

ctDNA Defined MRD - Clinical Utility in Colorectal Cancer

Brian R. Kann, MD, FACS, FASCRS

Surgeon-in-Chief and Chair, Dept of Colon &
Rectal Surgery, Ochsner Health

Academic Chair, Dept of Colon & Rectal
Surgery, Xavier Ochsner College of Medicine

Associate Professor of Colon & Rectal Surgery,
Xavier Ochsner College of Medicine

New Orleans, LA



No Financial Disclosures

- Not promoting a particular assay
- Acknowledgment: Lingling Du, MD
- Lots of data, not sure what to do with it
- I have more questions about ctDNA now than I used to

Learning Objectives:

- Describe the differences between tumor-informed vs tumor-agnostic ctDNA assays
- Describe the rationale and indications for utilizing ctDNA in:
 - Making decisions regarding post-surgical treatment for colorectal cancer
 - Post-operative surveillance following curative surgery for colorectal cancer
- Understand a potential strategy for utilization of ctDNA in a rectal cancer “watch and wait” surveillance protocol

- Minimal Residual Disease (MRD) – neoplastic cells that persist below detectable levels after therapy completion
 - Initially used in Acute Lymphoblastic Leukemia
- Circulating Tumor DNA (ctDNA) – MRD that is cell-free DNA originating from tumor cells
 - Half-life approx. 2 hours
 - Arises from apoptosis, necrosis, or phagocytosis of tumor cells

Potential Clinical Uses of ctDNA

- MRD-assessment after surgery
 - Adjuvant therapy guidance
 - Recurrence risk prediction
 - Early recurrence detection during surveillance
-
- Main advantage: ctDNA can potentially detect microscopic disease **months before radiologic recurrence.**

Tumor-Informed Assays

- Next-generation sequencing or digital droplet PCR assays developed from the whole exome or targeted sequencing of a patient's primary tumor
- Advantages:
 - High analytic sensitivity
 - Low probability of false negatives
- Disadvantages:
 - Longer turnaround time for assay development
 - Potential for non-detection of MRD after residual clonal evolution
- Examples: Signatera™ (Natera), RaDaR™ (Inovata/NeoGenetics)

Tumor-Agnostic Assays

- Do not require sequencing of tumor tissue
- Broad panel-based assays – look for genomic alterations and aberrant methylation patterns
- Advantages:
 - Rapid turnaround
 - Simplicity
 - No need for primary tumor tissue
 - Ability to continue to monitor for MRD even after residual tumor clonal evolution
- Disadvantage:
 - Lack of personalized genetic information specific to a patient's tumor
- Example : Guardant Reveal™ (Guardant), Tempus xM MRD™ (Tempus)

Prognostic risk stratification after surgery

- Most mature evidence
- Well-established that patients who are ctDNA (+) post-op have higher risk of recurrence

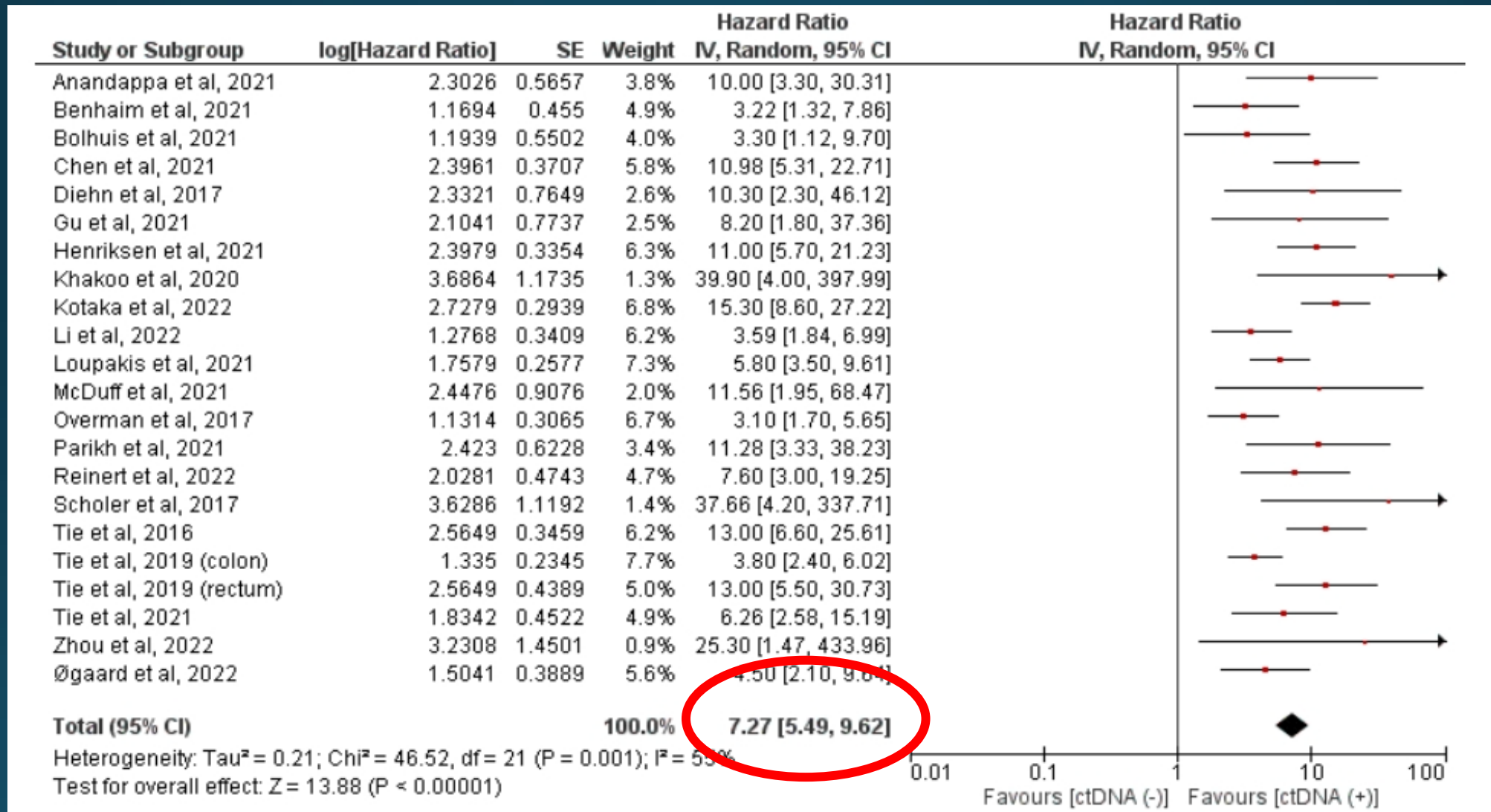
Circulating Tumor DNA as a Minimal Residual Disease Assessment and Recurrence Risk in Patients Undergoing Curative-Intent Resection with or without Adjuvant Chemotherapy in Colorectal Cancer: A Systematic Review and Meta-Analysis

Anusha Chidharla ^{1,*,+}, Eliot Rapoport ^{2,+}, Kriti Agarwal ³, Samragnyi Madala ⁴, Brenda Linares ⁵, Weijing Sun ¹, Sakti Chakrabarti ⁶  and Anup Kasi ^{1,*,\$}

Int. J. Mol. Sci. **2023**, *24*, 10230

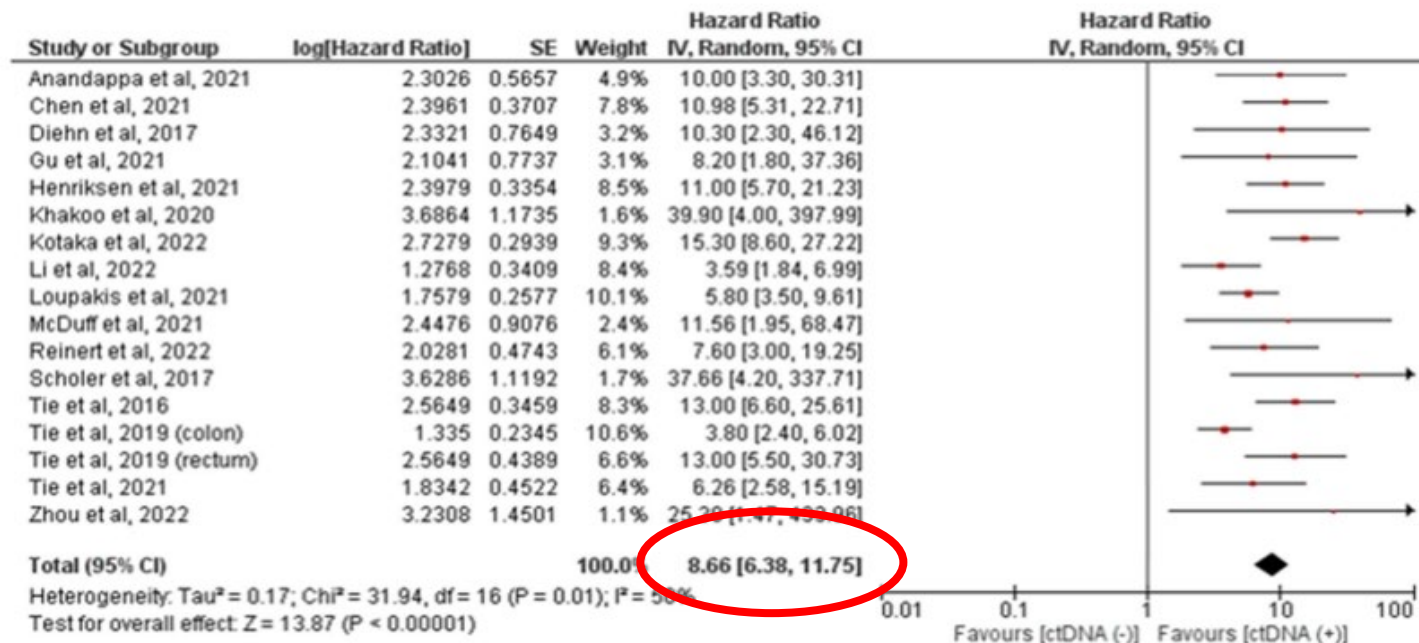
- Investigated impact of post-surgery ctDNA status on recurrence-free survival
- 23 studies, 3568 patients with stage I–III and oligometastatic stage IV colorectal cancer undergoing curative-intent resection.
- Mix of tumor-informed and tumor-agnostic assays
- 13.4% (477) positive for ctDNA post-operatively in MRD window

Post-surgical ctDNA (+) status imparted a significant negative effect on prognosis (HR 7.27)

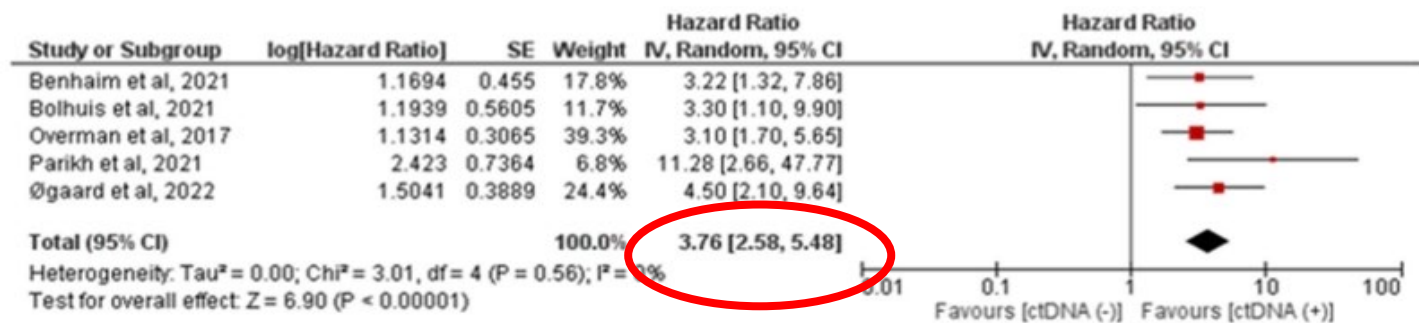


Tumor-Informed Assays (A) vs Tumor-Agnostic Agnostic (B)

A



B



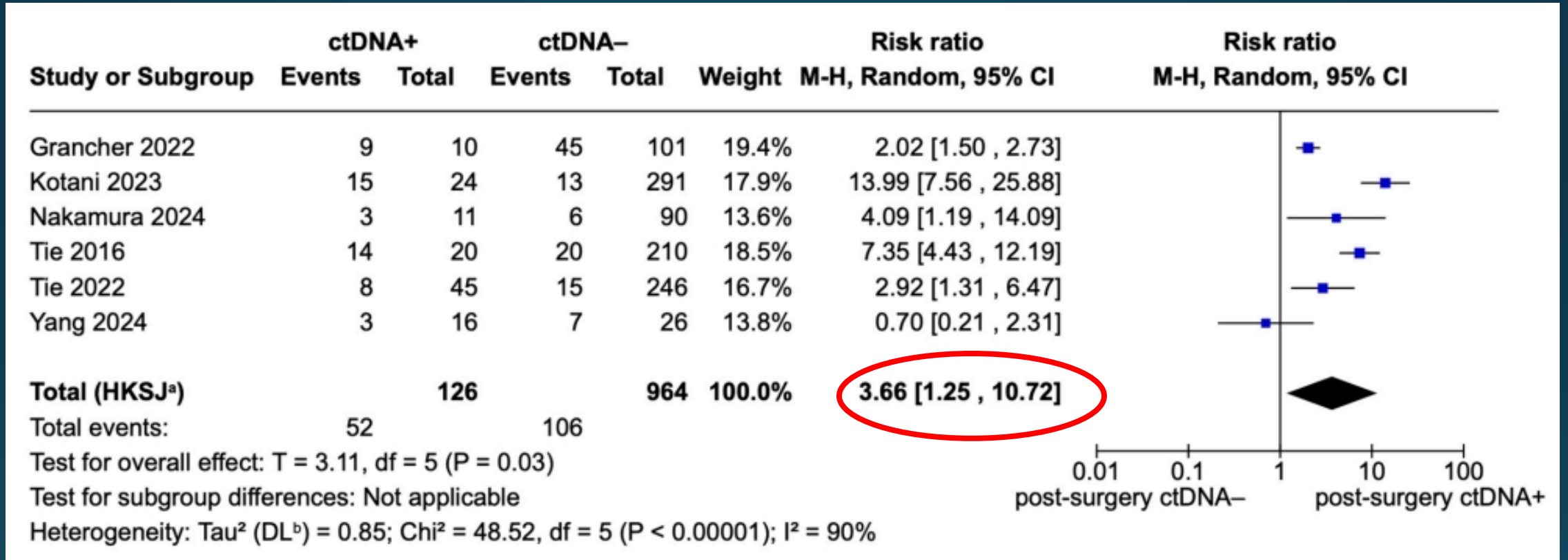
Circulating Tumor DNA as a Real-Time Biomarker for Minimal Residual Disease and Recurrence Prediction in Stage II Colorectal Cancer: A Systematic Review and Meta-Analysis

Silvia Negro ^{1,*} , Alessandra Pulvirenti ¹, Chiara Trento ² , Stefano Indraccolo ^{2,3} , Stefania Ferrari ¹ ,
Marco Scarpa ¹, Emanuele Damiano Luca Urso ¹ , Francesca Bergamo ⁴, Salvatore Pucciarelli ¹ , Simona Deidda ⁵ ,
Angelo Restivo ⁵, Sara Lonardi ^{4,†}  and Gaya Spolverato ^{1,†} 

Int. J. Mol. Sci. **2025**, *26*, 2486

- Evaluate the clinical relevance of ctDNA as a biomarker for recurrence risk assessment and treatment stratification in stage II CRC.
- 7 studies, 1090 patients, 11.6% ctDNA+
 - 5 studies – tumor-informed assay
 - 1 study – tumor-agnostic assay
 - 1 study – mix of both

Post-operative ctDNA (+) had a significantly higher risk of recurrence compared to ctDNA (-) patients



ctDNA-Guided MRD Assessment to Help Guide Treatment Decision

- Use of ctDNA testing to detect persistent neoplastic disease after completion of therapy
- Potential to help inform decisions around ACT
- Typically performed 4-6 weeks after completion of therapy to ensure clearance of cell-free DNA (“MRD window” typically 2-10 weeks post-op)
- Shown to be superior to CEA as a biomarker for MRD
- Stage II colon cancer w high risk features – use ACT?
- “Low risk” stage III colon cancer – omit ACT?

ctDNA-Guided MRD Assessment to Help Guide Treatment Decisions

- Major Trials
 - CIRCULATE-Japan/GALAXY
 - DYNAMIC II
 - DYNAMIC III
 - COBRA
 - BESPOKE-CRC

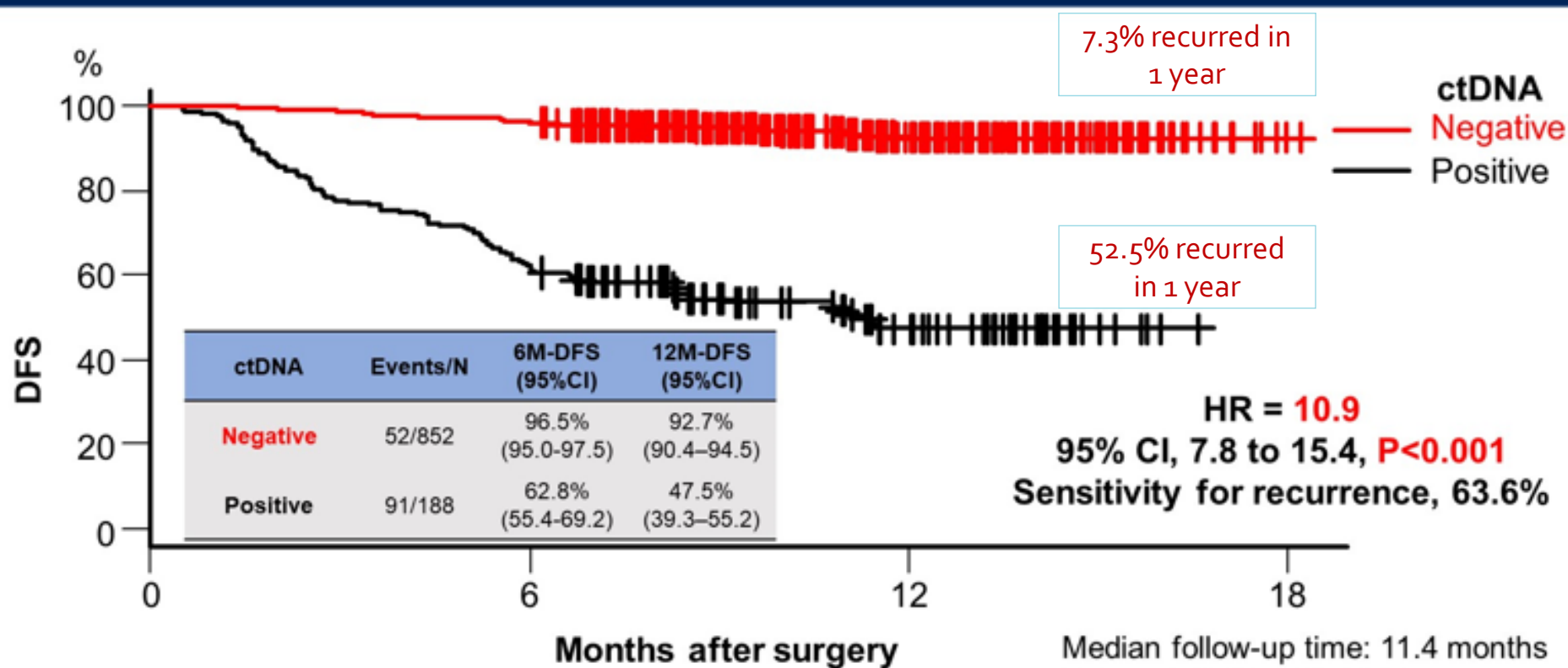
Association of circulating tumor DNA dynamics with clinical outcomes in the adjuvant setting for patients with colorectal cancer from an observational GALAXY study in CIRCULATE-Japan

Masahito Kotaka Gastrointestinal Cancer Center, Sano Hospital, Kobe, Japan

Co-authors; Hiromichi Shirasu, Jun Watanabe, Kentaro Yamazaki, Keiji Hirata, Naoya Akazawa, Nobuhisa Matsuhashi, Mitsuru Yokota, Masataka Ikeda, Kentaro Kato, Alexey Aleshin, Shruti Sharma, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Yoshiaki Nakamura, Hiroya Taniguchi, Masaki Mori, Takayuki Yoshino

- Observational study
- GALAXY utilized a personalized, tumor-informed ctDNA assay (Signatera). Blood samples collected before surgery and 4, 12, 24, 36, 48, 72 and 96 weeks after surgery.
- Patients with stage I-IV colon cancer (stage IV eligible for resection) were enrolled
- 1040 patients, median follow up time 11.4 months

DFS by post-op-4w ctDNA status in overall population (pStage I-IV)

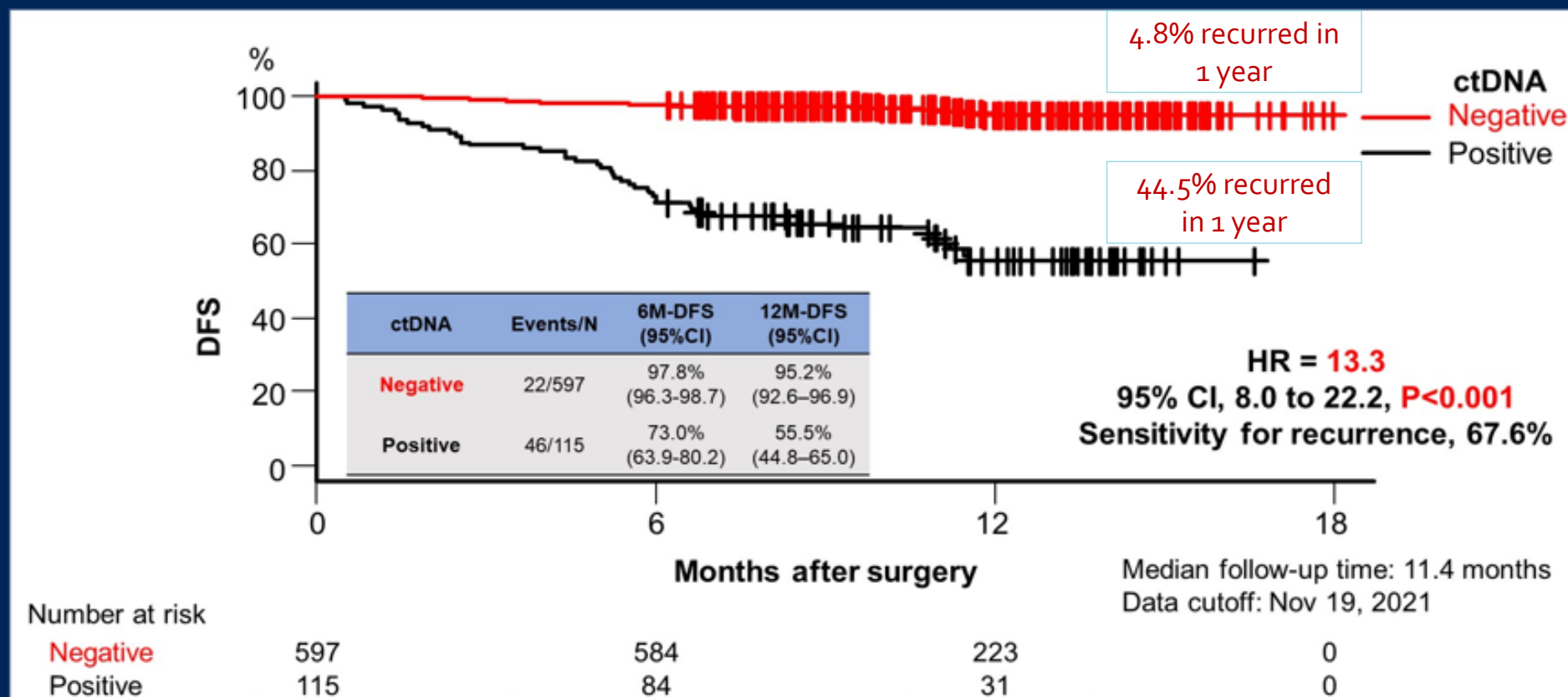


Number at risk

Negative	852	822	310	1
Positive	188	118	38	0

DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

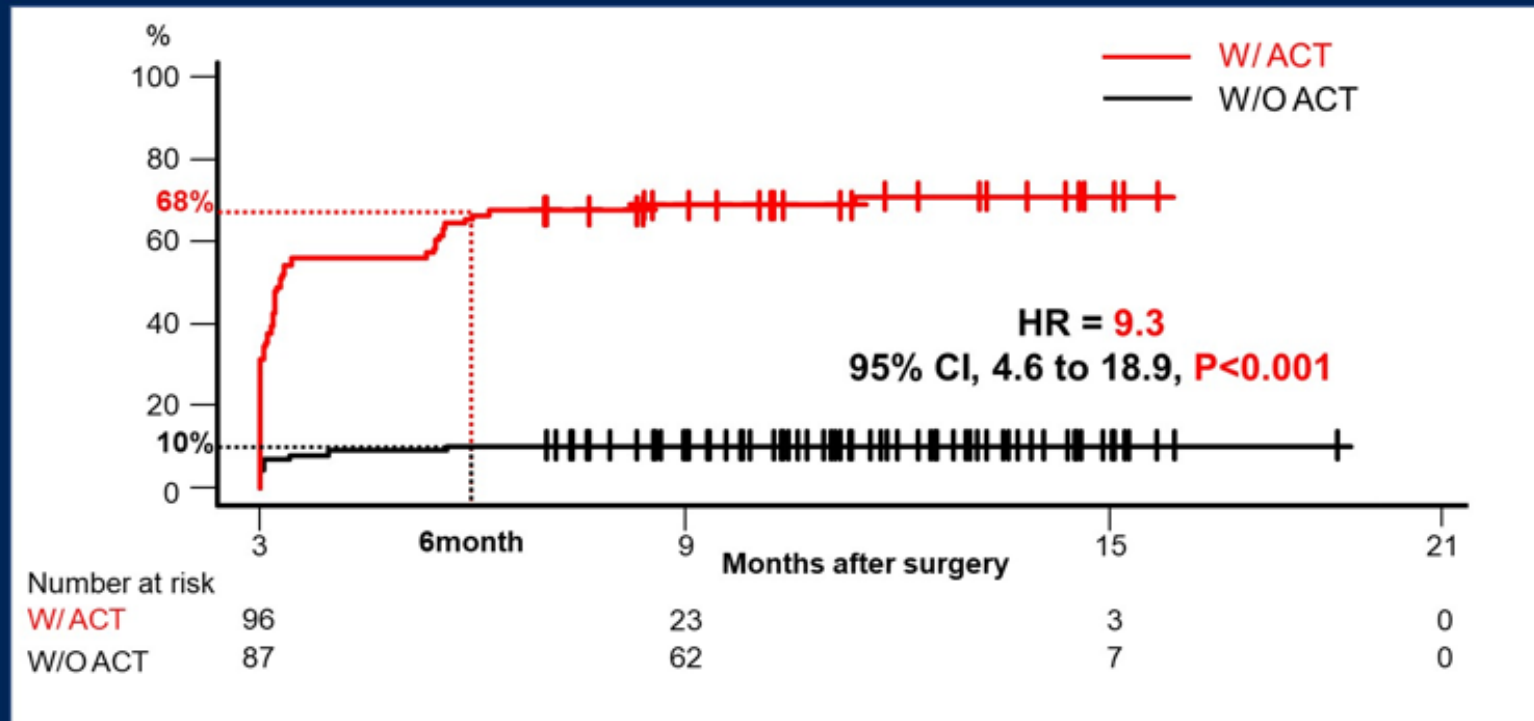
DFS by post-op-4w ctDNA status in overall population (pStage II-III)



DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

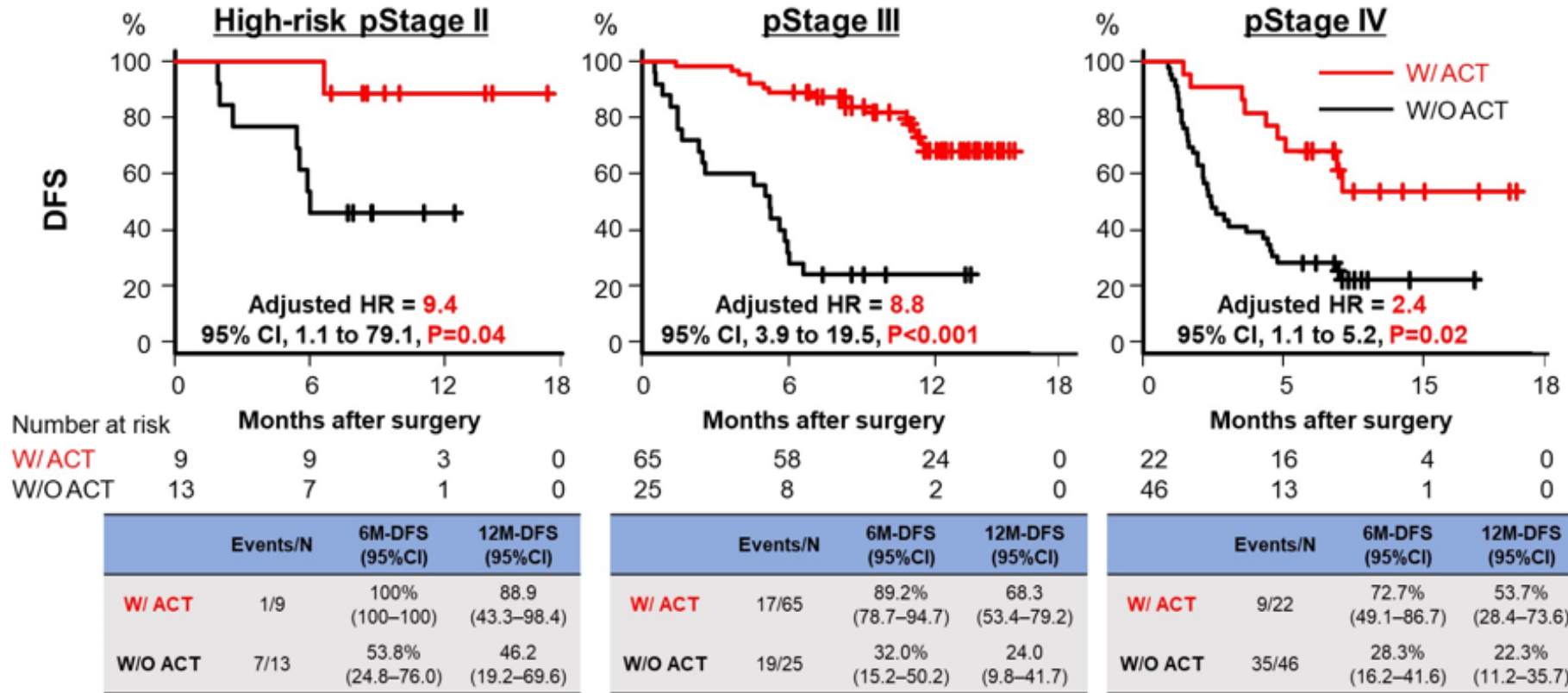
ctDNA clearance rate

Cumulative Incidence of ctDNA clearance pStage I-IV



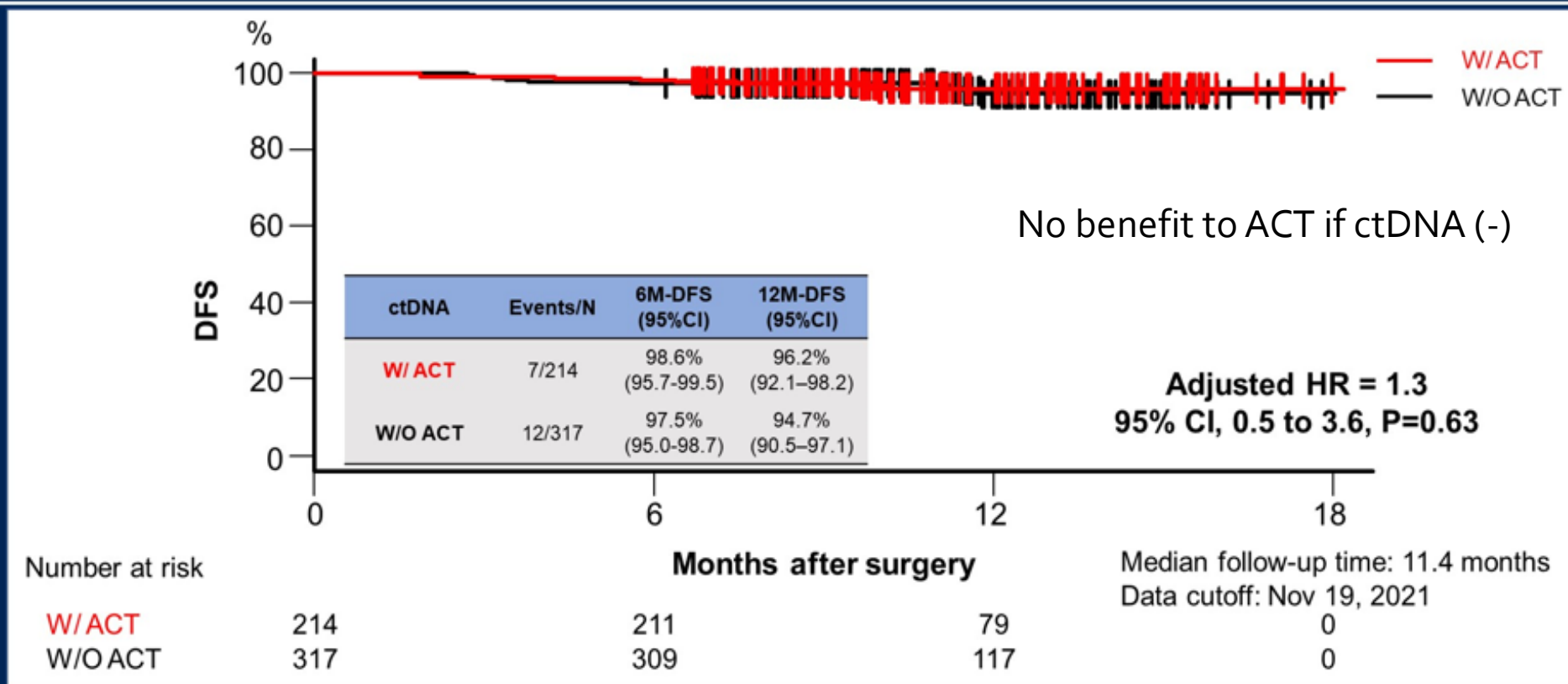
Landmark analysis at the post-op-12w was performed. HR was adjusted by sex, performance status, and pStage. ACT, adjuvant chemotherapy; HR, hazard ratio, cumulative curve was estimated by the gray's test. HR and 95%CI were calculated by Fine-Gray sub-distribution hazard model.

DFS by pStage in post-op-4w ctDNA positive population



HR was adjusted by sex, and performance status. ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval. DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

DFS by ACT in post-op-4w ctDNA negative population (High-risk pStage II-III)



Median follow up less than 1 year

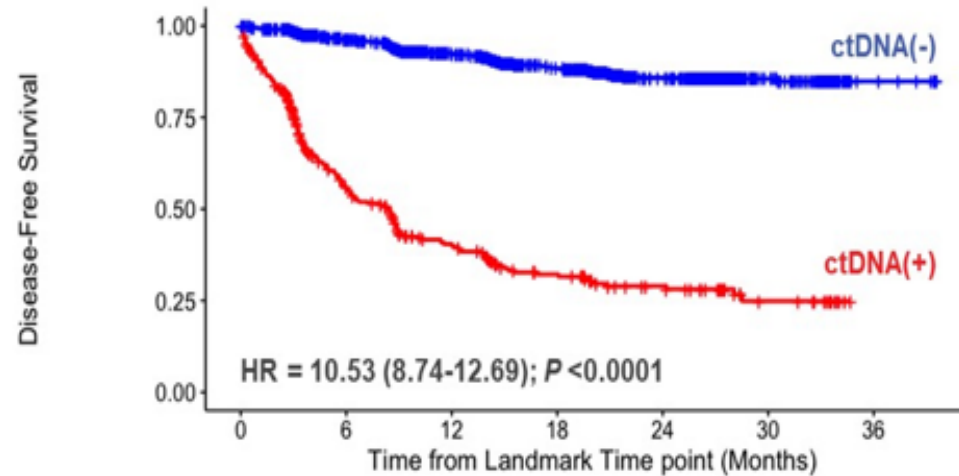
Circulating tumor DNA (ctDNA) dynamics in colorectal cancer (CRC) patients with molecular residual disease: Updated analysis from GALAXY study in the CIRCULATE-JAPAN

Presenting Author: Hiroki Yukami, MD, PhD

Co-authors: Yoshiaki Nakamura, Saori Mishima, Koji Ando, Hideaki Bando, Jun Watanabe, Keiji Hirata, Naoya Akazawa, Masataka Ikeda, Mitsuru Yokota, Kentaro Kato, George Laliotis, Vasily N. Aushev, Adham A. Jurdi, Minetta C. Liu, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Takayuki Yoshino

- Updated 24-month DFS analysis in stage I-IV patients with radically resected CRC participating in the prospective, observational GALAXY study

DFS according to status in the MRD window in all stages



Number at risk

ctDNA Negative	2491	2031	1441	1041	495	135	8
ctDNA Positive	369	165	98	59	35	13	0

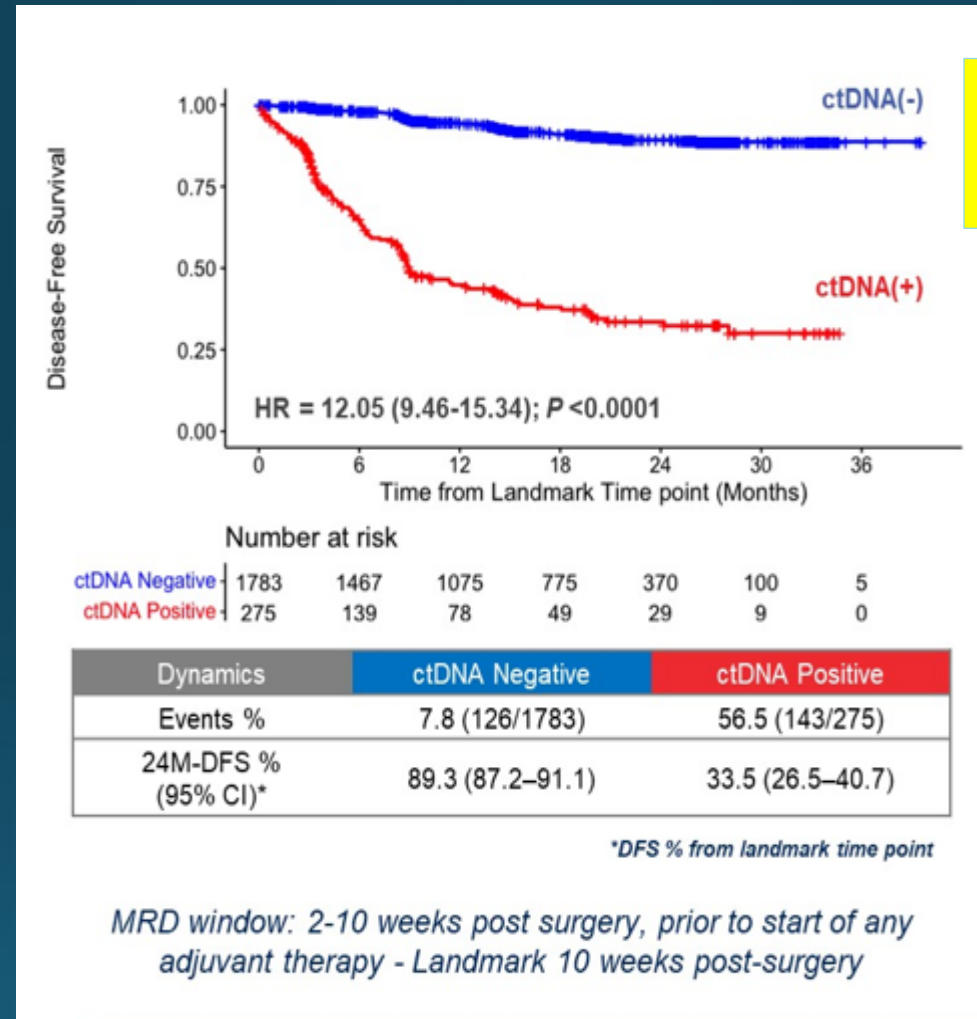
ctDNA status	Negative	Positive
Events %	9.4 (235/2491)	58.8 (217/369)
24M-DFS % (95% CI)*	85.9 (83.9–87.7)	28.9 (23.4–34.8)

*DFS % from landmark time point

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

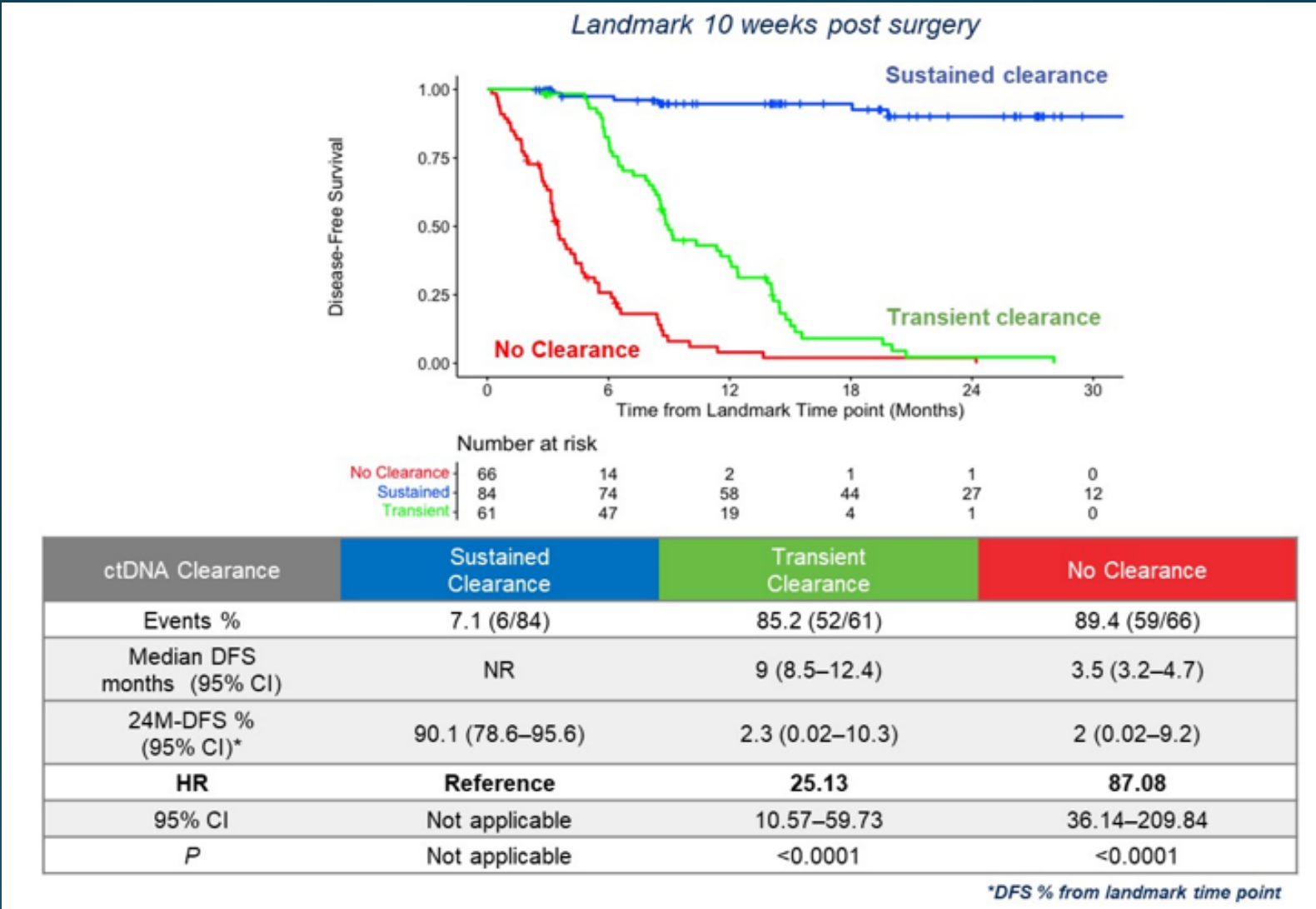
14% of pts recurred at 2 years

DFS according to status in the MRD window in pStage II/III



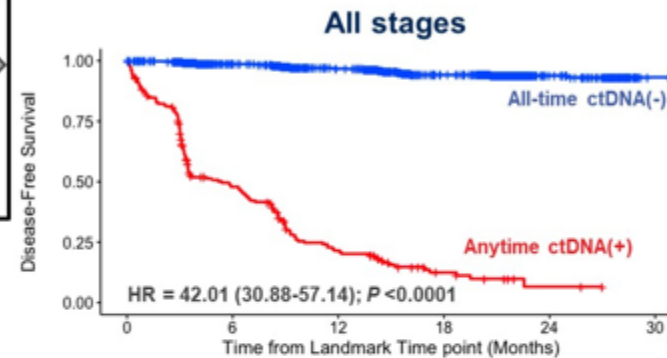
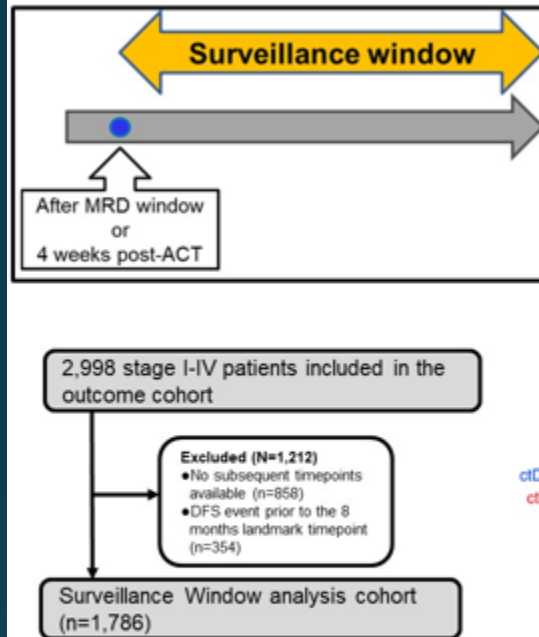
11% of pts recurred at 2 years

DFS according to ctDNA clearance in pts with ctDNA positive in the MRD window



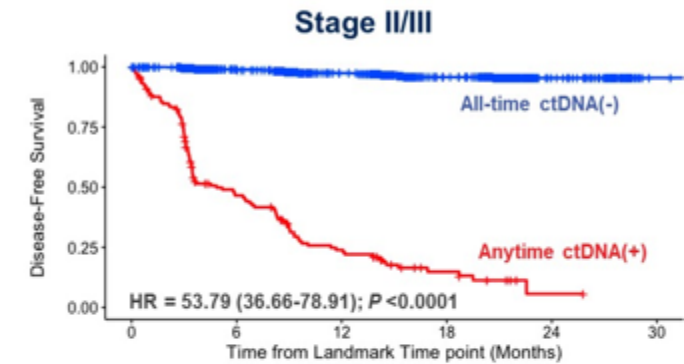
DFS according to ctDNA status in the Surveillance window

10



Number at risk						
ctDNA Negative	1582	1211	885	432	125	8
ctDNA Positive	204	84	33	10	2	0

ctDNA status	All-time Negative	Anytime Positive
Events %	3.7 (58/1582)	77.5 (158/204)
24M-DFS % (95% CI)*	93.9 (92-95.4)	6.6 (2-14.9)



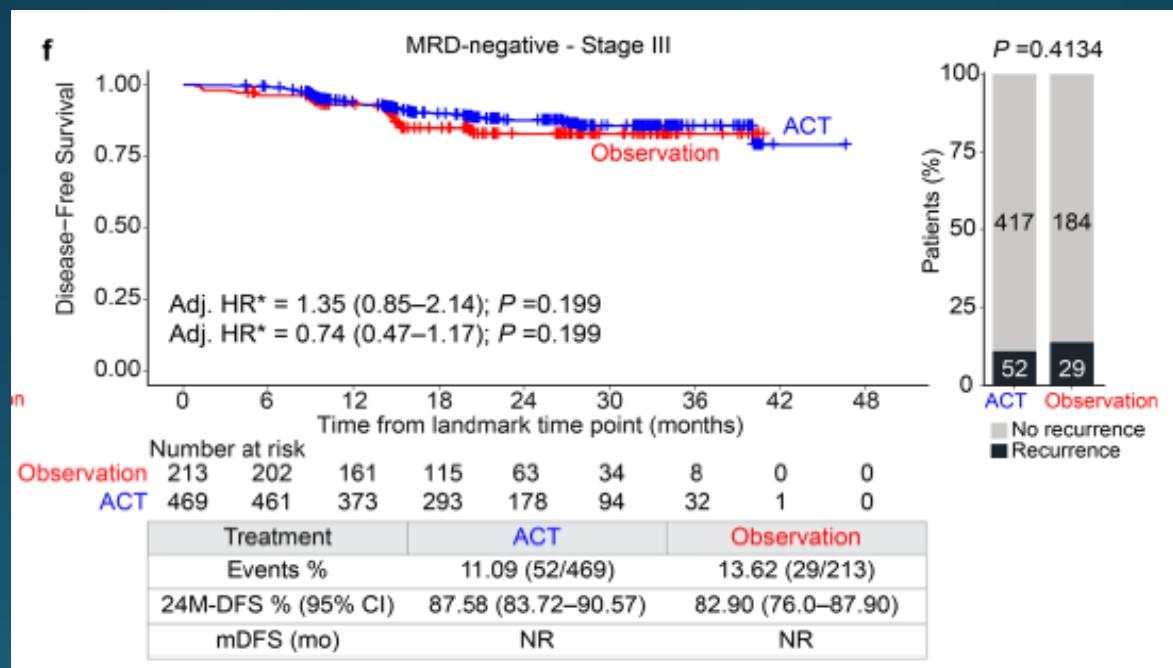
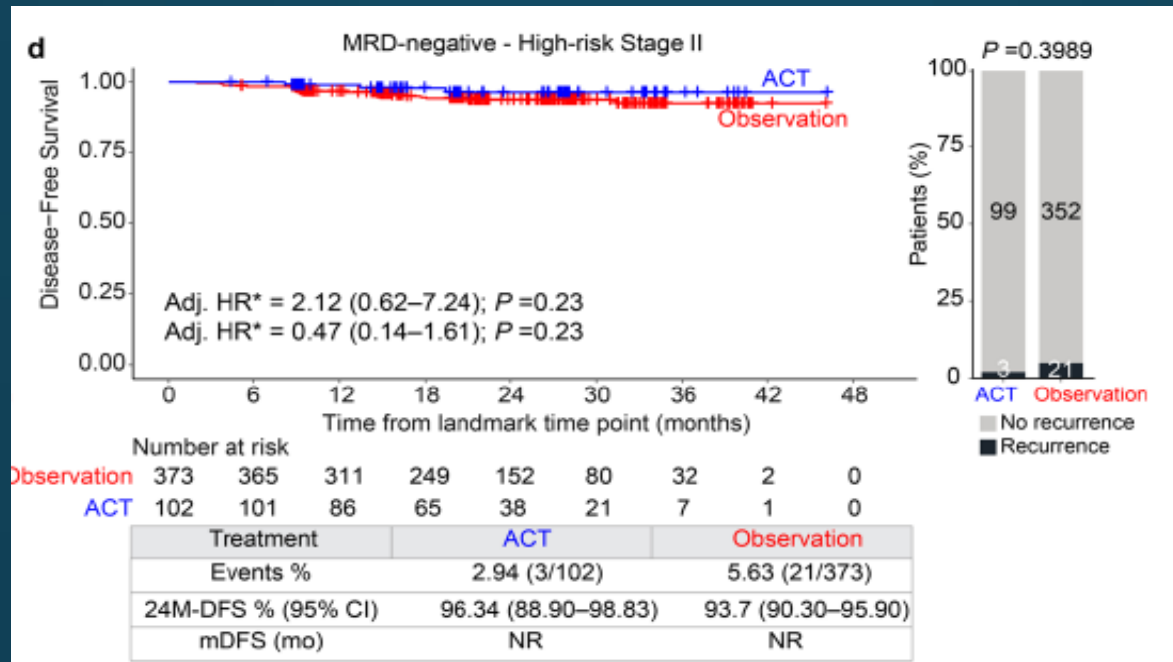
Number at risk						
ctDNA Negative	1326	1022	737	355	97	5
ctDNA Positive	146	57	26	9	1	0

ctDNA status	All-time Negative	Anytime Positive
Events %	2.7 (36/1326)	75.3 (110/146)
24M-DFS % (95% CI)*	95.4 (93.5-96.8)	5.6 (0.8-18.3)

*DFS % from landmark time point

- 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)

ctDNA-positive in the surveillance window is predictive of inferior DFS



Take-home messages from GALAXY

- Non-randomized, observational study
- Post-op ctDNA (-) is good.
 - Still associated with risk of recurrence (7% at 1 yr, 14% at 2 yr)
- Post-op ctDNA (+) predicts poor prognosis.
 - If ctDNA clears with ACT, prognosis DFS approaches that of ctDNA (-)
- Lack of benefit from ACT in high-risk stage II/III pts with post-op ctDNA (-)
 - Median follow up of 2 years, await longer follow up

The NEW ENGLAND JOURNAL *of* MEDICINE

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Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Jeanne Tie, M.D., Joshua D. Cohen, M.Phil., Kamel Lahouel, Ph.D., Serigne N. Lo, Ph.D., Yuxuan Wang, M.D., Ph.D., Suzanne Kosmider, M.B., B.S., Rachel Wong, M.B., B.S., Jeremy Shapiro, M.B., B.S., Margaret Lee, M.B., B.S., Sam Harris, M.B., B.S., Adnan Khattak, M.B., B.S., Matthew Burge, M.B., B.S., Marion Harris, M.B., B.S., James Lynam, M.B., B.S., Louise Nott, M.B., B.S., Fiona Day, Ph.D., Theresa Hayes, M.B., B.S., Sue-Anne McLachlan, M.B., B.S., Belinda Lee, M.B., B.S., Janine Ptak, M.S., Natalie Silliman, B.S., Lisa Dobbyn, B.A., Maria Popoli, M.S., Ralph Hruban, M.D., Anne Marie Lennon, M.D., Ph.D., Nicholas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Bert Vogelstein, M.D., Cristian Tomasetti, Ph.D., and Peter Gibbs, M.D., for the DYNAMIC Investigators*

2022 ASCO[®]
ANNUAL MEETING

**Adjuvant Chemotherapy Guided by Circulating Tumor
DNA Analysis in Stage II Colon Cancer**

The Randomized DYNAMIC Trial

Background: Stage II Colon Cancer

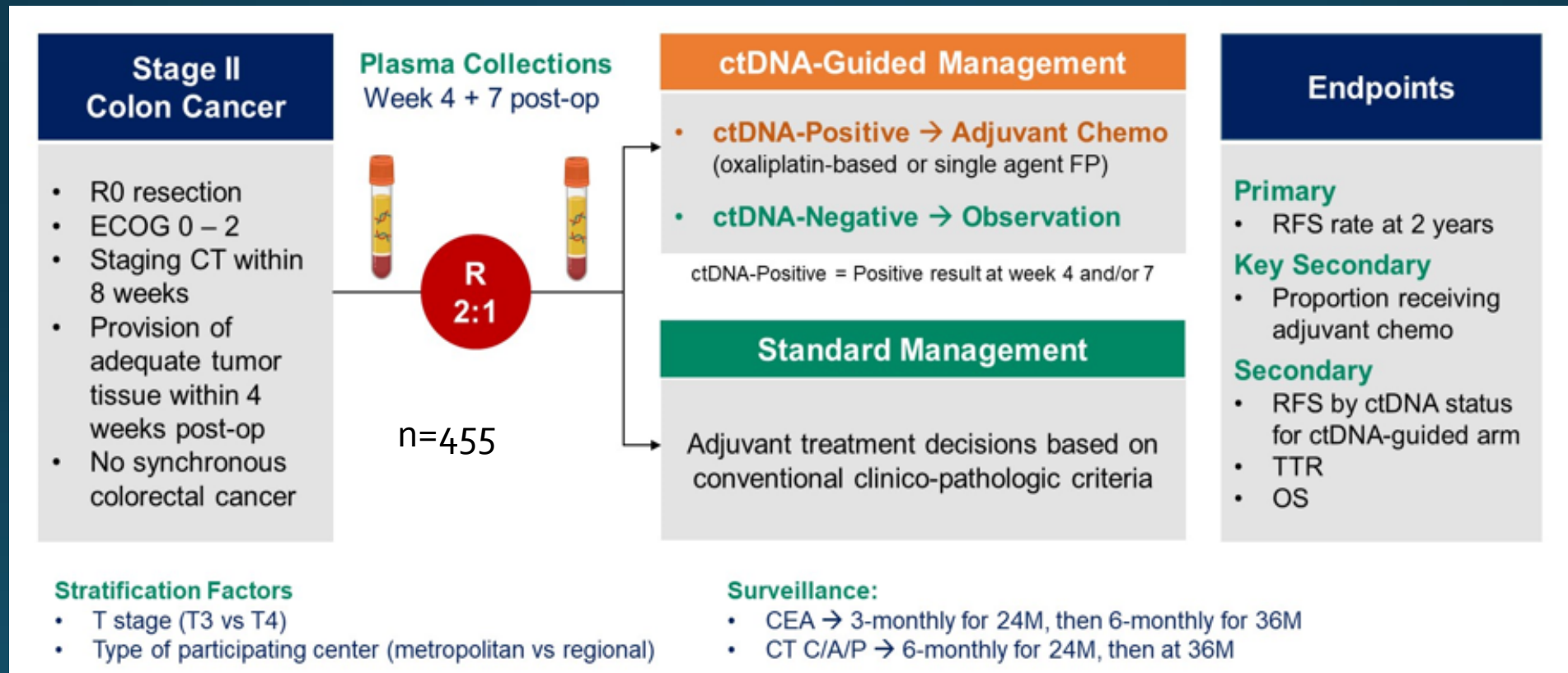
- Benefit of ACT controversial in average-risk stage II colon cancer
- ACT generally considered for pts with high-risk features
 - T₄
 - <12 LN removed
 - Perforation/obstruction
 - LVI/PNI
 - Poorly differentiated histology
- Can we use post-op ctDNA status to help decide which stage II colon cancer patients will benefit from ACT after curative surgery?

DYNAMIC II Trial

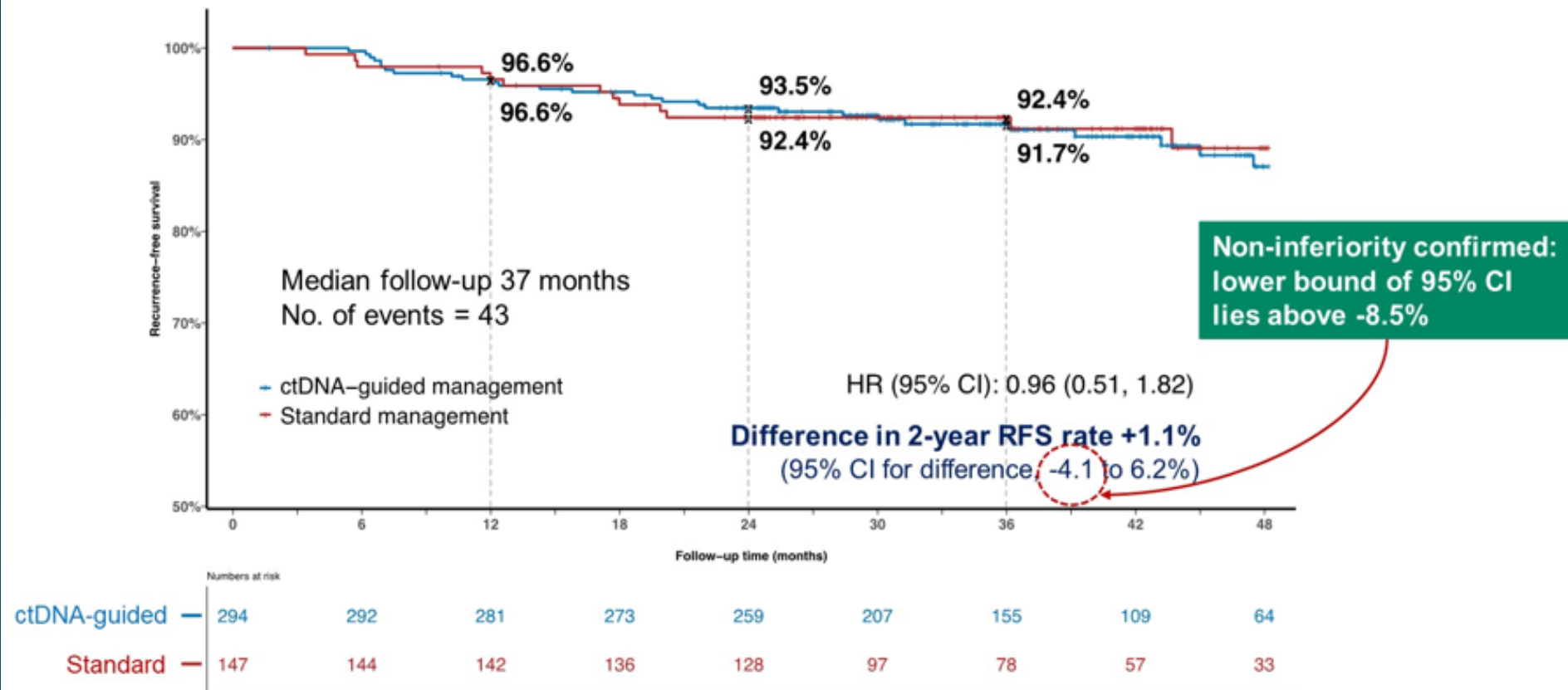
- Phase II, multicenter, randomized controlled non-inferiority trial comparing ctDNA informed treatment strategy with “standard” treatment strategy

Adjuvant Chemotherapy Guided by Circulating Tumor DNA Analysis in Stage II Colon Cancer

The Randomized DYNAMIC Trial

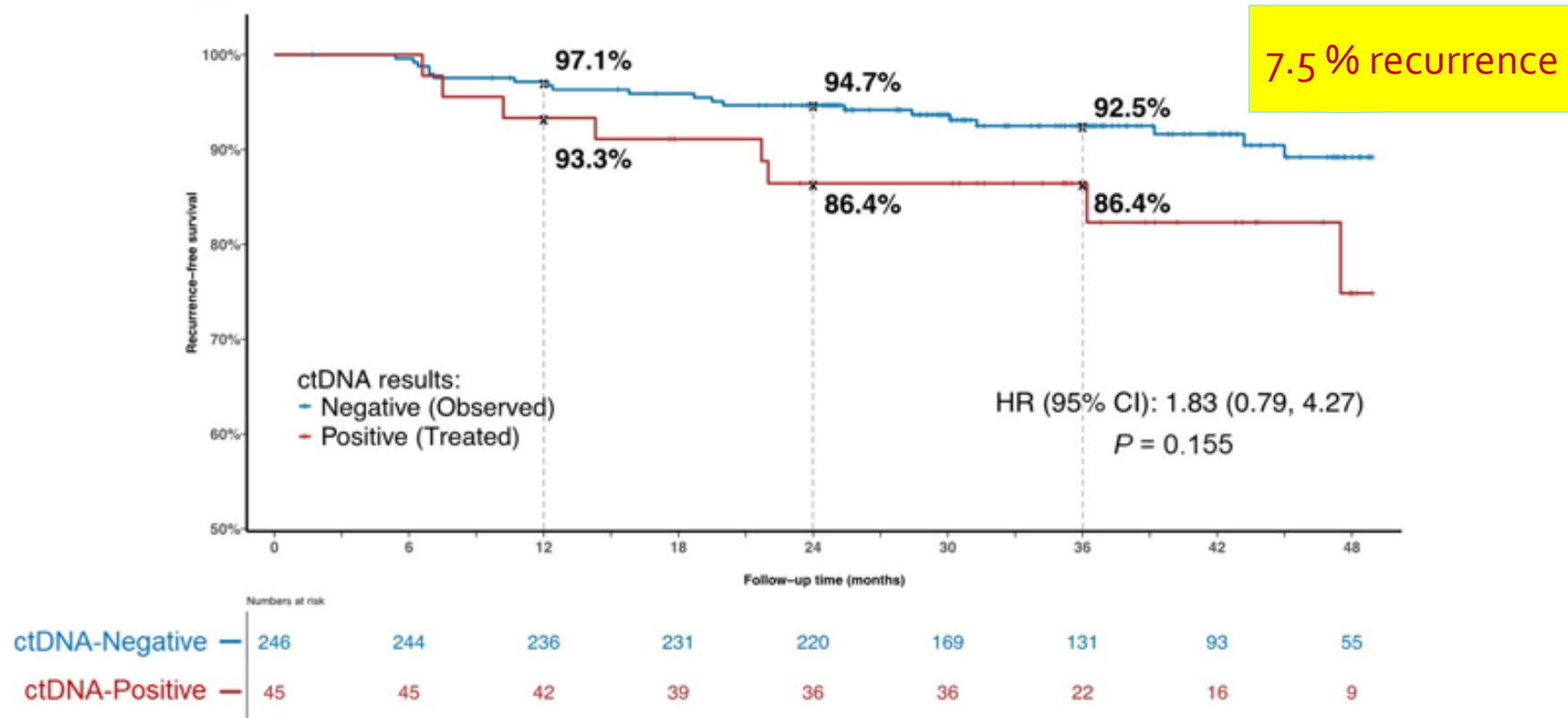


Recurrence-Free Survival



Recurrence-Free Survival: ctDNA-Guided Management

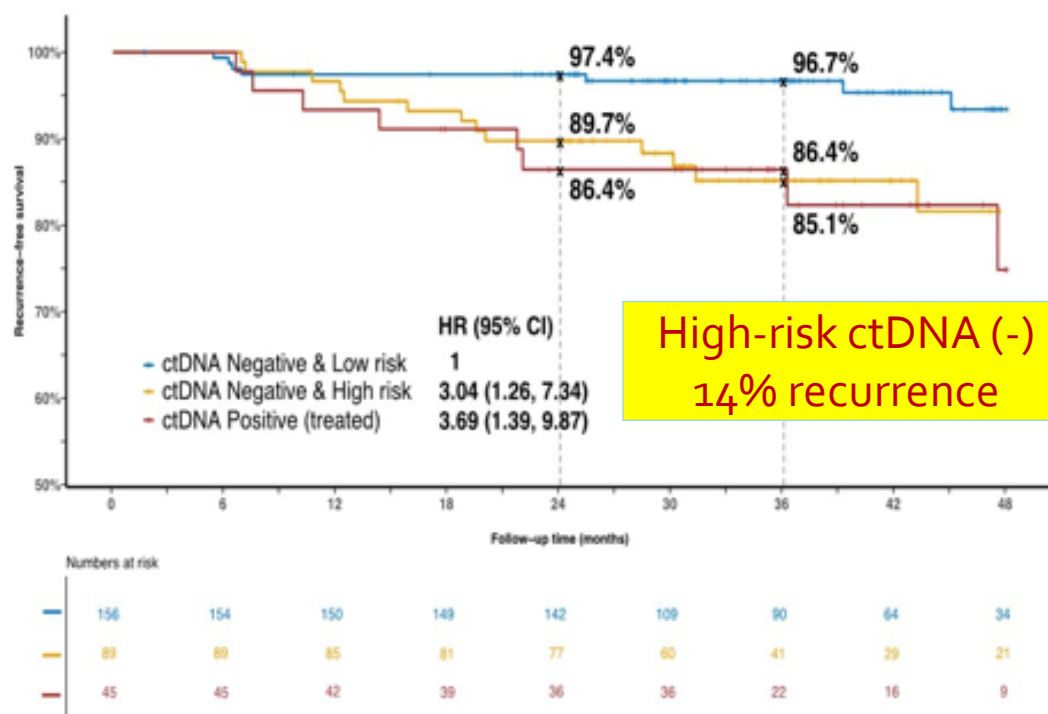
ctDNA Negative vs Positive



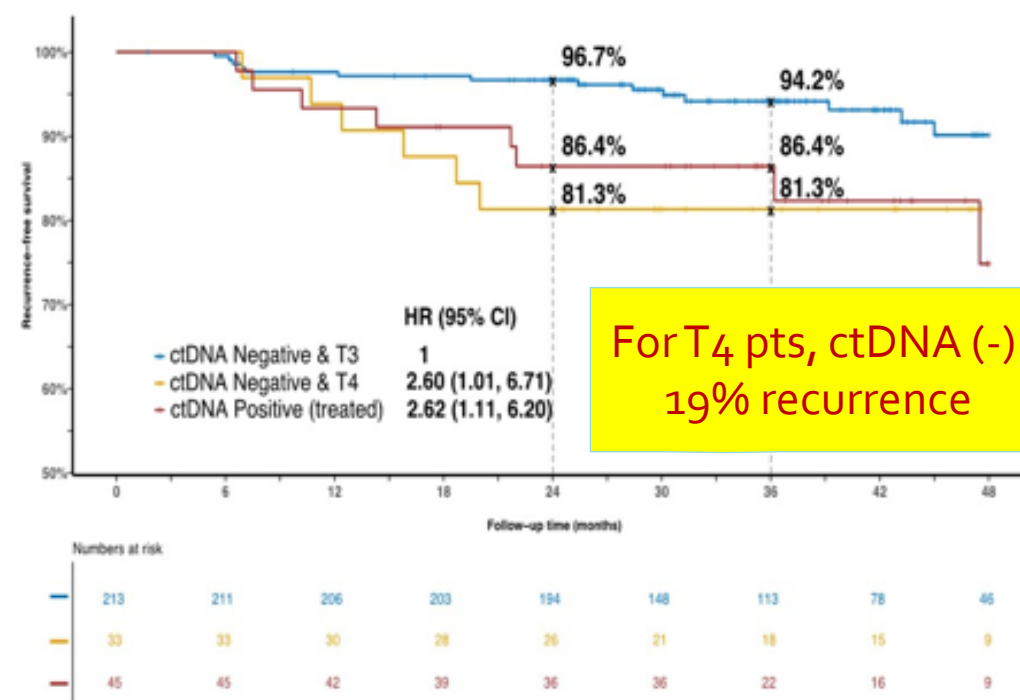
Recurrence-Free Survival: ctDNA-Guided Management

ctDNA, Clinical Risk and T Stage

ctDNA and Clinical Risk



ctDNA and T Stage



Take-home messages from DYNAMIC II

- ctDNA-guided treatment strategy is non-inferior to “standard” treatment strategy
- ctDNA (+) patients saw benefit from ACT
- In ctDNA-guided treatment arm, ctDNA (-) patients with high-risk features/T₄, had 14-19% risk of recurrence at 2 years
 - Would these patients have benefitted from ACT?

Criticisms - DYNAMIC

- Did not examine the effect of a ctDNA-guided approach beyond the initial decision for adjuvant chemotherapy
- Did not randomly assign the ctDNA-positive and ctDNA-negative patients to receive treatment or no treatment, a trial design that would have provided more definitive evidence of the effect of treatment or lack thereof in each subgroup.
- Ultimate question - If Stage II pts are ctDNA (-), is it safe to skip ACT, especially for clinically high-risk pts?
 - Not addressed by this study design.

Circulating tumor DNA-guided adjuvant therapy in locally advanced colon cancer: the randomized phase 2/3 DYNAMIC-III trial

DYNAMIC III

- Multicenter, randomized, phase 2/3 trial
- Patients with stage III colon cancer underwent ctDNA testing 5–6 weeks post-op
- Assigned (1:1) to ctDNA-guided or standard management.
- ctDNA-guided arm:
 - ctDNA (-) received de-escalated therapy
 - ctDNA(+) received escalated therapy.
- Primary endpoints:
 - 3-year RFS for ctDNA (-) patients
 - 2-year RFS for ctDNA (+) patients

DYNAMIC III

- 968 evaluable stage III colon cancer patients
- 702 (72.5%) were ctDNA-negative and randomized to de-escalation vs. standard management
- **At median follow-up of 47 months:**
 - 3-year RFS:
 - **85.3% with ctDNA-guided de-escalation**
 - **88.1% with standard management**
 - Non-inferiority NOT met (absolute difference -2.8%; 97.5% lower CI -8.0%, narrowly crossing the prespecified -7.5% non-inferiority margin)

DYNAMIC III

- **Strong prognostic separation confirmed**
 - ctDNA-negative patients had markedly better 3-year RFS than ctDNA-positive patients (**87% vs. 49%; $P < 0.001$**).
- **Substantial reduction in treatment intensity and toxicity.**
 - De-escalation cut oxaliplatin use from **88.6% to 34.8%** and reduced treatment-related hospitalization from **13.2% to 8.5%**
- Among the 702 ctDNA (-) negative patients:
 - 95 (13.5%) still recurred
 - Predominance of lung (39%) and peritoneal (34%) relapses — sites that shed less ctDNA
 - Some "negatives" reflect assay false negatives rather than cure

DYNAMIC III - Conclusions

- ctDNA is validated as a strong prognostic classifier
- ctDNA-guided de-escalation reduced oxaliplatin exposure and adverse events with outcomes approaching standard of care

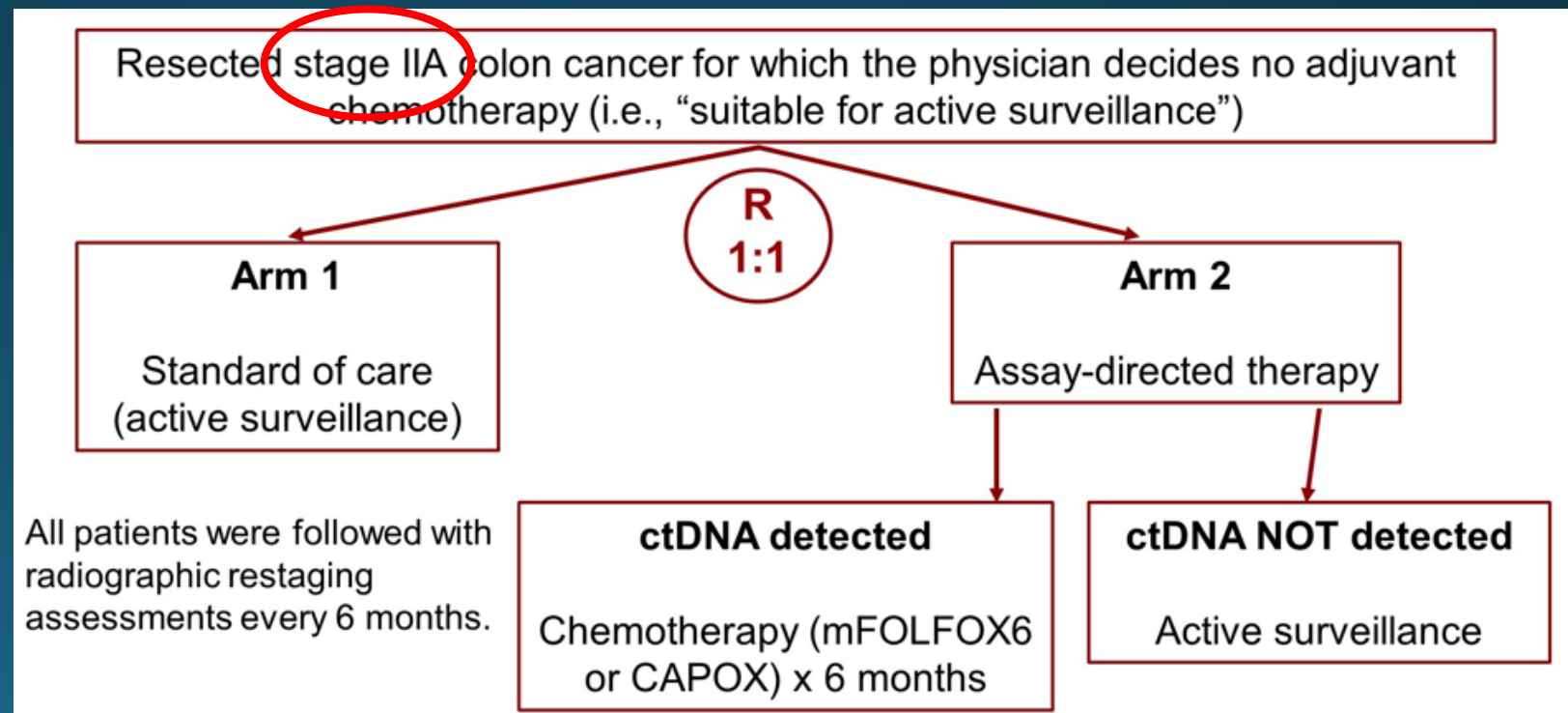
Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study.

Authors: [Van K. Morris](#), [Greg Yothers](#), [Scott Kopetz](#), [Shannon L. Puhalla](#), [Peter C. Lucas](#), [Atif Iqbal](#), [Patrick M Boland](#), ... [SHOW ALL](#) ... , and [Thomas J. George](#) | [AUTHORS INFO & AFFILIATIONS](#)

J Clin Oncol 42, 5(2024) • Volume 42, Number 3_suppl • DOI: 10.1200/JCO.2024.42.3_suppl.5

- Prospective phase II/III clinical trial
- 635 pts randomized (Arm A: 318; Arm B: 317)

Primary endpoint: compare rates of ctDNA clearance between ctDNA (+) cohorts at 6 months after randomization



Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study.

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J Clin Oncol 42, 5(2024) • [Volume 42, Number 3_suppl](#) • [DOI: 10.1200/JCO.2024.42.3_suppl.5](#)

- In the first 16 pts with ctDNA detected at baseline (interim analysis), clearance of ctDNA after 6 mos was:
 - Standard therapy arm – 43% (3/7)
 - ctDNA guided therapy arm – 11% (1/9)

P=0.98
- No improvement in ctDNA clearance was observed after 6 mos of chemotherapy for pts with ctDNA detected following resection of stage II colon cancer.
- The phase II endpoint was not met and further enrollment was halted.

Circulating tumor DNA (ctDNA) for informing adjuvant chemotherapy (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of BESPOKE CRC study.

Pashtoon Murtaza Kasi, Vasily N. Aushev, Joe Ensor, Nathan Langer, Christopher Gene Wang, Timothy Lewis Cannon, Lyudmyla Derby Berim, Trevor Feinstein, Axel Grothey, Joseph William McCollom, Sujith R. Kalmadi, Ahmed Zakari, Farshid Dayyani, Donald Gravenor, Janelle Marie Meyer, Saima Sharif, Adham A Jurdi, Minetta C. Liu, Alexey Aleshin, Scott Kopetz; Weill Cornell Medicine, Englander Institute of Precision Medicine, NewYork-Presbyterian Hospital, New York, NY; Natera, Inc., Austin, TX; Virginia Cancer Institute (QCCA), Richmond, VA; Alabama Oncology, Birmingham, AL; Inova Schar Cancer Institute, Fairfax, VA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Piedmont Cancer Institute, Atlanta, GA; West Cancer Center, Germantown, TN; Parkview Cancer Institute, Fort Wayne, IN; Ironwood Cancer & Research Centers, Chandler, AZ; Adventhealth Cancer Institute, Orlando, FL; Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA; Baptist Cancer Center, Memphis, TN; Oregon Oncology Specialists, Salem, OR; University of Iowa, Iowa City, IA; The University of Texas MD Anderson Cancer Center, Houston, TX

- Multicenter, prospective, observational study evaluating use of tumor-informed ctDNA assay to inform treatment decisions in stage II/III CRC
- 1792 pts enrolled between July 2020 and Aug 2022, tumor-informed ctDNA levels quantified post-op in the first 350 patients with stage II/III CRC
- Following curative resection, 232 pts received ACT and 118 underwent observation.
- 15.6% of pts were ctDNA + at post-op time point (Stage II – 6.9%, Stage III – 22.4%)
- Median follow-up 24.8 months

Circulating tumor DNA (ctDNA) for informing adjuvant chemotherapy (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of BESPOKE CRC study.

Pashtoon Murtaza Kasi, Vasily N. Aushev, Joe Ensor, Nathan Langer, Christopher Gene Wang, Timothy Lewis Cannon, Lyudmyla Derby Berim, Trevor Feinstein, Axel Grothey, Joseph William McCollom, Sujith R. Kalmadi, Ahmed Zakari, Farshid Dayyani, Donald Gravenor, Janelle Marie Meyer, Saima Sharif, Adham A Jurdi, Minetta C. Liu, Alexey Aleshin, Scott Kopetz; Weill Cornell Medicine, Englander Institute of Precision Medicine, NewYork-Presbyterian Hospital, New York, NY; Natera, Inc., Austin, TX; Virginia Cancer Institute (QCCA), Richmond, VA; Alabama Oncology, Birmingham, AL; Inova Schar Cancer Institute, Fairfax, VA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Piedmont Cancer Institute, Atlanta, GA; West Cancer Center, Germantown, TN; Parkview Cancer Institute, Fort Wayne, IN; Ironwood Cancer & Research Centers, Chandler, AZ; Adventhealth Cancer Institute, Orlando, FL; Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA; Baptist Cancer Center, Memphis, TN; Oregon Oncology Specialists, Salem, OR; University of Iowa, Iowa City, IA; The University of Texas MD Anderson Cancer Center, Houston, TX

- MRD-positivity associated with inferior DFS in stages II-III combined and in stage-stratified subgroups
- Within the MRD+ group, pts receiving ACT had longer DFS compared to those in the observation group
- In contrast, no benefit of ACT was observed in MRD- pts
- Of the MRD+ pts, 39.1% (18/46) had ctDNA clearance at 12-weeks post-surgery.
- Pts with ctDNA clearance had longer DFS compared to those who remained positive however, had worse DFS than pts who were ctDNA- at both 4- and 12-weeks
- 44.4% (8/18) of pts with ctDNA clearance recurred - all 8 turned ctDNA+ before radiological detection of relapse.
- ctDNA results during surveillance were available for 339 pts, of whom 8.3% were ctDNA+ and had significantly worse DFS compared to serially ctDNA- pts

Circulating tumor DNA (ctDNA) for informing adjuvant chemotherapy (ACT) in stage II/III colorectal cancer (CRC): Interim analysis of BESPOKE CRC study.

Pashtoon Murtaza Kasi, Vasily N. Aushev, Joe Ensor, Nathan Langer, Christopher Gene Wang, Timothy Lewis Cannon, Lyudmyla Derby Berim, Trevor Feinstein, Axel Grothey, Joseph William McCollom, Sujith R. Kalmadi, Ahmed Zakari, Farshid Dayyani, Donald Gravenor, Janelle Marie Meyer, Saima Sharif, Adham A Jurdi, Minetta C. Liu, Alexey Aleshin, Scott Kopetz; Weill Cornell Medicine, Englander Institute of Precision Medicine, NewYork-Presbyterian Hospital, New York, NY; Natera, Inc., Austin, TX; Virginia Cancer Institute (QCCA), Richmond, VA; Alabama Oncology, Birmingham, AL; Inova Schar Cancer Institute, Fairfax, VA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Piedmont Cancer Institue, Atlanta, GA; West Cancer Center, Germantown, TN; Parkview Cancer Institute, Fort Wayne, IN; Ironwood Cancer & Research Centers, Chandler, AZ; Adventhealth Cancer Institute, Orlando, FL; Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, Orange, CA; Baptist Cancer Center, Memphis, TN; Oregon Oncology Specialists, Salem, OR; University of Iowa, Iowa City, IA; The University of Texas MD Anderson Cancer Center, Houston, TX

- **Conclusions:**
 - ctDNA-based MRD detection was highly prognostic of recurrence
 - Significant benefit from adjuvant chemotherapy was observed in MRD+ but not in MRD- pts.
 - Early ctDNA clearance in response to adjuvant therapy and ctDNA status during surveillance were prognostic of outcomes.

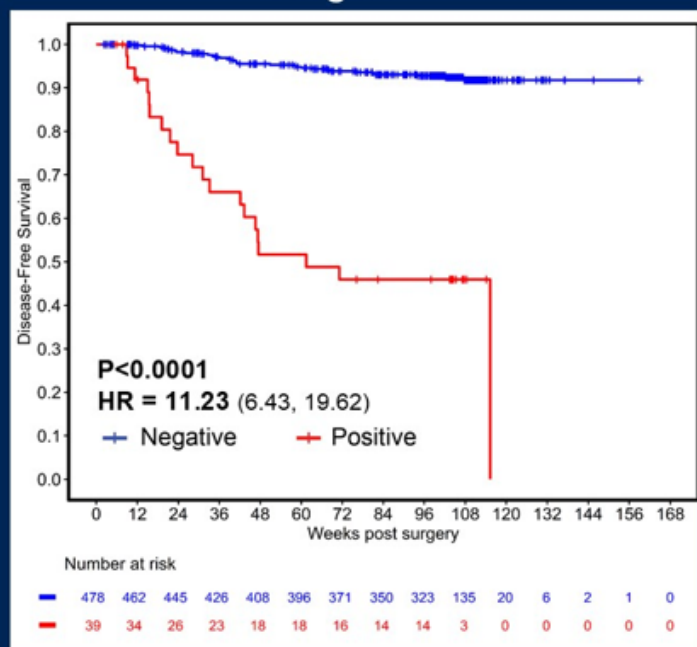
Circulating tumor DNA for detection of molecular residual disease (MRD) in patients (pts) with stage II/III colorectal cancer (CRC): Final analysis of the BESPOKE CRC sub-cohort.

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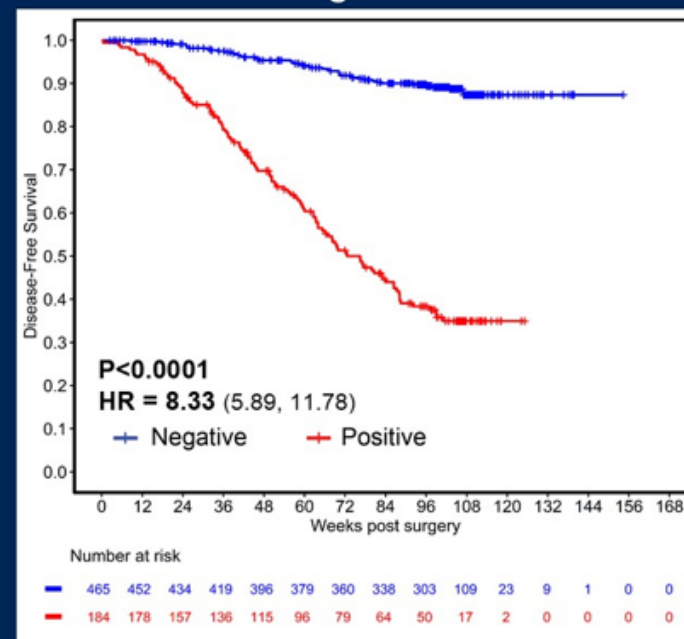
- Final analysis of 1001 patients with surgically resected stage II/III colorectal cancer
- 62.4% (625/1001) received adjuvant chemotherapy
 - 25.9% (115/443) stage II
 - 91.3% (510/558) stage III.

Post-operative ctDNA positivity predicts inferior DFS

Stage II



Stage III



ctDNA Status	Events	Median DFS post surgery, months (95% CI)	2-year DFS post surgery, % (95% CI)
Negative	33	NE (NE-NE)	91.8 (NE-NE)
Positive	20	12.7 (8.3-NE)	45.9 (32.1-65.8)

ctDNA Status	# Events	Median DFS post surgery, months (95% CI)	2-year DFS post surgery, % (95% CI)
Negative	47	NE (NE-NE)	87.4 (83.8-91.1)
Positive	105	16.2 (13.6-18.9)	35.5 (28.6-44.2)

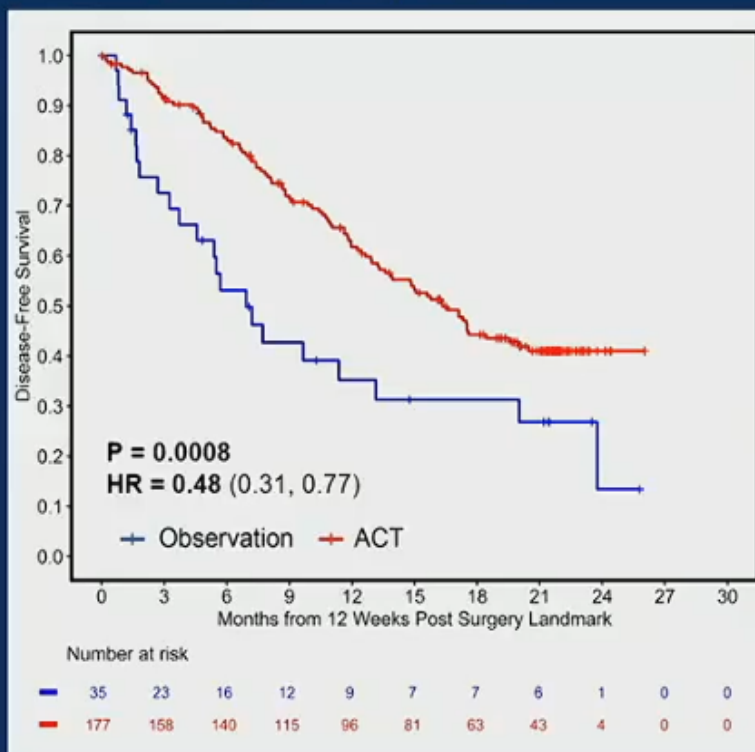
Landmark DFS Analysis at 6 weeks (42 Days). NE: Not Estimable

13% recurred

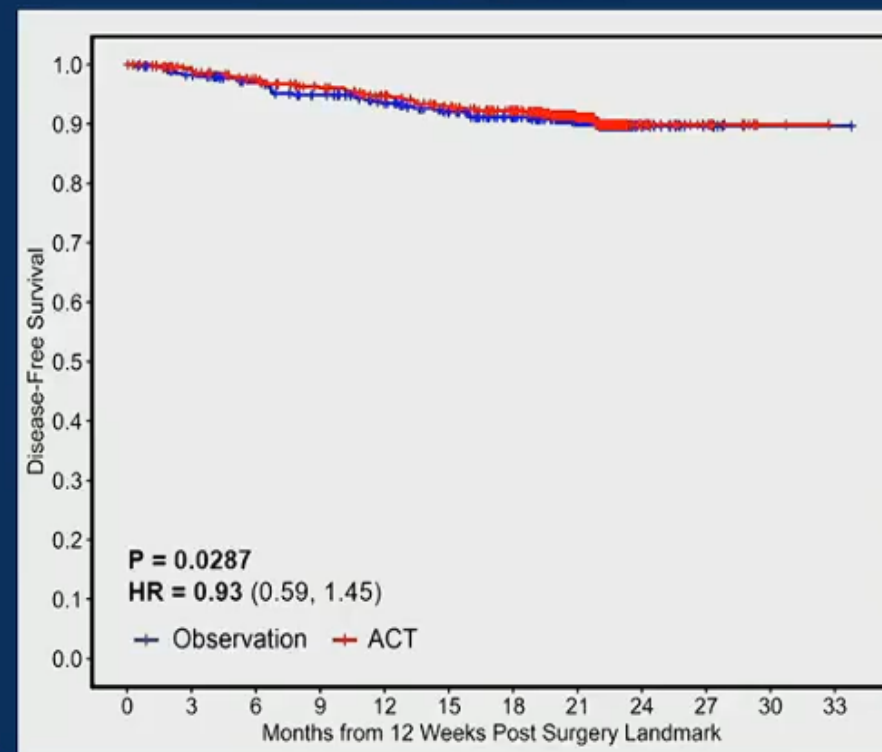
ctDNA MRD testing is predictive of the benefit of ACT

12

MRD-positive patients



MRD-negative patients

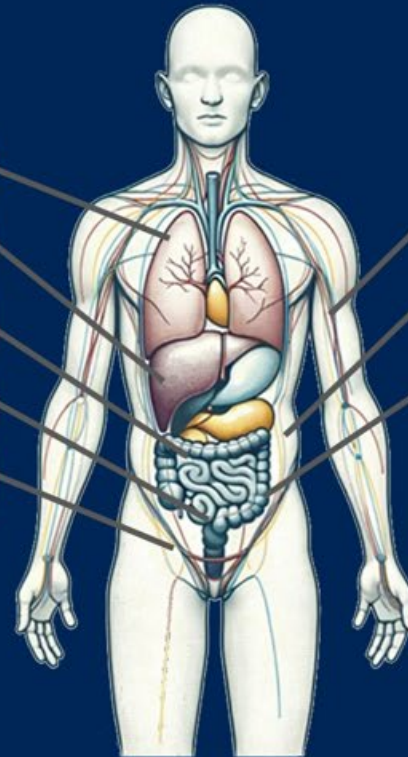
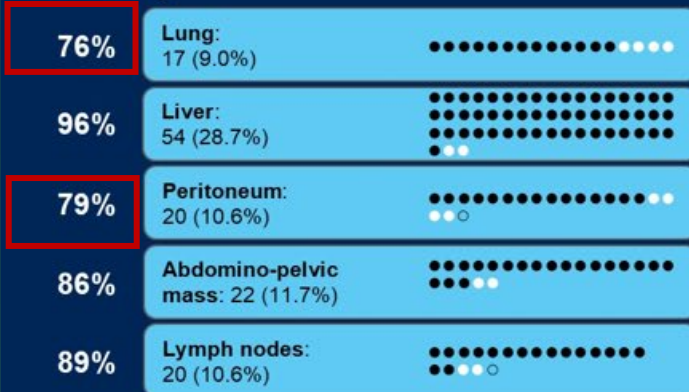


Adjuvant strategy	ACT	Observation
Numbers of events (%)	96/177 (54.24)	29/35 (82.86)
2-year DFS post surgery, % (95% CI)	40.3 (33.3 - 48.9)	24.7 (13.2 - 46.3)
Median DFS post surgery, months (95%)	17.7 (14.6 - 21.4)	7.1 (4.6 - 21.4)

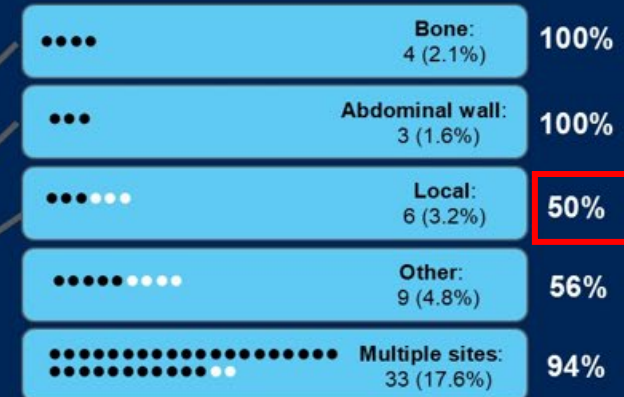
Adjuvant strategy	ACT	Observation
Numbers of events (%)	43/506 (8.50)	37/408 (9.07)
2-year DFS post surgery, % (95% CI)	89.7 (86.7 - 92.9)	89.5 (86.2 - 92.9)
Median DFS post surgery, months (95%)	Not reached	Not reached

Recurrence sites (N=188)

Sensitivity



Sensitivity



● ctDNA-pos within 24w before recurrence
 ○ ctDNA-neg within 24w before recurrence
 ○ ctDNA not available within 24w before recurrence

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- Analysis of surveillance was performed separately for pts observed (N=368) vs. chemotherapy-treated (N=597).
- If ctDNA turned positive during surveillance, DFS was worse in both arms:
 - Observation cohort
 - Stage II - 6.8% turned ctDNA(+) [HR=34.9; p<0.0001]
 - Stage III – 33.3% turned ctDNA (+) [HR=34.1; p=0.0008]
 - Chemotherapy cohort:
 - Stage II – 10.9% turned ctDNA (+) [HR=131.4; p<0.0001]
 - Stage III – 21.1% turned ctDNA (+) [HR=54.6; p<0.0001]

Circulating tumor DNA for detection of molecular residual disease (MRD) in patients (pts) with stage II/III colorectal cancer (CRC): Final analysis of the BESPOKE CRC sub-cohort.

Purvi K. Shah, Vasily N. Aushev, Joe Ensor, Stephanie A Sanchez, Christopher Gene Wang, Timothy Lewis Cannon, Lyudmyla Derby Berim, Trevor Feinstein, Axel Grothey, Joseph William McCollom, Sujith R. Kalmadi, Ahmed Zakari, Farshid Dayyani, Don Gravenor, Minetta C. Liu, Adham A Jurdi, Alexey Aleshin, Janelle Marie Meyer, Saima Sharif, Scott Kopetz; Virginia Cancer Institute, Richmond, VA; Natera, Inc., Austin, TX; Alabama Oncology, Birmingham, AL; Inova Schar Cancer Institute, Fairfax, VA; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; Piedmont Cancer Institute, Atlanta, GA; West Cancer Center and Research Institute, Germantown, TN; Parkview Cancer Institute, Fort Wayne, IN; Ironwood Cancer & Research Centers, Chandler, AZ; AdventHealth Cancer Institute, Orlando, FL; University of California, Irvine Medical Center, Irvine, CA; Baptist Cancer Center, Memphis, TN; Oregon Oncology Specialists, Salem, OR; University of Iowa, Iowa City, IA; The University of Texas MD Anderson Cancer Center, Houston, TX

- ctDNA clearance was associated with superior DFS.
 - Clearance by month 3 = HR 0.43 (95% CI, 0.29-0.64; $P < .0001$)
 - Clearance by month 6 = HR 0.31 (95% CI, 0.19-0.52; $P < .0001$).

Take-home messages from BESPOKE-CRC

- Observational study
- ctDNA positivity was highly prognostic of DFS within in a subset of stages II-III colorectal cancer patients
- Patients who were ctDNA (+) in MRD window had high risk of recurrence
 - MRD+ patients who received ACT saw a benefit
- In ctDNA (-) patients there was still a recurrence rate of ~10%
- ctDNA clearance after ACT resulted in better DFS
- In patients who turned ctDNA(+) during surveillance, prognosis was worse, even in those who received ACT
- ctDNA less specific for pulmonary, peritoneal, & local recurrences
- Question remains: For high-risk patient Stage II and Stage III ctDNA (-) patients, do we feel comfortable not offering ACT?

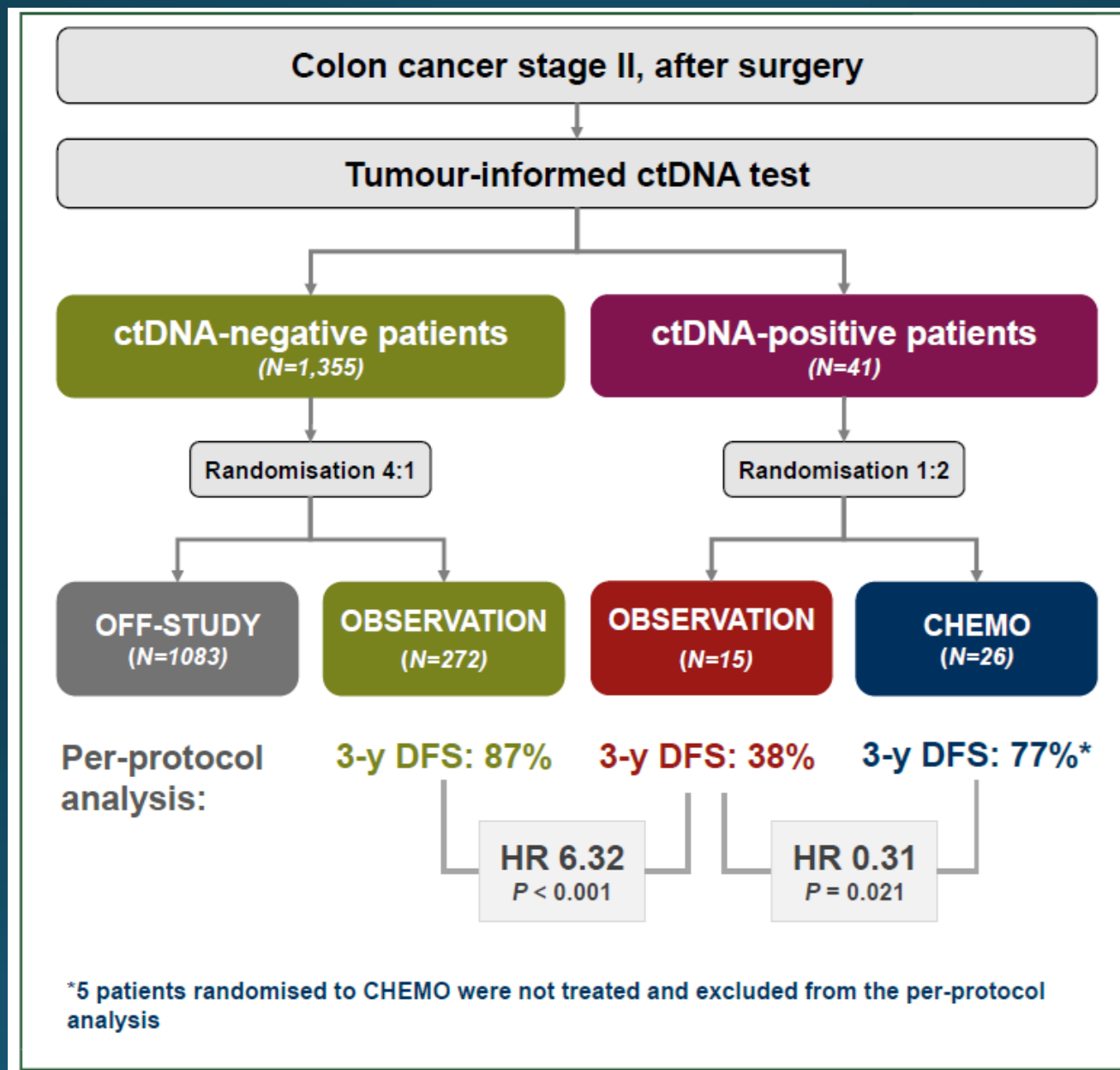
CIRCULATE-NORTH AMERICA (NRG GI-008) Trial

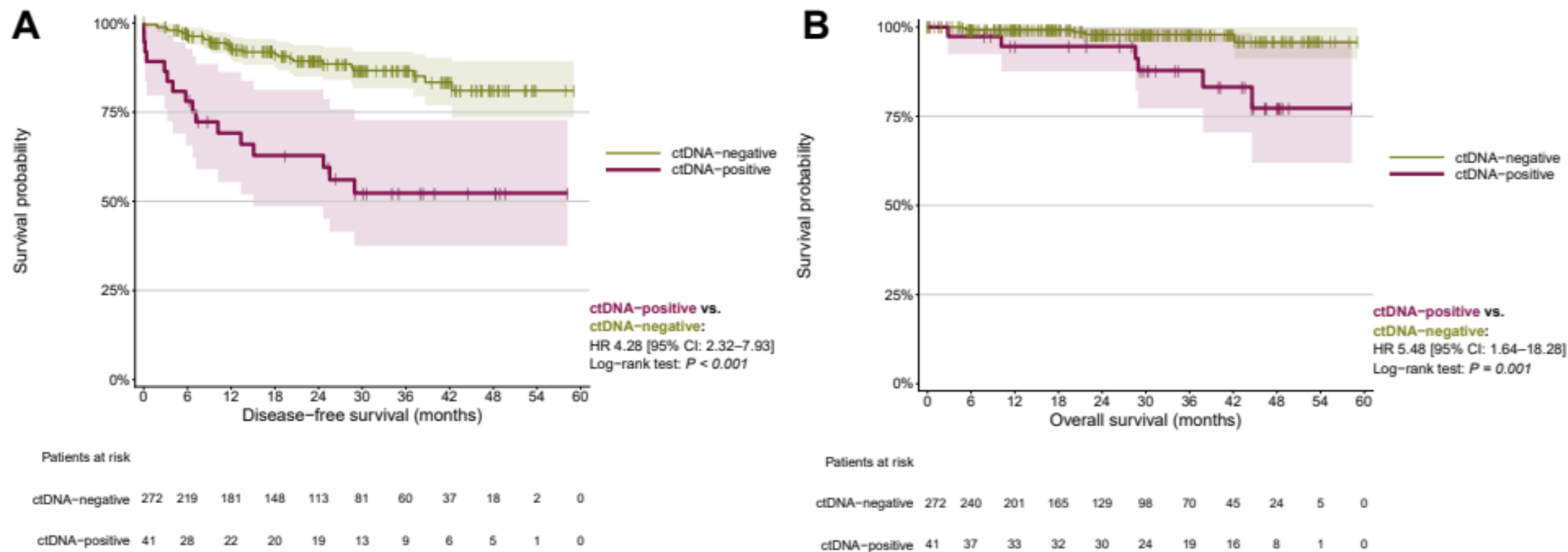
- Phase II/III multi-center trial RCT
- Stage IIB, IIC, or III colon cancer
- ctDNA positive patients randomized to mFOLFOX6 or CAPOX vs mFOLFIRINOX x 6 months
- ctDNA negative patients randomized to mFOLFOX6 (3-6 months) or CAPOX (3 months) vs no treatment/serial ctDNA monitoring
- Enrollment started June 2022
- Target enrollment – 1912 patients

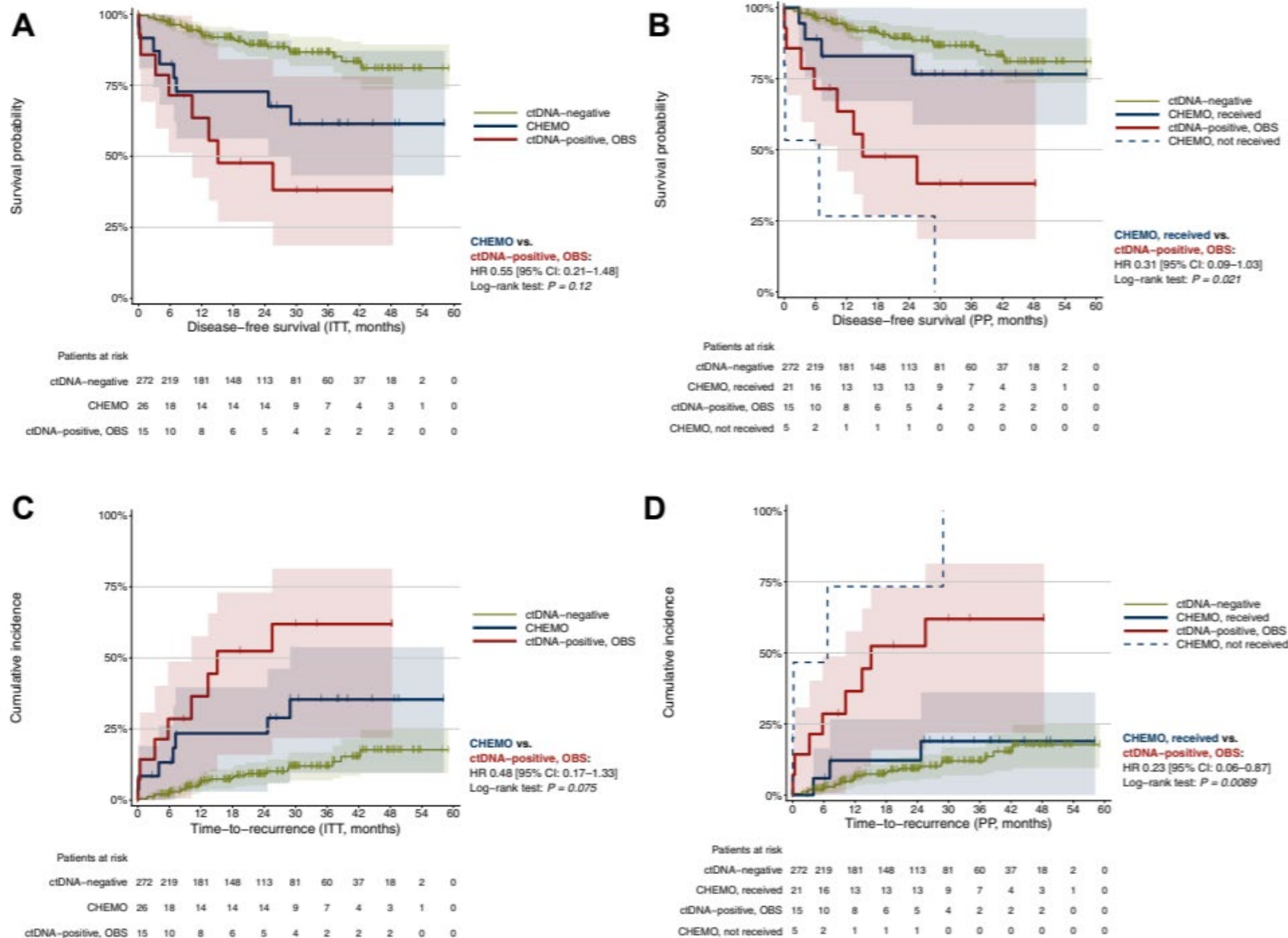
ORIGINAL ARTICLE

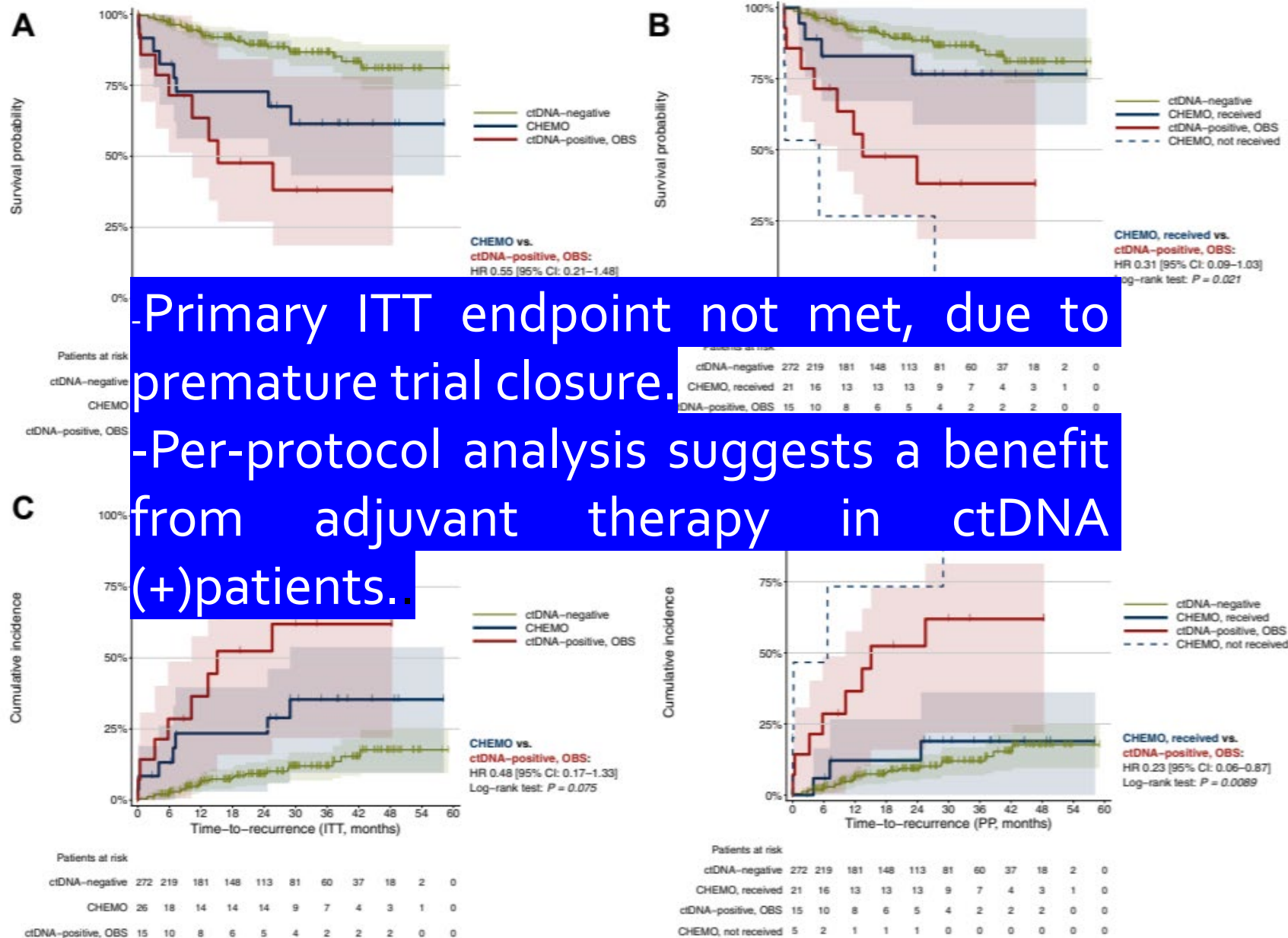
Chemotherapy for patients with circulating tumour DNA-positive, stage II colon cancer (CIRCULATE)—an AIO/ABCSG trial

G. Folprecht^{1*}, S. Stasik², A. Reinacher-Schick^{3,4}, L. Weiss^{5,6}, E. Goekkurt⁷, L. Jacobasch⁸, L. Conradi⁹, A. Kröcher¹, R.-D. Hofheinz¹⁰, R. Liersch¹¹, U. M. Martens¹², J. Chater¹³, M. Fuchs¹⁴, J. U. Riera Knorrenschild¹⁵, J. Schubert¹⁶, A. Klimova^{17,18}, L. Reinhardt¹, C. Sperling¹, J. von Tresckow^{3,4}, J. Weitz¹⁹, D. E. Aust²⁰, A. Tannapfel^{4,21}, J. Christmann^{4,21†} & C. Thiede^{2†}









-Primary ITT endpoint not met, due to premature trial closure.

-Per-protocol analysis suggests a benefit from adjuvant therapy in ctDNA (+)patients.

- Multiple other trials currently recruiting patients looking at use of ctDNA to inform decisions regarding adjuvant therapy for nonmetastatic colon cancer, including therapeutic approaches in patients who remain ctDNA (+) after completing standard adjuvant therapy
 - NCT03803553 - FOLFIRI or Nivolumab vs observation for persistent ctDNA (+) after surgery and standard ACT in stage III MSI-H colon cancer
 - NCT03832569 - Pembrolizumab vs placebo for persistent ctDNA (+) after surgery and standard ACT in non-metastatic MSI-H colon cancer

ctDNA and Rectal Cancer “Watch & Wait”

- Many studies have shown:
 - ctDNA can predict response to TNT for locally advanced rectal cancer
 - patients who are ctDNA (+) after TNT have higher risk of recurrence after surgery
- Is there a role for routine use of ctDNA monitoring in patients with complete clinical response after TNT who are in a watch and wait protocol?
 - How do we manage patient with CCR but is ctDNA (+)
 - How do we manage patient with CCR who is ctDNA (-) but turns ctDNA (+) during watch and wait if flex sig & imaging show no clear recurrence?
 - Local recurrence vs distant?

Article

Circulating Tumor DNA Detects Minimal Residual Disease in Patients with Locally Advanced Rectal Cancer After Total Neoadjuvant Therapy

Jin K. Kim ¹, Ashley J. Alden ¹, Sarah Knaus ¹, Rishabh Thakkar ¹, Lisa Moudgill ^{1,2}, Allen Chudzinski ¹, Paul Cavallaro ¹, Carolina Martinez ¹, Robert D. Bennett ¹ and Jorge Marcet ^{1,*}

Cancers **2025**, *17*, 2560

- Single-institution retrospective case series
- Locally-advanced rectal cancer patients treated with TNT with CCR from 2019 to 2023 (n=28)
- ctDNA testing used as an adjunct to standard clinical response assessments.
- 9 patients ctDNA (+) – 6 required surgery for residual disease (4 TME, 2 local excision)
- 19 patients ctDNA (-) - 4 required surgery for residual disease (all TME)

Utility of Circulating Tumor DNA to Assess Tumor Response in Patients with Locally Advanced Rectal Cancer Undergoing Neoadjuvant Therapy

Sakti Chakrabarti ^{1,*†}, Stacey A. Cohen ^{2,†} , Antony Tin ³, Autumn Dangl ³, Ki Y. Chung ⁴, Mohamedtaki A. Tejani ⁵, Marwan G. Fakih ⁶ , Sreenivasa R. Chandana ⁷ , Colleen A. Donahue ⁸ , Virgilio George ⁸, Midhun Malla ⁹, Vasily N. Aushev ³ , Giby V. George ³, J. Bryce Ortiz ³ , Whitney K. Herter ³, Arun Nagarajan ¹⁰, Benjamin A. Weinberg ¹¹, Vivek R. Sharma ¹² , Gregory P. Botta ¹³ , May Cho ¹⁴, Georges Azzi ¹⁵, Anup Kasi ¹⁶, Farshid Dayyani ¹⁷ , Diana L. Hanna ¹⁸, Bradley G. Somer ¹⁹, Meenakshi Malhotra ³ , Shruti Sharma ³, Adham Jurdi ³ , Minetta C. Liu ³ , Ron G. Landmann ²⁰ and Arvind Dasari ²¹

Cancers 2026, 18, 589

- Retrospective study, 220 patients with locally advanced rectal cancer
- 148 (67.3%) underwent neoadjuvant treatment (TNT or CRT) followed by surgery
- 72 (32.7%) underwent neoadjuvant treatment followed by non-operative management (NOM)
- ctDNA assay (Signatera™) obtained at discretion of ordering physician
- In the surgery cohort, ctDNA positivity at the post-operative MRD timepoint was a strong predictor of recurrence, with an 88.3% relapse rate compared to 11.5% in ctDNA-negative patients ($p < 0.001$).

Utility of Circulating Tumor DNA to Assess Tumor Response in Patients with Locally Advanced Rectal Cancer Undergoing Neoadjuvant Therapy

Sakti Chakrabarti ^{1,*†}, Stacey A. Cohen ^{2,†} , Antony Tin ³, Autumn Dangl ³, Ki Y. Chung ⁴, Mohamedtaki A. Tejani ⁵, Marwan G. Fakih ⁶ , Sreenivasa R. Chandana ⁷ , Colleen A. Donahue ⁸ , Virgilio George ⁸, Midhun Malla ⁹, Vasily N. Aushev ³ , Giby V. George ³, J. Bryce Ortiz ³ , Whitney K. Herter ³, Arun Nagarajan ¹⁰, Benjamin A. Weinberg ¹¹, Vivek R. Sharma ¹² , Gregory P. Botta ¹³ , May Cho ¹⁴, Georges Azzi ¹⁵, Anup Kasi ¹⁶, Farshid Dayyani ¹⁷ , Diana L. Hanna ¹⁸, Bradley G. Somer ¹⁹, Meenakshi Malhotra ³ , Shruti Sharma ³, Adham Jurdi ³ , Minetta C. Liu ³ , Ron G. Landmann ²⁰ and Arvind Dasari ²¹

Cancers 2026, 18, 589

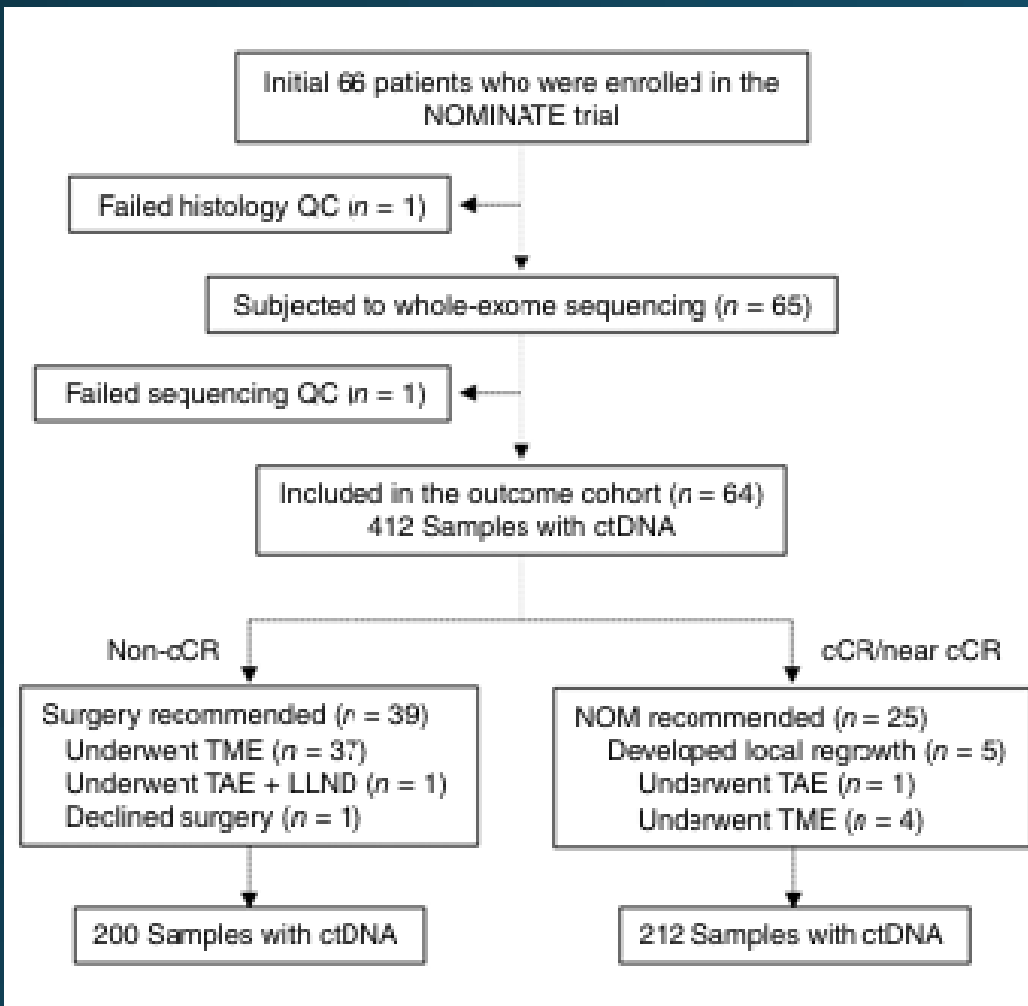
- Among the 64 NOM patients with post-neoadjuvant treatment ctDNA, 21.9% (14/64) were ctDNA-positive
 - 100% (14/14) relapsed (13 local, 1 distant)
- Only 10% (5/50) of the ctDNA-negative NOM patients experienced local recurrence ($p < 0.0001$).
- ctDNA positivity post-NAT was associated with inferior DFS ($p = 0.003$).
- Conclusion: ctDNA was a strong predictor of recurrence in rectal cancer, including in NOM settings. In NOM patients, ctDNA detected recurrences, highlighting its potential to guide post-NAT surveillance and treatment.

ctDNA Longitudinal Analysis during Total Neoadjuvant Therapy and Nonoperative Management for Locally Advanced Rectal Cancer: A Biomarker Study from the NOMINATE Trial



Takashi Akiyoshi^{1,2}, Eiji Shinozaki^{2,3}, Yusuke Maeda⁴, Senzo Taguchi⁵, Akiko Chino^{2,6}, Yutaka Hanaoka⁴, Shigeo Toda⁴, Shuichiro Matoba⁴, Antony Tin⁷, Erik Spickard⁷, Tetsuro Tominaga⁸, Kohei Shigeta⁹, Koji Okabayashi⁹, Shimpei Matsui^{1,2}, Toshiki Mukai^{1,2}, Tomohiro Yamaguchi^{1,2}, Hiroki Osumi^{2,3}, Adham Jurdi⁷, Minetta C. Liu⁷, Naoki Miyazaki¹⁰, and Kensei Yamaguchi^{2,3}

- Prospective, multicenter randomized phase II study of patients with stage II/III locally advanced rectal cancer (LARC), evaluating association between ctDNA status during TNT and NOM and clinical outcomes
 - Companion analysis of NOMINATE trial (comparing 2 TNT regimens within framework of NOM of LARC)



To – pre-treatment

T₁ – interim evaluation

T₂ – interim evaluation

T₃ – final re-staging

T₄ – after surgery or NOM

- Baseline ctDNA detection - 98.4%
 - Decreased to 32% at T₁, 15% at T₂, 30% at T₃, and 5% at T₄
- 25 patients achieving cCR or near-cCR with NOM, ctDNA clearance = 100% at T₂ to T₄
- 39 non-cCR patients - lower clearance rates (75% at T₂ and 51% at T₃)
- ctDNA (+) at T₃ had 100% specificity and PPV for pathologic residual disease and was associated with shorter DFS (HR = 6.7, P = 0.005).
- Local regrowth occurred in 5 NOM patients, with ctDNA detected in two during surveillance.
- CONCLUSION – Highlights potential of ctDNA as predictive/prognostic biomarker BUT modest sensitivity highlights need for technological improvements

Recruiting



Establishing a ctDNA Biomarker to Improve Organ Preserving Strategies in Patients With Rectal Cancer

ClinicalTrials.gov ID  NCT05081024

Sponsor  OHSU Knight Cancer Institute

Information provided by  Adel Kardosh M.D., Ph.D., OHSU Knight Cancer Institute (Responsible Party)

Last Update Posted  2025-09-25

- ctDNA for MRD is not FDA approved for routine clinical use in colon cancer
- “Breakthrough device designation” granted for the Haystack MRD[®] test (Quest Diagnostics) in Aug 2025 (tumor-informed ctDNA assay)

Minimal Residual Disease Testing for the Early Detection of Cancer Recurrence in Resectable Stage II-IV Colorectal Cancer Patients

ClinicalTrials.gov ID ⓘ NCT07125729

Sponsor ⓘ City of Hope Medical Center

- Primary objective: Compare the clinical performance of the Haystack MRD test and the Signatera® test in patients with stage II-IV CRC patients treated with curative intent surgery with or without adjuvant therapy.
- Secondary objective: Calculate the lead time (months) of recurrence detection by the Haystack MRD test in curatively resected colorectal cancer patients to 1) radiological recurrence time 2) Signatera® test positivity.
- *** Patients with TNT for rectal cancer and CCR with plans of watchful waiting may also be enrolled as long as there is adequate tissue from prior endoscopic biopsies to allow for Signatera® and Haystack MRD assays

PATHOLOGIC STAGE	SURVEILLANCE ^b	Serial CEA elevation or documented recurrence	Workup and treatment (COL-9)
Stage I	• Colonoscopy^a at 1 y after surgery ▶ If advanced adenoma, repeat in 1 y ▶ If no advanced adenoma,^{ff} repeat in 3 y, then every 5 y^{gg}		
Stage II, III ^{ee}	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA^{hh} every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • C/A/P CT every 6–12 mo (category 2B for frequency <12 mo) from date of surgery for a total of 5 y • Colonoscopy^a in 1 y after surgery except if no complete preoperative colonoscopy, then colonoscopy in 3–6 mo ▶ If advanced adenoma, repeat in 1 y ▶ If no advanced adenoma,^{ff} repeat in 3 y, then every 5 y^{gg} • FDG-PET/CT is not indicated • Principles of Survivorship (COL-H)		
Stage IV	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA^{hh} every 3–6 mo x 2 y, then every 6 mo for a total of 5 y • C/A/P CT every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y • Colonoscopy^{a,ii} in 1 y after surgery except if no complete preoperative colonoscopy, then colonoscopy in 3–6 mo ▶ If advanced adenoma, repeat in 1 y ▶ If no advanced adenoma,^{ff} repeat in 3 y, then every 5 y^{gg} • FDG-PET/CT is not indicated • Principles of Survivorship (COL-H)		

^a All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected LS, FAP, and attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric](#).

^b [Principles of Imaging \(COL-A\)](#).

^{ee} ctDNA is not recommended for surveillance.

^{ff} Villous polyp, polyp ≥1 cm, or high-grade dysplasia.

^{gg} Kahi CJ, et al. Gastroenterology 2016;150:758-768.

^{hh} If patient is a potential candidate for further intervention.

ⁱⁱ In patients with stage IV disease managed nonoperatively with complete clinical response, initiate colonoscopy surveillance from first documentation of complete response.

Note: All recommendations are category 2A unless otherwise indicated.



PRINCIPLES OF NONOPERATIVE MANAGEMENT

To provide nonoperative management (NOM) for patients with rectal cancer, the multidisciplinary team's diagnostic skills are crucial. They must accurately assess clinical, radiologic, and pathologic findings, determining patient eligibility for NOM and closely monitoring progress. The team's expertise extends to tracking treatment responses, identifying surgical needs promptly, and adjusting the management plan as necessary. Additionally, the team should maintain a comprehensive understanding of the watchful waiting literature and surveillance methodology, adeptly treating patients with complete or near-complete clinical responses and regularly monitoring for potential tumor recurrence or progression. Given this, NOM is recommended only at centers with experienced multidisciplinary teams and for patients committed to intensive surveillance.

Criteria for Complete Clinical Response

- High-definition flexible endoscopy¹
 - Pale smooth scar with or without telangiectasia
 - No ulceration, nodularity, or mucosal irregularities
 - No stricture
- DRE¹
 - Smooth, flat scar
 - No nodularity
- Diffusion-weighted MRI²
 - Fibrotic, linear scar with low signal intensity on T2-weighted images
 - No diffusion restriction
 - No suspicious lymph nodes
- All of the criteria must be satisfied in order to define a complete clinical response
- Biopsy offers no added diagnostic value if the criteria are met^{3,4}
- ctDNA has no proven role in the NOM of patients

Timing of Assessment for Complete Clinical Response

- For patients treated with chemotherapy first followed by radiation (induction chemotherapy), assessment should be performed no earlier than 8 weeks after completion of radiotherapy to allow time for delayed response to radiation.⁵
- For patients treated with radiation first followed by chemotherapy (consolidation chemotherapy), assessment should be completed within a month of completion of chemotherapy.

Near Complete Response^{6,7}

- If the patient has had a nCR and wishes to avoid surgery, then an additional 8 weeks of observation followed by reassessment can be considered.
- An nCR is defined by:
 - ◊ Smooth induration or superficial minor mucosal irregularity on DRE
 - ◊ Endoscopic appearance with irregular small mucosal nodules, superficial ulceration, or mild persistent erythema
 - ◊ T2-weighted MRI with downstaging with or without residual fibrosis, small area of residual signal, and complete or partial regression of lymph nodes
 - ◊ Diffusion-weighted MRI with small area of residual high signal intensity

Indications for Surgery

- Radical surgery is indicated for patients who do not ultimately achieve a complete clinical response based on the above criteria or patients who have tumor regrowth after a clinical response.
- If residual tumor or regrowth is suspected at the time of assessment, it is not necessary to perform biopsies. False-negative biopsies are common in this scenario and a high degree of suspicion for tumor is sufficient as an indication for surgery.⁸

Note: All recommendations are category 2A unless otherwise indicated.

References

Conclusions

- ctDNA (-) after surgery predicts improved survival
 - BUT recurrences DO occur
- ctDNA (+) after surgery probably benefits from ACT
- ctDNA (-) after surgery probably do not benefit from ACT
- ctDNA clearance after ACT predicts improved survival
- Unclear which high risk Stage II & III ctDNA (-) patients will benefit from ACT
- ctDNA-guided strategy may allow for reduction in chemotherapy
- In patients who turn ctDNA(+) during surveillance, prognosis is worse
- Unclear what to do for patients who remain ctDNA+ after standard ACT
- ctDNA less specific for pulmonary, peritoneal, and local recurrences
- Role of ctDNA in rectal cancer watch and wait not defined
- Routine ctDNA monitoring for surveillance or rectal cancer NOM not recommended by NCCN

