Multidisciplinary Approaches to Cancer Symposium

ctDNA Should Be Incorporated Into Active Management of Colorectal Cancer Patients

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Disclosures

- Consultant for AbbVie, Adagene, Bayer. BMS, Delcath Systems, Iterion Therapeutics, Janssen, Merck, Mirati, Microbial Machines, Roche/Genentech, Summit Therapeutics, Taiho, Tempus, Totus Medicines, Xilio Therapeutics

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Understand the limitations of circulating tumor DNA in the management of colorectal cancer*

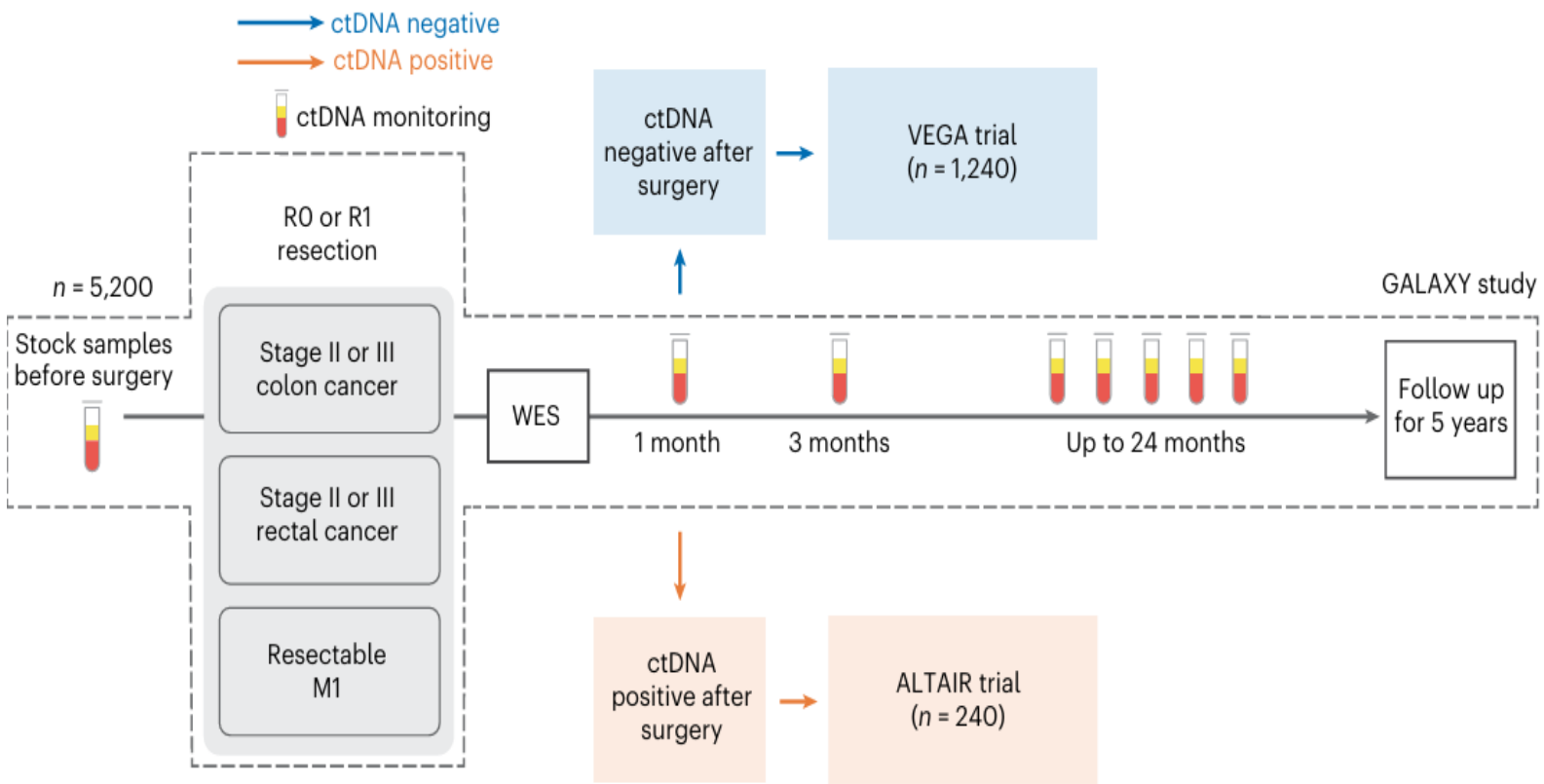
ctDNA of unproven benefit in managing CRC

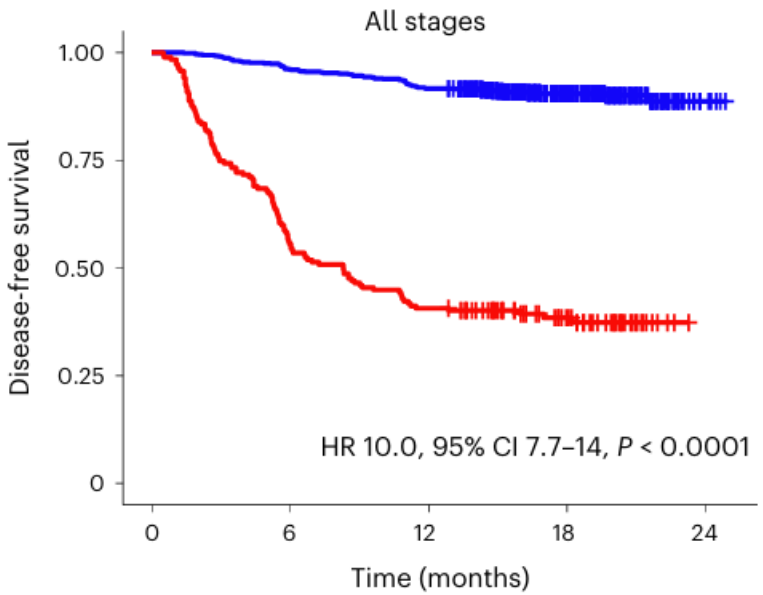
- To impact clinical outcome and enhance health care, the integration of a biomarker should:
  - Improve clinical outcome, specifically overall survival
  - Reduce toxicity by sparing unnecessary treatment
  - Reduce the cost of health care

Myth, Myth, and Myth!!

- **Myth #1: post-op ctDNA should direct adjuvant therapy and will guide intensification and de-intensification**
- Myth #2: surveillance ctDNA is better that imaging in finding recurrence and that will improve outcomes
- Myth #3: surveillance ctDNA will allow salvage chemotherapy post-op which will improve outcome

GALAXY Study



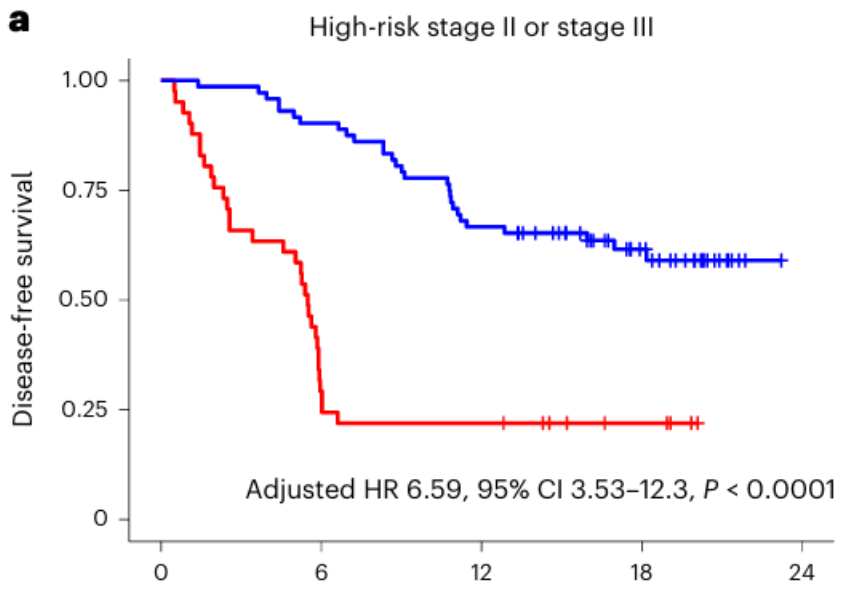


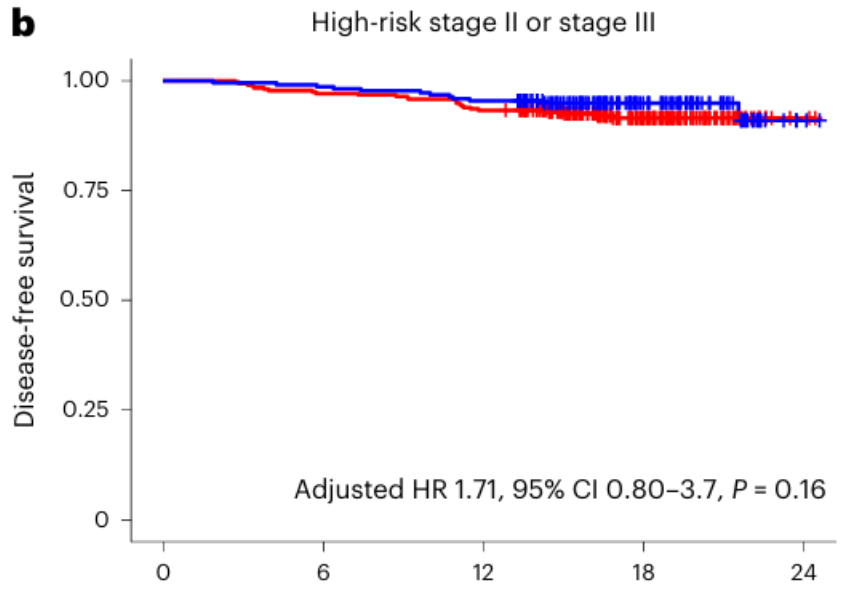
Number at risk

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)

GALAXY: DFS with Adj Rx in ctDNA+/-

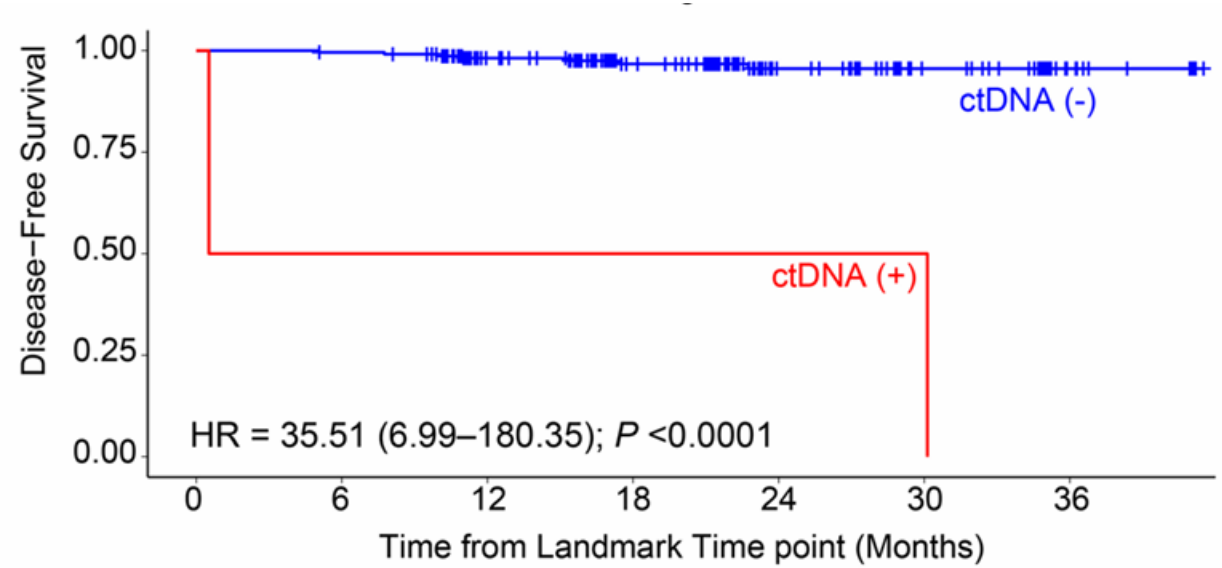




So What?
These were all high-risk stage 2 and stage 3 and hence they all needed chemo
They would have received chemotherapy anyway!!!
There is likely an imbalance in pt characteristics or else why would you deny a stage 3 disease chemotherapy???

So What?
This is NOT evidence of non-inferiority
Strong trend in favor of chemotherapy: HR = 1.7
That is 70% less recurrence and the findings would likely have been SS had the sample size been larger!!

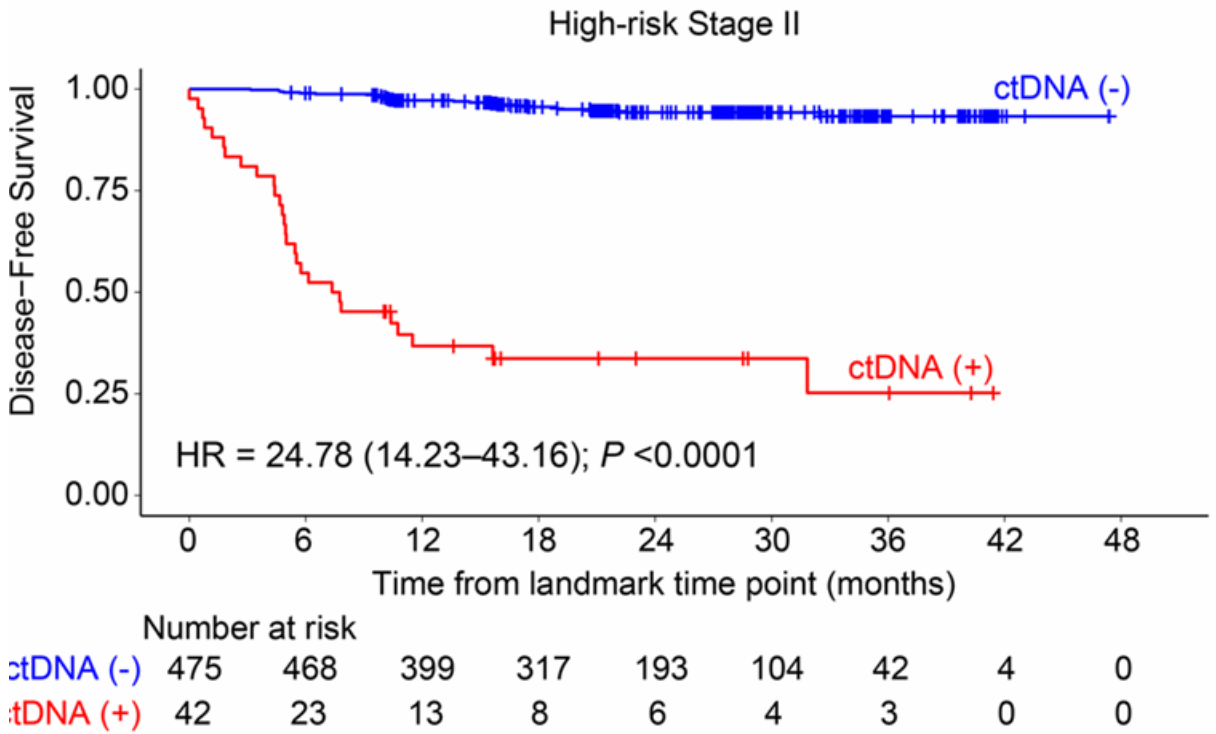
Galaxy: Update on Stage 1 Disease



ctDNA status	Negative	Positive
Events %	3.10 (7/226)	100 (2/2)
24M-DFS % (95% CI)	95.56 (90.43–97.97)	50.0 (0.60–91.04)
mDFS (mo)	NR	15.30 (0.53–NR)

- Not cost-effective (< 1% will be ctDNA ++
- Arguably bad biology for a stage 1 to recur and benefit of chemo would have been unknown
- Assuming chemotherapy cures 30% of ctDNA+, would have to survey 600 patients for ONE curative outcome – and unclear if that pt would have been salvaged by surgery anyway

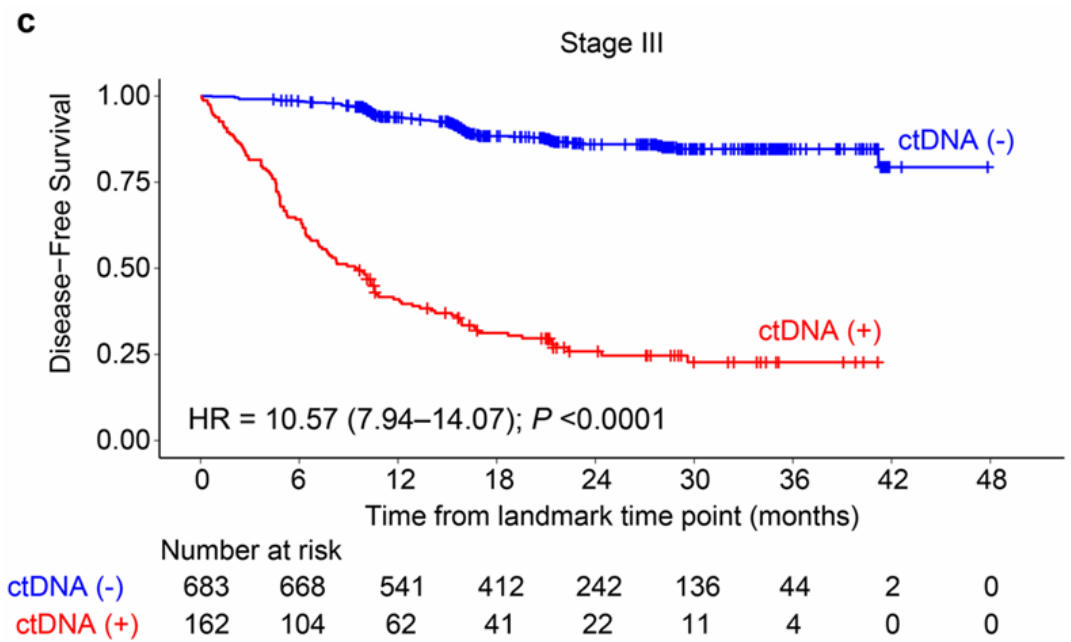
Galaxy: Update on high-risk Stage 2



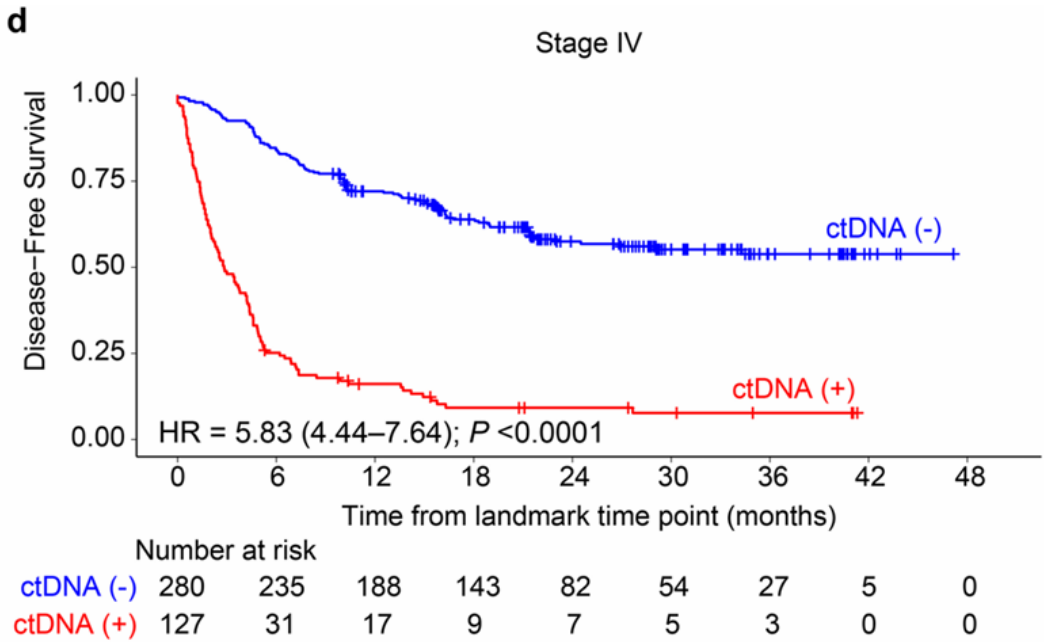
ctDNA status	Negative	Positive
Events %	5.05 (24/475)	66.67 (28/42)
24M-DFS % (95% CI)	94.20 (91.40–96.20)	33.70 (19.50–48.40)
mDFS (mo)	NR	7.56 (4.99–NR)

- Hard to interpret as many received chemotherapy
- Recurrence of 5% at 2 years is compelling but this may have been ameliorated by chemo in this group of patients
- Possible confounding variables: ctDNA+ patients are more likely to have more unfavorable high-risk features (no all high-risk are created equal) and may have more advanced co-morbidities (perforation, post op complications, T4B, etc…)

Galaxy: Update on Stage 3 and 4 Disease



ctDNA status	Negative	Positive
Events %	12.01 (82/683)	72.22 (117/162)
24M-DFS % (95% CI)	86.0 (82.72–88.70)	25.90 (19.0–33.40)
mDFS (mo)	NR	9.48 (7.16–11.70)



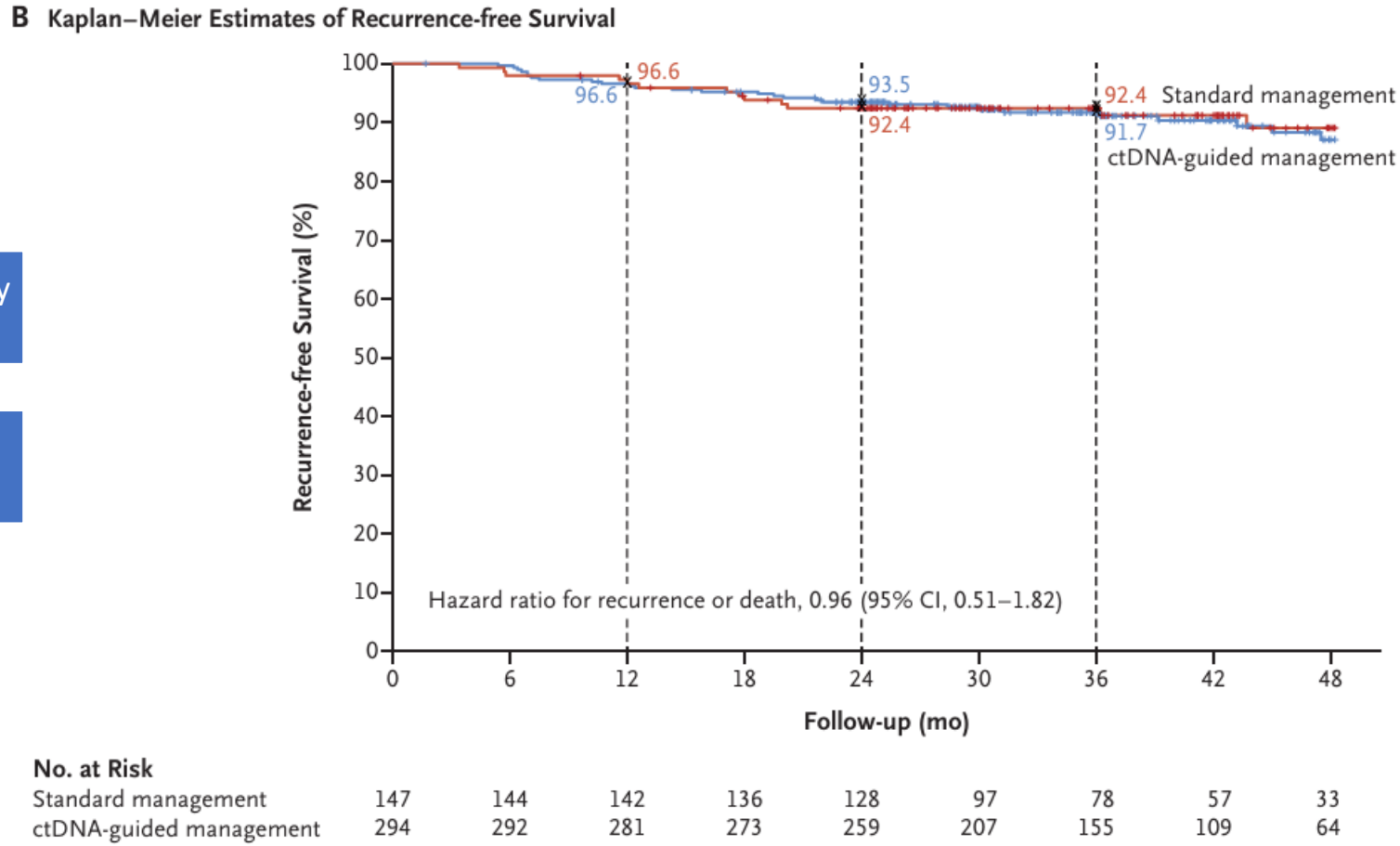
ctDNA status	Negative	Positive
Events %	40.71 (114/280)	89.76 (114/127)
24M-DFS % (95% CI)	57.48 (50.97–63.44)	9.24 (4.79–15.48)
mDFS (mo)	NR (26.91–NR)	2.83 (2.17–4.21)

- ALL PATIENTS ARE HIGH RISK. 12% recurrence at 2 years despite chemo in ctDNA- stage 3 and 41% at 2 years in resected ctDNA- stage 4 disease!! NOT READY TO EXCLUDE ADJ Treatment!

Prospective Studies: Dynamic

Stage 2
2:1 Randomization

- ctDNA directed adj (only ctDNA+ receive RX)
- SOC: physician choice



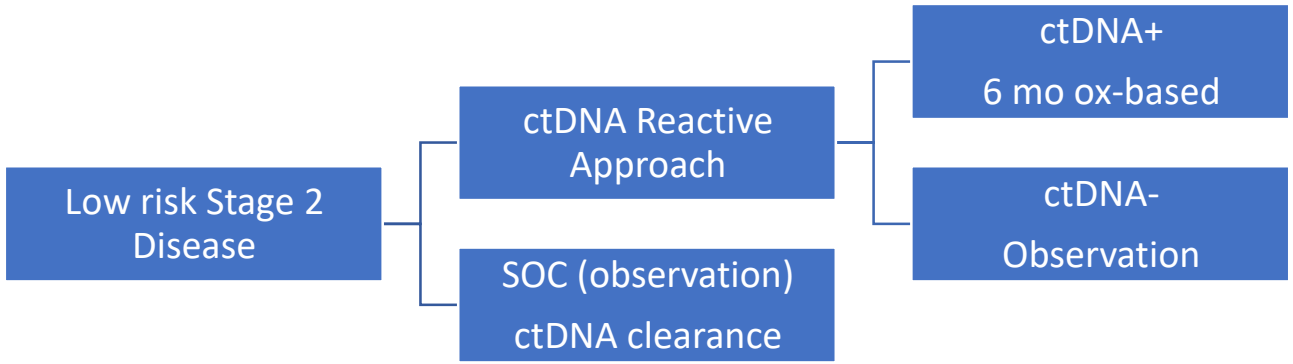
DYNAMIC: Pitfalls

- Phase 2 trial (not powered to set SOC)
- Confidence interval for inferiority are wild +/-8% difference in OS
- 1/3 of the high-risk (clinical) in the control arm did not received adjuvant RX
- Major discordance in the nature of adjuvant treatment between arms

Treatment Characteristic	Standard Management (N=147)	ctDNA-Guided Management (N=294)	Relative Risk (95% CI)
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)
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)

Treatment imbalance may have led to an overestimation of the benefit of ctDNA directed strategy!

Why is it important to conduct confirmatory clinical trials: GI005 (COBRA)- Van Morris, MD- ASCO 2024



Gardant Lunar assay (not Reveal)
Estimated sensitivity 56%
Estimated specificity 95%

596 patients with baseline ctDNA assessment

- 16 + ctDNA at baseline
  - 9 ctDNA+ on the reactive chemo arm, only 1 cleared
  - 7ctDNA+ on the observation arm, 3/7 cleared

- STUDY CLOSED FOR FUTILITY

Morris, V. ASCO 2024

DYNAMIC III: Intensification vs SOC in ctDNA+ Stage III CRC

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumor-Informed ctDNA Analysis
(SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- **ctDNA-Negative → De-escalate**
- **ctDNA-Positive → Escalate**

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Pre-Planned SoC → Escalation

No chemotherapy → 5FU/Cape
5FU/Cape → 6M Oxaliplatin doublet
3M Oxaliplatin doublet → 6M Doublet or ≥ 3M FOLFOXIRI
6M Oxaliplatin doublet → ≥ 3M FOLFOXIRI

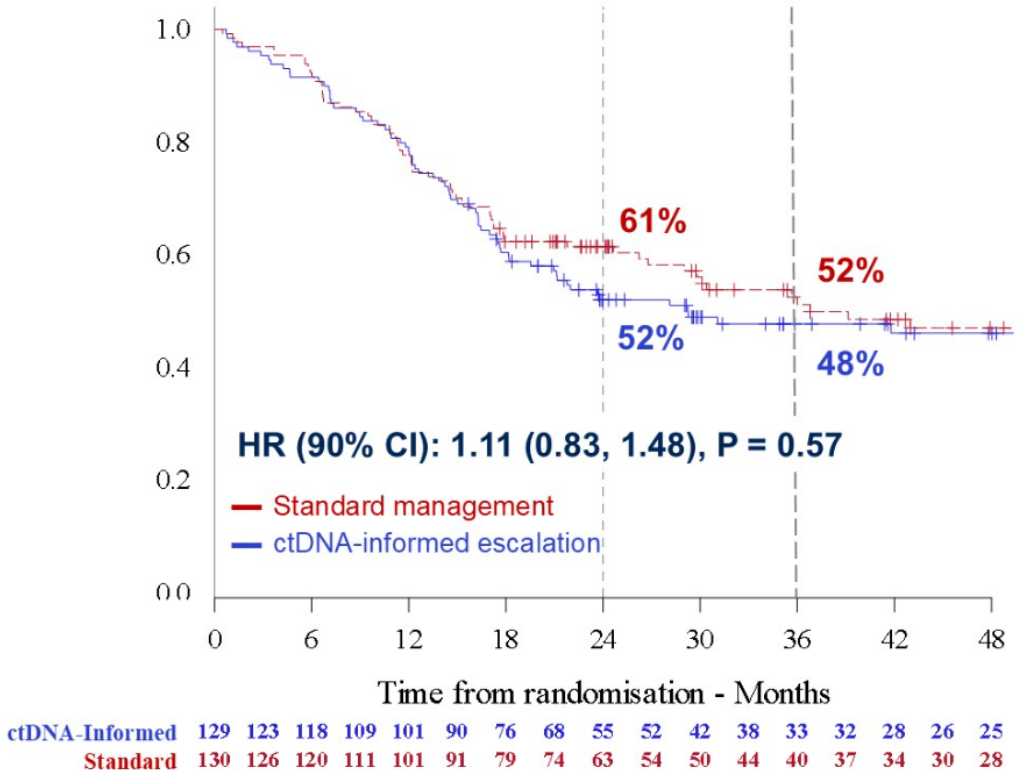
Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

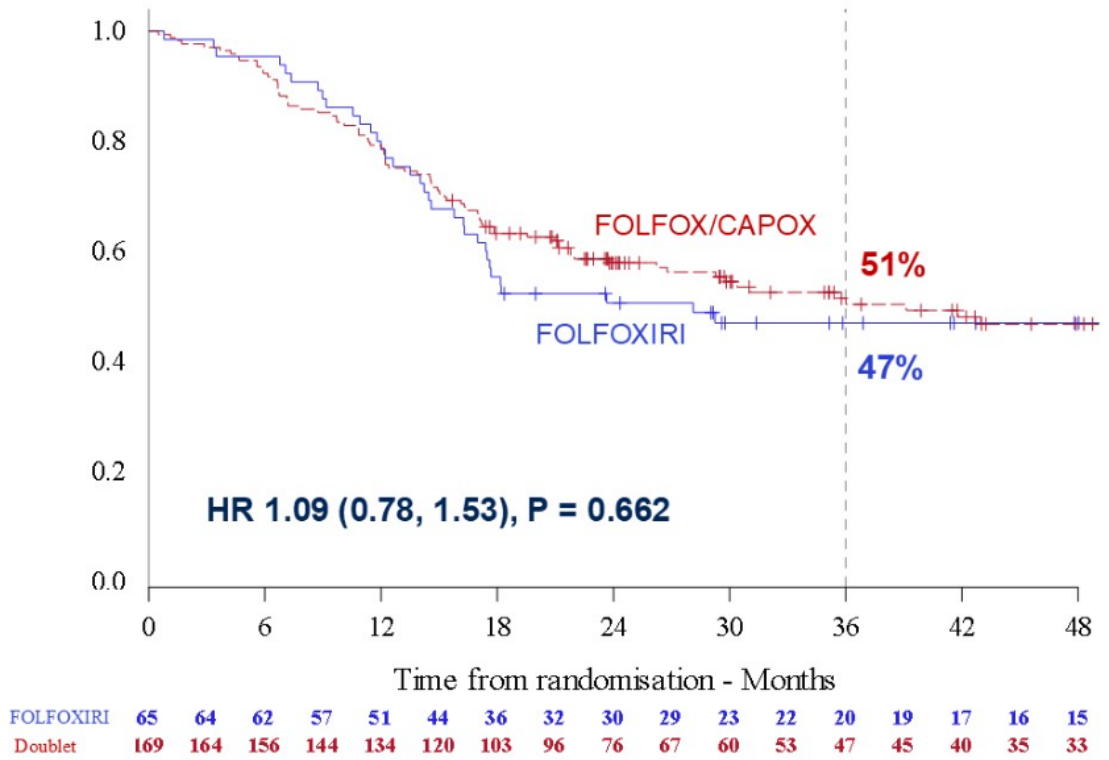
Stratified by clinical risk (low vs high) and sites

DYNAMIC III: Relapse Free Survival

RFS in Intensification vs SOC



RFS in FOLFOXIRI vs SOC



Myth, Myth, and Myth!!

- Myth #1: post-op ctDNA should direct adjuvant therapy and will guide intensification and de-intensification
- **Myth #2: surveillance ctDNA is better than imaging in finding recurrence which will improve outcomes**
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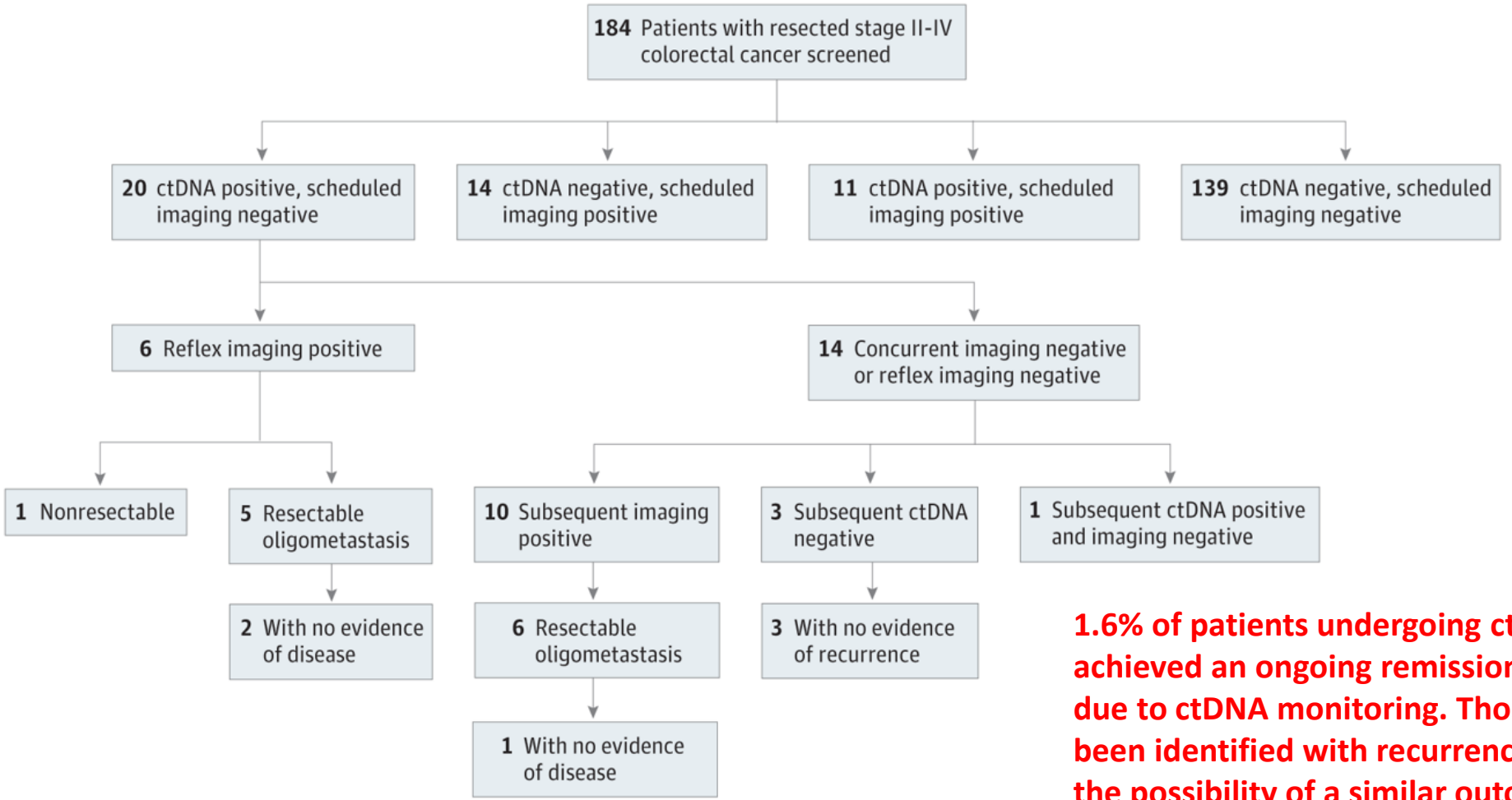
ctDNA Surveillance in CRC and Subsequent Curative Outcome of Salvage Surgery (COH experience)



1.6% of patients undergoing ctDNA (Signatera) achieved an ongoing remission following surgery due to ctDNA monitoring. Those pts may still have been identified with recurrence at a later date with the possibility of a similar outcome (early detection may not have impacted outcome)

Fakih et al. JAMA Network, 2024

COH Experience

- 45/184 pts on surveillance had + recurrence by imaging or ctDNA
- 14/45 had only Imaging Recurrence
- Lung only mets predominantly negative by ctDNA
- No difference in time to recurrence by imaging or ctDNA

Table 4. Surveillance Details for Patients in the Circulating Tumor DNA–Negative and Imaging-Positive Cohort

Patient No.	Stage at diagnosis	Neoadjuvant or adjuvant chemotherapy	Time from surgery to imaging positive, mo	Site of recurrence
1	II	Yes	21	Abdominal wall
2	II	Yes	9	Lung
3	III	Yes	17	Lung
4	III	Yes	6	Lung
5	III	Yes	15	Pelvis or peritoneum
6	III	Yes	17	Lung
7	III	No	15	Lung
8	III	Yes	2	Pelvic lymph node
9	III	Yes	12	Lung
10	III	Yes	9	Lung
11	IV	Yes	8	Lung
12	IV	Yes	19	Lung
13	IV	Yes	16	Lung
14	IV	Yes	5	Liver

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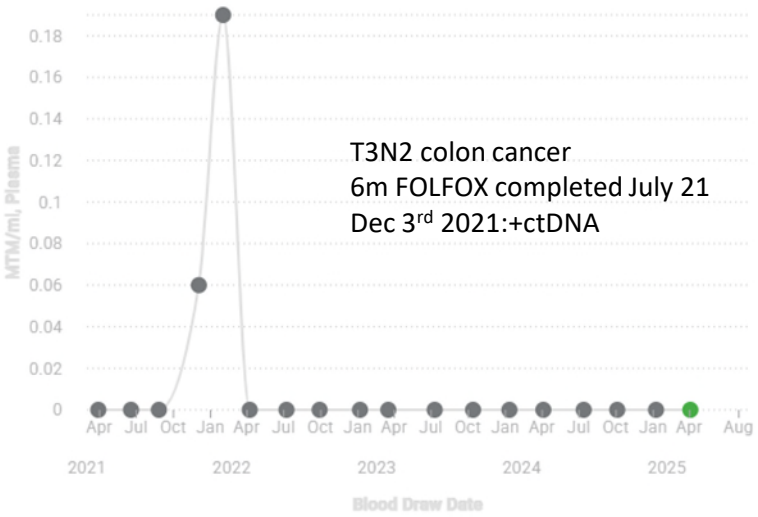
PEGASUS Trial: ctDNA guiding switch therapy in the adjuvant setting

"After 3 months of CAPOX, 11/35 LB+ pts were converted to LB- (31%), but 8/11 relapsed or LB re-positivized. Of the 23 LB+ pts receiving FOLFIRI after CAPOX, 12 remained LB+ (52%) among which 6 relapsed, while 11 were converted to LB- remaining relapse-free at the time of analysis (48%), thus suggesting an effect of FOLFIRI in the MRD setting."

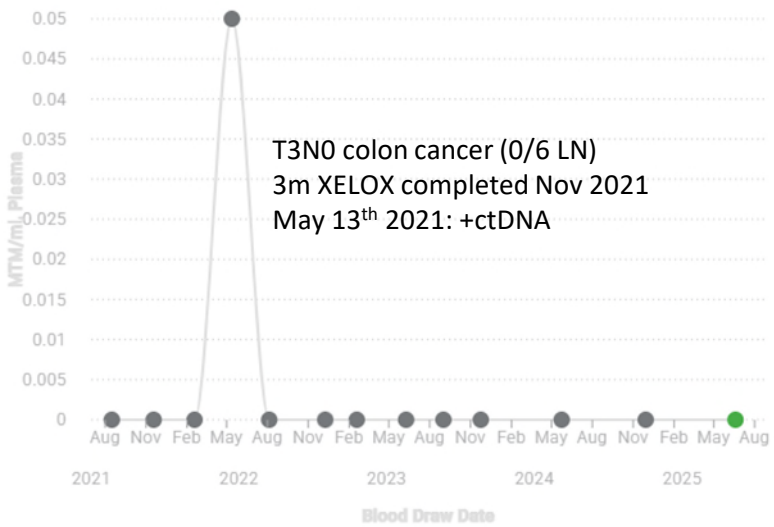
MY CRITIQUE:

- Irinotecan does not work in the adjuvant setting
    - Irinotecan does not work in the adjuvant settings
    - Dynamic III was negative (adding irinotecan did not help)
    - Does not account for spontaneous clearance of ctDNA post adjuvant therapy
    - No supporting long-term followup

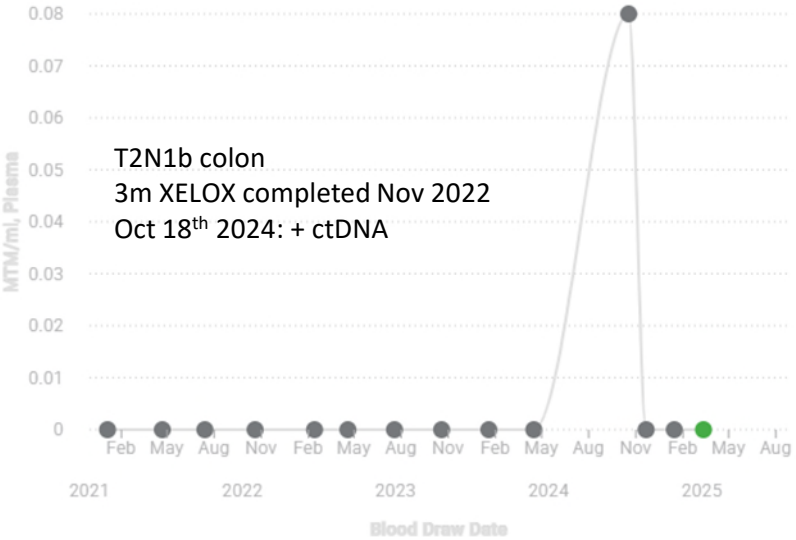
Adjuvant Oxaliplatin-Based Therapy is Associated with Transient Positive ctDNA Conversion after Treatment Completion and without Disease Recurrence in MSS CRC



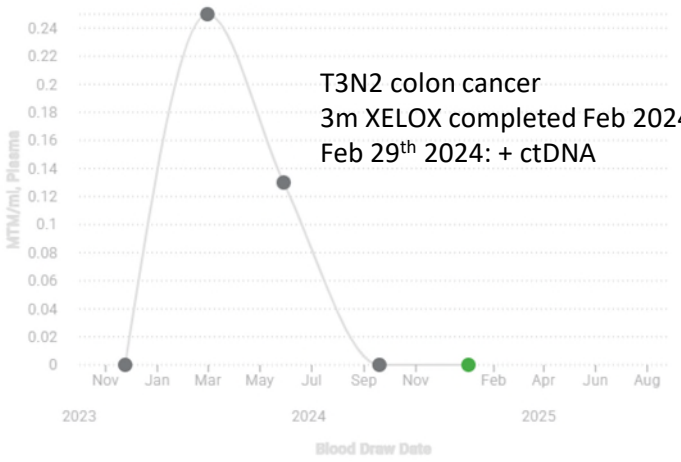
T3N2 colon cancer
6m FOLFOX completed July 21
Dec 3rd 2021:+ctDNA



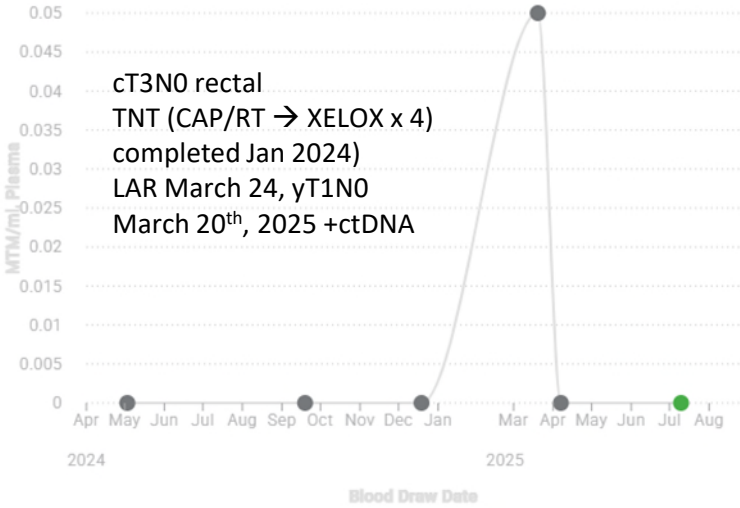
T3N0 colon cancer (0/6 LN)
3m XELOX completed Nov 2021
May 13th 2021: +ctDNA



T2N1b colon
3m XELOX completed Nov 2022
Oct 18th 2024: + ctDNA



T3N2 colon cancer
3m XELOX completed Feb 2024
Feb 29th 2024: + ctDNA



cT3N0 rectal
TNT (CAP/RT → XELOX x 4)
completed Jan 2024)
LAR March 24, yT1N0
March 20th, 2025 +ctDNA

COST to society

150,000 colon cancers per year

- Assuming 100,000 undergo surveillance
- Assuming pre-op testing and then Q3 m x 2 years and Q6 m x 3 years = 15 assays
- 15 x 100,000 x 3500 =

5.25 BILLION DOLLARS:

Does not include indirect costs of additional testing and treatments

CHAT GPT

what is the cost of signatera

The cost of the **Signatera™ test**—a personalized blood test used to detect molecular residual disease (MRD)—can vary significantly depending on your insurance coverage and eligibility for financial assistance.

💰 Estimated Pricing Breakdown

- **List Price (CMS Fee Schedule)**: Around **$3,500 to $3,920** per test, based on recent updates to the Medicare fee schedule [1].
- **With Insurance**:
  - If your plan is **in-network** with Natera, over **60% of patients pay nothing out-of-pocket** [2].
  - If you haven't met your deductible, you may have some out-of-pocket costs.
- **Without Insurance or Financial Assistance**:
  - You may be eligible for a **reduced price of $149 or less** per test through Natera's financial assistance program [2].