ctDNA Based decision making for adjuvant colon cancer: Ready for primetime?

Valerie Lee, MD
Assistant Professor of Medical Oncology

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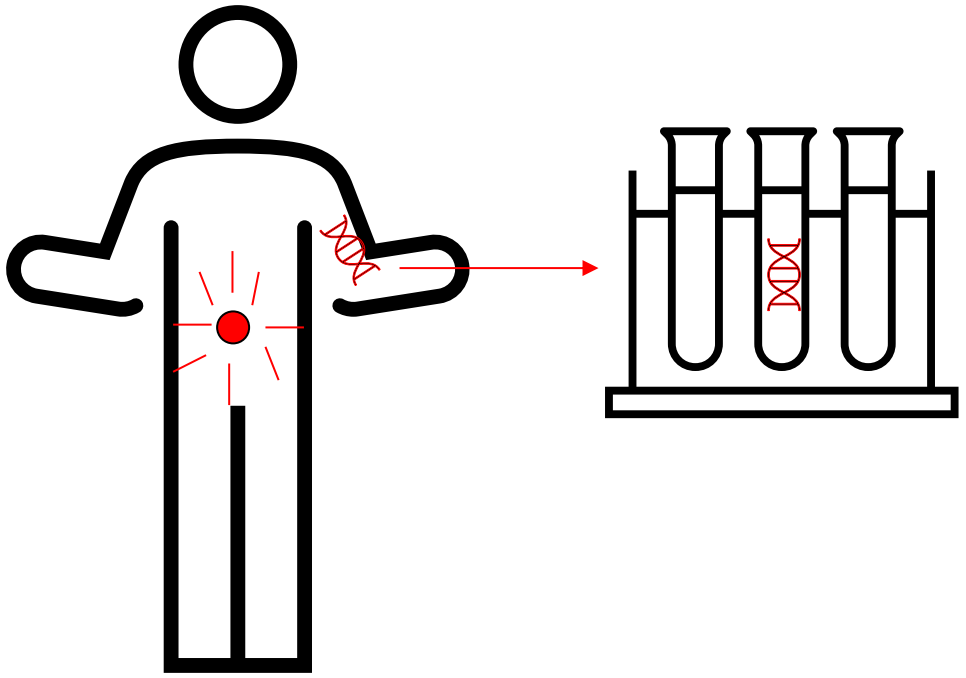
Disclosures

- Research Funding: Merck
- Advisory Board: Sirtex, Incyte

Outline

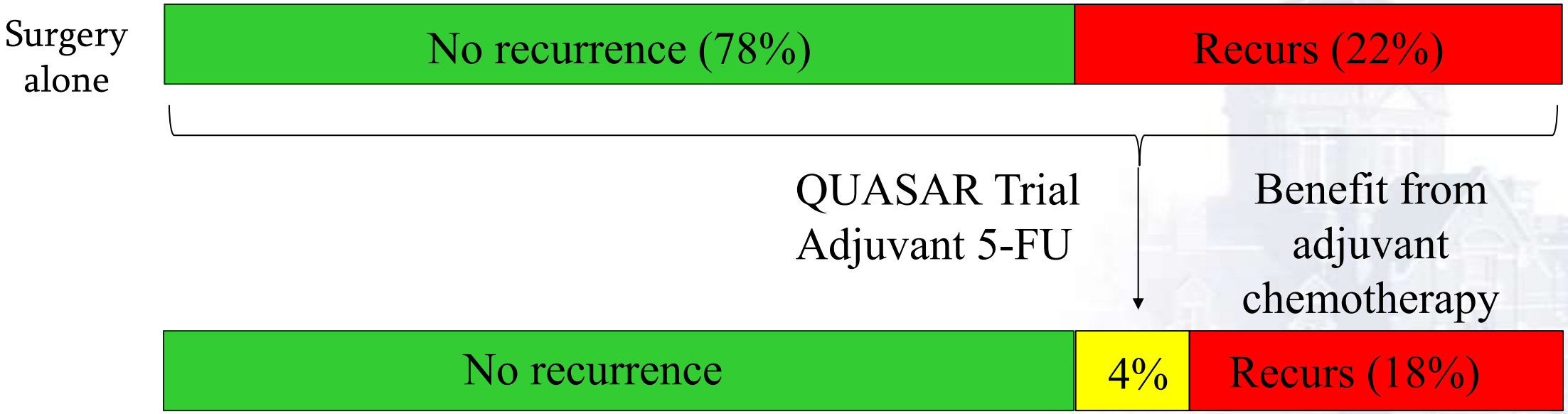
- What is ctDNA?
- Role in stage II disease
- Role in stage III disease



Tumor Agnostic	Tumor Specific/Informed
Blood (or other liquid) based testing for predefined panels of genomic/epigenomic changes consistent with malignancy	Tumor testing to develop personalized assay that is then assessed in the blood
Rapid (1-2 weeks)	Slower (4-6 weeks)
Assess dynamic changes in types of mutations/resistance over time May pick up other malignancies Allows NGS when tumor insufficient	Specific and sensitive to just the tumor
Less specificity due to clonal hematopoeisis or other underlying disease	Requires sufficient tumor sample
Goals: • Identify minimal residual disease for prognostic and predictive decision making	

Wills et al Curr Prob in Cancer. Nov 2018
Chan et al Front Onc. Feb 2023

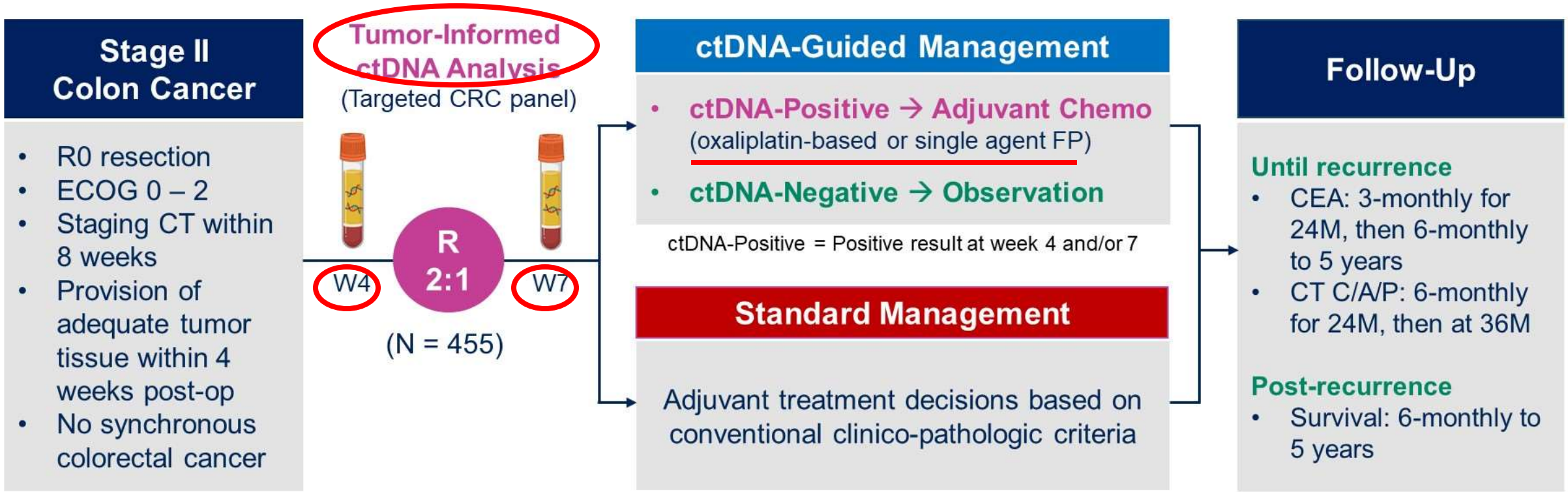
Stage II Colon Cancer



Adjuvant chemotherapy provides 3.6% OS benefit in stage II colon cancer

QUASAR Lancet 2007

DYNAMIC Study Design



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455 patients enrolled from 2015-2019

Treatment Delivery and Adherence.

Table 2. Treatment Delivery and Adherence.*

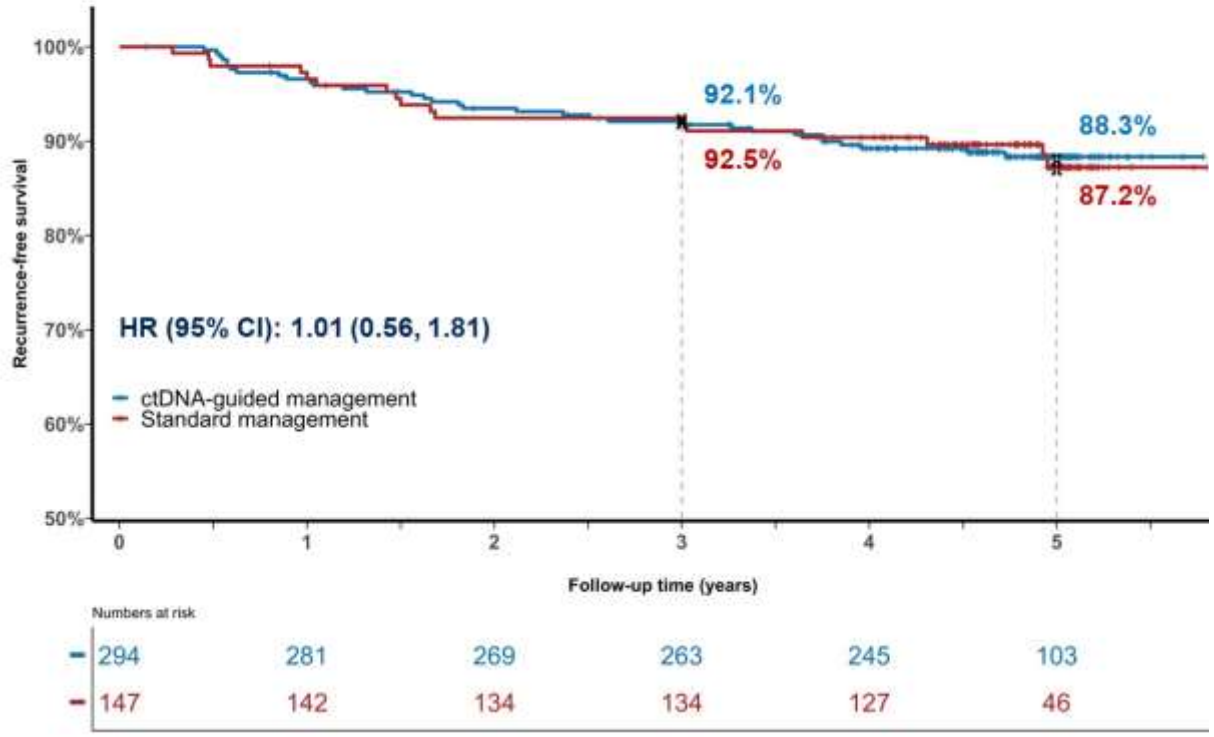
Treatment Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Relative Risk (95% CI)
Adjuvant chemotherapy received — no. (%)			
No	106 (72)	249 (85)	
Yes	41 (28)	45 (15)	1.82 (1.25–2.65)

Only half as many people ended up getting chemotherapy

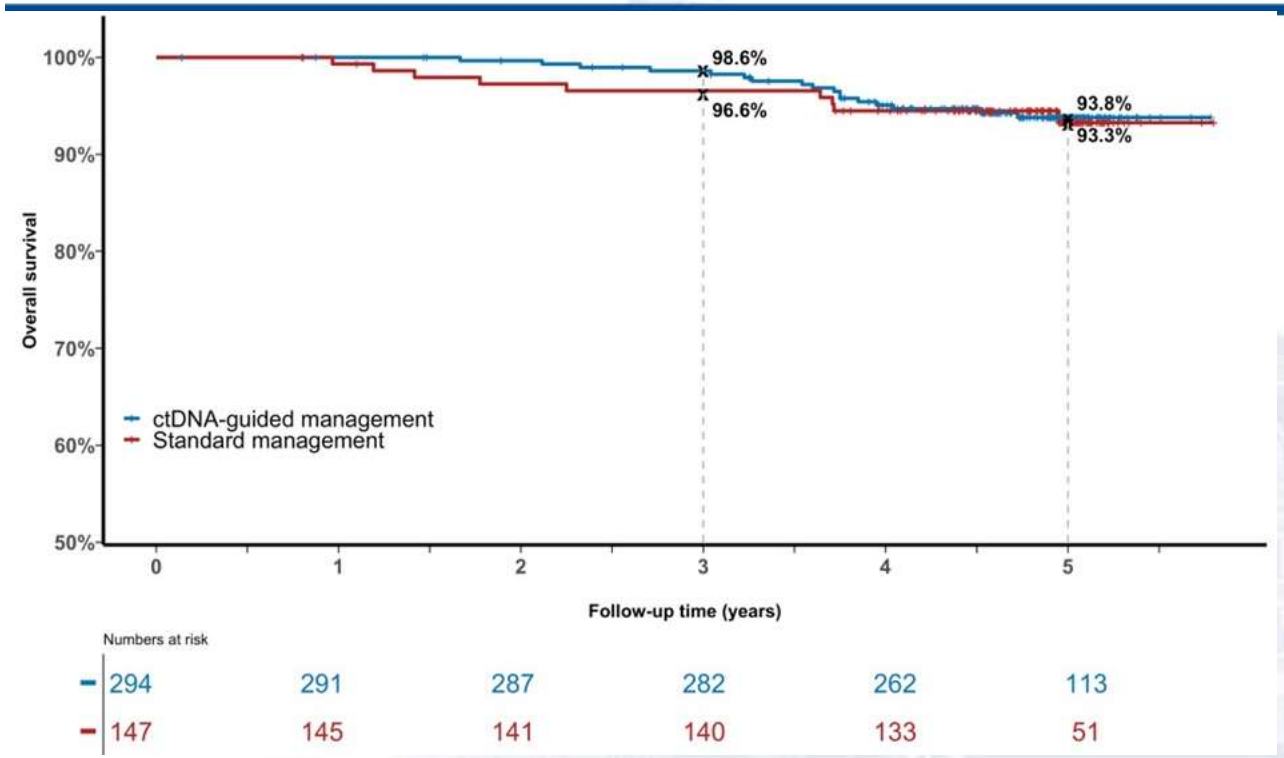
Tie J et al. N Engl J Med2022;386:2261-2272

The NEW ENGLAND JOURNAL of MEDICINE

Updated 5-Year RFS Analysis



Overall Survival



Outcomes almost identical with only half as many people getting chemotherapy!

BUT…..

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)	

2.3%

9.5%

6 months of therapy!

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

9.5% of ctDNA guided patients:

- +/- mediport
- 8-12 infusions (depending upon CapOx v FOLFOX)
- Risk of neuropathy, myelosuppression, and infusion reactions

97.7% of standard management:

- Single agent 5-FU (?oral capecitabine)

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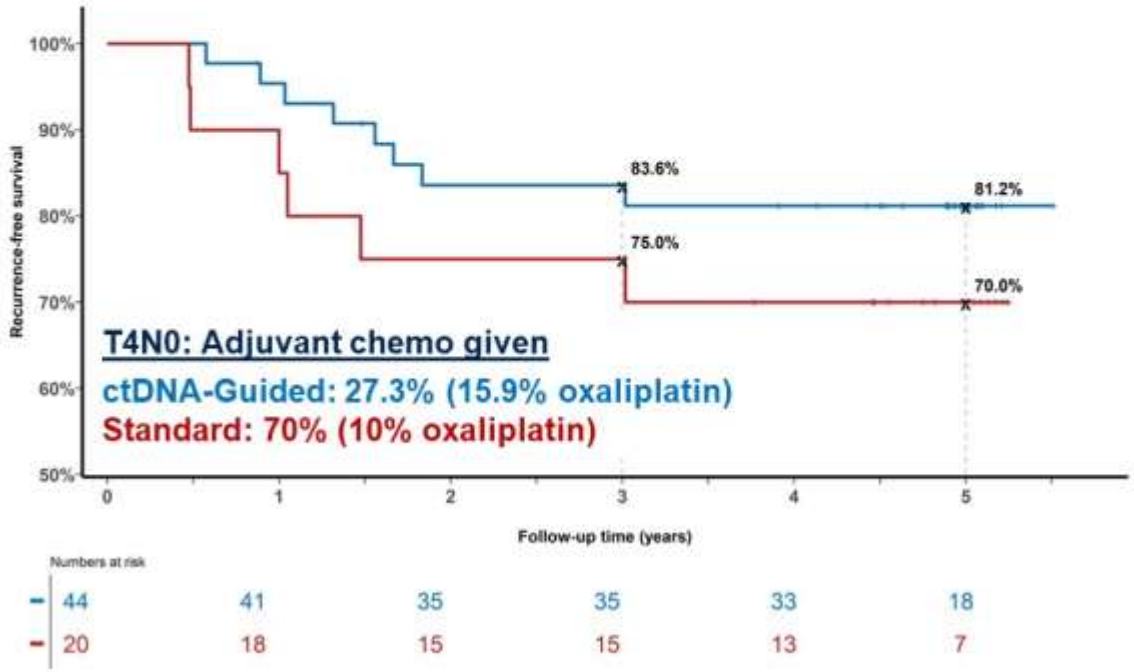
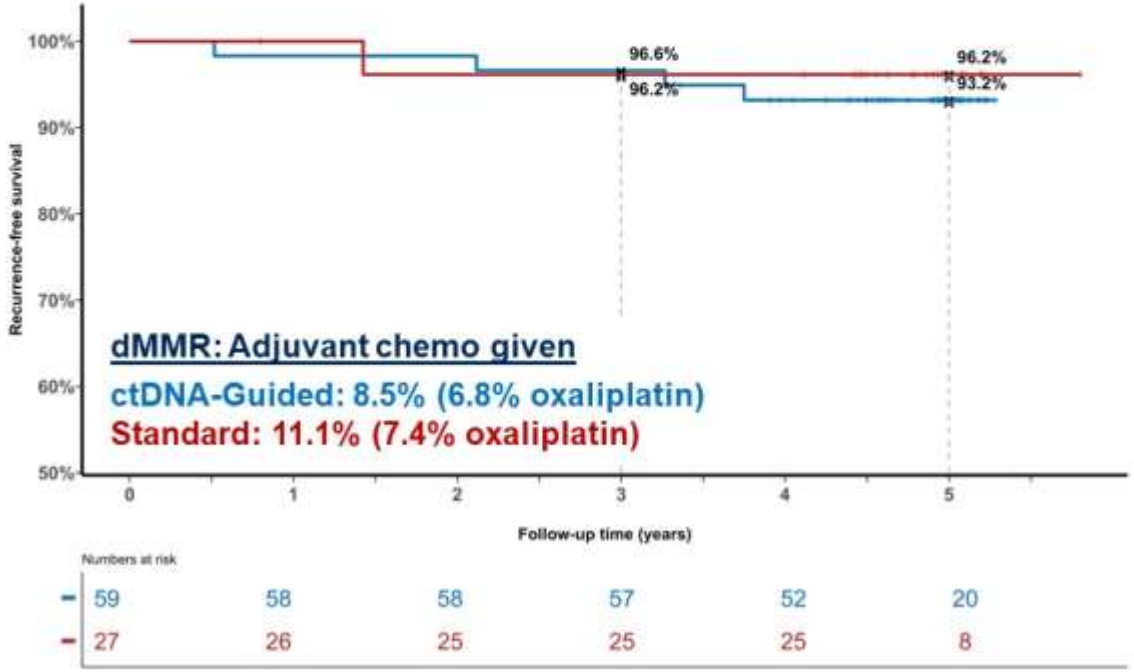
Tie J et al. N Engl J Med2022;386:2261-2272

RFS by Subgroup: T4N0 and dMMR

T4N0 5-Year RFS Rate, %		Recurrence, N (%)	Death w/o recur, N (%)
ctDNA (N = 44)	**81.2**	7 (15.9)	1 (2.3)
SoC (N = 20)	**70.0**	6 (30.0)	0 (0)
HR (95% CI): 1.79 (0.62, 5.15), p = 0.275			

dMMR 5-Year RFS Rate, %		Recurrence, N (%)	Death w/o recur, N (%)
ctDNA (N = 59)	**93.2**	1 (1.7)	3 (5.1)
SoC (N = 27)	**96.2**	1 (3.7)	0 (0)
HR (95% CI): 0.48 (0.05, 4.27), p = 0.512			





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Is ctDNA decision making for Stage II pts be cost effective?

Early evaluation of the effectiveness and cost-effectiveness of ctDNA-guided selection for adjuvant chemotherapy in stage II colon cancer

Astrid Kramer, Marjolein J. E. Greuter, Suzanna J. Schraa, Geraldine R. Vink, Jillian Phallen, Victor E. Velculescu, Gerrit A. Meijer, Daan van den Broek, Miriam Koopman, Jeanine M. L. Roodhart, Remond J. A. Fijneman, Valesca P. Retèl and Veerle M. H. Coupé

Ther Adv Med Oncol

2024, Vol. 16: 1–16

DOI: 10.1177/17588359241266164

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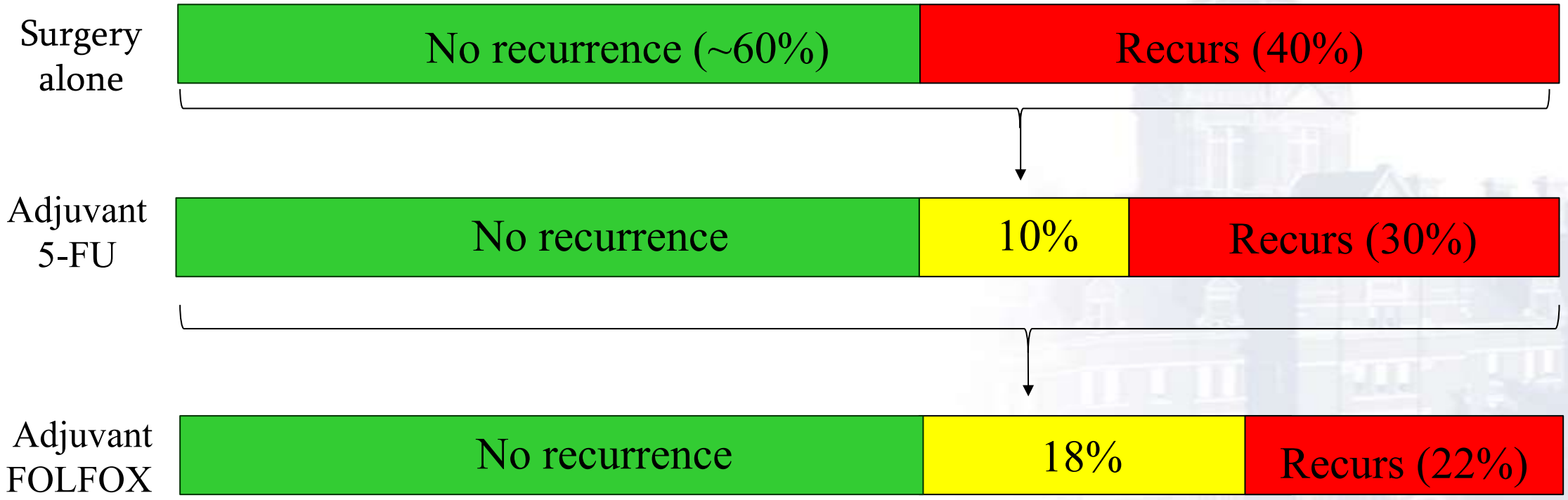
Stage II colon cancer recap

- Can we switch to ONLY ctDNA based testing now?
  - Not quite
  - Were outcomes in +ctDNA group improved only because they received intensified (oxaliplatin) based therapy?
  - Is it cost effective?
  - It can help reinforce most low risk (dMMR) and moderate risk patients who would not be offered therapy. However, patients must be willing to consider physician recommendations to escalate therapy if +
- T4 patients got surprisingly low % oxaliplatin in both arms – would intensification help?
- Shared decision making is a must
  - What is the mental wear on a person who does not undergo adjuvant therapy and then has recurrence?

Stage III Colon Cancer



Stakes are higher if you forego adjuvant therapy as there is a higher risk of recurrence!

NSABP C-03 (Wolmark JCO 1993), IMPACT (Lancet 1995), Intergroup (JCO 1995), MOSAIC (Andre NEJM 2005)

The data for ctDNA in stage III disease

CIRCULATE-Japan trial - using tumor informed ctDNA

– 3 trials:

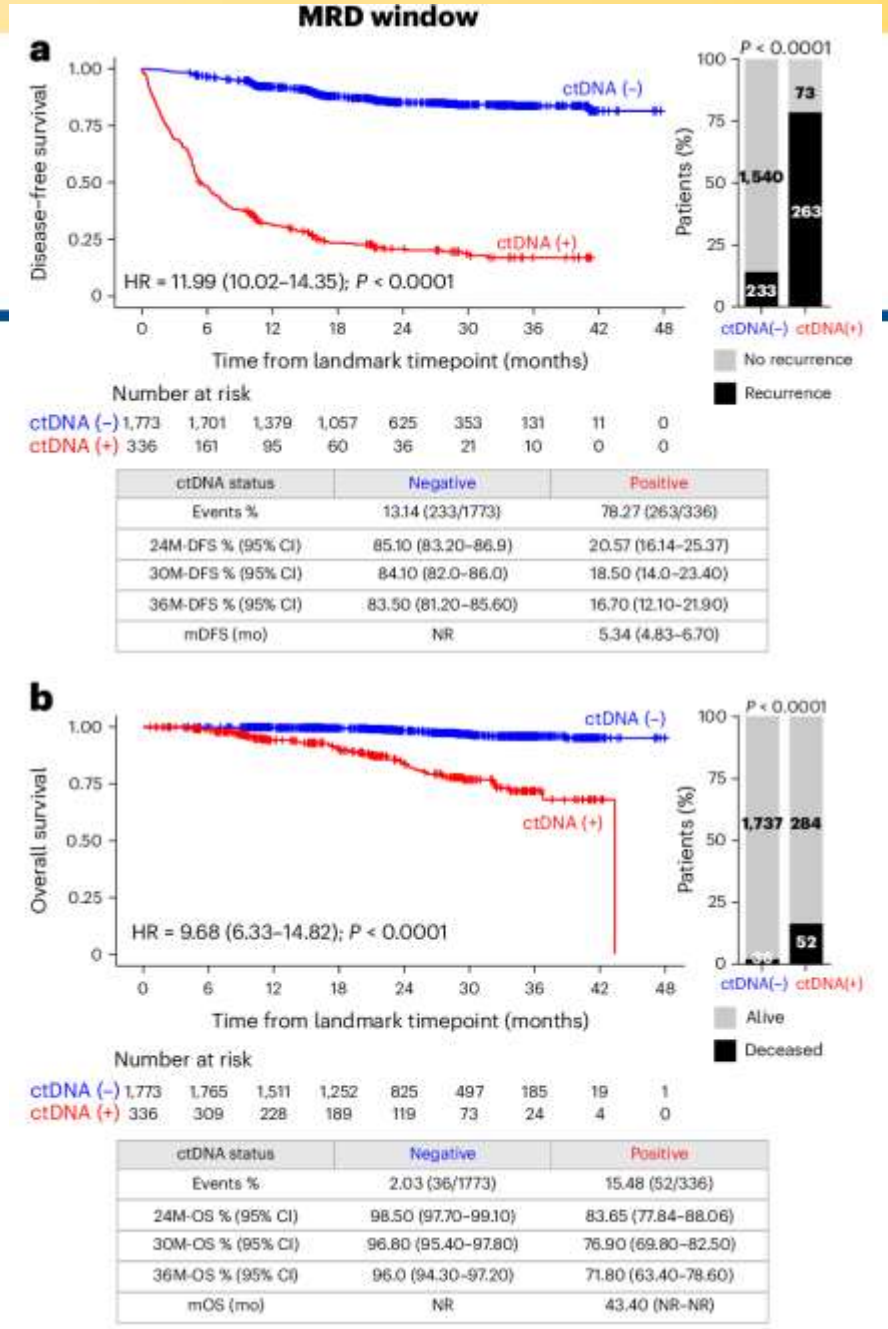
- GALAXY – prospective registry study for stage II-IV resected CRC
- VEGA – randomized phIII trial of observation versus CapOx x 3 months after surgery for stage III and high risk stage II CRC with negative ctDNA at 4 weeks postop
- ALTAIR – randomized phIII trial of observation for TAS-102 for those with +ctDNA, BUT NED on imaging, in 2 years following surgery/adjuvant chemotherapy

BESPOKE – North American data

INTERCEPT – Single center MDACC

Taniguchi H, et al.*Cancer Sci*. 2021;112:2915–2920.
Kasi P et al. *JCO Abstract GI ASCO 2024*
Dasari et al. JCO Abstract GI ASCO 2023

CIRCULATE-JAPAN GALAXY Interim Analysis



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)

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)

CIRCULATE-Japan trial - using tumor informed ctDNA

- 2,240 patients analyzed, 42% stage III
- 15.93% MRD positive → 78.27% recurred
- 84% MRD negative → 13.14% recurrence
- Adjuvant ctDNA is prognostic

Nakamura Y et al. Nature Medicine 2024.

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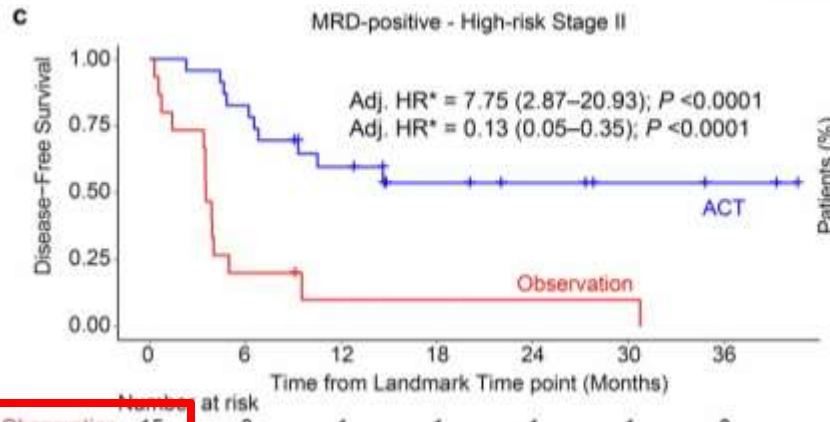
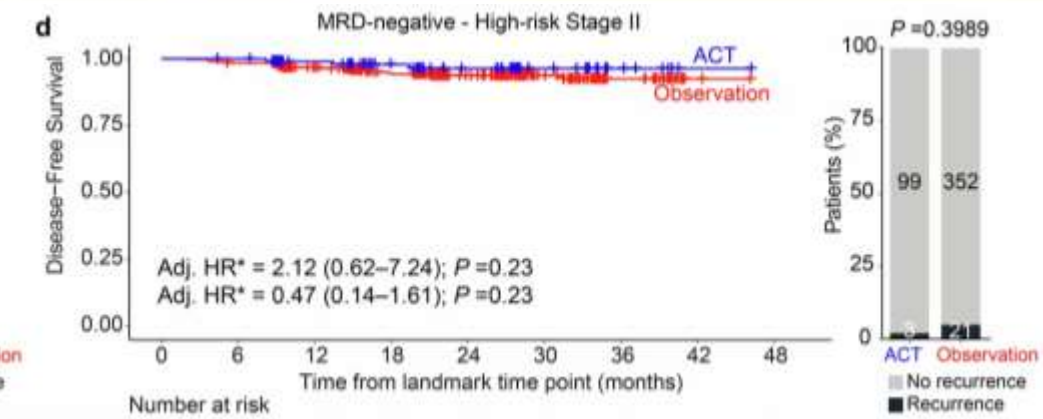
Stage II





Number at risk

Observation	15	3	1	1	1	1	0
ACT	23	19	12	7	5	3	2

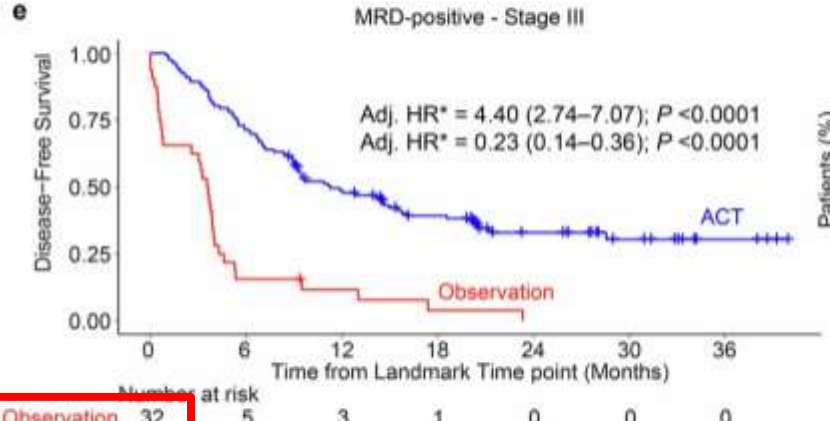
Treatment	ACT	Observation
Events %	43.48 (10/23)	93.33 (14/15)
24M-DFS % (95% CI)	53.70 (30.50–72.20)	10.0 (0.78–33.53)
mDFS (mo)	NR (9.30–NR)	3.52 (3.39–NR)

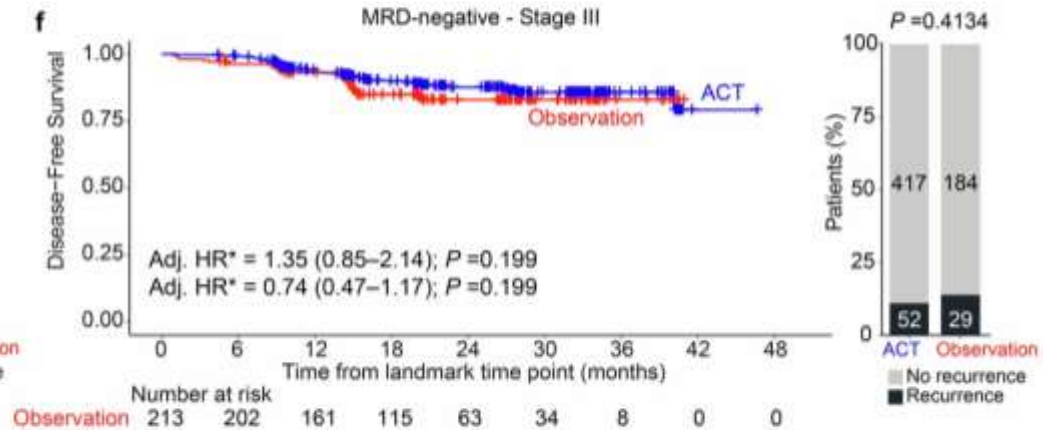
Number at risk

Observation	373	365	311	249	152	80	32	2	0
ACT	102	101	86	65	38	21	7	1	0

Treatment	ACT	Observation
Events %	2.94 (3/102)	5.63 (21/373)
24M-DFS % (95% CI)	96.34 (88.90–98.83)	93.7 (90.30–95.90)
mDFS (mo)	NR	NR

Stage III





Number at risk

Observation	32	5	3	1	0	0	0
ACT	122	87	56	39	20	11	4

Treatment	ACT	Observation
Events %	63.93 (78/122)	96.88 (31/32)
24M-DFS % (95% CI)	33.0 (24.1–42.1)	NR
mDFS (mo)	11.27 (9.1–16.07)	3.58 (2.57–4.01)

Number at risk

Observation	213	202	161	115	63	34	8	0	0
ACT	469	461	373	293	178	94	32	1	0

Treatment	ACT	Observation
Events %	11.09 (52/469)	13.62 (29/213)
24M-DFS % (95% CI)	87.58 (83.72–90.57)	82.90 (76.0–87.90)
mDFS (mo)	NR	NR

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Nakamura Y et al. Nature Medicine 2024.

Ongoing Trials

CORRECT Study of Minimal Residual Disease Detection in Colorectal Cancer (MRD)

ClinicalTrials.gov I

Circulating Cell-Free Tumor DNA Testing in Guiding Treatment for Patients With Advanced or Metastatic Colorectal Cancer

A Phase II Clinical Trial Comparing the Efficacy of RO7198457 Versus Watchful Waiting in Patients With ctDNA-positive, Resected Stage II (High Risk) and Stage III Colorectal Cancer

C

Epidemiological Study to Monitor Study Participants With Resected Stage II (High Risk) or Stage III Colorectal Cancer for Circulating Tumor DNA Before, During and After Their Treatment With Adjuvant Chemotherapy

ClinicalTrials.gov ID NCT04813627

IIA Colon Cancer

ClinicalTrials.gov ID NCT04068103

Minimal Residual Disease Assessment in Patients with Colorectal Cancer, the MiRDA-C Study

ClinicalTrials.gov ID NCT04739072

Colon Adjuvan

ClinicalTrials.gov ID NCT05174169

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The role of ctDNA in adjuvant colon cancer

- Is it ready for prime time?
  - Not quite yet – but so soon! Proven for prognostic, big decisions on predictive aspect
  - Might be reasonable for reinforcement in those for whom we hope not to administer chemotherapy (ie in setting of medical comorbidities)
  - More compelling for stage II disease with lower risk, but likely upcoming for stage III disease
  - Does not represent discussions for surveillance or for those with metastatic disease