Atrium Health
Wake Forest Baptist

ctDNA Adjuvant and Oligometastasis Colon Ca **YES!**

Caio Max S. Rocha Lima, M.D.

Professor of Medical Oncology
GI DOT and Phase I DOT co-leader
Department Internal Medicine
Division of Hematology and Oncology

Stage II

- Stage II – not high risk – adjuvant therapy unclear to be beneficial.

- High risk patients may benefit from adjuvant therapy
  - Lymphovascular invasion, perineural invasion, bowel obstruction, <12 lymph nodes examined, perforation, and close, indeterminate or positive margins

- Multi-gene assays (ColonPrint and Oncotype) may be predictive of risk of recurrence
  - However, they do not predict benefit to adjuvant chemotherapy

- ctDNA ???????-YES

J Clin Oncol. 2022;40(8):892. Epub 2021 Dec 22.

Stage III

- Stage III Colon Cancer has lots of heterogeneity
- FOLFOX, XELOX, 5FU, Capecitabine are options
- IDEA trial 3 months =/~ 6 months of adjuvant chemotherapy
  - Except for high risk: T4 and/or N2
    - If 3 months subset analysis of IDEA collaboration suggests that CAPOX/XELOX may be a better than FOLFOX
- Still, we treat many to only benefit few
  - Analysis of 12,834, the absolute DFS gain between T1N1a and T4N2b were 8% and 20%, respectively.

N Engl J Med 2004; 350:2343-2351. J Clin Oncol. 2011 Apr 10;29(11):1465-71
Lancet Oncol 2020; 21:1620. J Clin Oncol. 2022;40(8):892. Epub 2021 Dec 22.

CT DNA
The tests

- Tumor Informed: Signatera, RaDaR, Assure, Haystack Oncology, MAESTRO…

- Tumor Uninformed: Reveal, Galleri

Sensitivity ctDNA increases with frequency testing

- Sensitivity of ct DNA within 8 weeks from surgery is between 40 and 50%. JAMA Onc 2019, Clin Cancer Res 2021, GI ASCO 2021.
- Sensitivity goes up to over 80 % with serial testing. JAMA 2019, Cancers (Basel) 2020, GALAXI ASCO GI 2024

A Few Concepts

- MRD Window: 2-12 weeks post-surgery and before the start of chemotherapy
- Surveillance Window: > 2 weeks post adjuvant therapy or > 12 weeks post surgery if patient goes for observation

ct DNA positive at MRD point is Predictive of Recurrence Stage II Retrospective Data

- Postoperarive Colon Cancer :
  - No Adjuvant (Stage II) : ctDNA + (14 pts) and ctDNA – (164 pts):HR 18 (CI 7.9-40) independent predicting recurrence
    - **ALL 14 PATIENTS RELAPSED within 2 years**
  - Adjuvant : ctDNA + (3 pts) and ctDNA – (41 pts):HR 11 (CI 1.8-68) independent predicting recurrence
    - **ALL 3 PATIENTS RELAPSED within 10 months**

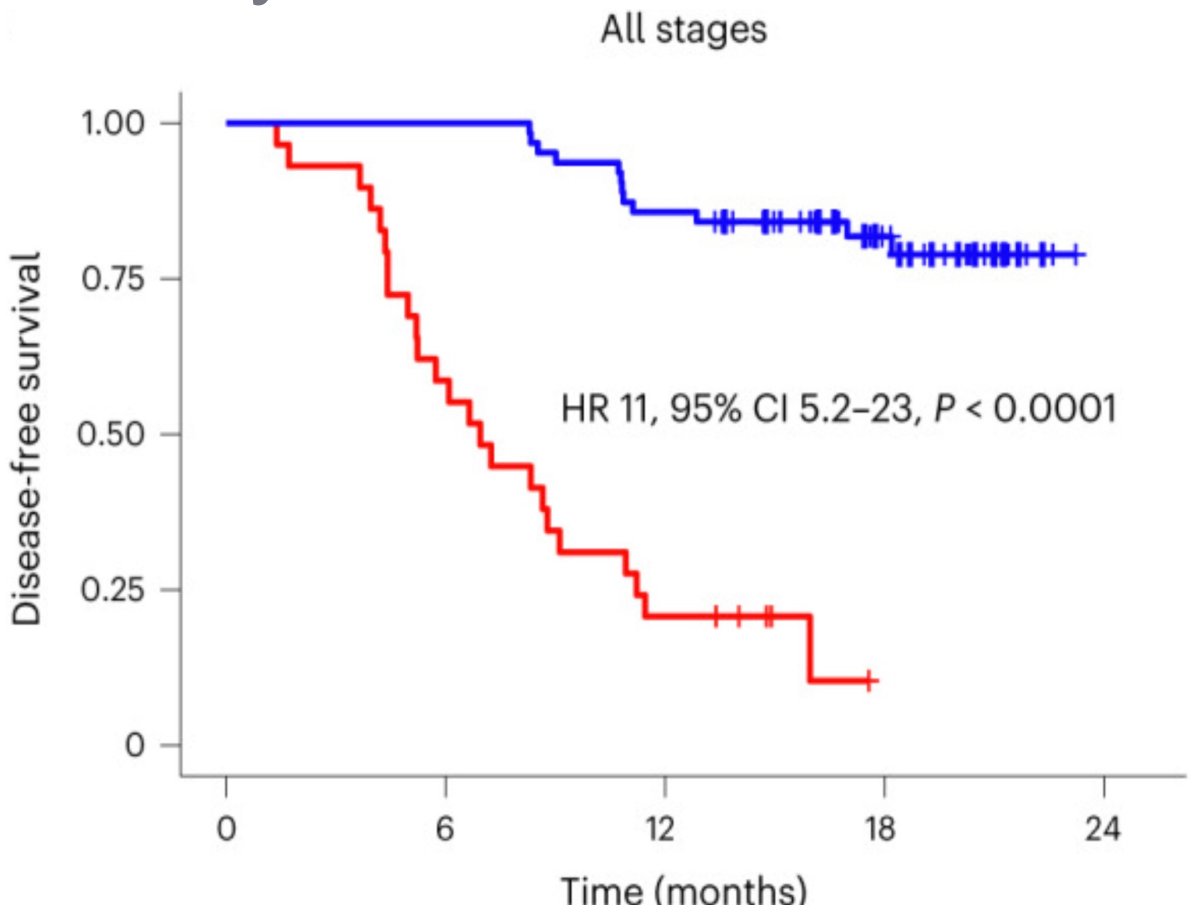
Tie et al. Sci Transl Med, 2016

ctDNA Predictive of Relapse confirmed in multiple trials stages I-IV

- Stage I-III
  - Henriksen ASCO GI 2021: HR 11
  - Parikh Clin Can Res 2021: HR 11.2
  - Henriksen ASCO 2021: HR 7.2
- Stage IV Post Liver Mets Resection
  - Overman ASCO 2017 : HR 3.1
  - Tie PLOS One 2021: HR 6.3

ct DNA is Predictive of Recurrence Independent of Stage GALAXY study

- **2,998 ctDNA-+ resected stage I-IV (t**umor-informed Signatera assay) Median FU 16.7 M
  - ctDNA cleared in 68% of chemo-treated patients by 6 months after surgery
  - HR 11 (CI 5.2-23, p<0.0001) favoring clearance



Kotani D et al. Nat Med. 2023 Jan;29(1):127-134

Atrium Health Wake Forest Baptist

Is positive ctDNA sufficient to recommend adjuvant chemo in stage II? DYNAMIC

- 455 stage II 1:2 ratio
  - standard risk-factor–guided chemotherapy or
  - ctDNA positive adjuvant and ctDNA negative no.
    - The trial had a dual objective:
      - ctDNA-guided would be noninferior to standard management at 2-year RFS (primary)
      - Less chemotherapy would be used with the ctDNA-guided approach (secondary).

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

DYNAMIC
The results confirmed both hypotheses:

- The 2-year recurrence-free survival was 93.5% with ctDNA-guided management and 92.4% with standard management.
- Chemotherapy use was indicated in 15% of the patients in the ctDNA-guided group and 28% of the patients in the standard-management group

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

Is positive ctDNA sufficient to recommend adjuvant chemo in stage II?

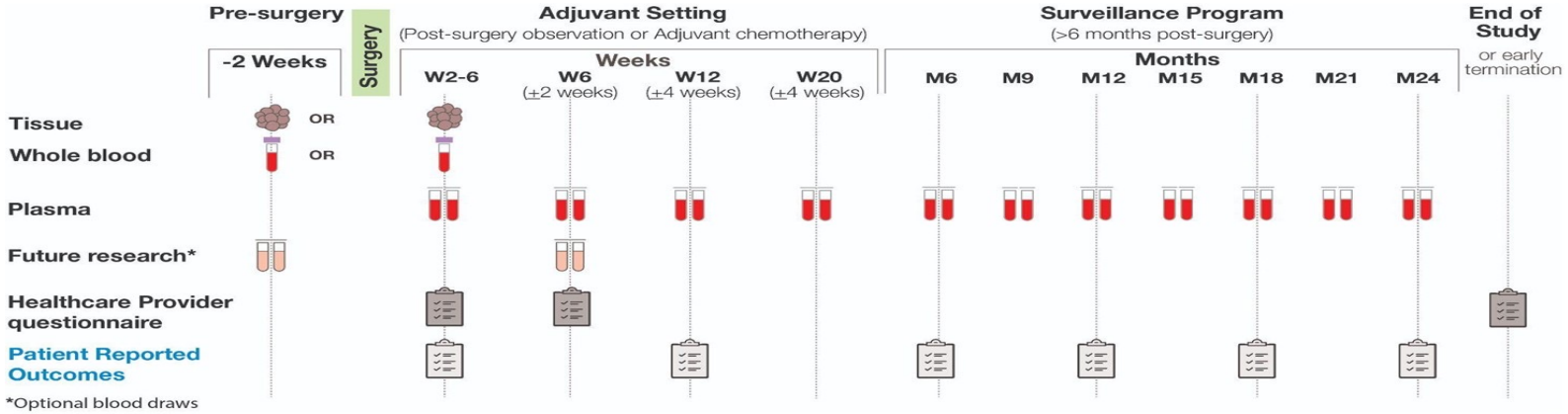
- YES

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

Is negative ctDNA sufficient to not recommend adjuvant chemo in stage II?

BESPOKE CRC study schema

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]



[1]Kasi et al. *BMJ Open* 2021;11:e047831.

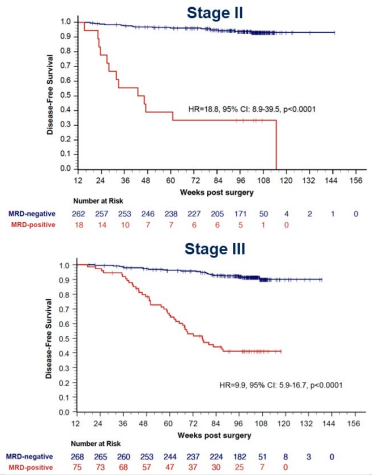
Is negative ctDNA sufficient to not recommend adjuvant chemo in stage II?

ctDNA-positivity at MRD time point is predictive of inferior DFS

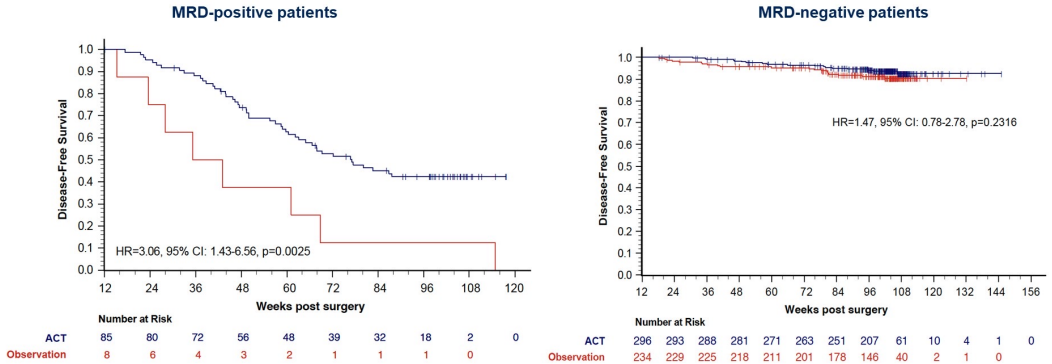
MRD-positivity rate by stage II-III

Stage	Total, N	MRD-negative, n (%)	MRD-positive, n (%)	95% CI for positivity rate
II	280	262 (93.57)	18 (6.43)	4.10-9.93
III	343	268 (78.13)	75 (21.87)	17.82-26.54
Total	623	530	93	

Benchmark for proportion (%) of patients who are MRD-positive with stage II and III colorectal cancer.



Benefit from ACT observed in MRD-positive but not MRD-negative patients



Adjuvant strategy	ACT	Observation
Numbers of events (%)	47/85 (55.29)	8/8 (100)
2-year DFS post surgery, % (95% CI)	42.44 (31.55-52.91)	12.50 (0.66-42.27)
Median DFS post surgery, months (95%)	17.78 (14.37-not reached)	7.52 (3.52-15.88)

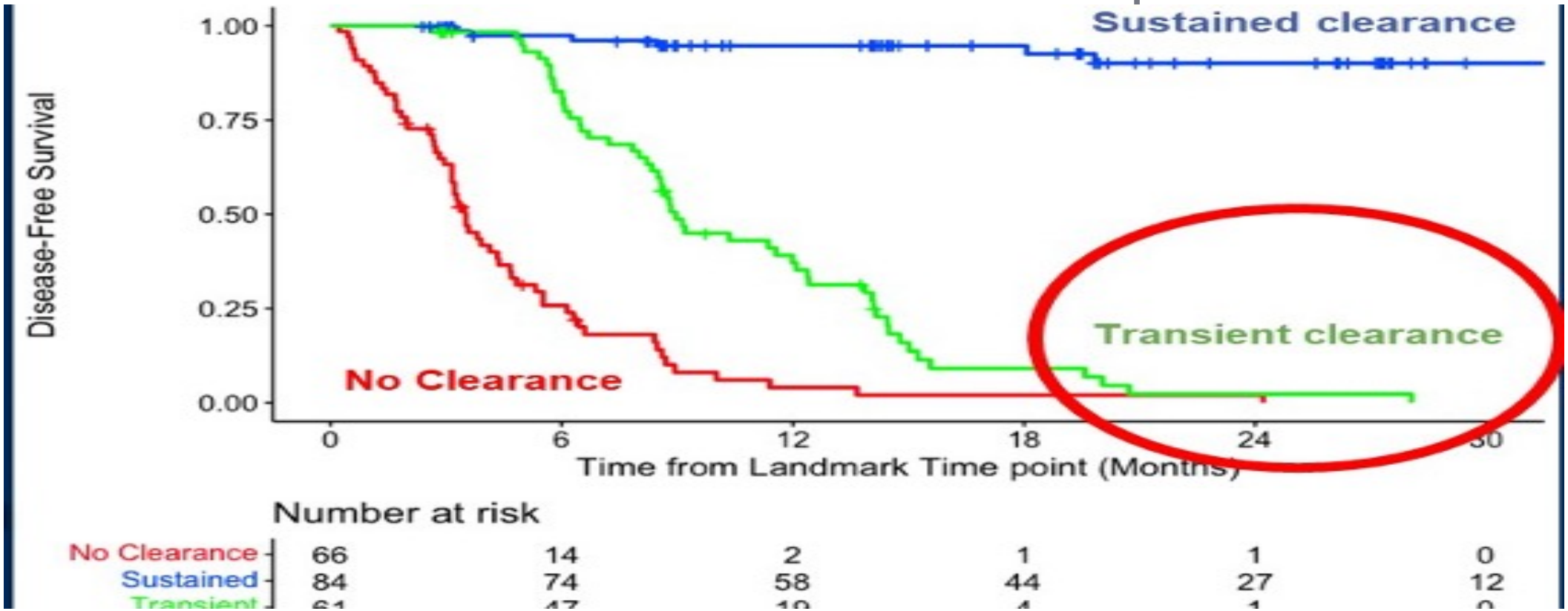
Adjuvant strategy	ACT	Observation
Numbers of events (%)	18/296 (6.08)	20/234 (8.55)
2-year DFS post surgery, % (95% CI)	93.70 (90.03-96.05)	90.39 (85.38-93.75)
Median DFS post surgery, months (95%)	Not reached	Not reached

Is negative ctDNA sufficient to not recommend adjuvant chemo in stage II?

- May be – Dynamic data support this assumption but not applicable for T4 pts

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

ct DNA is Predictive of Recurrence Independent of transient clearance
GALAXY 24 month follow up

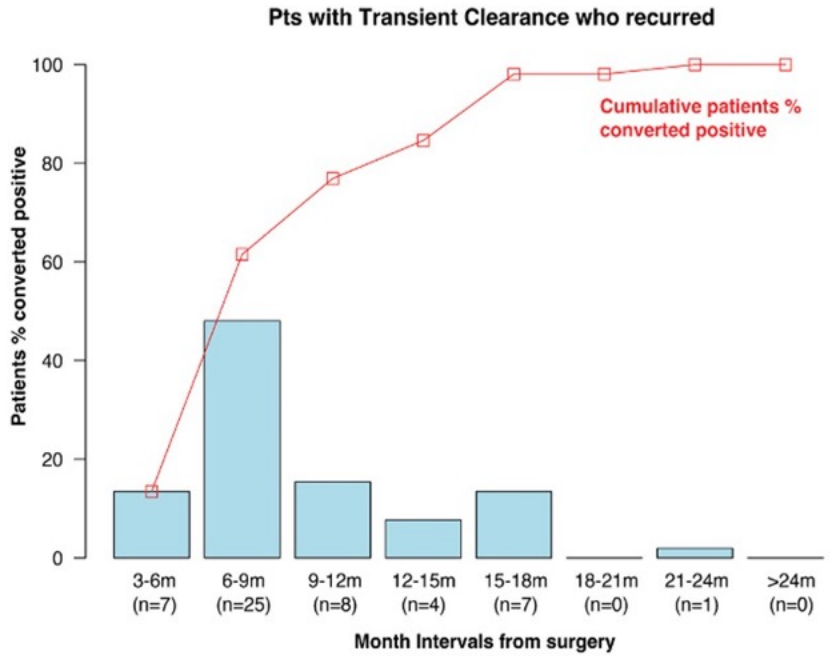


Nakamura et al ASCO GI 2024

Atrium Health Wake Forest Baptist

GALAXY 24 month follow up
Chemotherapy may be suppressing rather than completely eradicating MRD

ctDNA Clearance	Sustained Clearance	Transient Clearance	No Clearance
Events %	7.1 (6/84)	85.2 (52/61)	89.4 (59/66)
Median DFS months (95% CI)	NR	9 (8.5–12.4)	3.5 (3.2–4.7)
24M-DFS % (95% CI)*	90.1 (78.6–95.6)	2.3 (0.02–10.3)	2 (0.02–9.2)
HR	Reference	25.13	87.08
95% CI	Not applicable	10.57–59.73	36.14–209.84
P	Not applicable	<0.0001	<0.0001



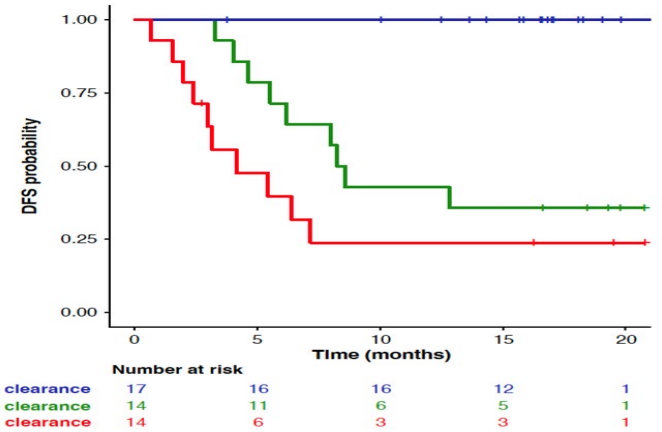
Nakamura et al ASCO GI 2024

Atrium Health Wake Forest Baptist

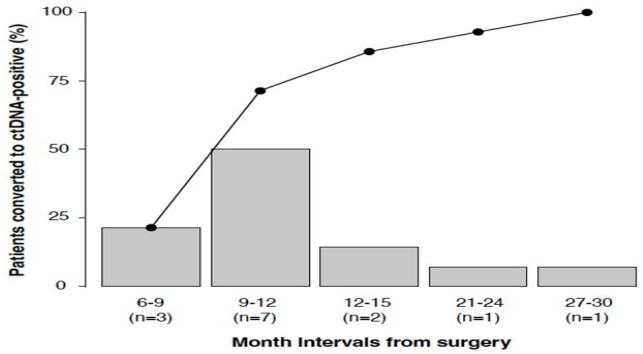
BESPOKE TRIAL
Chemotherapy may be suppressing rather than completely eradicating MRD

Sustained ctDNA clearance is associated with superior DFS when compared to transient or no clearance [8]

DFS by ctDNA clearance patterns



85% of patients with transient clearance develop molecular recurrence by the 15th month



ASCO Gastrointestinal Cancers Symposium #GI24

PRESENTED BY: Pashtoon Kasi, MD, MS

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

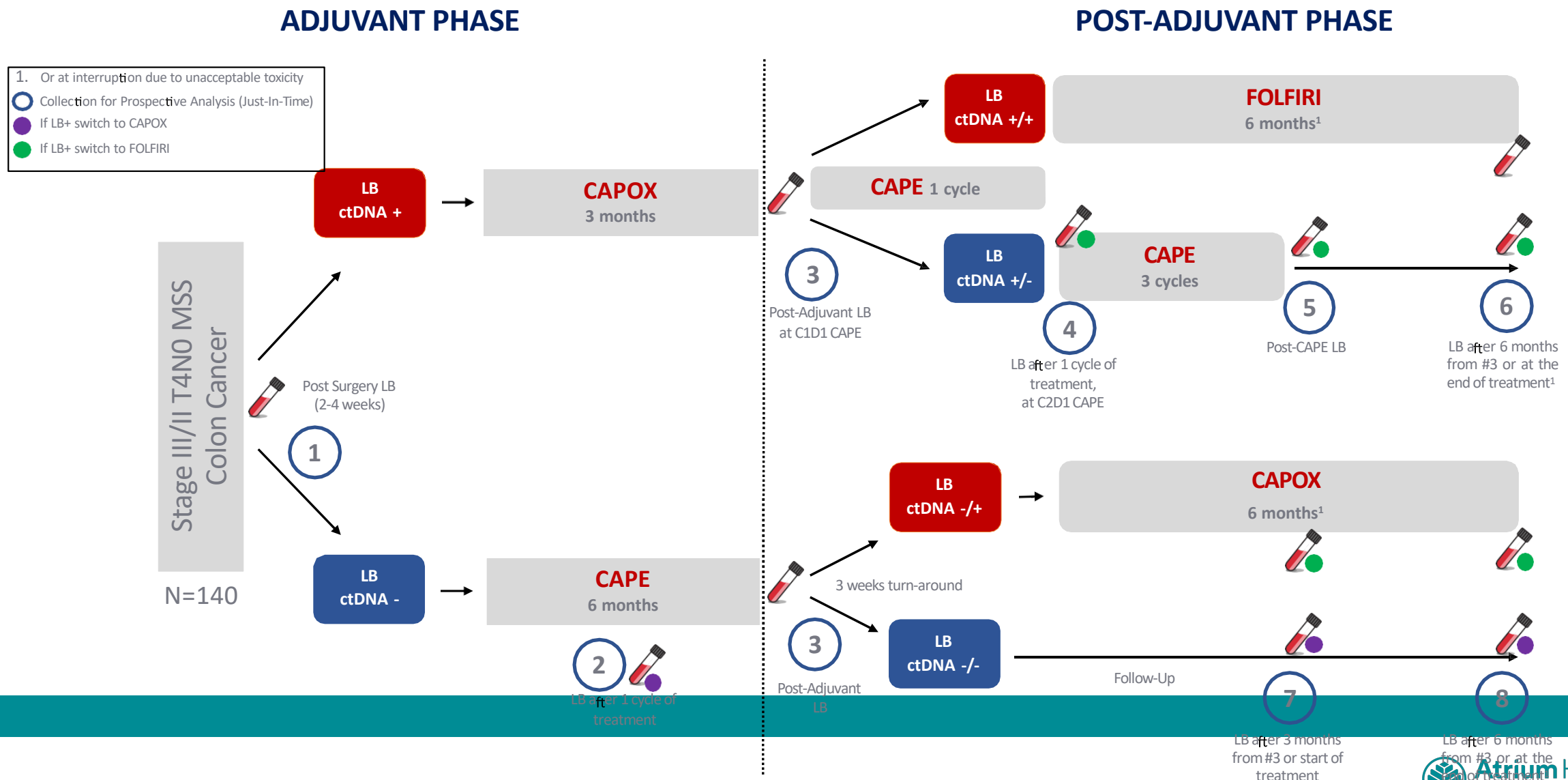
Nakamura et al ASCO GI 2024

Atrium Health Wake Forest Baptist

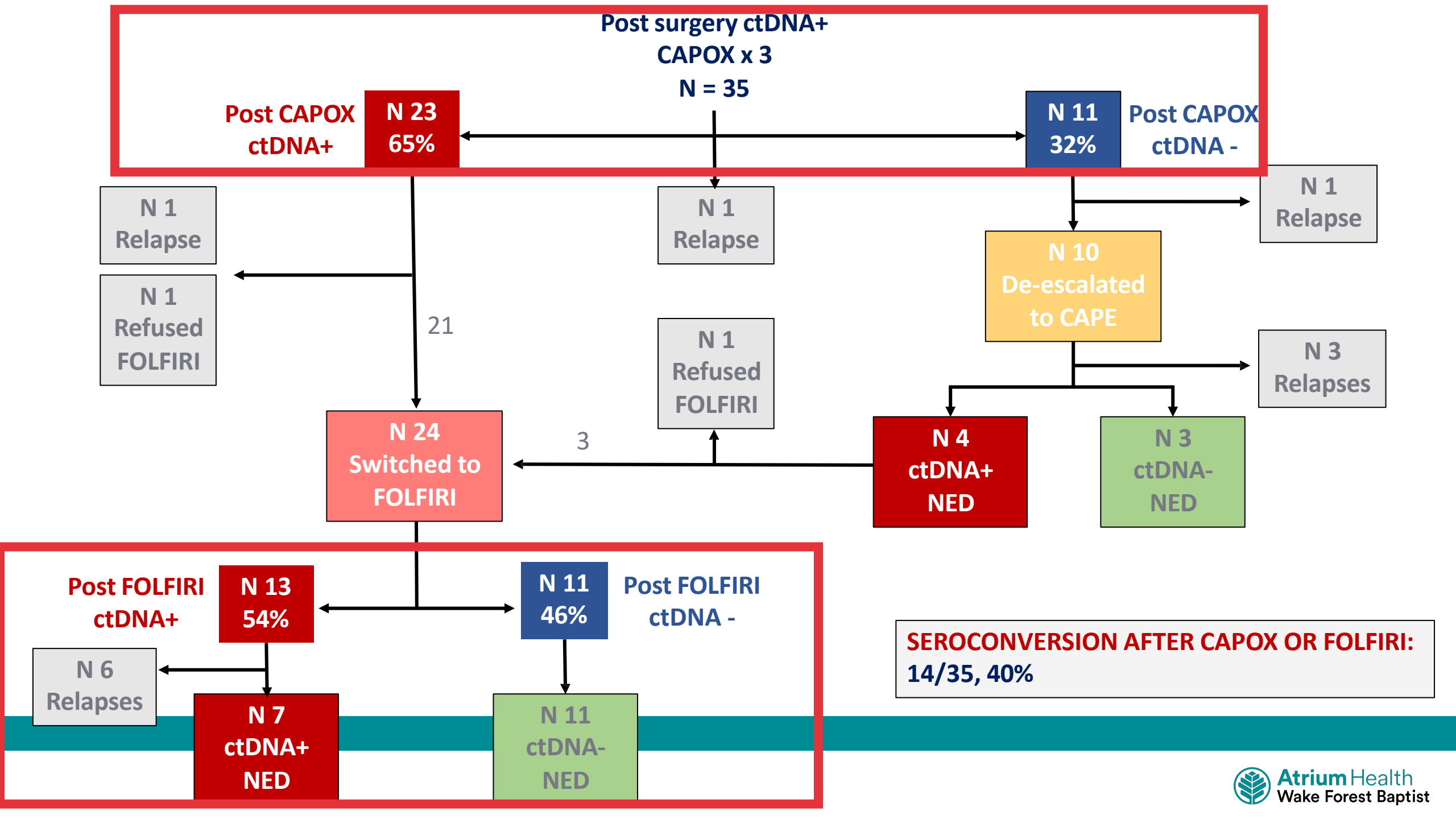
Should we intensify, de-intensify, or change adjuvant therapy based on ctDNA ?

- PEGASUS TRIAL
  - Feasibility 140 pts
  - Primary Endpoint **False negative cases**
  - **Intensifying Cape to CAPOX or changing CAPOX to FOLFIRI**
  - **De-intensify CAPOX to Cape**

Study Design



Atrium Health Wake Forest Baptist



Atrium Health
Wake Forest Baptist

Conclusions

- Please do not listen to Dr Cusnir remarks
  - The sample sizes of the trials are too small…
  - Follow up is not long enough and data are not mature…
  - The trials to answer these questions are still ongoing….
- ctDNA is the strongest prognosticator for recurrence and data strongly suggest it is predictor in the adjuvant setting
- ctDNA MRD should be considered in colon cancer patients with stage II, III, and stage IV post potentially curative surgery
  - Consider escalation of therapy
  - However, negative ct DNA data not sufficient to deescalate therapy at this time

Many Things We Do Not Know

- What do we do when ctDNA remains or become + after adjuvant therapy
- Should we intensify adjuvant chemotherapy if ctDNA+ after 2 or 3 Months adjuvant therapy
- Should we favor tumor informed or not informed ctDNA?
- When should ctDNA be measured?
- Would ct DNA value change according to: cytotoxic X immunotherapy X targeted therapy?

Thanks For The Attention!!!