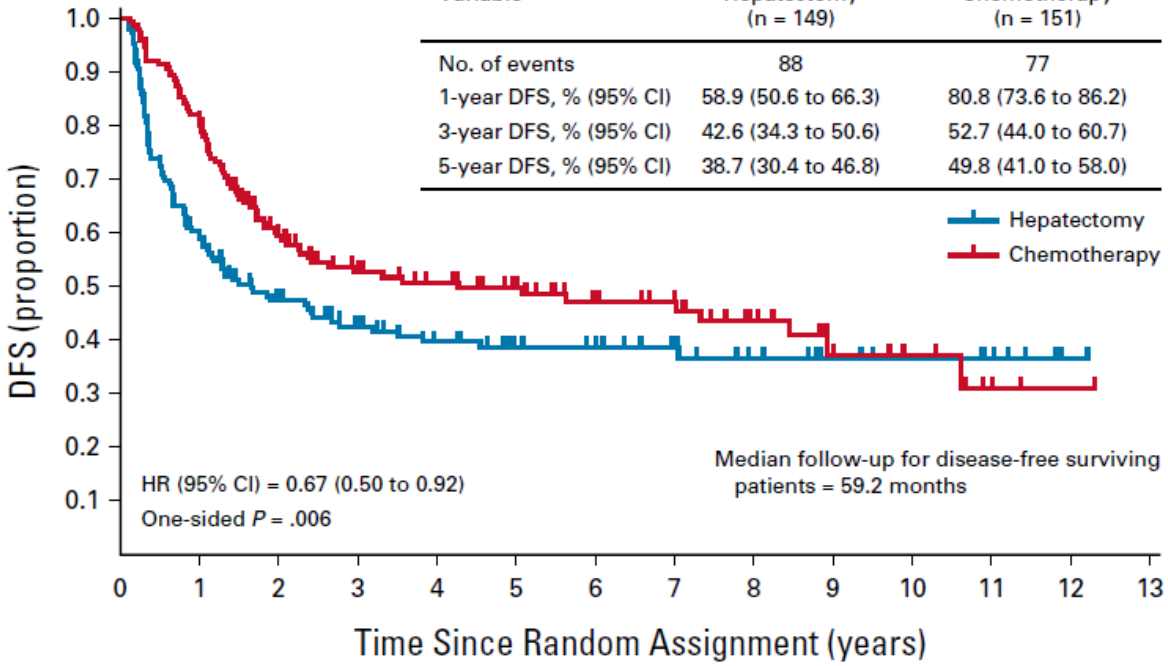
JCOG0603: Does adjuvant chemotherapy after CRC liver metastasis resection improve survival?



Kanemitsu et. al., J Clin Oncol 2021 39:3789-3799

JCOG0603: DFS superior for adjuvant chemotherapy

Variable	Hepatectomy (n = 149)	Chemotherapy (n = 151)
No. of events	88	77
1-year DFS, % (95% CI)	58.9 (50.6 to 66.3)	80.8 (73.6 to 86.2)
3-year DFS, % (95% CI)	42.6 (34.3 to 50.6)	52.7 (44.0 to 60.7)
5-year DFS, % (95% CI)	38.7 (30.4 to 46.8)	49.8 (41.0 to 58.0)

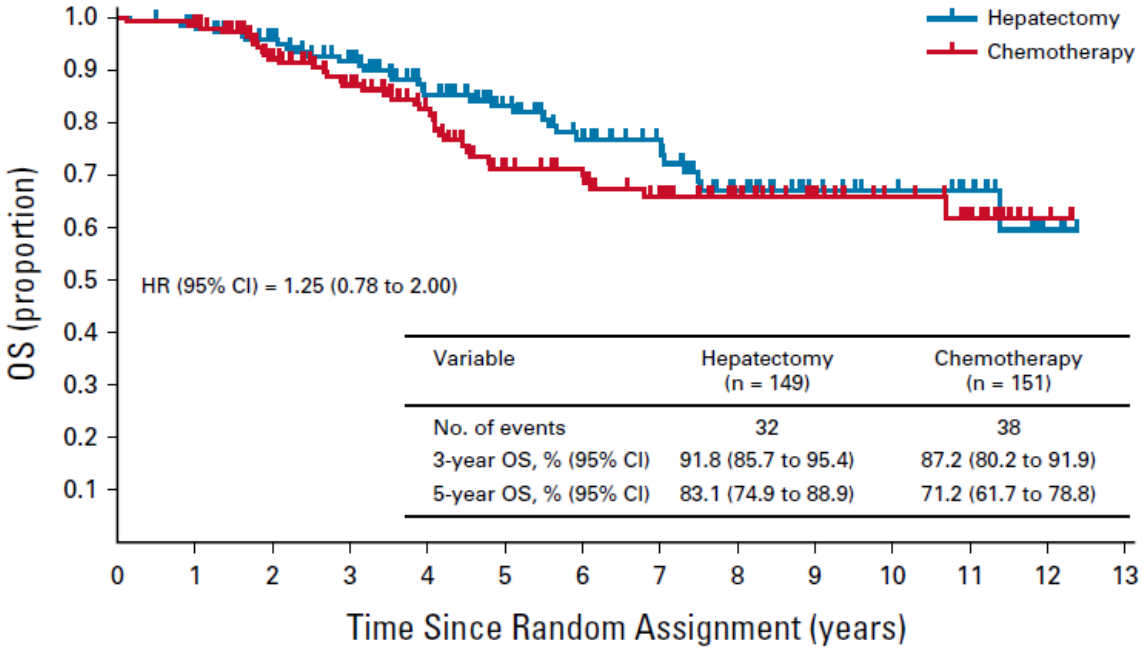


No. at risk:

Hepatectomy (censored)	149(0)	86(2)	61(9)	49(6)	39(7)	30(8)	28(2)	21(7)	16(4)	12(4)	10(2)	7(3)	1(6)	0(1)
Chemotherapy (censored)	151(0)	121(1)	75(16)	59(8)	51(6)	42(8)	33(7)	29(4)	19(8)	10(7)	7(3)	3(3)	1(2)	0(1)

Kanemitsu et. al., J Clin Oncol 39:3789-3799

JCOG0603: No survival benefit for adjuvant chemotherapy



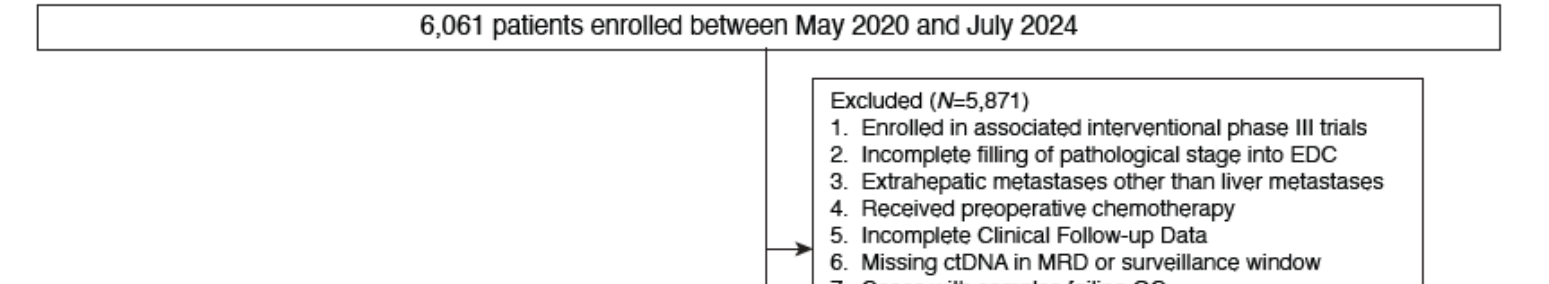
Variable	Hepatectomy (n = 149)	Chemotherapy (n = 151)
No. of events	32	38
3-year OS, % (95% CI)	91.8 (85.7 to 95.4)	87.2 (80.2 to 91.9)
5-year OS, % (95% CI)	83.1 (74.9 to 88.9)	71.2 (61.7 to 78.8)

No. at risk:

Hepatectomy (censored)	149(0)	144(3)	124(16)	108(11)	86(15)	71(13)	59(7)	50(9)	33(11)	23(10)	19(4)	13(6)	3(9)	0(3)
Chemotherapy (censored)	151(0)	148(1)	121(18)	102(13)	84(13)	61(12)	55(5)	45(7)	35(10)	24(11)	18(6)	12(5)	2(10)	0(2)

Kanemitsu et. al., J Clin Oncol 39:3789-3799

GALAXY: Outcomes for patients with colorectal cancer liver metastases following surgical resection

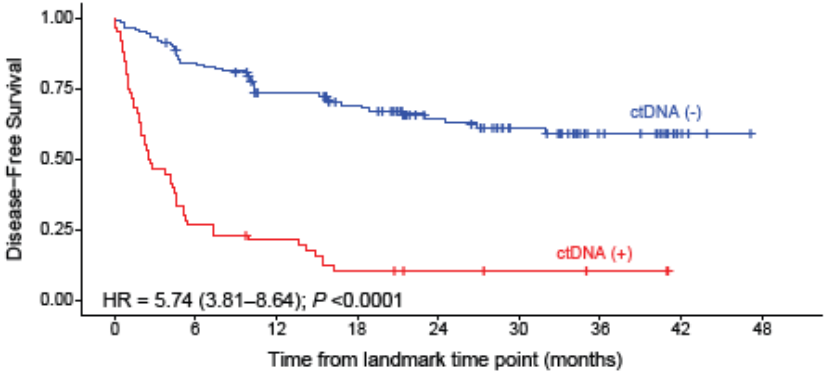


	All Patients	ctDNA status in the MRD Window	
Characteristic	**N = 190[1]**	**ctDNA(-)**, N = 129[1]	**ctDNA(+)**, N = 61[1]

Kataoka et. al., Annals of Oncology 2024 (in press) presented at 2024 ESMO Annual Congress

Colorectal liver mets s/p resection: ctDNA status in the MRD and surveillance windows is strongly prognostic for DFS

MRD Window

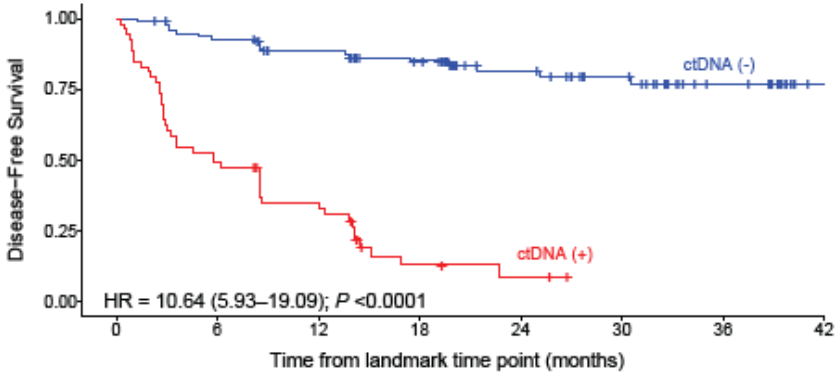


Number at risk

ctDNA negative	129	107	87	70	41	29	15	4	0
ctDNA positive	60	16	12	6	4	3	2	0	0

ctDNA status	Negative	Positive
Events %	34.88 (45/129)	88.33 (53/60)
24M-DFS % (95% CI)	64.50 (54.80–72.60)	10.80 (4.45–20.30); *P* <0.0001
30M-DFS % (95% CI)	61.30 (51.10–70.0)	10.80 (4.45–20.30); *P* <0.0001
36M-DFS % (95% CI)	59.20 (48.40–68.40)	10.80 (4.45–20.30); *P* <0.0001
mDFS (mo)	NR (32.0–NR)	2.56 (2.0–4.60)

Surveillance Window



Number at risk

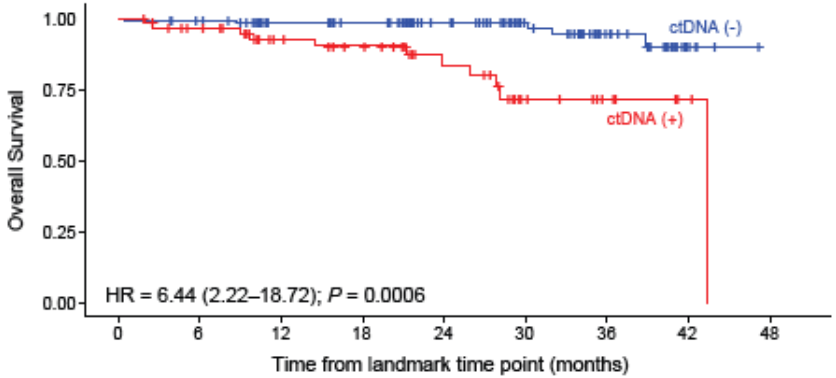
ctDNA negative	99	90	80	68	41	31	15	1
ctDNA positive	53	26	17	4	2	0	0	0

ctDNA status	Negative	Positive
Events %	18.18 (18/99)	83.02 (44/53)
24M-DFS % (95% CI)	81.50 (71.10–88.40)	8.59 (2.0–21.42); *P* <0.0001
30M-DFS % (95% CI)	79.50 (68.40–87.0)	NR
36M-DFS % (95% CI)	76.80 (64.60–85.30)	NR
mDFS (mo)	NR	5.81 (3.05–12.10)

Kataoka et. al., Annals of Oncology 2024 (in press) presented at 2024 ESMO Annual Congress

Colorectal liver mets s/p resection: ctDNA status in the MRD and surveillance windows is strongly prognostic for survival

MRD Window

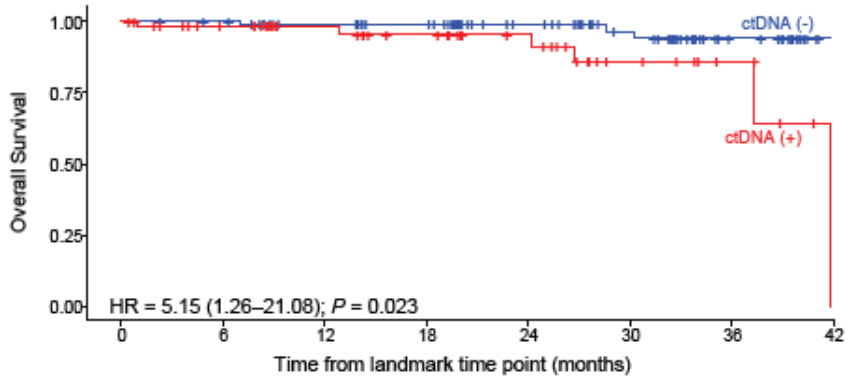


Number at risk

ctDNA negative	129	125	108	97	71	48	26	5	0
ctDNA positive	61	54	40	35	23	12	6	2	0

ctDNA status	Negative	Positive
Events %	3.88 (5/129)	18.03 (11/61)
24M-OS % (95% CI)	98.40 (93.80–99.60)	83.6 (67.4–92.1); P=0.016
30M-OS % (95% CI)	98.40 (93.80–99.60)	71.7 (52.1–84.4); P=0.0007
36M-OS % (95% CI)	94.30 (84.10–98.0)	71.7 (52.1–84.4); P=0.006
mOS (mo)	NR	43.4 (NR–NR)

Surveillance Window



Number at risk

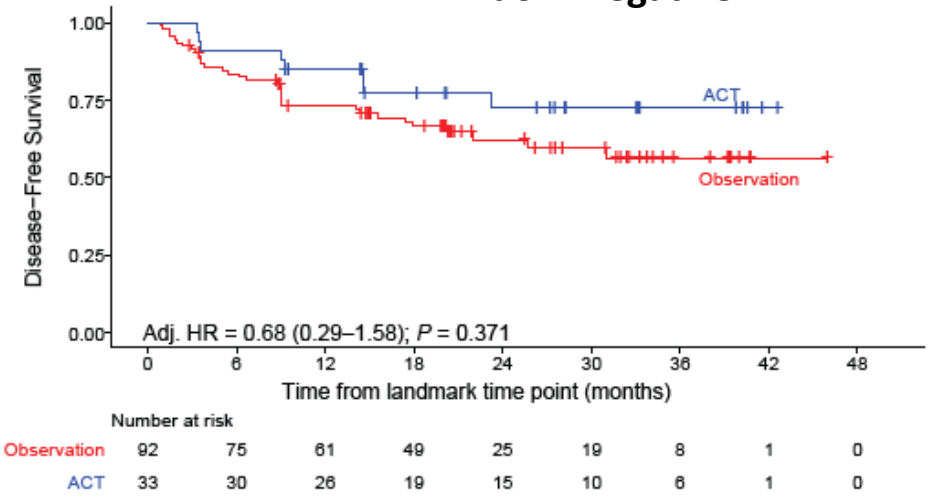
ctDNA negative	99	97	88	81	55	39	18	1
ctDNA positive	55	46	37	30	22	11	5	0

ctDNA status	Negative	Positive
Events %	3.03 (3/99)	10.91 (6/55)
24M-OS % (95% CI)	99.0 (92.80–99.90)	95.5 (82.7–98.9); P=0.368
30M-OS % (95% CI)	96.50 (85.50–99.20)	85.8 (64.1–94.8); P=0.065
36M-OS % (95% CI)	94.10 (81.70–98.20)	85.8 (64.1–94.8); P=0.128
mOS (mo)	NR	41.8 (37.3–NR)

Kataoka et. al., Annals of Oncology 2024 (in press) presented at 2024 ESMO Annual Congress

Colorectal liver mets s/p resection: ctDNA status in the MRD window may predict benefit from adjuvant chemo

MRD Window Negative

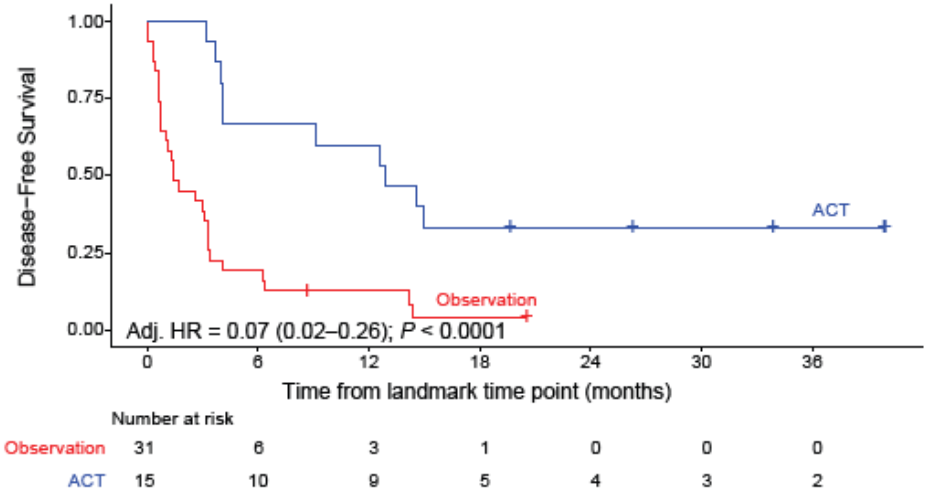


Number at risk

Observation	92	75	61	49	25	19	8	1	0
ACT	33	30	26	19	15	10	6	1	0

ctDNA status	ACT	Observation
Events %	24.24 (8/33)	35.87 (33/92)
24M-DFS % (95% CI)	72.31 (51.43–85.38)	62.22 (50.11–72.18); P = 0.384
mDFS (mo)	NR	NR (25.6–NR)

MRD Window Positive



Number at risk

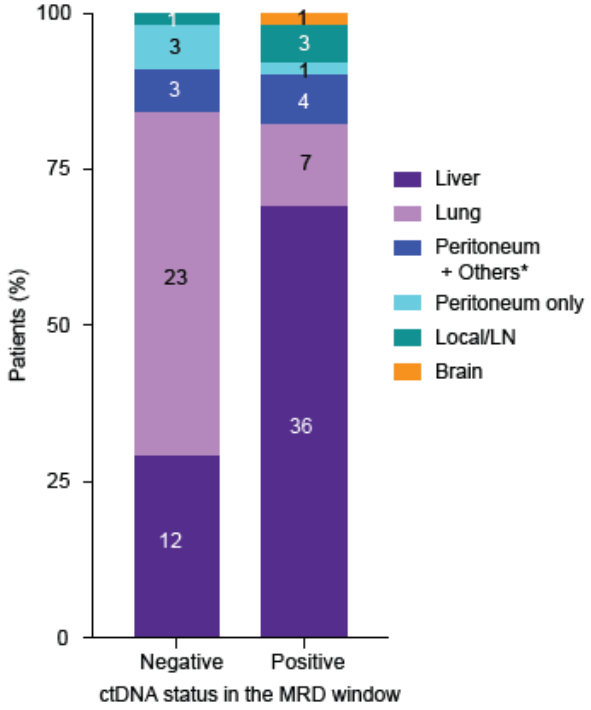
Observation	31	6	3	1	0	0	0
ACT	15	10	9	5	4	3	2

ctDNA status	ACT	Observation
Events %	66.67 (10/15)	93.55 (29/31)
24M-DFS % (95% CI)	33.33 (12.2–56.4)	NE
mDFS (mo)	12.92 (4.11–NR)	1.45 (0.76–3.32)

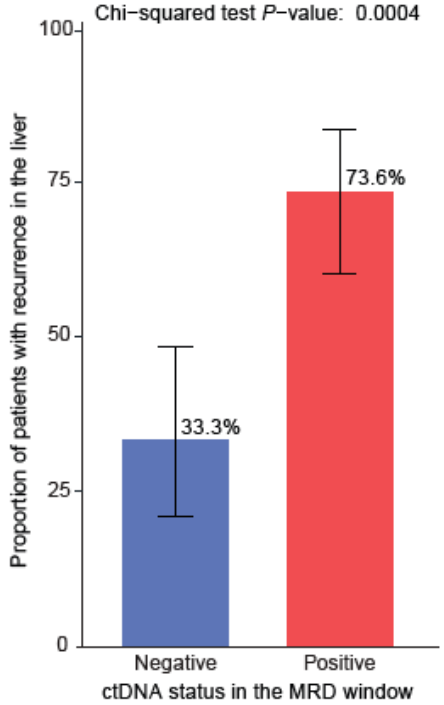
Kataoka et. al., Annals of Oncology 2024 (in press) presented at 2024 ESMO Annual Congress

Colorectal liver mets s/p resection: ctDNA detection and site of recurrence

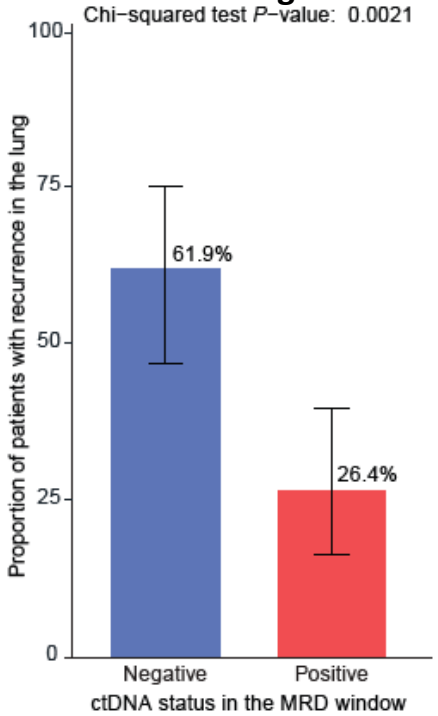
Site of recurrence and ctDNA status in the MRD window



Patients with recurrence in the liver



Patients with recurrence in the lung



Kataoka et. al., Annals of Oncology 2024 (in press) presented at 2024 ESMO Annual Congress

CASE

68-year-old man undergoes sigmoid colectomy for sigmoid mass.

- Pathology with T3N2 (4/17 LN)M0 moderately diff adenocarcinoma of colon.
- Offered Circulate trial, but ineligible due to anemia.

Do you still obtain ctDNA?

We did – positive at baseline.

- FOLFOX started – still positive at 3 months.
- No metastatic disease.
- Now what?

CASE

- 55 year old musician presents with BRBPR
- Colonoscopy- Ffungating nonobstructive mass in the distal sigmoid colon
- LAR. Path: Moderately-differentiated colonic adenocarcinoma. Surgical margins negative, 0/22 lymph nodes, 1 tumor deposit. Pathologic stage: pT3N1c, MSS
- CT c/a/p after surgery: no evidence of metastatic disease
- Adjuvant FOLFOX advised. Pt declines and requests Signatera.
- 4 week post op: Negative
- 8 weeks postop: Negative.
- 3 months postop: Negative. Pt declines adjuvant chemotherapy again

Pt sees you 5 months after surgery requesting opinion about adjuvant chemotherapy

Timing of adjuvant chemotherapy is critical to survival benefit

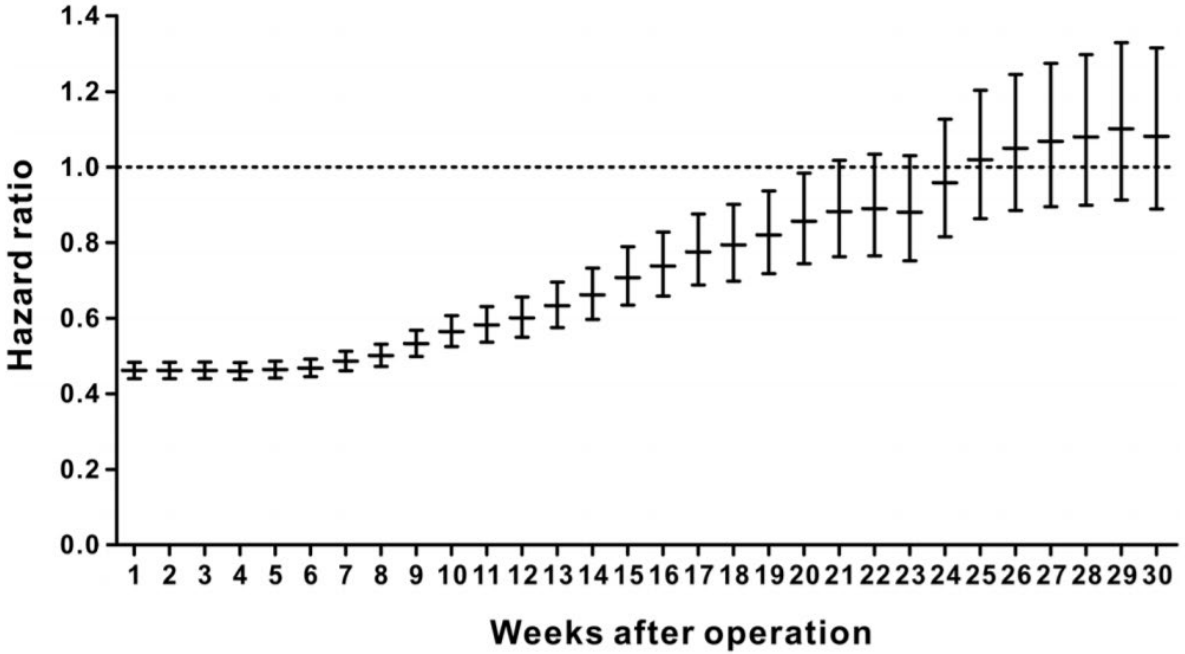


Fig. 3 Hazard ratio plot for the relationship between timing of chemotherapy and overall survival compared with the non-chemotherapy group

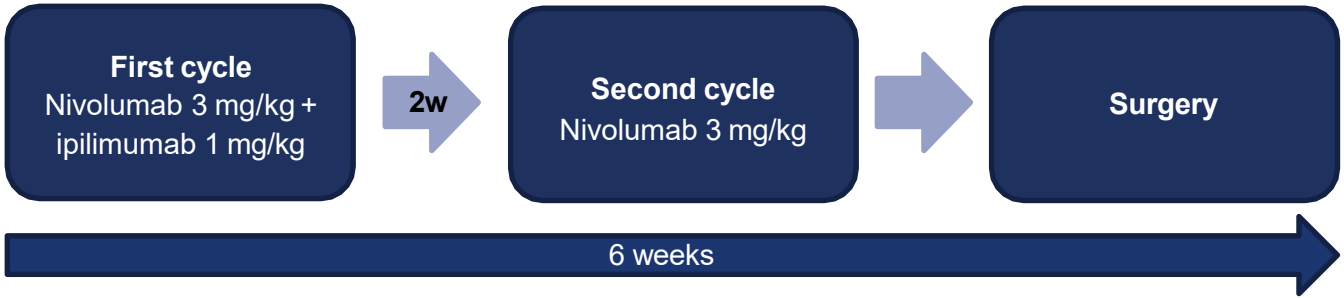
Gao, et al., BMC Cancer. 2018 Mar 1;18(1):234.

NICHE-2 study design

Investigator-initiated, non-randomized multicenter study

Key eligibility criteria

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



Endpoints and statistical design

- Two primary endpoints
  - Safety
  - **3-year disease free survival (DFS)**
- Secondary endpoints
  - Pathologic response rate
  - Translational research
  - **Circulating tumor DNA dynamics**

A 3-year DFS of 93% would be deemed successful, at a power of 80% and a two-sided alpha of 0.025 using a one-sample log rank test assuming a historical 82% DFS[1]

[1]Historical 82% DFS was calculated with the assumption of 60% stage III and 40% stage II tumors. The historical 3-year DFS used for these calculations was 75% for stage III tumors and 90% for stage II disease.

Baseline characteristics

Characteristic	All patients, *n* = 115
Median age (range) – yr	60 (20-82)
Female sex – no. (%)	67 (58)
Tumor stage – no. (%)	
cT2	17 (15)
cT3 or cT3-4	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status – no. (%)	
cN0	38 (33)
cN+	77 (67)
Lynch syndrome – no. (%)	37 (33)

Chalabi et al. NEJM 2024

Pathologic responses in NICHE-2

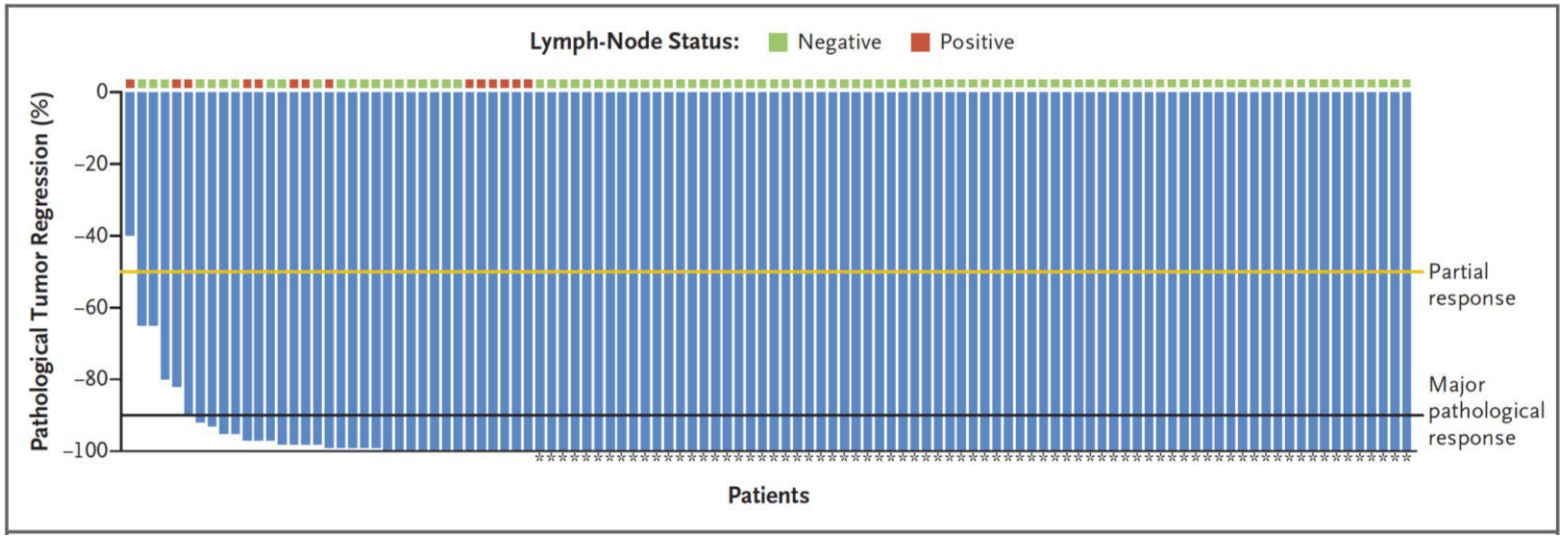
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., Nikè V. Büller, M.D., Ph.D., Brechtje A. Grotenhuis, M.D., Ph.D., Koert Kuhlmann, M.D., Ph.D., Jacobus W. Burger, M.D., Ph.D., Inge L. Huibregtse, M.D., Ph.D., Tjeerd S. Aukema, M.D., Ph.D., Eduard R. Hendriks, M.D., Steven J. Oosterling, M.D., Ph.D., Petur Snaebjornsson, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Lodewyk F. Wessels, Ph.D., Regina G. Beets-Tan, M.D., Ph.D., Monique E. Van Leerdam, M.D., Ph.D., Ton N. Schumacher, Ph.D., José G. van den Berg, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D., and John B. Haanen, M.D., Ph.D.

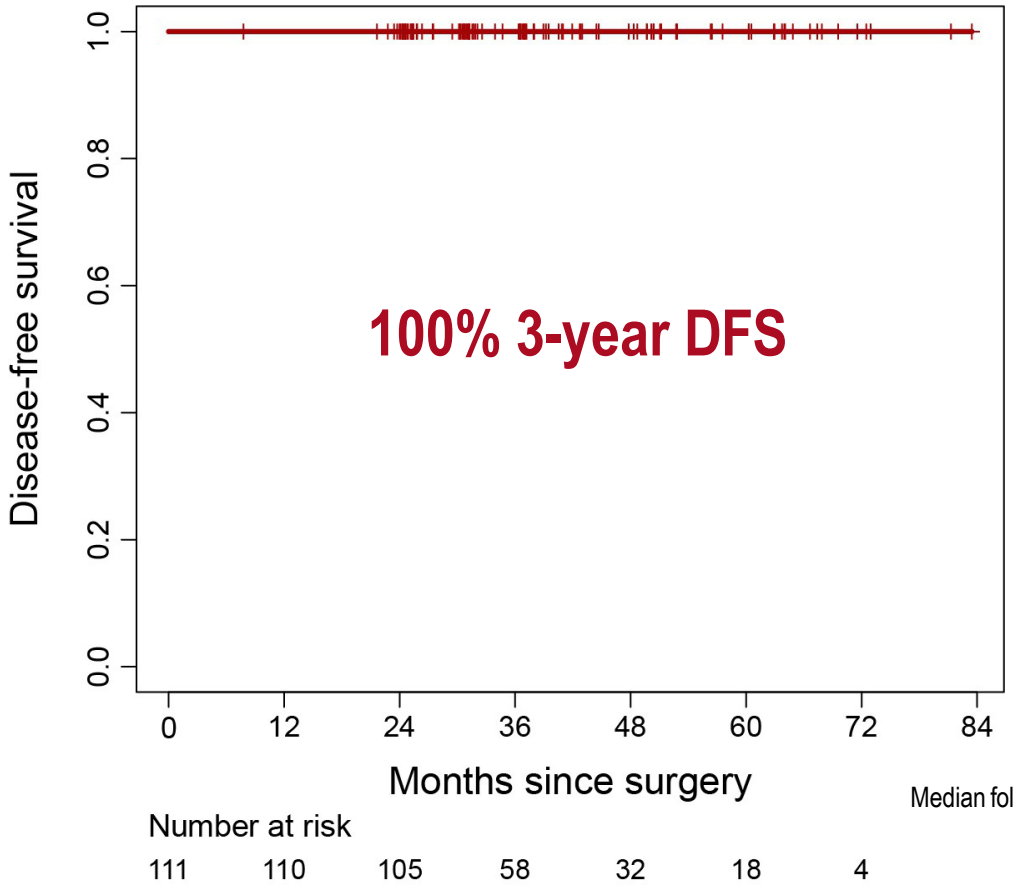
Pathologic response in **98%** of 111 patients in efficacy analysis

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



Chalabi et al. NEJM 2024

Results – 3-year disease-free survival 100%



Median follow-up after surgery: 36.6 months (7.8 - 83.4)

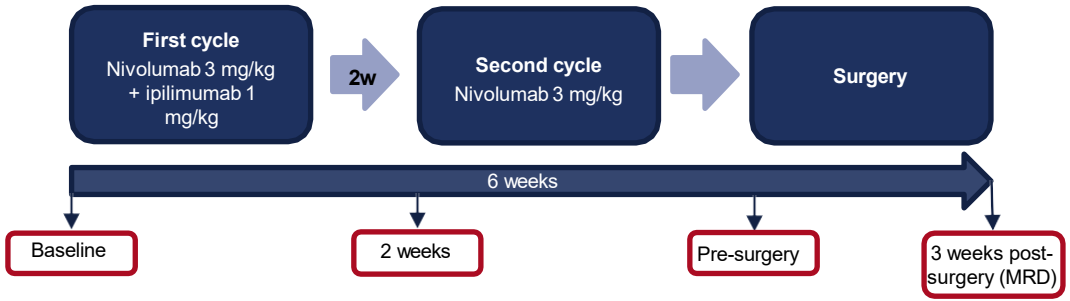
BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

Circulating tumor DNA in NICHE-2

1. Assess ctDNA at minimal residual disease (MRD) timepoint

2. Can ctDNA accurately predict pCR?
   - In NICHE-2: despite high pCR and MPR rates, inability to predict pathologic response with radiographic imaging



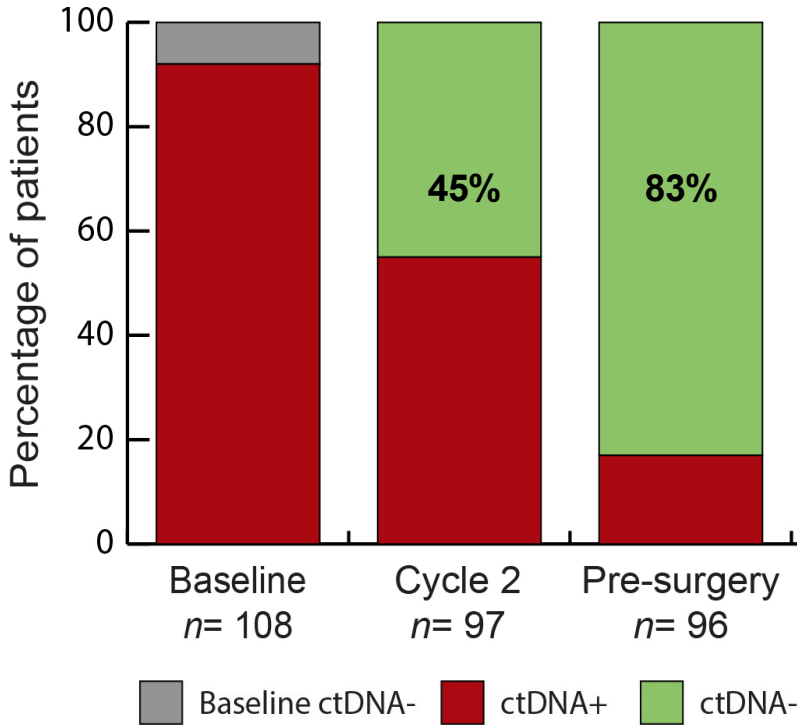
Tissue-informed Signatera ctDNA assay

Chalabi et al. NEJM 2024; Hofste et al. Eur J Surg Oncol. 2023; Alden et al. Oncologist 2024; Kasi et al. ASCO GI 2024;

Circulating tumor DNA detection

- Baseline detection in 99/108 (92%) of patients
- 45% of patients cleared ctDNA after only 1 cycle

	ctDNA – Cycle 2	ctDNA – Pre-surgery
pCR	**58%**	**92%**
MPR	**19%**	**70%**



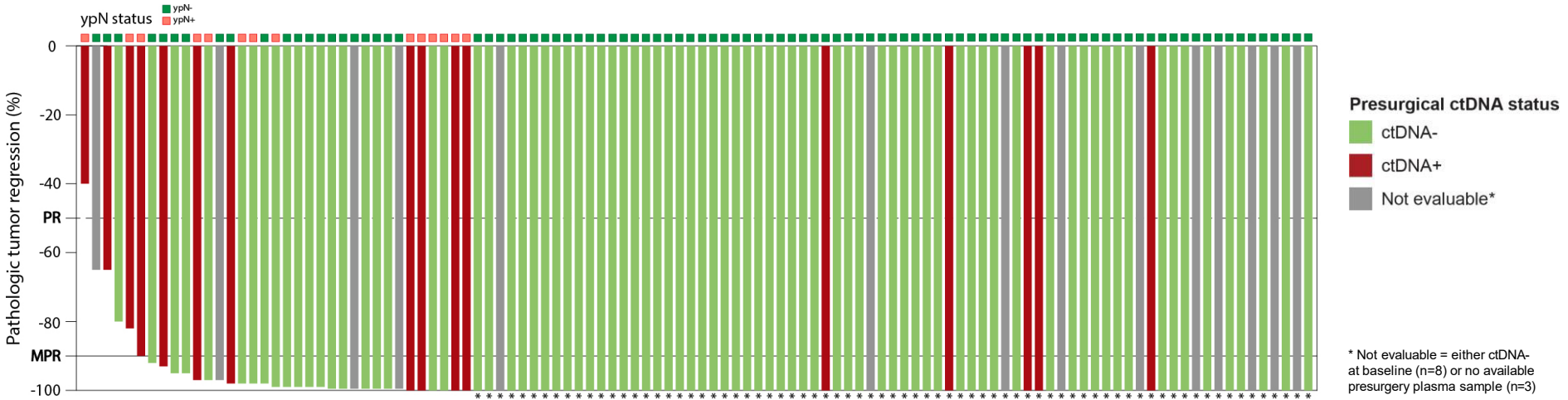
Pre-surgery ctDNA status and pathologic response

BARCELONA 2024 ESMO congress

ctDNA pre-surgery		
Response group	**ctDNA-**	**ctDNA+**
pCR (*n* = 65)	60 (92%)	5 (8%)
MPR (*n* = 27)	19 (70%)	8 (30%)
PR (*n* = 3)	1 (33%)	2 (67%)
NR (*n* = 1)	0	1 (100%)

16 patients remained ctDNA positive pre-surgery

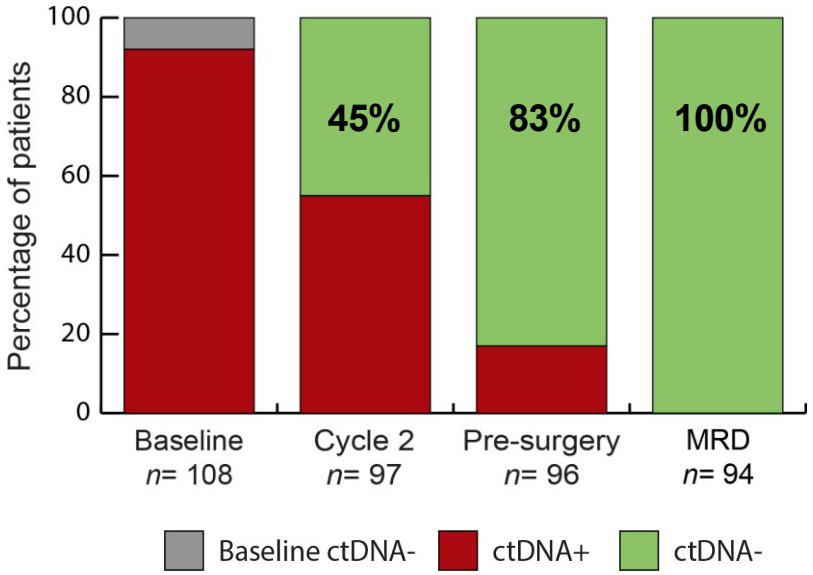
8/14 ypN+ patients

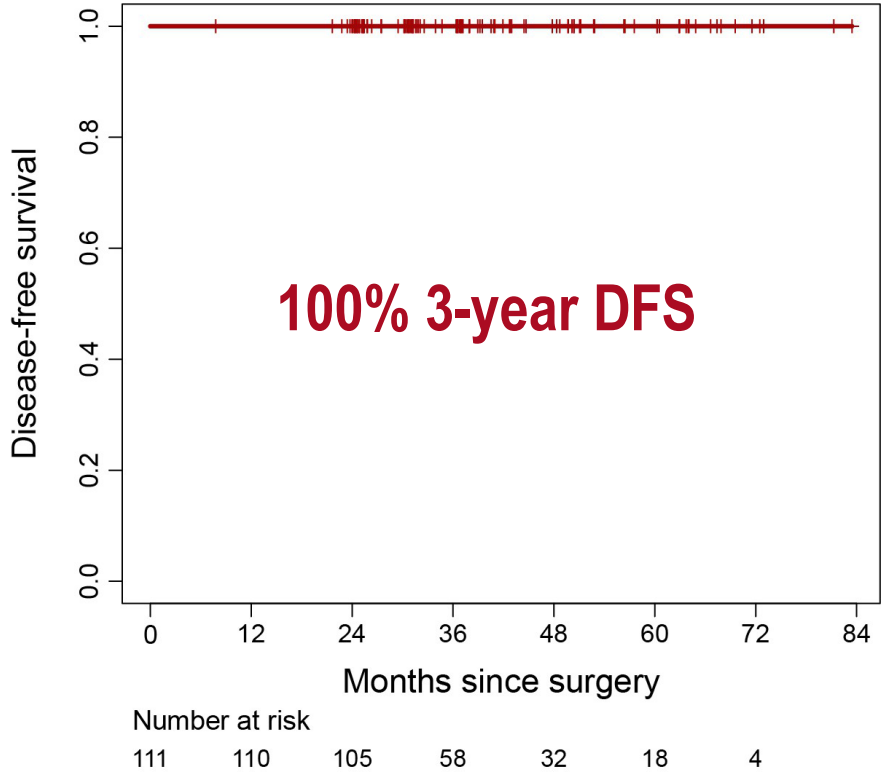


* Not evaluable = either ctDNA- at baseline (n=8) or no available presurgery plasma sample (n=3)

Minimal residual disease

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





Myriam Chalabi, MD PhD

Final thoughts

- MRD testing is a fit-for-purpose tool to risk-stratify patients with colorectal cancer in various clinical scenarios

- Results now show prognostic impact of ctDNA status on survival

- MRD testing is most sensitive for detection of liver metastases– lung metastases tend to be indolent and may escape detection