Controversies in Colon Cancer:

Ct-DNA in the Adjuvant Therapy of Colon Cancer
And in the Management of Oligometastases

" in Favor ☺"

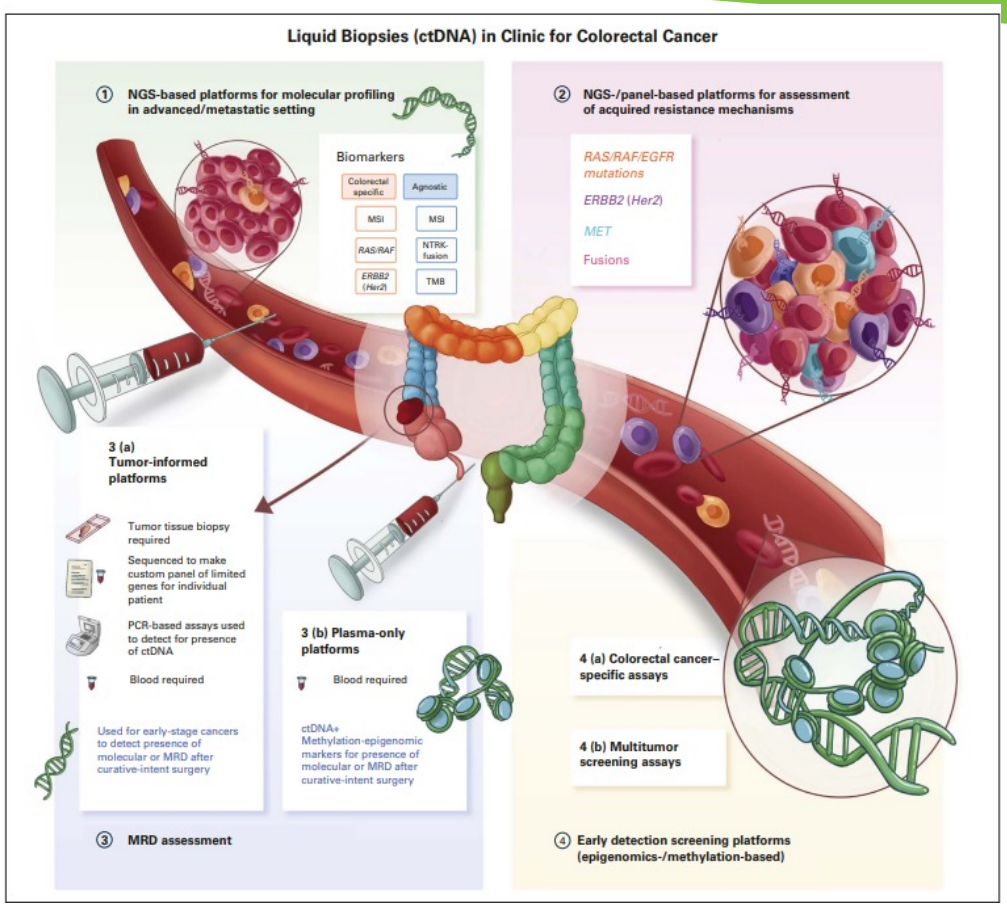
- ***Ahmed Zakari, MD***
- *Department Chair, Hematology AdventHealth Orlando*
- *Clinical Director GI Cancer Program at AHCI*
- *Associate Professor, School of Medicine University of Central Florida*

Introduction

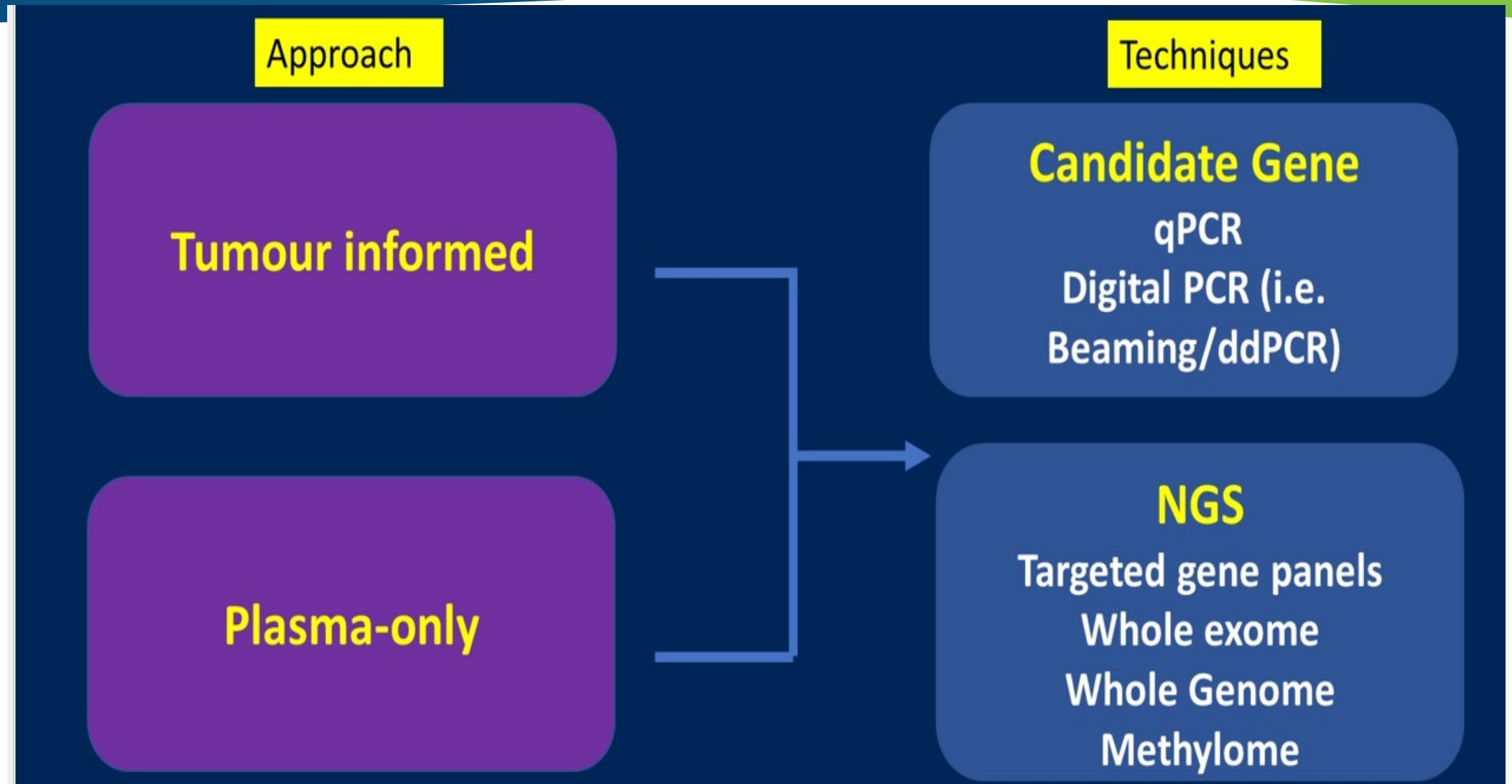
- The role of adjuvant chemotherapy (ACT) in stage II, III Colorectal who had undergone curative Surgical Resection, is to eradicate micro-metastatic disease.
  - The recurrence of disease is estimated around 15% and 25-50% for stage II and III CRC respectively
- For clinical stage IV or relapsed CRC pMMR with oligometastasis, perioperative chemotherapy with metastasectomy is the only curative option
  - Almost 60–70% of stage IV after oligometastatic resection experience recurrence
- Per the IDEA Consortium/ Trial the 5- year DFS rate for stage III Colon Cancer:
  - 89% for lowest-risk stage III (T1N1a) group , 31% for Highest-risk cohort (T4N2b)
- The absolute DFS benefit of ACT <u>3 months Vs 6 months</u>:
  - The lowest-risk stage III → 8 % , The highest-risk group→ 20%, ACT with
  - 5FU improves the OS by 10% to 15% after Surgery
  - Oxaliplatin will add 4% to 6% to the 5FU benefit

Circulating Tumor DNA for MRD

- Ct-DNA technology represents an emerging tool in GI cancer diagnostics to detect MRD
- Ct-DNA fragments harbor the same somatic genomic alterations as a patient's tumor.
- Ct-DNA analysis Methods:
  - PCR-based → Allele-specific assays
  - Next-generation sequencing (NGS)-based targeted and whole-genome approaches
  - Methylation Analysis Epigenetic Information



Circulating Tumor DNA Methodologies



Clinical Applications of ct-DNA

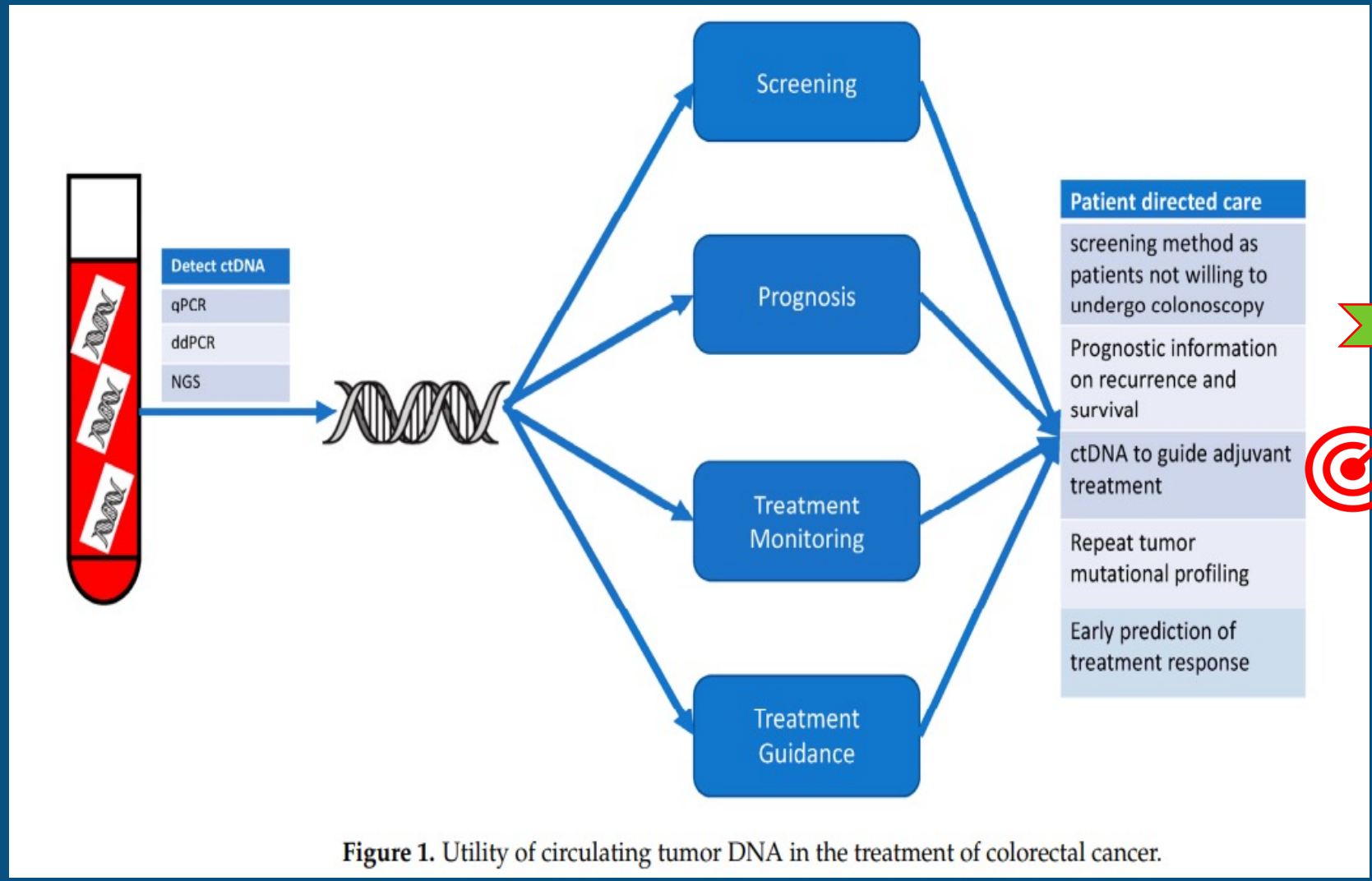


Figure 1. Utility of circulating tumor DNA in the treatment of colorectal cancer.

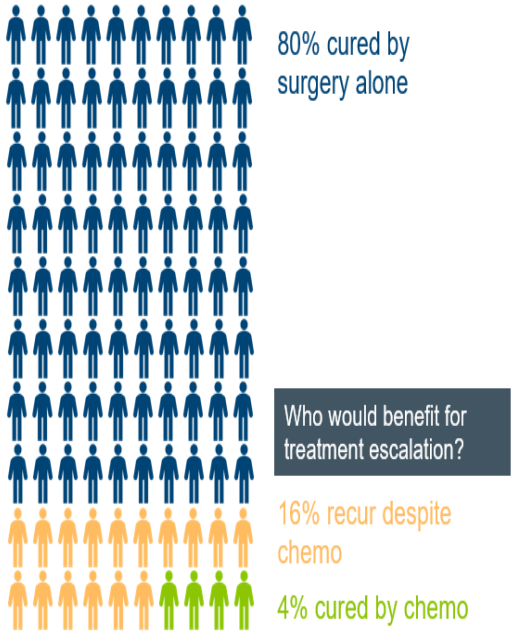
- MRD refers to persistent cancer after treatment that cannot be detected with current imaging tools (occult metastatic disease)[1]
- ctDNA dynamics can be used to assess disease burden in real-time
- Helps to inform treatment decisions along the continuum of care

Risk Stratification and ACT: Should we us ct-DNA as Biomarker

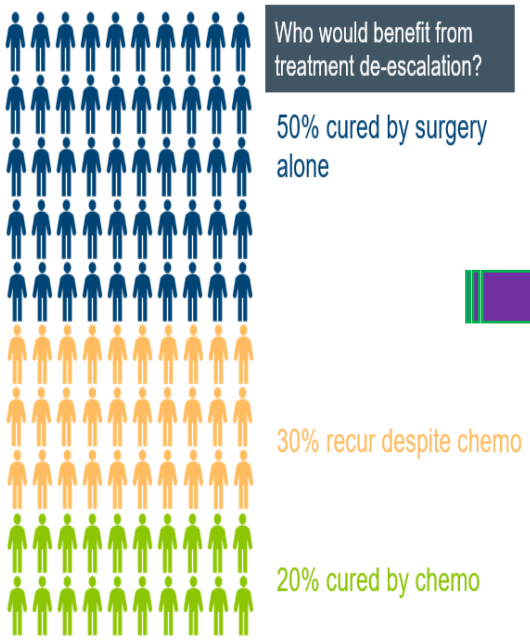
- Do All Patients with stage II Colon Cancer benefits from adjuvant Chemotherapy after Curative Surgery
- Could we select out patients with stage III who may be low risk and tailor the need for ACT or even omit ACT
- For stage IV CRC Resected is there any additional benefit of ACT
  - EORTC Controversies?
- <u>There is a great need to use ct-DNA to stratify who will benefit from treatment for stage II , and/or De-escalation for stages III or IV</u>

Stratification Clinicopathologic Risk Factors: Good Enough ??

Clinical dilemma in CRC Stage II



Clinical dilemma in CRC Stage III



Limitations in current methods of measuring disease burden or risk of relapse in patients with solid tumors

	Imaging	Clinicopathologic characteristics	Serum-based protein biomarkers
Examples	CT and PET/CT scans	ECOG PS, age, comorbidities, lymph node status, histology	PSA, CA-125, AFP, CEA
Limitations	Inability to detect micrometastatic disease, exposure to radiation	Risks features can be subjective and may not correlate to outcomes after treatment	Low sensitivity and specificity

1. Iversen LH, et al. *Acta Oncol.* 2016; 55(suppl 2):10-23. 2. Labianca R, et al. *Ann Oncol.* 2013; 24(suppl 6):vi64-vi72. 3. Glynne-Jones R, et al. *Ann Oncol.* 2018; 29(suppl 4):iv263. 4. Påhlman LA, et al. *J Clin Oncol.* 2016; 34(12):1297-1299.
5. Böckelman C, et al. *Acta Oncol.* 2015; 54(1):5-16.

DYNAMIC STUDY STAGE II COLON CANCER

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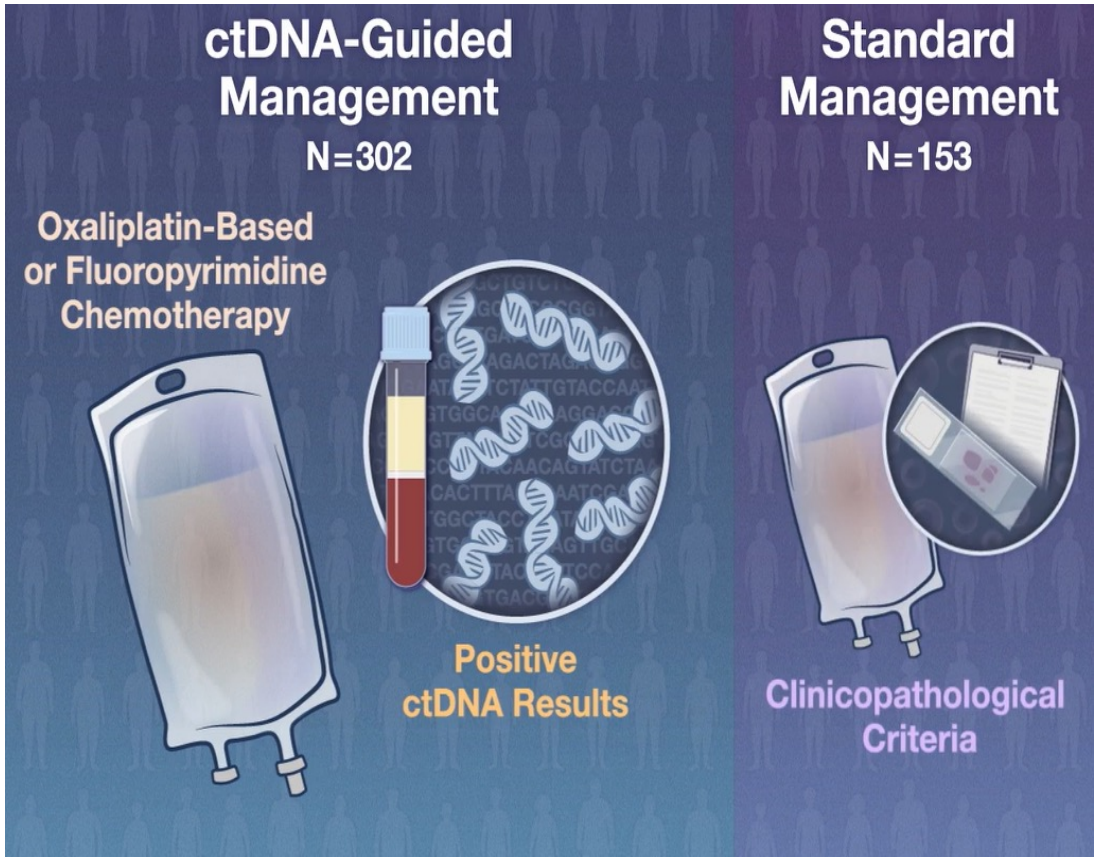
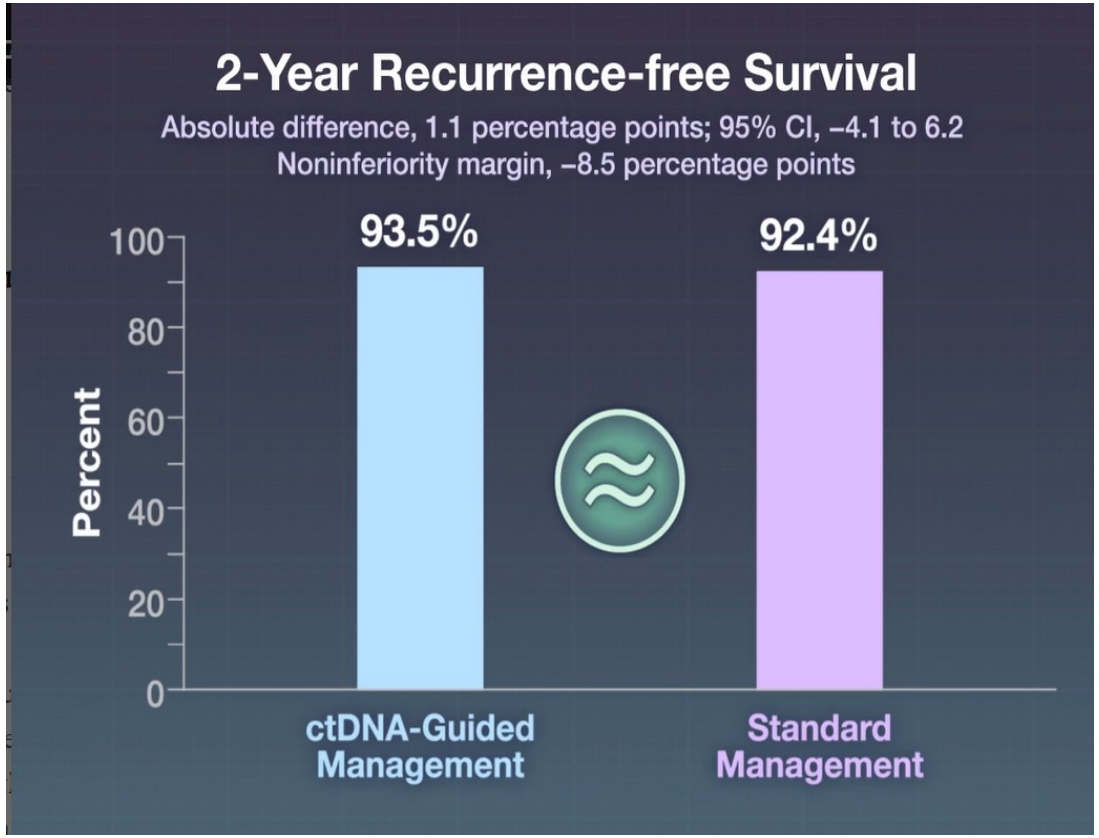
Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

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.,



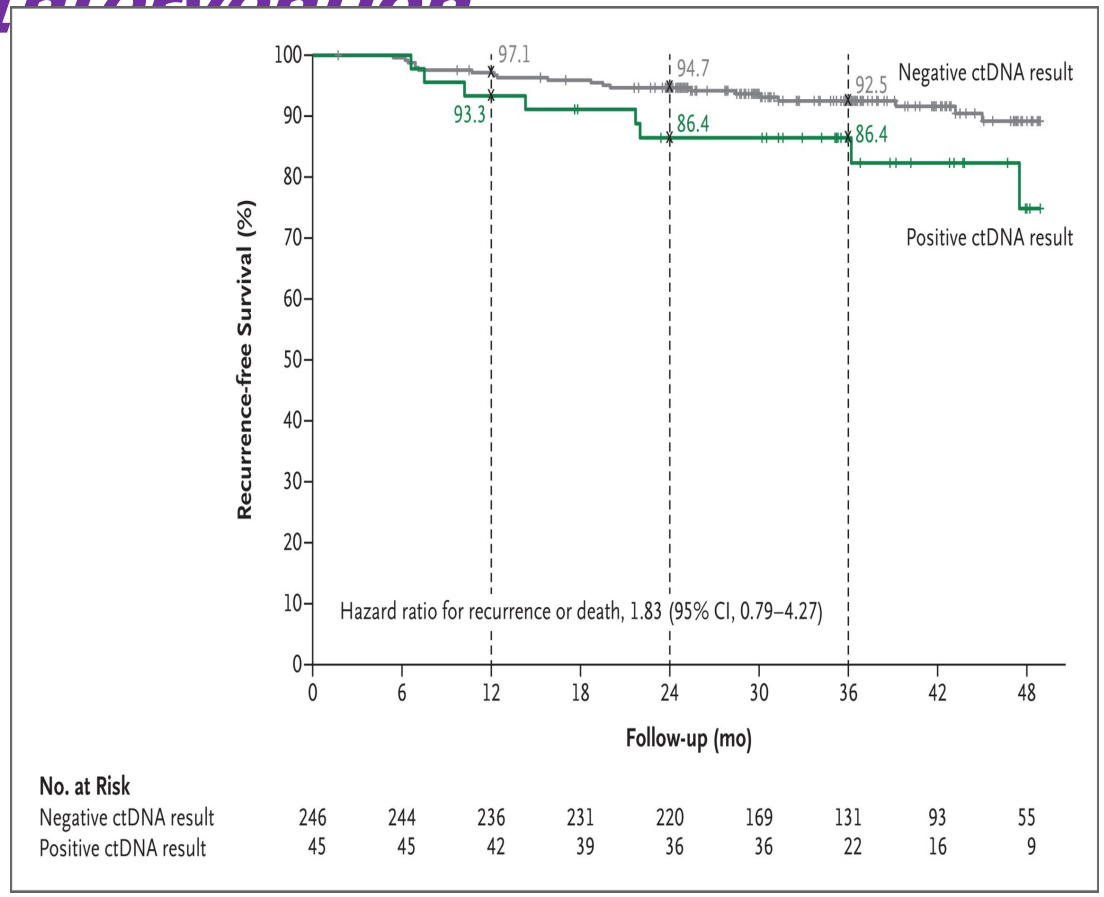
DYNAMIC STUDY STAGE II COLON CANCER

- A lower percentage of patients in the ct-DNA guided group than in the standard-management group received adjuvant chemotherapy 15% vs. 28%
- In 2-year recurrence-free survival→ ct-DNA-guided management was noninferior to standard management

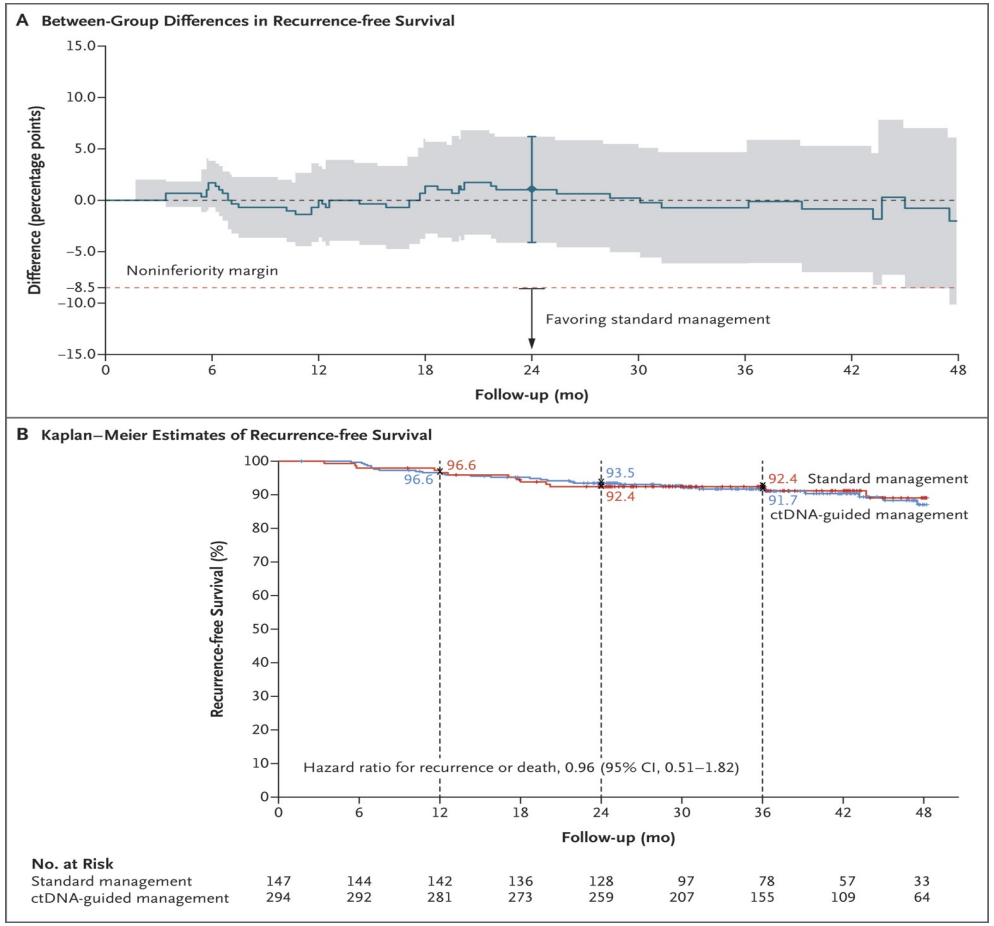


DYNAMIC STUDY STAGE II COLON CANCER

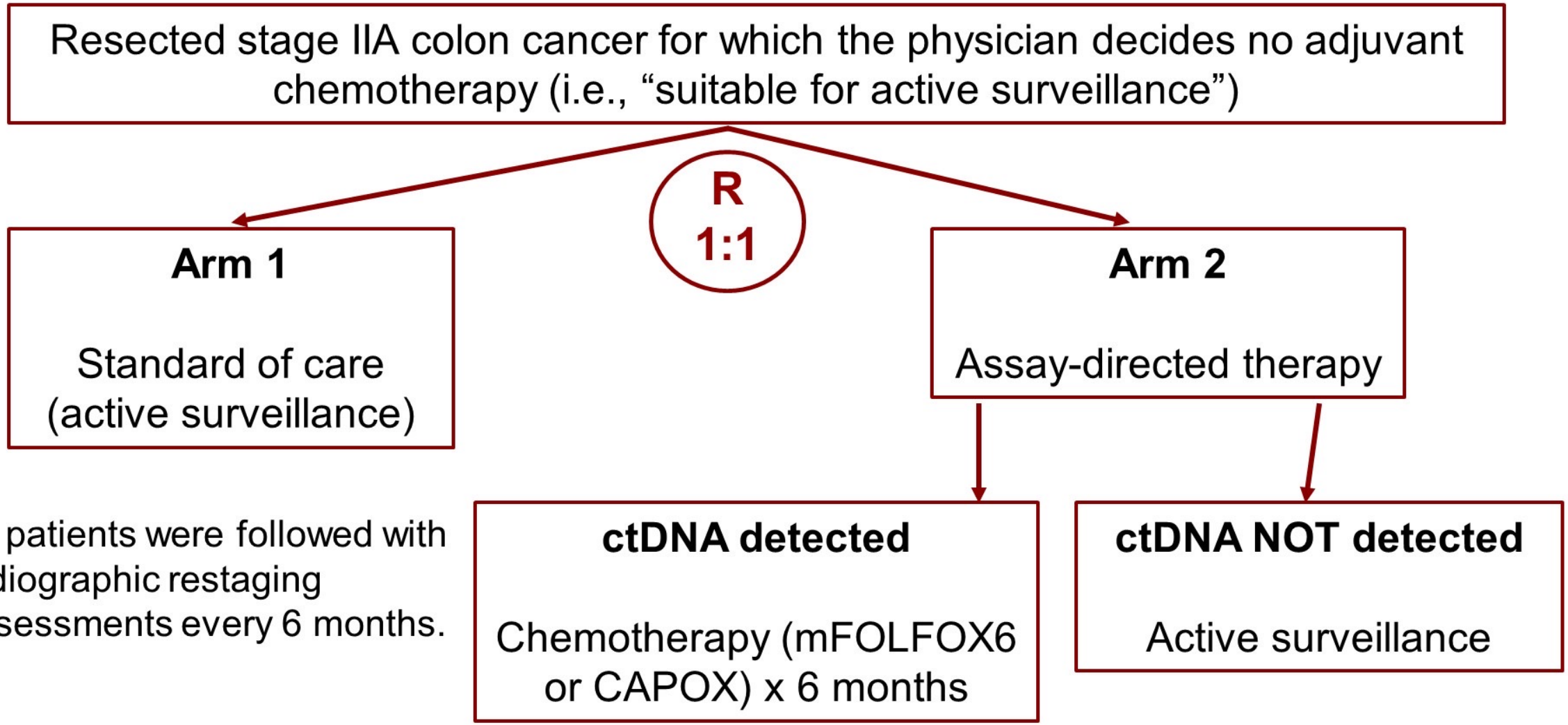
Recurrence Free Survival Intervention



RFS with



NRG-GI005 (COBRA) Study Schema



Phase II Endpoint Analysis: ctDNA(+) baseline participants

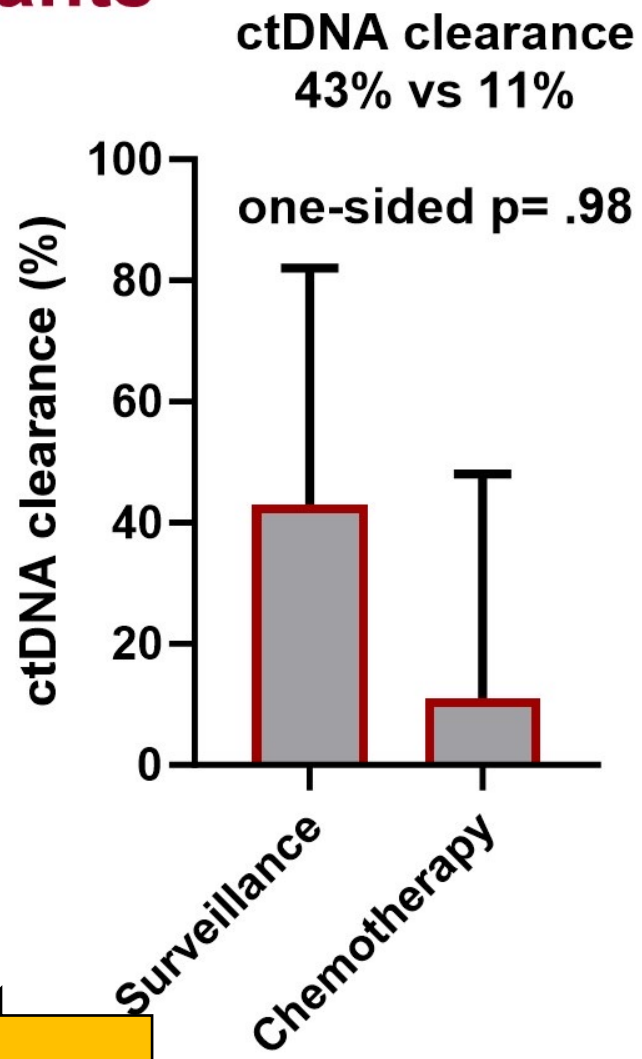
- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).

16 participants with "ctDNA detected" status at baseline

- Arm 1: Surveillance 7 participants
- Arm 2: Chemotherapy 9 participants

- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeded 0.35, H_o was not rejected, and the decision rule calls for early stopping due to futility.**



ASCO® Gastrointestinal Cancers Symposium

CIRCULATE Japan

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

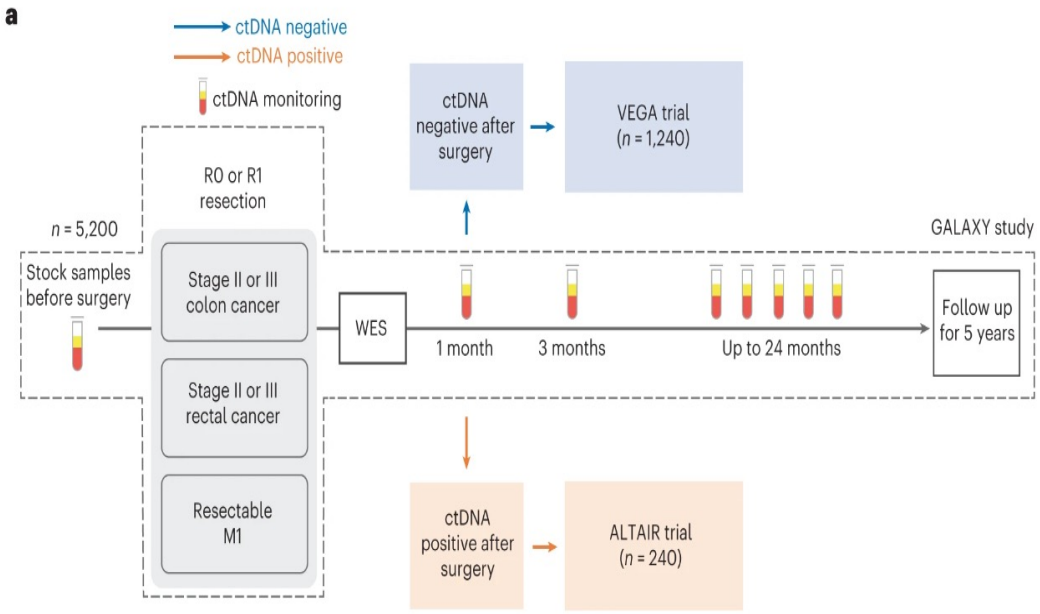
Co-authors; Hiromichi Shirasu, Jun Watanabe, Kentaro Yamazaki, Keiji Hirata, Naoya Akazawa, Nobuhisa Matsuhashi, Mitsuru Yokota, Masataka Ikeda, Kentaro Kato, Alexey Aleshin, Shruti Sharma, Daisuke Kotani, Eiji Oki, Ichiro Takemasa, Takeshi Kato, Yoshiaki Nakamura, Hiroya Taniguchi, Masaki Mori, Takayuki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

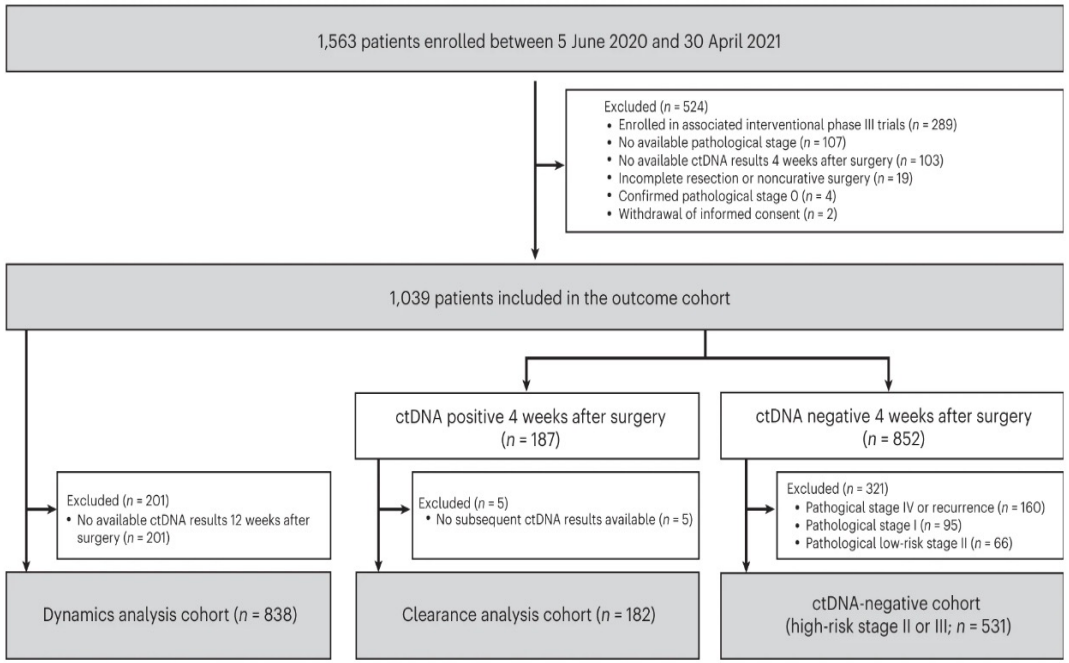
On behalf of the CIRCULATE-Japan Investigators

GALAXY STUDY /CIRCULATE JAPAN

Fig. 1: Study design and population.

From: Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer



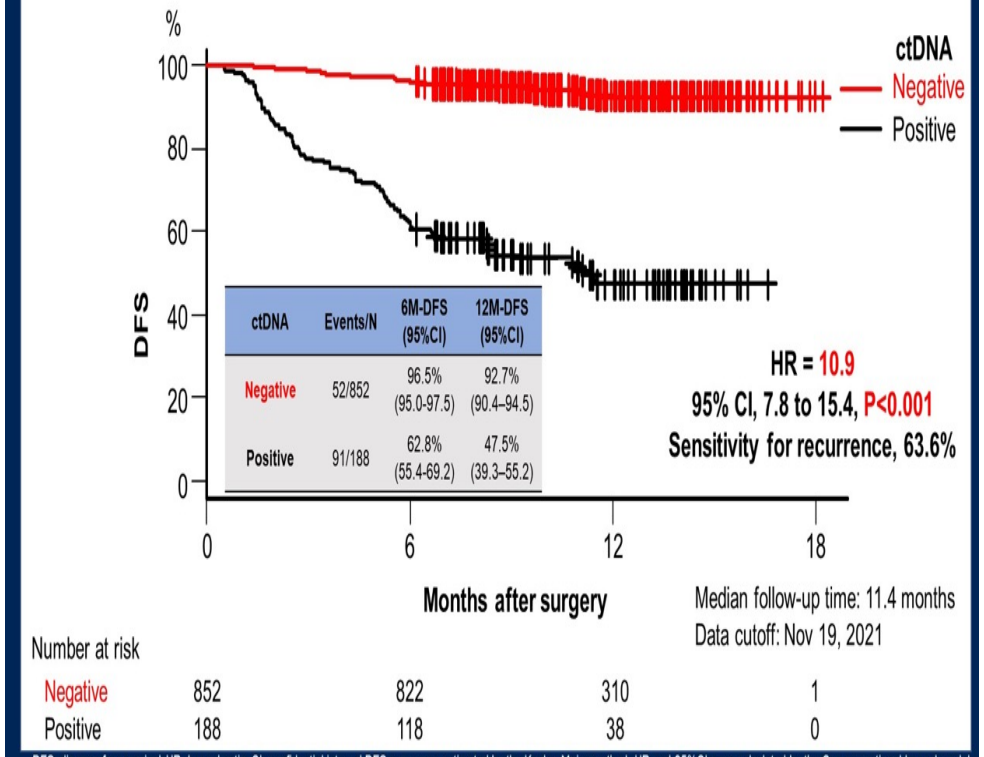


a, Overview of CIRCULATE-Japan study, illustrating the observational GALAXY protocol with sample collection schema. **b**, CONSORT (Consolidated Standards of Reporting Trials) diagram illustrating patient inclusion and exclusion criteria for sub-analyses.

GLAXY Study in CIRCULATE Japan

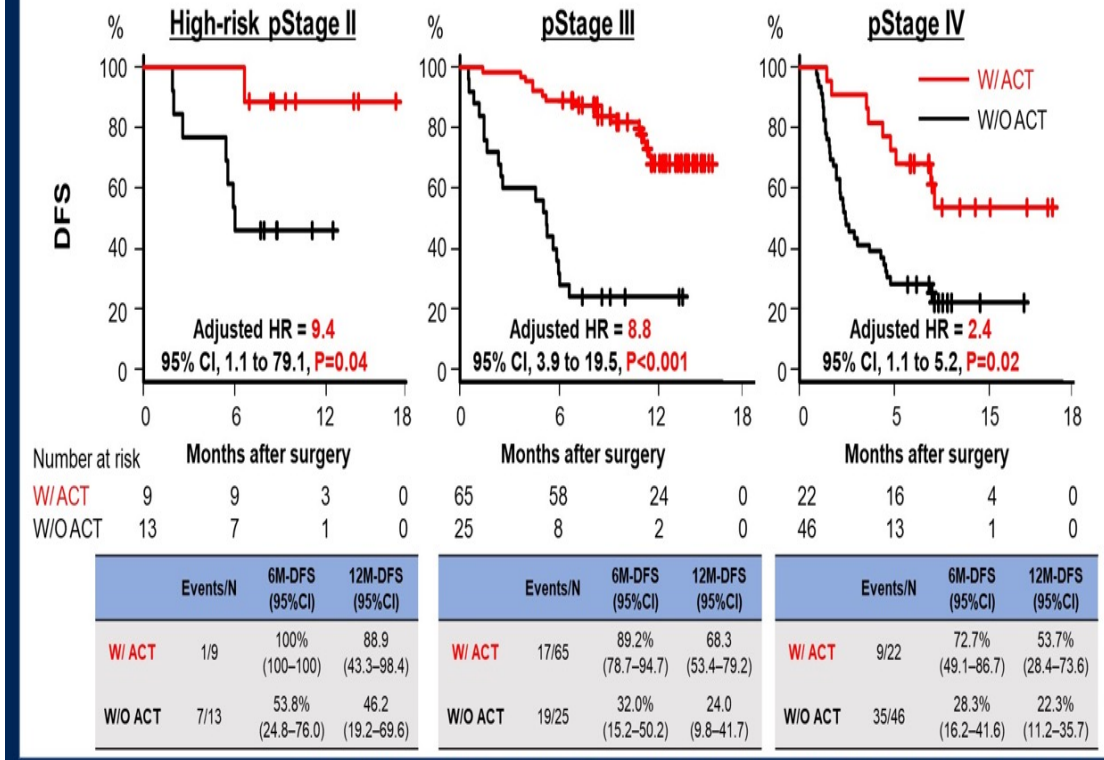
GI ASCO 2022

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



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 pStage in post-op-4w ctDNA positive population



	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	1/9	100% (100–100)	88.9 (43.3–98.4)
W/O ACT	7/13	53.8% (24.8–76.0)	46.2 (19.2–69.6)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	17/65	89.2% (78.7–94.7)	68.3 (53.4–79.2)
W/O ACT	19/25	32.0% (15.2–50.2)	24.0 (9.8–41.7)

	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	9/22	72.7% (49.1–86.7)	53.7% (28.4–73.6)
W/O ACT	35/46	28.3% (16.2–41.6)	22.3% (11.2–35.7)

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.

GLAXY Study in CIRCULATE Japan

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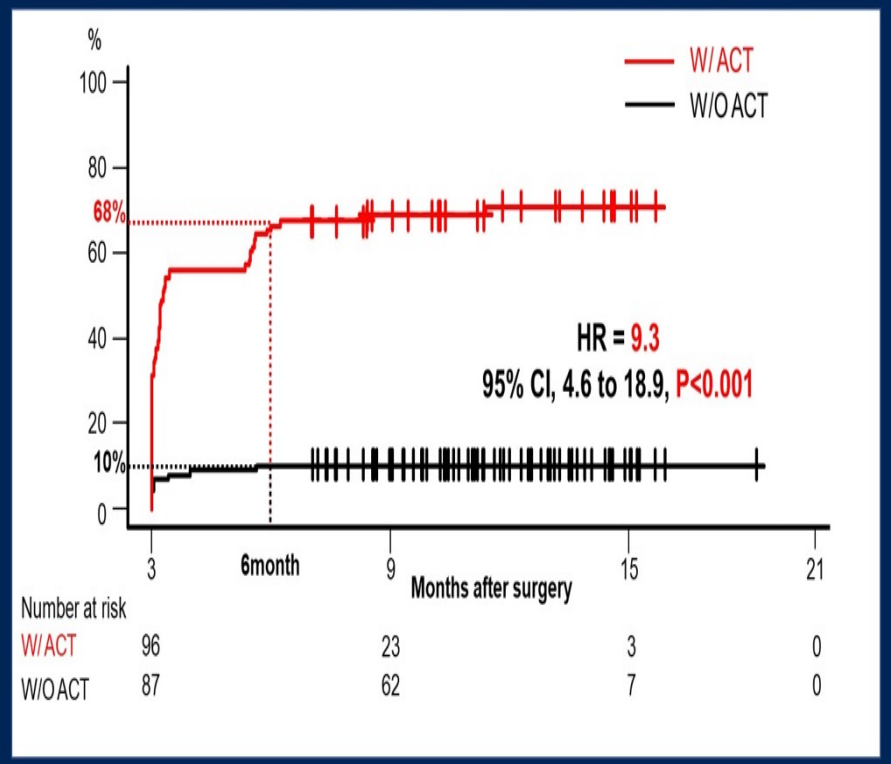
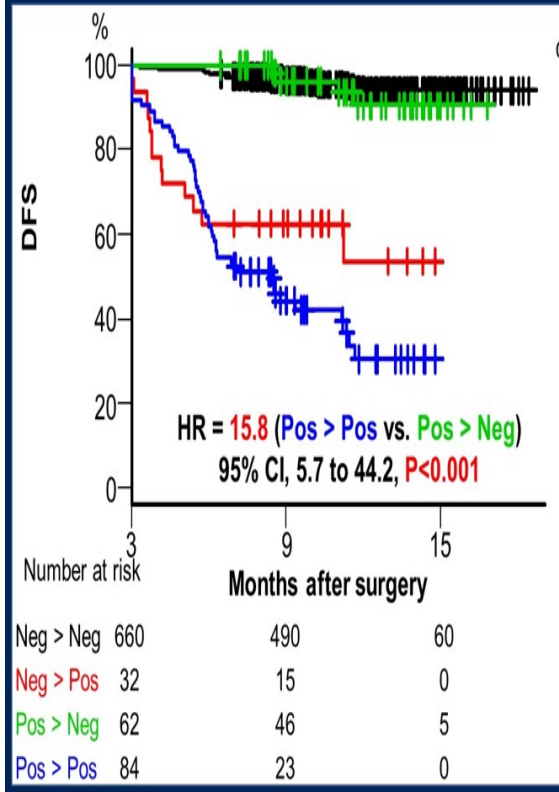
Cumulative Incidence of ctDNA clearance pStage I-IV



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 ctDNA dynamics from post-op-4w to 12w



dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27–2.15	3.0–28.4	-	5.7-44.2
P	0.60	<0.001	-	<0.001

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Landmark analysis at the post-op-12w was performed.
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.

GLAXY Study in CIRCULATE Japan

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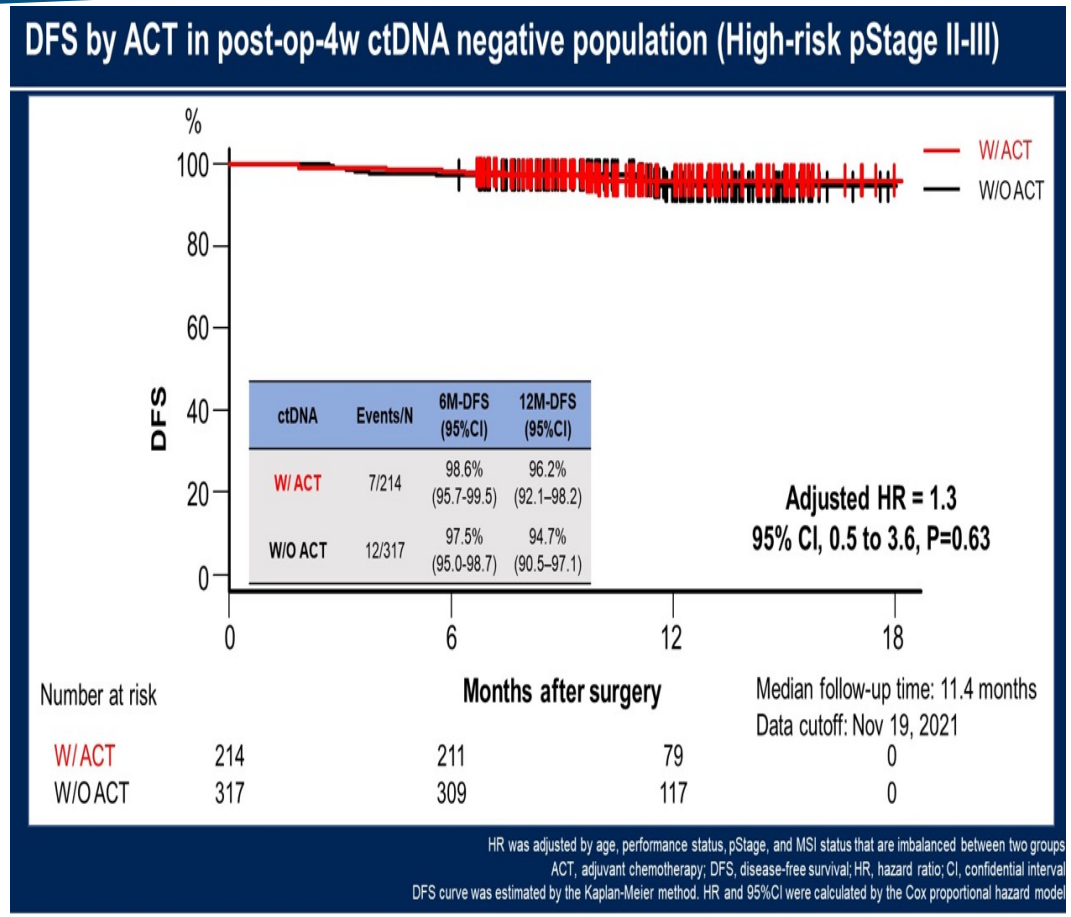
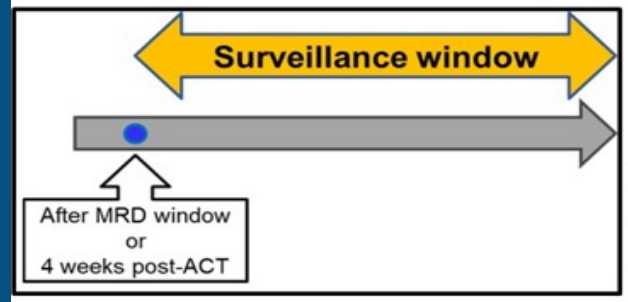


- Lower DFS → if ct DNA (+) 4week post-Op
- DFS significantly different in 6 months, 12M with post-op4w-12w ctDNA :
  - if was (+)→ (-) Vs (+)→ (+)
- 68% of ctDNA (+)
- Patients stage II, III with ct DNA (-) DID NOTwith HR 1.3 derive benefit from ACT

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

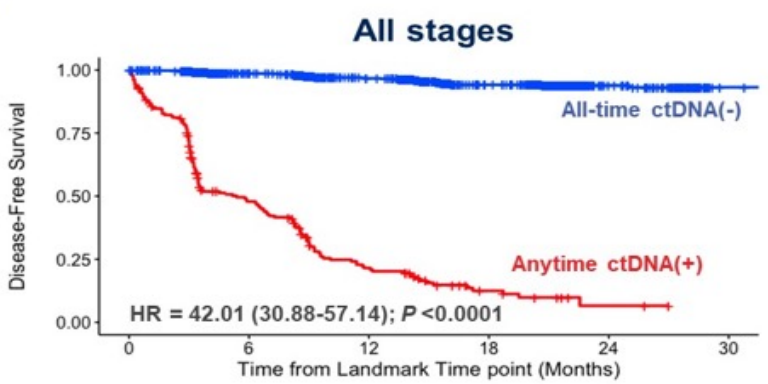
DFS according to ctDNA status in the Surveillance window



2,998 stage I-IV patients included in the outcome cohort

Excluded (N=1,212)
- No subsequent timepoints available (n=858)
- DFS event prior to the 8 months landmark timepoint (n=354)

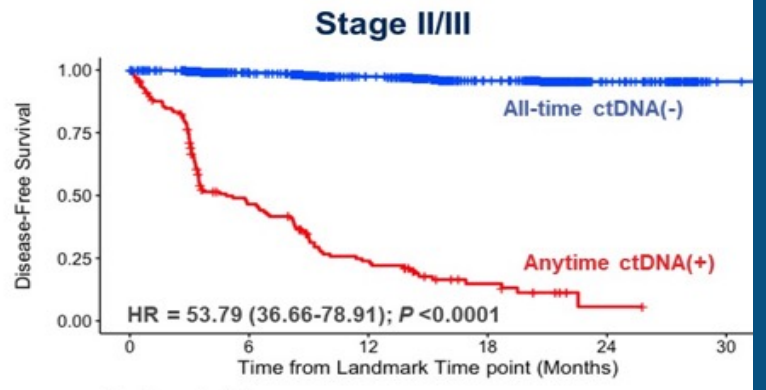
Surveillance Window analysis cohort (n=1,786)



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

PRESENTED BY: Hiroki Yukami, MD, PhD

Galaxy Trial / Circulate Japan Takeaway

- The largest trial with 3000 patients to demonstrate a Prognostic value of ct-DNA detection at 24m
- Sustained ct-DNA clearance is associated with > 90% DFS
- Transient clearance on ACT is better than Non-Cleared but carries poor prognosis→ 90 % will have recurrence by 18m
- The DFS for Stage I-IV at 24m for ct DNA (+) Vs ct DNA (-) is 29% Vs 86%
- Randomized Trials VEGA & ALTAIR are ongoing in hope to result on ct-DNA Guided ACT in resected CRC

ASCO Gastrointestinal Cancers Symposium

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

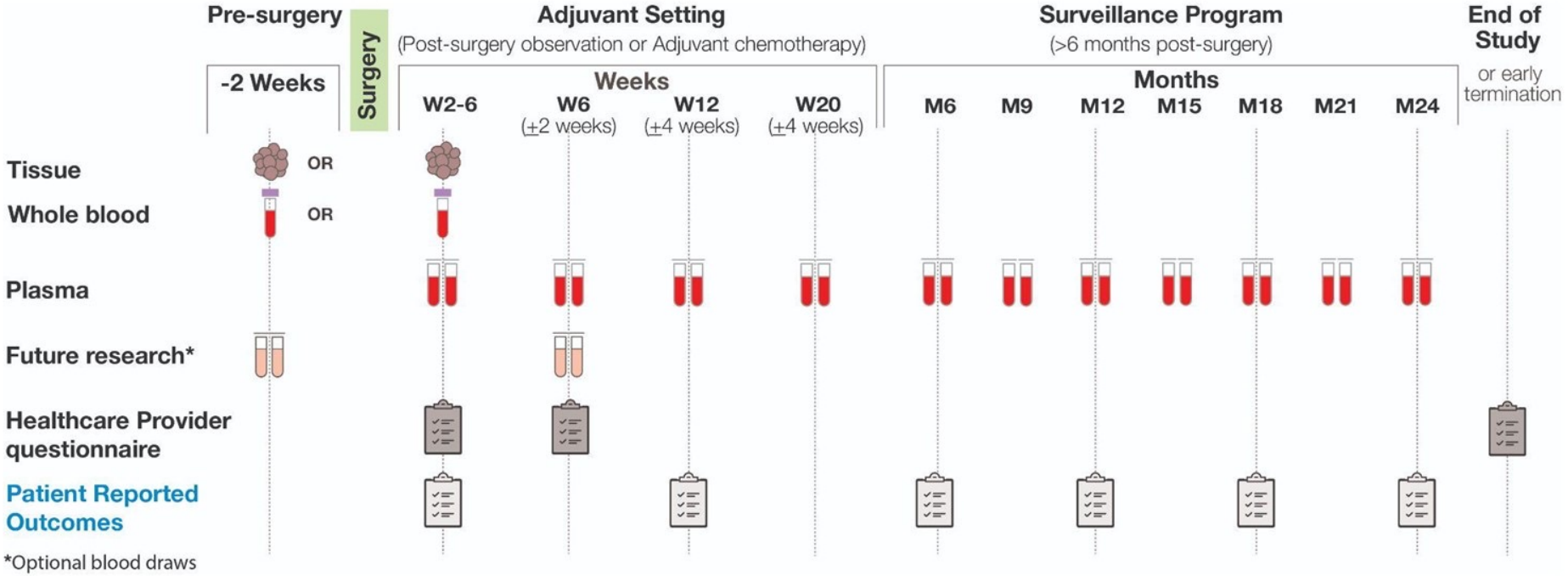
Presenting author: Pashtoon Kasi[1], MD, MS

Co-authors: Vasily N Aushev[2], Joe Ensor[2], Nathan Langer[3], Christopher Wang[4], Timothy Cannon[5], Lyudmyla Berim[6], Trevor Feinstein[7], Axel Grothey[8], Joseph McCollom[9], Sujith Kalmadi1[0], Ahmed Zakari[11], Farshid Dayyani[12], Don Gravenor[13], Janelle Meyer[14], Saima Sharif[15], Adham Jurdi[2], Minetta C Liu[2], Alexey Aleshin[2], Scott Kopetz[16]

[1]Department Weill Cornell Medicine, Englander Institute of Precision Medicine, New York Presbyterian Hospital, New York, NY; [2]Natera, Inc., Austin, TX; [3]Virginia Cancer Institute (QCCA), Richmond, VA; [4]Alabama Oncology, Birmingham, AL; [5]Inova Schar Cancer Institute, Fairfax, VA; [6]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ; [7]Piedmont Cancer Institue, Atlanta, GA; [8]West Cancer Center, Germantown, TN; [9]Parkview Cancer Institute, Fort Wayne, IN; [10]Ironwood Cancer & Research Centers, Chandler, AZ; [11]AdventHealth Cancer Institute, Montverde, FL; [12]Division of Haematology/Oncology, Department of Medicine, University of California Irvine, Orange, CA; [13]Baptist Cancer Center, Memphis, TN; [14]Hematology Oncology of Salem, LLP - Salem Office, Salem, OR; [15]University of Iowa, Iowa City, IA; [16]University of Texas MD Anderson Cancer Center, Houston, TX

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]



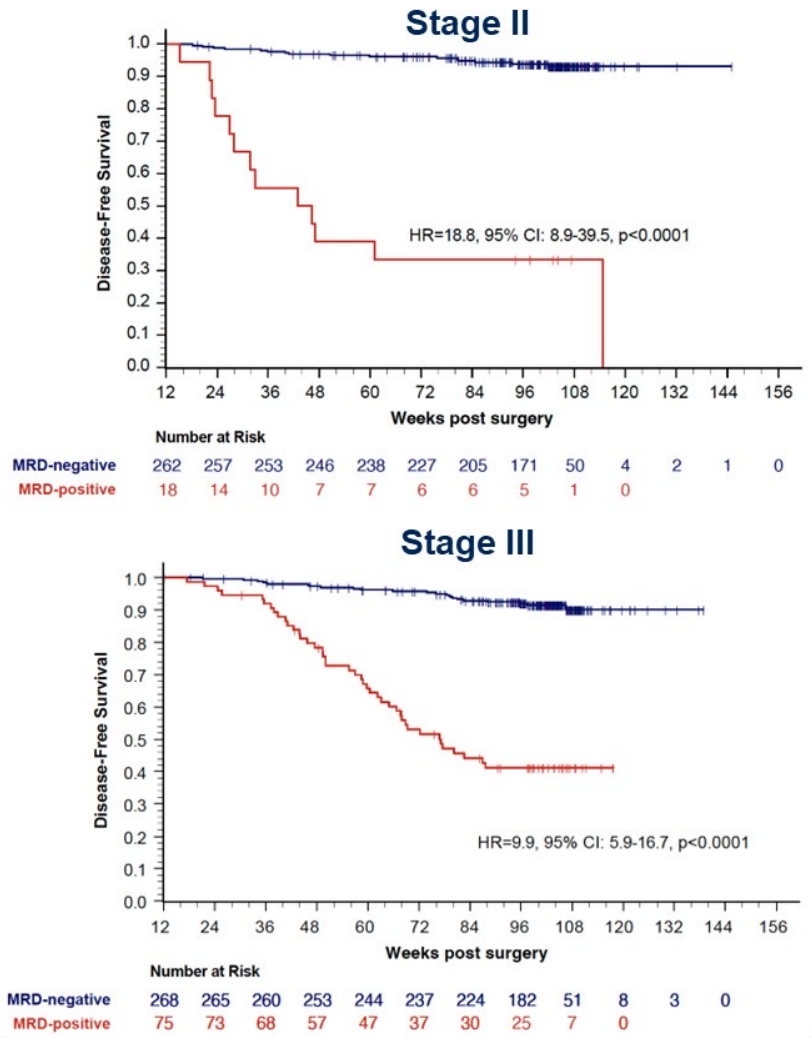
[1]Kasi et al. *BMJ Open* 2021;11:e047831.

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

MRD-positivity rate by stage II-III

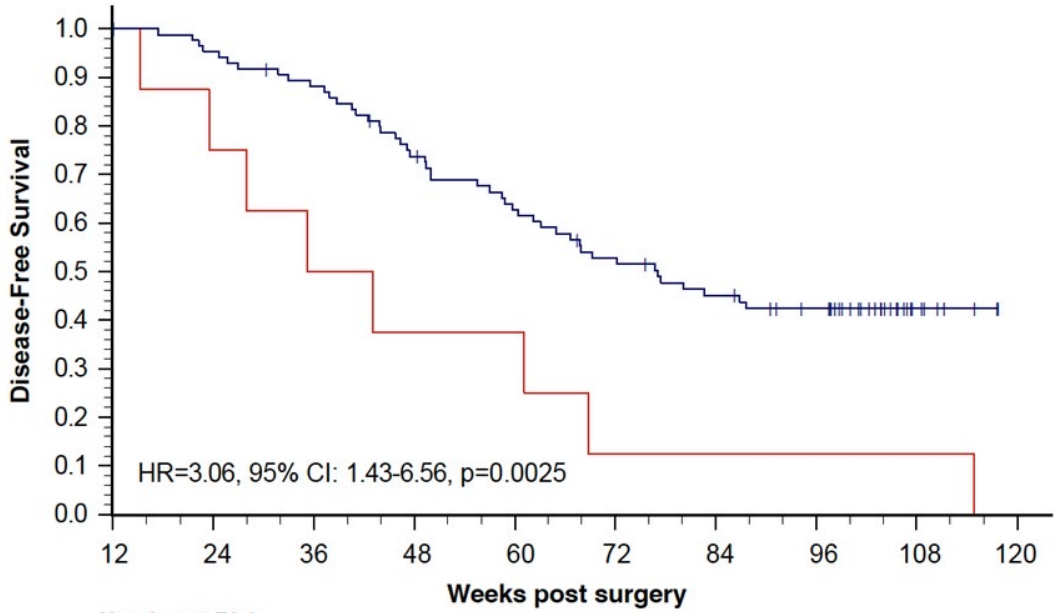
Stage	Total, N	MRD-negative, n (%)	MRD-positive, n (%)	95% CI for positivity rate
II	280	262 (93.57)	**18 (6.43)**	4.10-9.93
III	343	268 (78.13)	**75 (21.87)**	17.82-26.54
Total	623	530	93	

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

MRD-positive patients

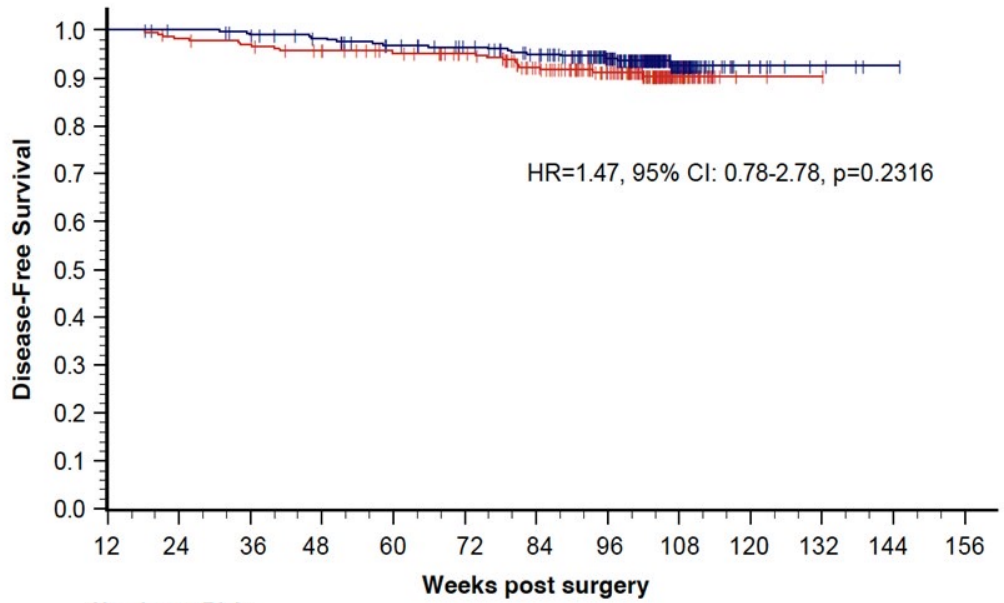


Number at Risk

ACT	85	80	72	56	48	39	32	18	2	0
Observation	8	6	4	3	2	1	1	1	0	

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)

MRD-negative patients



Number at Risk

ACT	296	293	288	281	271	263	251	207	61	10	4	1	0
Observation	234	229	225	218	211	201	178	146	40	2	1	0	

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

PRESENTED BY: Pashtoon Kasi, MD

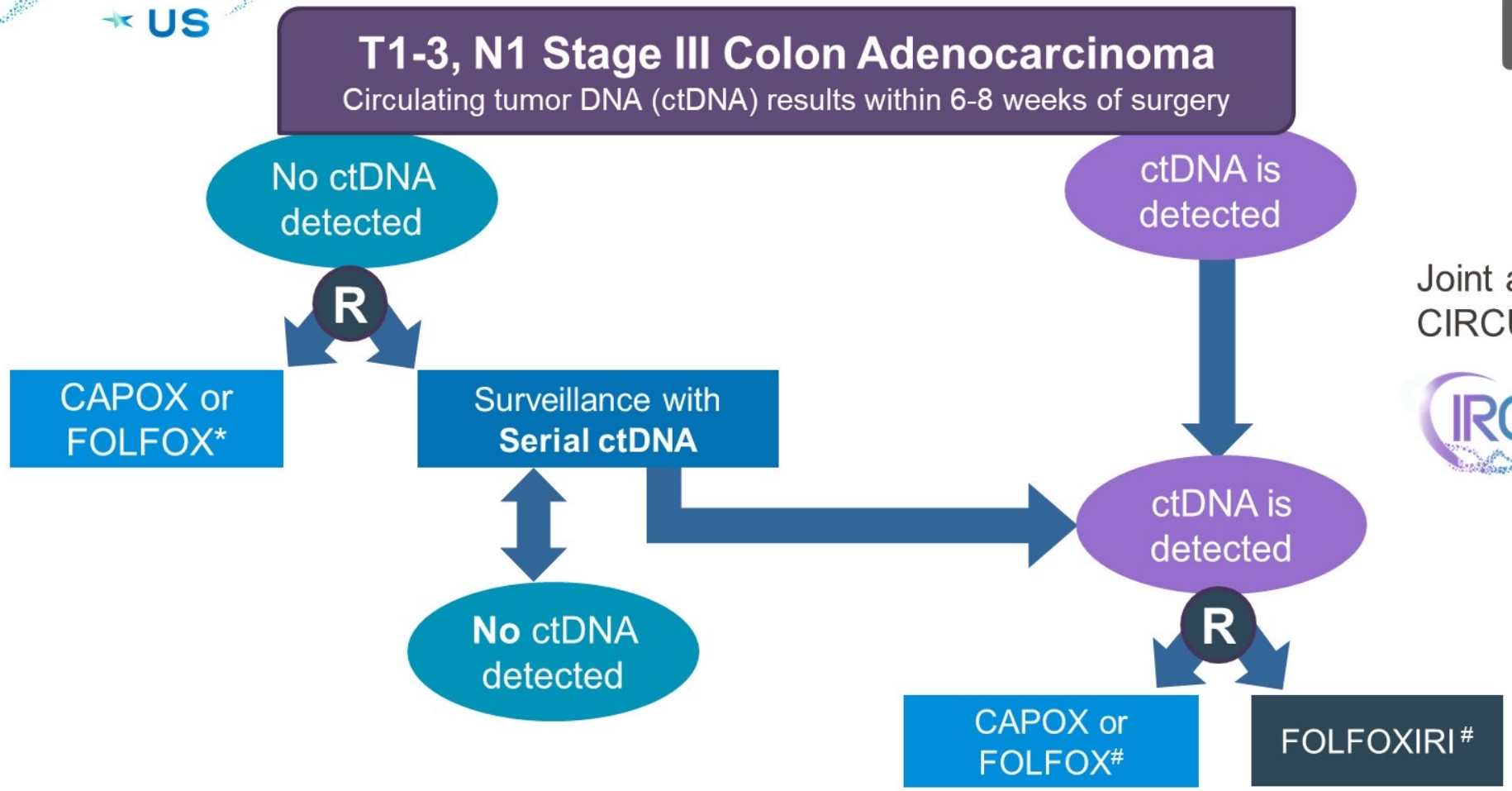
MD Anderson

CIRCULATE US

NRG ONCOLOGY
Advancing Research. Improving Lives.™

SWOG
Leading cancer research. Together.

NIH NATIONAL CANCER INSTITUTE



Joint analysis with CIRCULATE-Japan

CIRCULATE Japan

PIs:
Arvind Dasari (MDACC – NRG)
Christopher Lieu (UCCC – SWOG)

*: Duration and regimen per physician discretion
#: 6 months duration

NRG-GI008

Stage IV CRC and ct-DNA

- Could it be used as Biomarker for Treatment guidance and monitoring after Surgical Resection following peri-operative Chemotherapy
- SCRUM-Japan GOZILA study site of metastasis for CRC showed:
  - Lung metastasis and Peritoneal Mets significantly lower levels of ctDNA
- For mCRC there is High Correlation between ct-DNA response and OS
- Ct-DNA may also prove useful in treatment monitoring of acquired resistance mechanisms

Ongoing Trials ct DNA in Stage IV CRC

OPTIMISE: OPTIMIzation of Treatment SElection and Follow up in Oligometastatic Colorectal Cancer - NCT04680260

PI Karen-Lise Garm Spindler, Aarhus University Hospital, Aarhus, Denmark

Compares: ctDNA Guided vs Standard-of-Care treatment

ctDNA-Directed Post-Hepatectomy Chemotherapy for Patients With Resectable Colorectal Liver Metastases - NCT05062317

PI Timothy Newhook, M.D. Anderson Cancer Center, Houston, Texas, USA

Compares: Arm 1: ctDNA-low risk (Leucovorin + Capecitabine) versus

Arm 2: ctDNA-high risk (FOLFOX or FOLFIRI with/without bevacizumab)

Conclusion

- Ct-DNA could be a powerful" Biomarker" which may predict recurrence rate after Curative Surgery in stage II and III CRC
- Hence, Its utilization may play a major role on omitting ACT in Low risk stage II and stage III CRC, certain Young patients.
  - DYNAMIC, GALAXY BESPOKE ct-DNA (-) did not derive a significant improvement of ACT
- High Rate ct-DNA clearance correlates with improved RFS in stage II-III ct-DNA (+) population.
  - Could ct DNA Dynamic 4w Positive -12 w (-) become surrogate End Point like DFS for clinical Trials
- Future clinical Trials are needed to answer questions in High Risk patients and stage IV CRC with oligometastatic disease

Personal Take on ct-DNA

- Stage II:
  - Low Risk stage II Colon Cancer ct-DNA (-) → Offer surveillance
  - High Risk ct-DNA (-) → Risk & Benefit of ACT and neuropathy Discussion.
  - Stage II ct-DNA (+) ACT then De-escalate → (-)
- Stage III → Clinical trial Circulate-USA
  - Off trials Low Risk → 12 weeks of ACT.
    - If Hesitancy/ Concern about Adverse Events, Comorbidities… → ct DNA guided Rx
  - High Risk →12 weeks of ACT & De-Escalate therapy if ct-DNA becomes (-)
- Stage IV Resected after 12 wks of peri-operative chemoRX→ De-escalate and Close Surveillance if ct-DNA (-)