15th CONGRESS on Lung CANCER
MADRID
23&24 November 2023
#15CongressGECP

Fundación GECP lung cancer research

Minimal residual disease detection through comprehensive analyses of circulating tumor DNA for early stage non-small cell lung cancer

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Disclosures

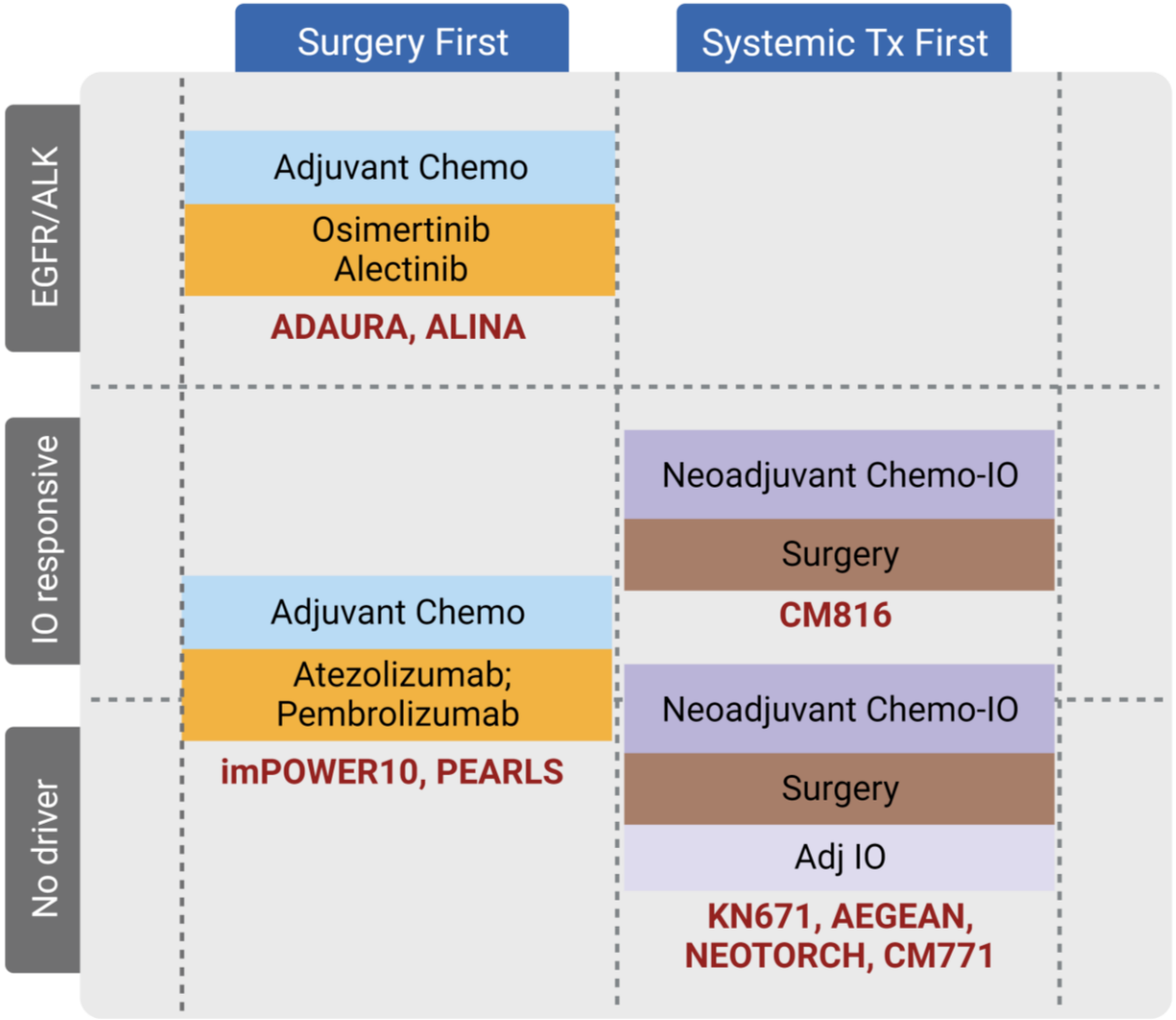
I have the following financial relationships to disclose:

Current/within the past 5 years: Grant/Research support (to Johns Hopkins) from: Astra Zeneca, Bristol-Myers Squibb, Personal Genome Diagnostics/Labcorp and Delfi Diagnostics; advisory board member for: Astra Zeneca and Neogenomics, honoraria for lectures: Foundation Medicine

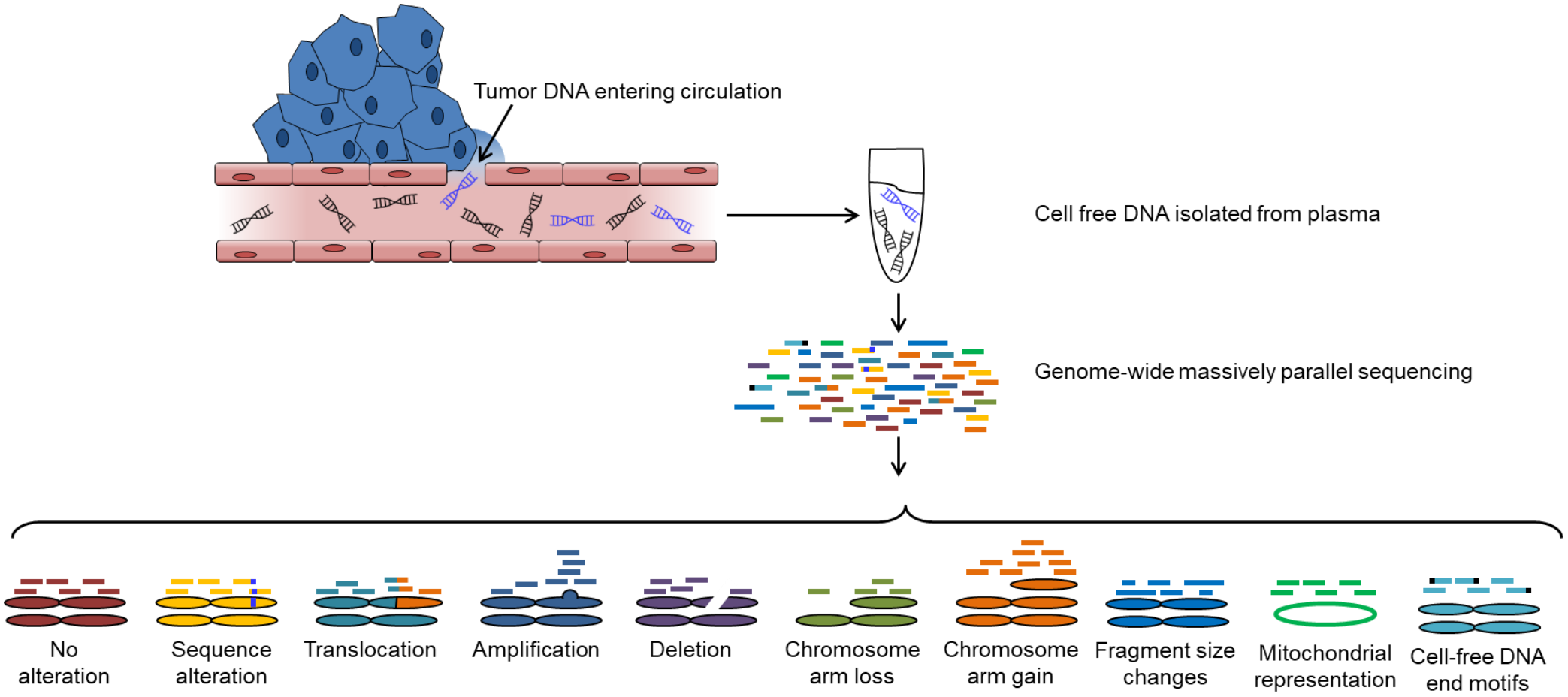
My additional financial relationship disclosures are:

I am an inventor on patent applications (63/276,525, 17/779,936, 16/312,152, 16/341,862, 17/047,006 and 17/598,690) submitted by Johns Hopkins University related to cancer genomic analyses, ctDNA therapeutic response monitoring and immunogenomic features of response to immunotherapy that have been licensed to one or more entities. Under the terms of these license agreements, the University and inventors are entitled to fees and royalty distributions.

The evolving therapeutic landscape of early stage NSCLC



Liquid biopsy approaches for detection of NSCLC

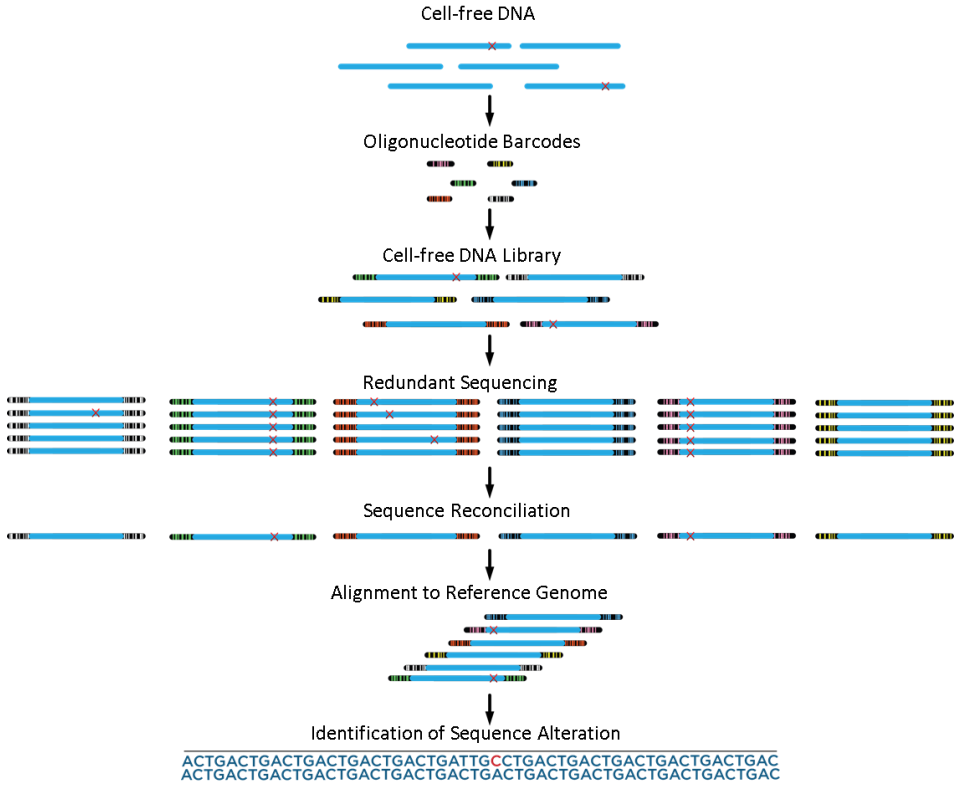


Bruhm et al., *Nat Genet*, 2023, Mattox et al., *Cancer Discov*, 2023, Wang et al., *PNAS*, 2023, Sivapalan et al., *Clin Can Res*, 2023, Foda et al., *Cancer Discov*, 2023
Cohen et al., *Nat Biotechnol*, 2021, Cristiano et al., *Nature*, 2019, Anagnostou et al., *Can Res*, 2019, 2020, Cohen et al., *Science*, 2018, Phallen et al., *Science TM*, 2017

ctDNA challenges: technical noise

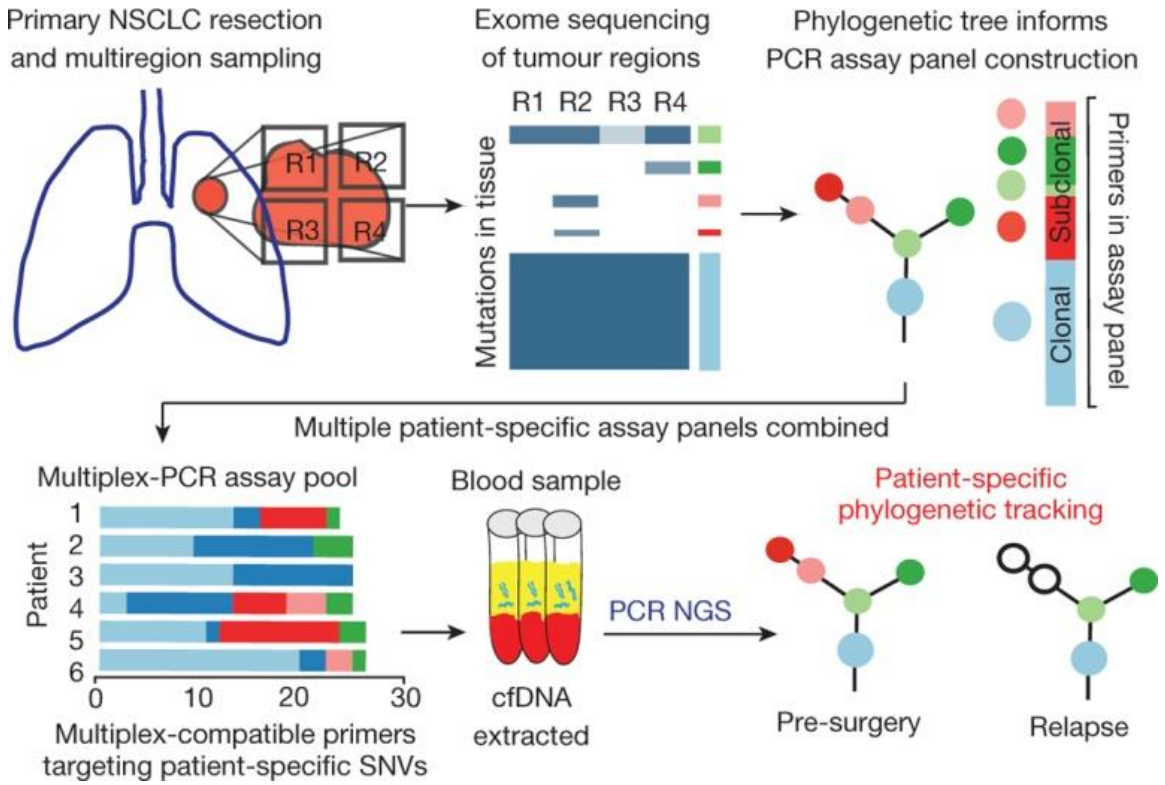
Hybrid capture NGS

TEC-Seq, Capp-Seq, Guardant360, F1 Liquid CDx, Tempus xF



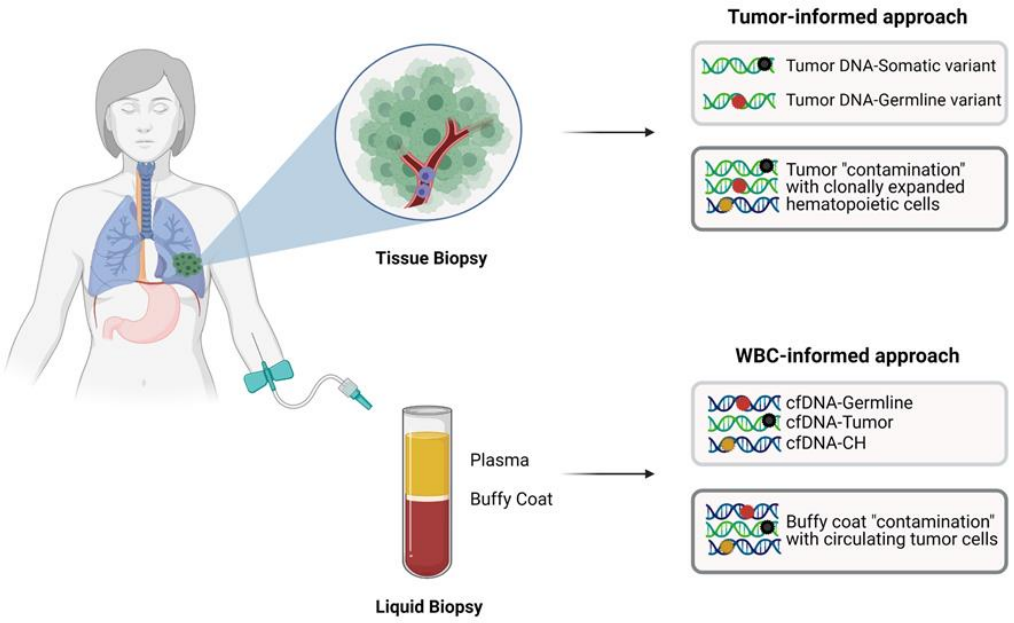
Multiplex PCR NGS

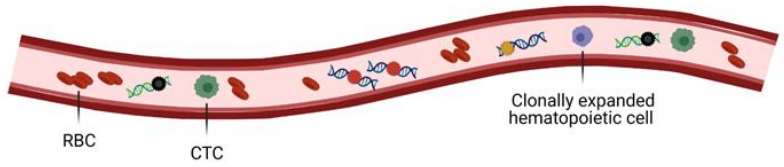
Safe(r)-Seq, HaystackNatera Signatera, FoundationOne Tracker, Inivata RaDar, Invitae personalized cancer monitoring, Personalis NeXT Personal Dx

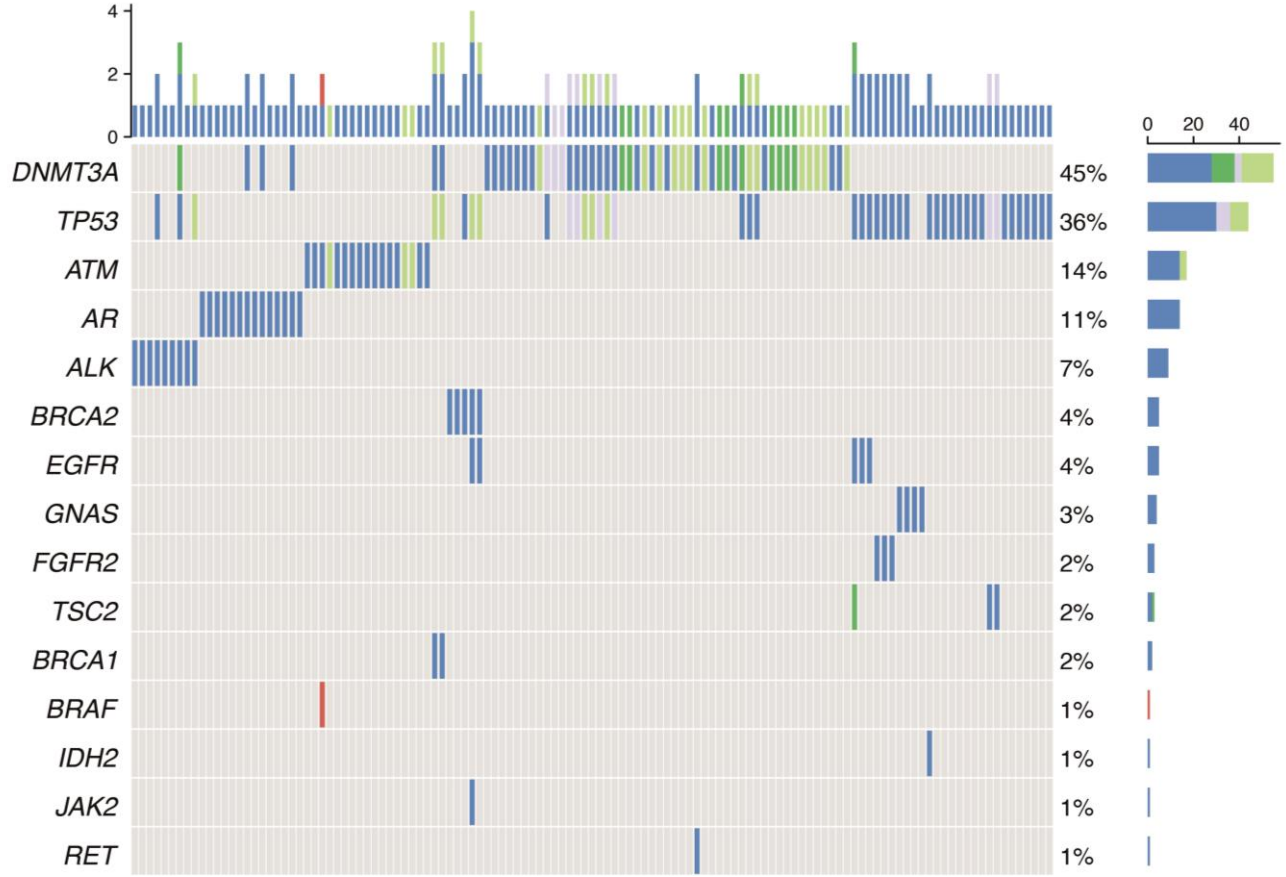


Newman et al., *Nat Med*, 2014, Phallen et al., *Science TM*, 2017, Forshew et al., *Science TM*, 2012, Kinde et al., *PNAS USA,* 2011, Cohen J, *Nat Biotechnol*, 2021

ctDNA challenges: biological noise



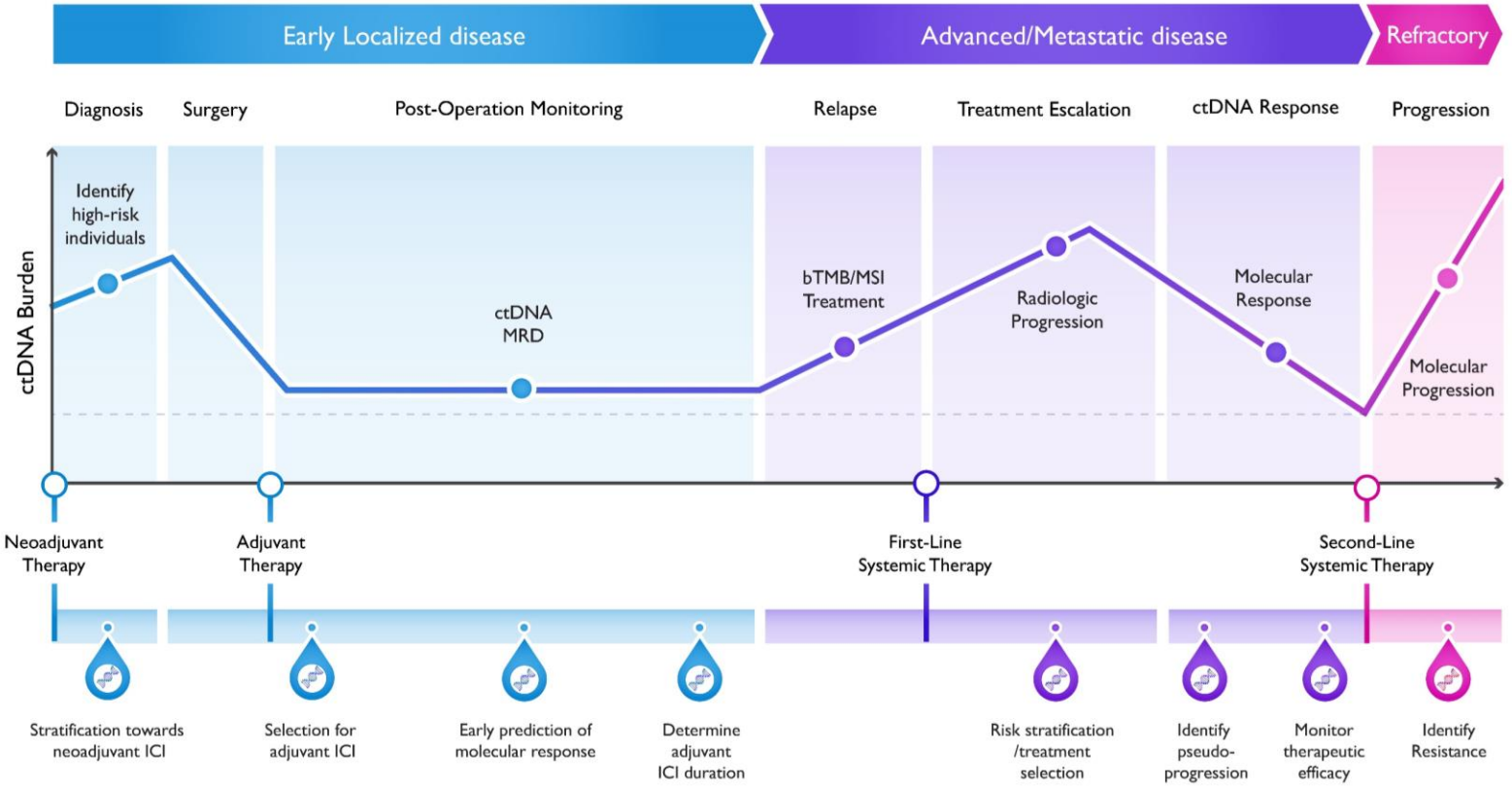




Leal et al., *Nat Commun*, 2020, Anagnostou et al., *Nat Med*, 2023, Sivapalan et al., *Clin Can Res*, 2023, Sivapalan et al., *JITC Review Series on Liquid Biopsies,* 2023

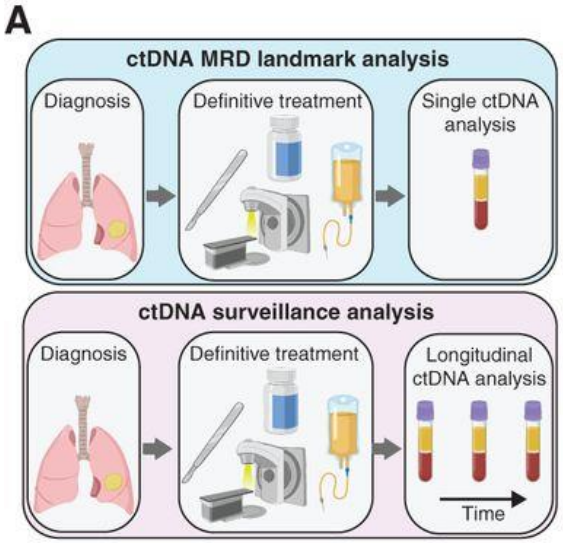
Integration of liquid biopsies in the NSCLC care continuum

T Tumor Size	N Lymph Node	M Metastasis	B Blood
T1 Tumor size/local invasion	N0 No regional lymph node invasion	M0 No distant metastasis	B0 No ctDNA mutations in blood
T2 Tumor size/local invasion	N1 Tumor spead to closest or small number of regional lymph nodes	M1 Distant metastasis	B1 ctDNA mutations in blood (can be further defined with more detailed quantification in the future)
T3 Tumor size/local invasion	N2 Tumor spead to an extent between N1 and N3		
T4 Tumor of any size that invades to other organs	N3 Tumor spead to more distant or regional numerous lymph nodes		



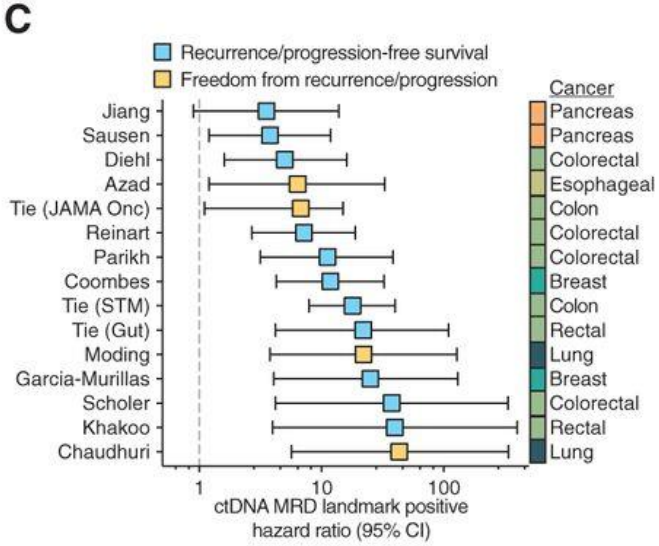
Yang et., *Ann Oncol,* 2018, Sivapalan et al., *JITC Special Review Series on Liquid Biopsies,* 2023

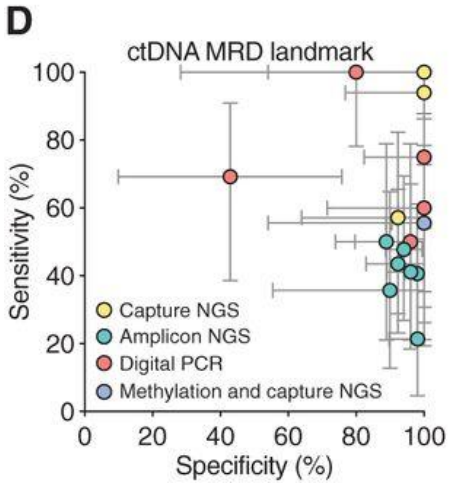
ctDNA MRD is prognostic

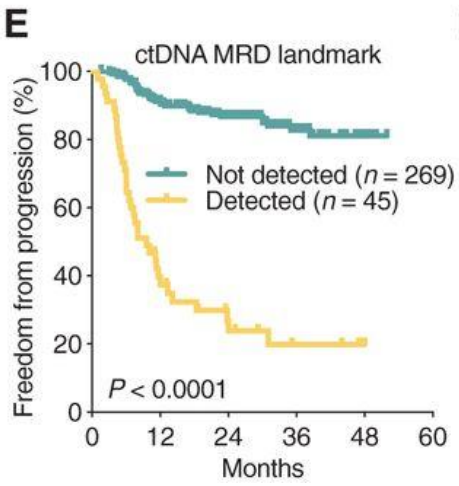


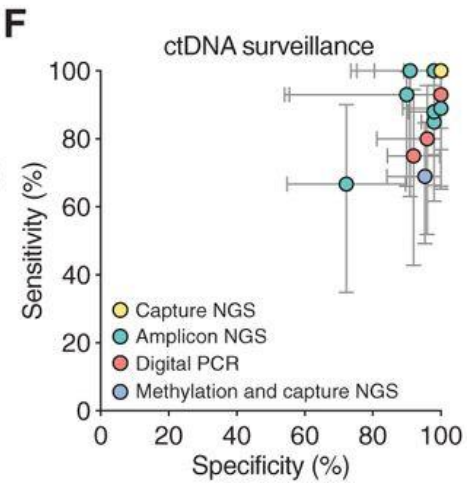
B

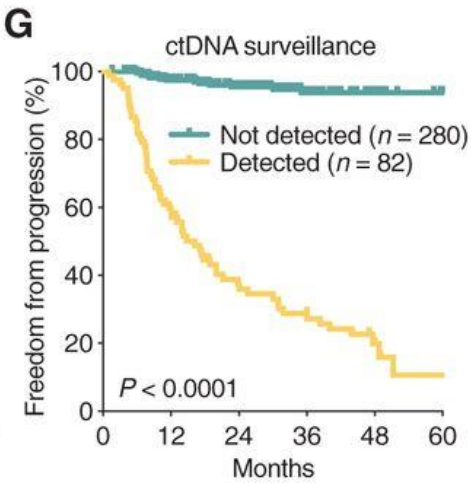
Cancer	Reference	# Patients	Analysis Landmark	Analysis Surveillance
Lung	Peng (111)	48	Yes	Yes
Lung	Chaudhuri (62)	37	Yes	Yes
Lung	Abbosh (31)	24	Yes	Yes
Lung	Moding (90)	12	Yes	No
Breast	Garcia-murillas (113)	101	No	Yes
Breast	Coombes (34)	49	Yes	Yes
Breast	Garcia-murillas (27)	43	Yes	Yes
Breast	Olsson (112)	20	No	Yes
Colon	Tie (91)	178	Yes	Yes
Rectal	Tie (89)	159	Yes	No
Colorectal	Reinert (36)	94	Yes	Yes
Colon	Tie (92)	88	Yes	No
Colorectal	Parikh (52)	72	Yes	Yes
Colon	Wang (114)	40	No	Yes
Colorectal	Schøler (28)	26	Yes	Yes
Rectal	Khakoo (109)	23	Yes	No
Colorectal	Diehl (107)	20	Yes	No
Esophageal	Azad (65)	20	Yes	No
Pancreas	Jiang (110)	27	Yes	No
Pancreas	Sausen (108)	20	Yes	No
Bladder	Christensen (35)	66	Yes	Yes
	Total	**1167**	**18**	**13**











Moding et al., *Cancer Discov,* 2021

Landmark ctDNA MRD for NSCLC

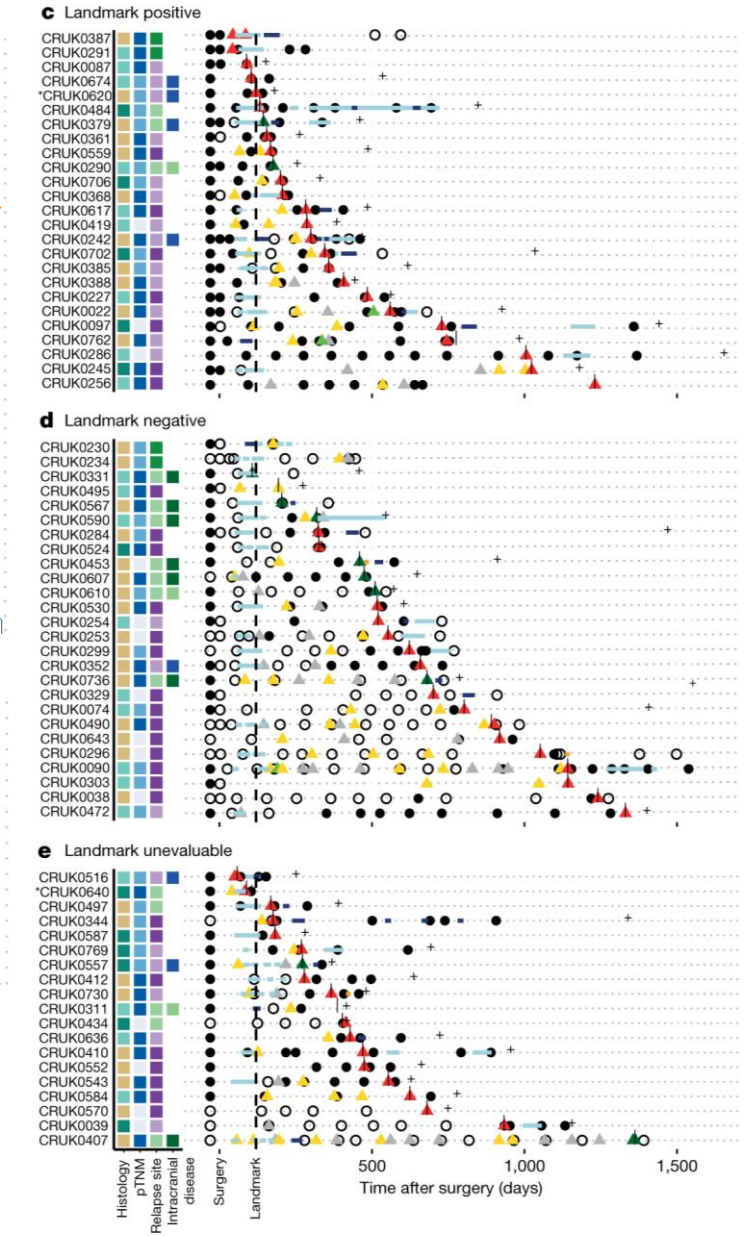
ctDNA MRD+
Recurrence +
(n=25)

Clinical sensitivity 49%

ctDNA MRD-
Recurrence +
(n=26)

51% discordance

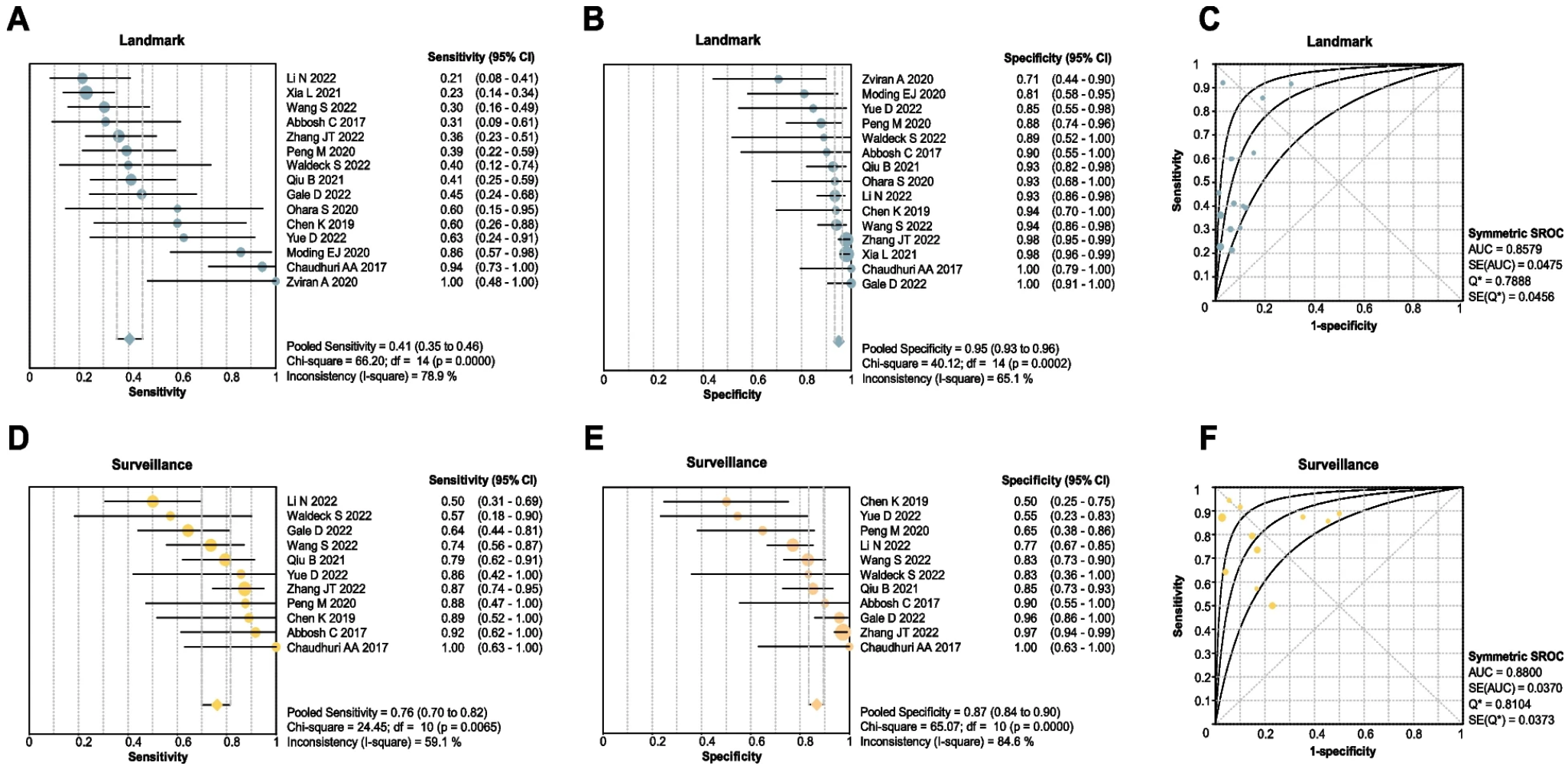
ctDNA in-evaluable
Recurrence +
(n=19)



- Tumor-informed anchored multiplex PCR enrichment
- Assay sensitivity using a 50-variant panel at 0.01% VAF was > 90% at DNA input > 20 ng
- LOD 95 VAF 0.008% (80 PPM)
- **Landmark ctDNA MRD assessed within 120 days of surgery: 25% ctDNA MRD+**
- **Clinical sensitivity 49% (fraction of ctDNA MRD+ among those who recurred)**
- Landmark ctDNA MRD+ patients had a hazard ratio of 5.3 for OS and a hazard ratio of 6.8 for freedom from relapse relative to MRD- (P<0.001)
- Landmark-positive patients had the longest lead times (228 days)
- Patients relapsing in the first year of surgery are more likely to be MRD positive

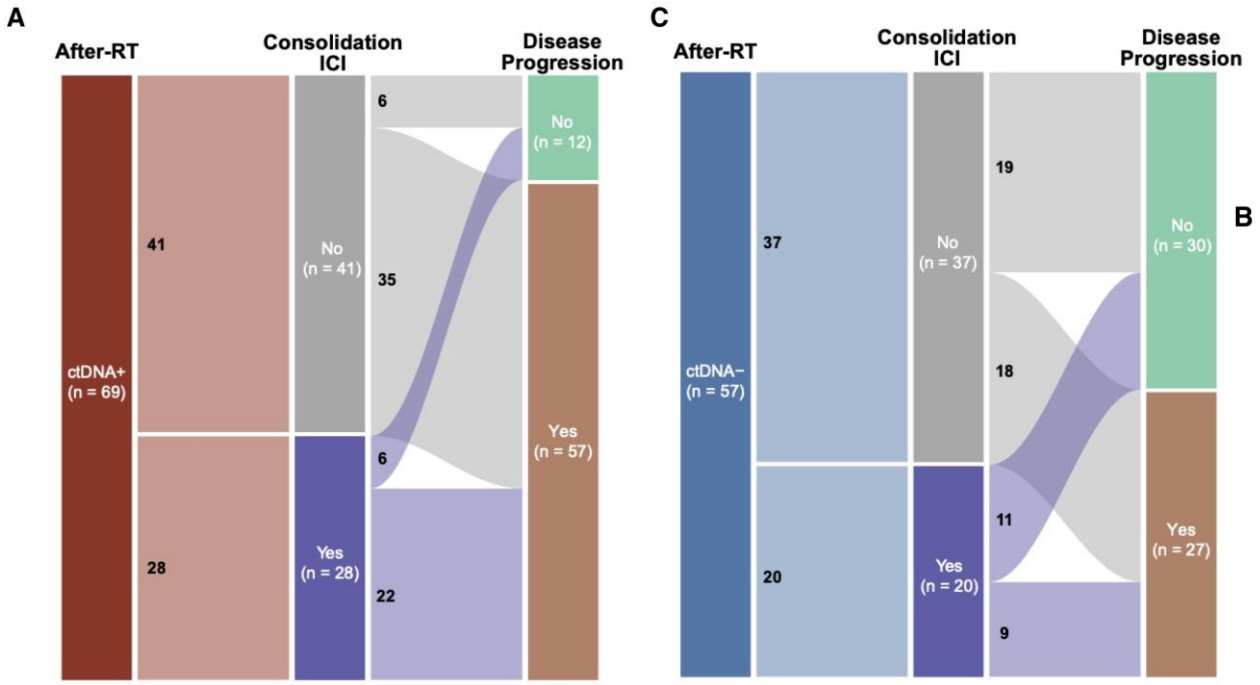
Abbosh et al., *Nature*, 2023

Clinical sensitivity of ctDNA MRD in NSCLC



Zhong et al. BMC Medicine 2023; 21:180

ctDNA MRD after definitive chemoradiation is predictive



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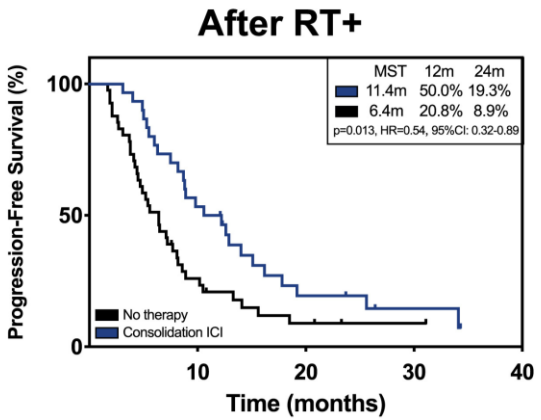
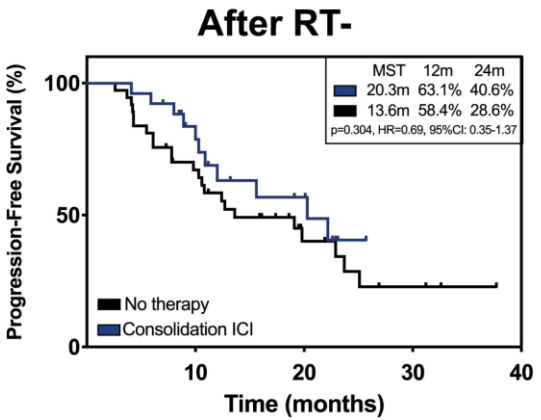
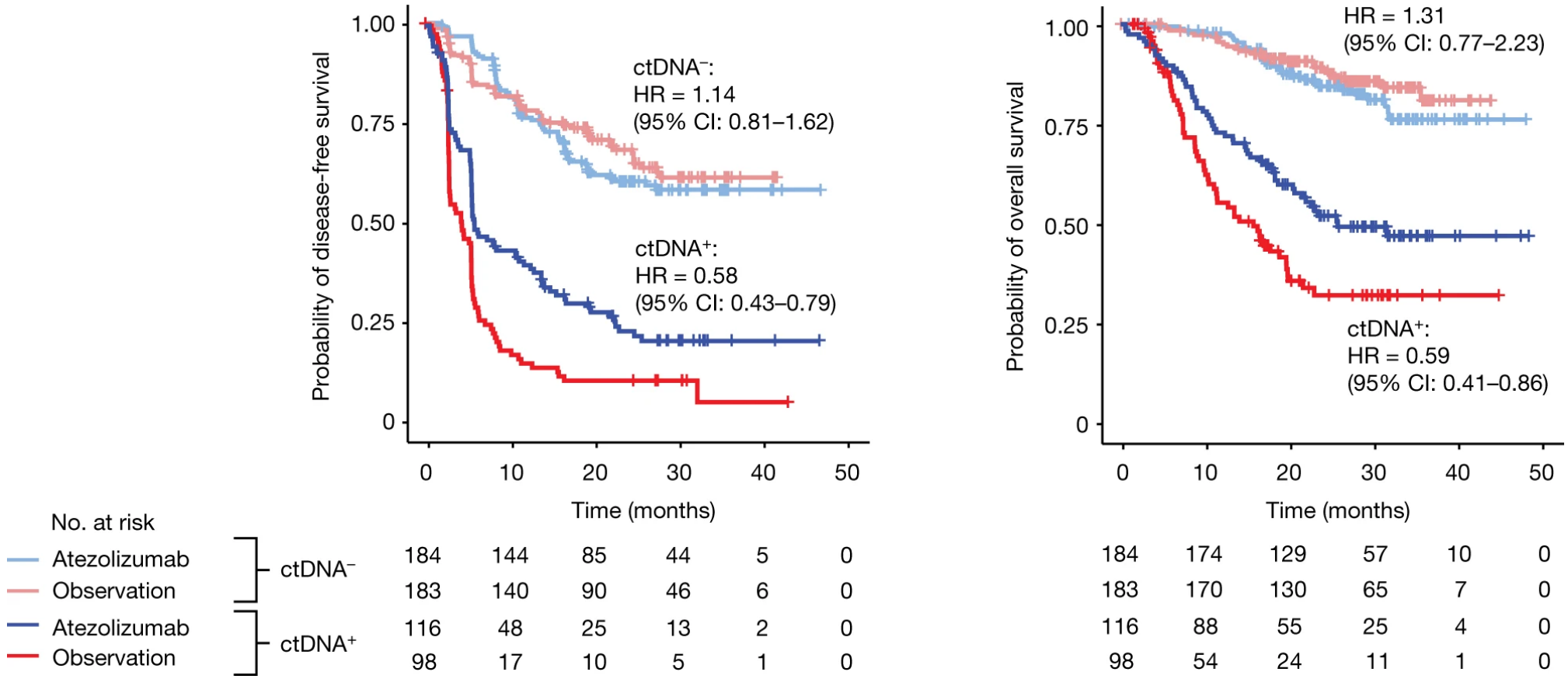


D



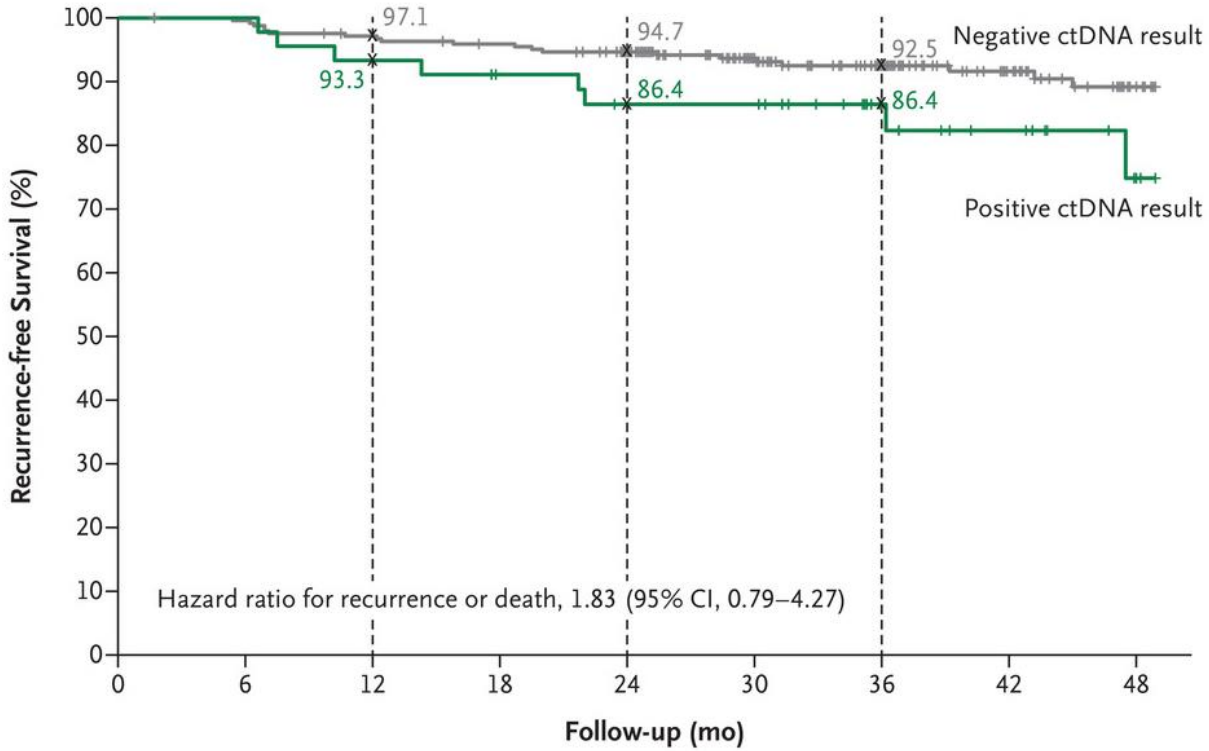
Moding et al., *Nat Cancer*, 2020, Pan et al., *Cancer Cell*, 2023

ctDNA MRD after curative-intent surgery is predictive



Powles et al., *Nature*, 2021

What does ctDNA MRD negative mean?



No. at Risk

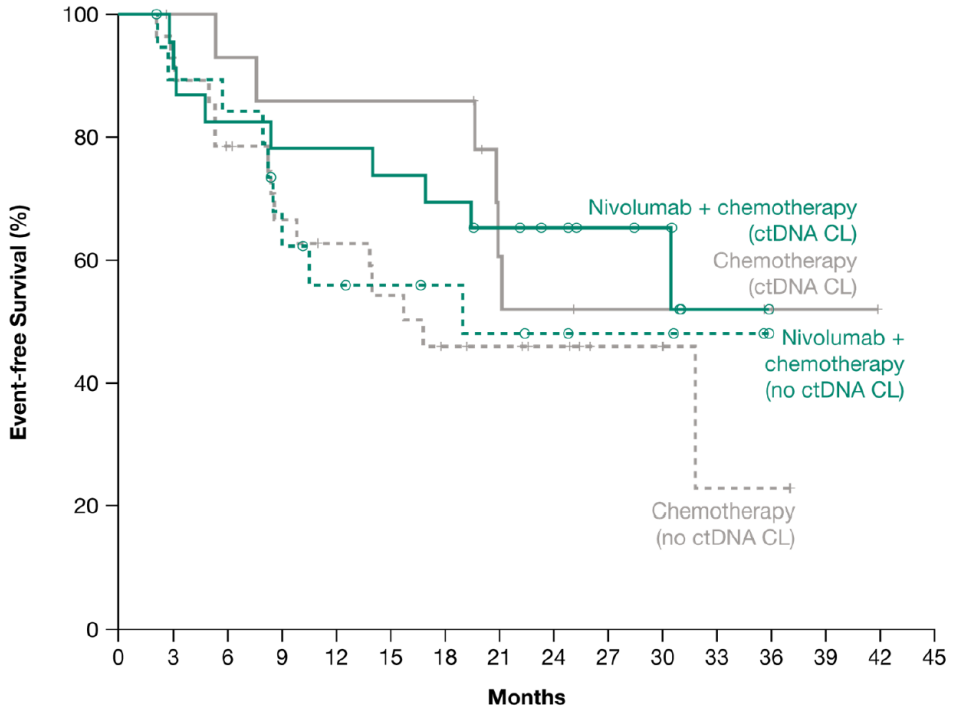
Negative ctDNA result	246	244	236	231	220	169	131	93	55
Positive ctDNA result	45	45	42	39	36	36	22	16	9

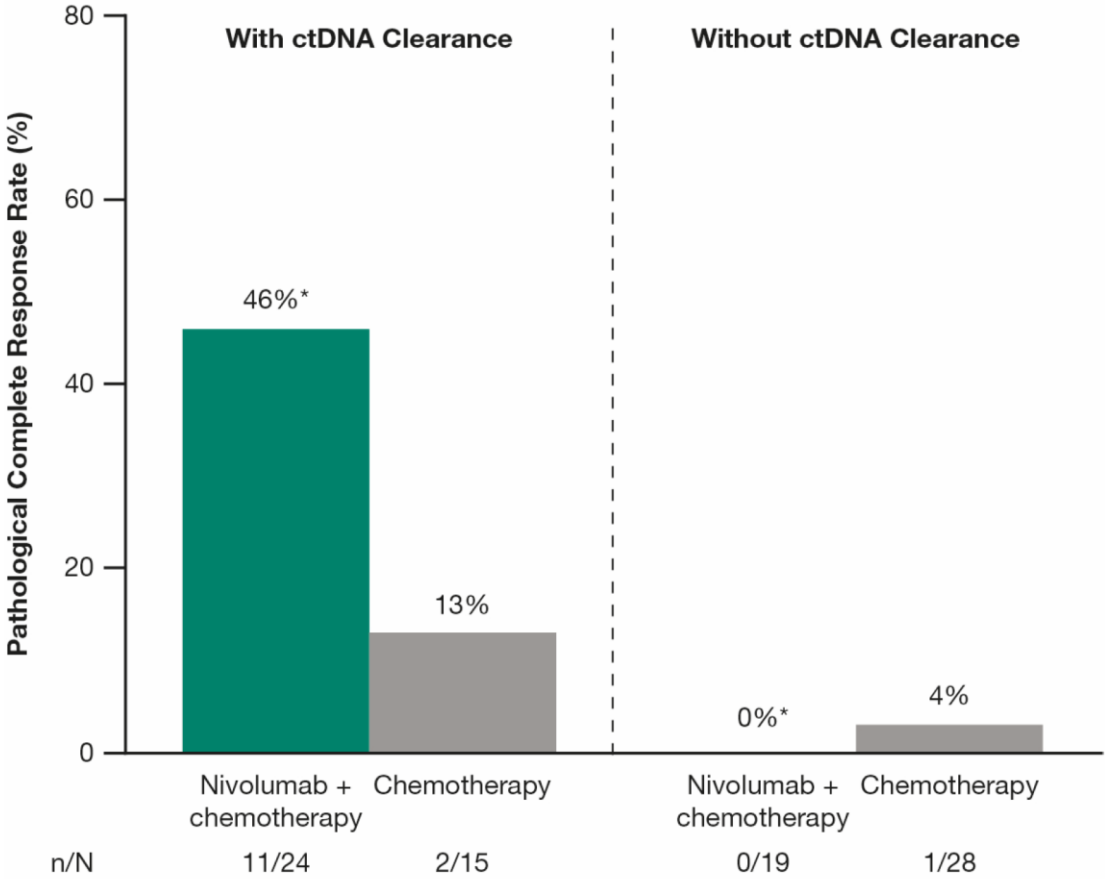
- In the ctDNA-guided group of the DYNAMIC trial, recurrence or death occurred in 15 of 246 ctDNA-negative patients (6%).
- **A fraction of ctDNA MRD-negative patients experience disease recurrence.**

Tie et al., *NEJM,* 2022

ctDNA post neoadjuvant IO predicts pCR

	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	

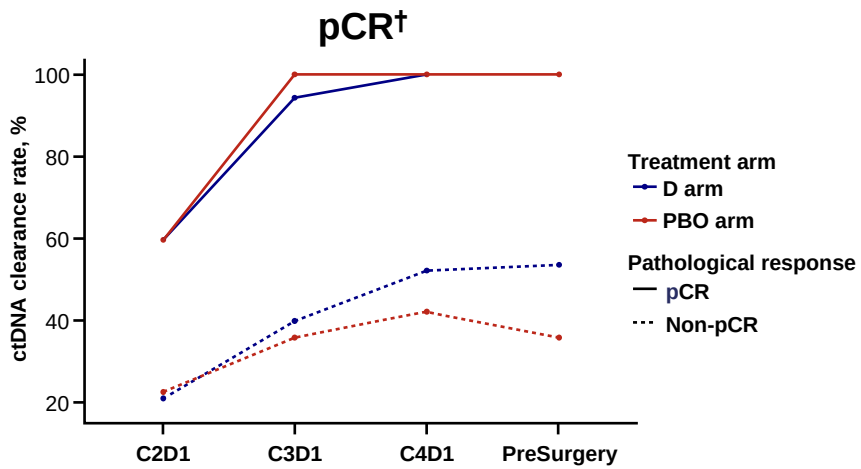


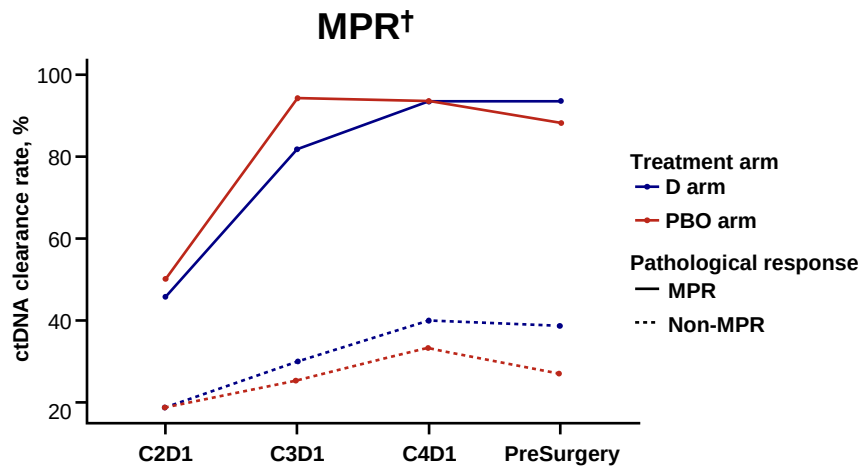


Forde et al., *NEJM*, 2022

ctDNA clearance predicts pCR with

- Among patients who were ctDNA-positive at baseline (C1D1), all patients achieving pCR and >90% of all patients achieving MPR had ctDNA clearance at C4D1*





- Patients without ctDNA clearance were unlikely to achieve pCR (NPV > 84.0% at C2D1 in both arms)
- Patients who achieved ctDNA clearance in the D arm vs the PBO arm were more likely to achieve pCR (PPV = 50.0% vs 14.3% at C2D1)

Predictive value of ctDNA clearance at different timepoints for pCR

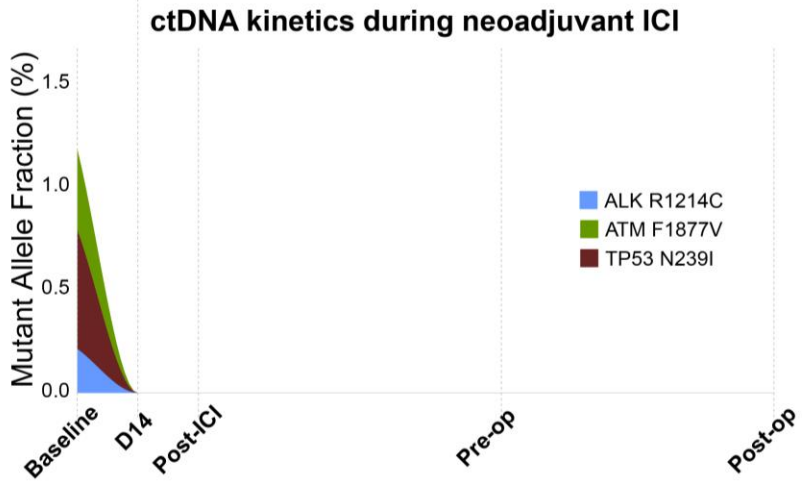
D arm	pCR	
	PPV	NPV
C2D1	50.0%	84.9%
C3D1	43.6%	97.1%
C4D1	40.5%	100.0%
PreSurgery	41.5%	100.0%

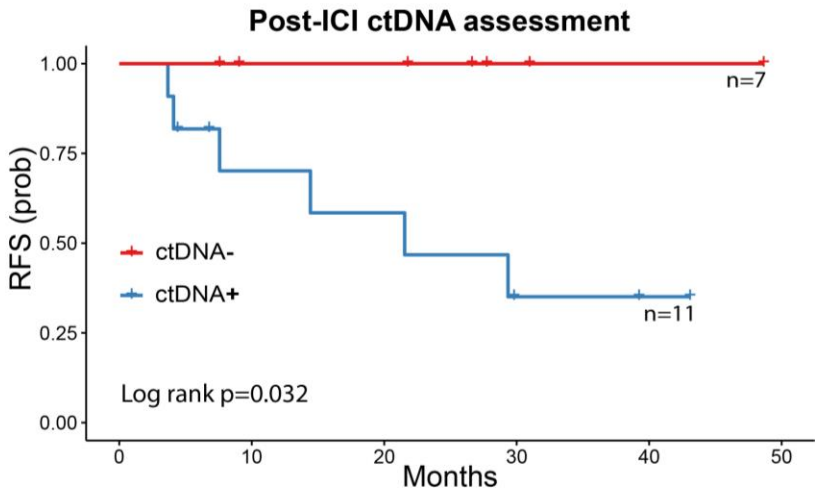
PBO arm	pCR	
	PPV	NPV
C2D1	14.3%	96.9%
C3D1	18.2%	100.0%
C4D1	18.2%	100.0%
PreSurgery	19.4%	100.0%

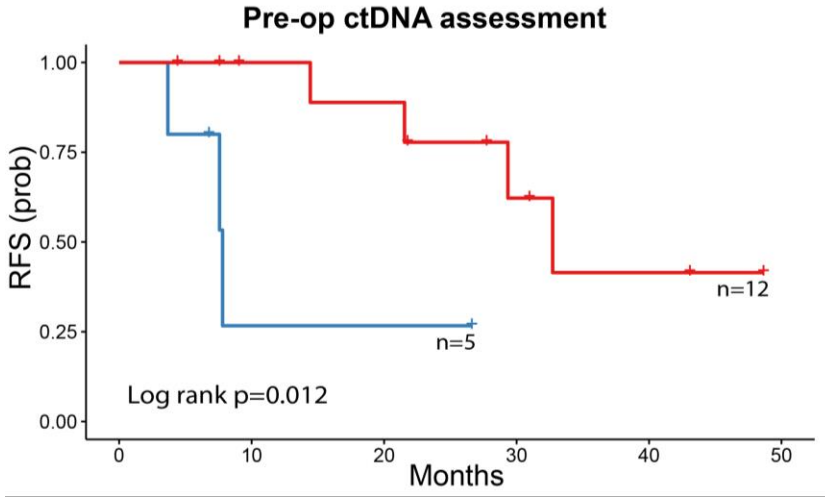
*In the BEP, pCR (25.6% vs 6.3%) and MPR (44.4% vs 18.8%) rates were higher in the D arm vs the PBO arm. †The plots include all evaluable patients at each timepoint. NPV, negative predictive value; PPV, positive predictive value.

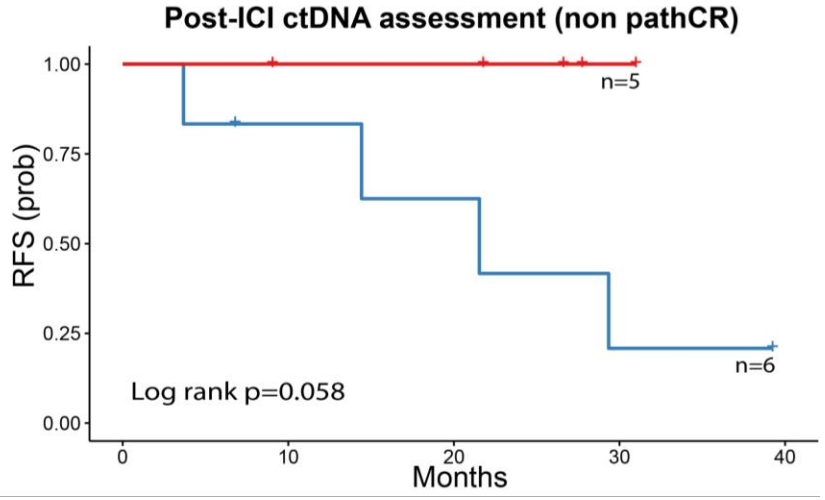
Reck et al., *presented at ESMO 2023*

ctDNA may help refine the heterogeneity of non pCR



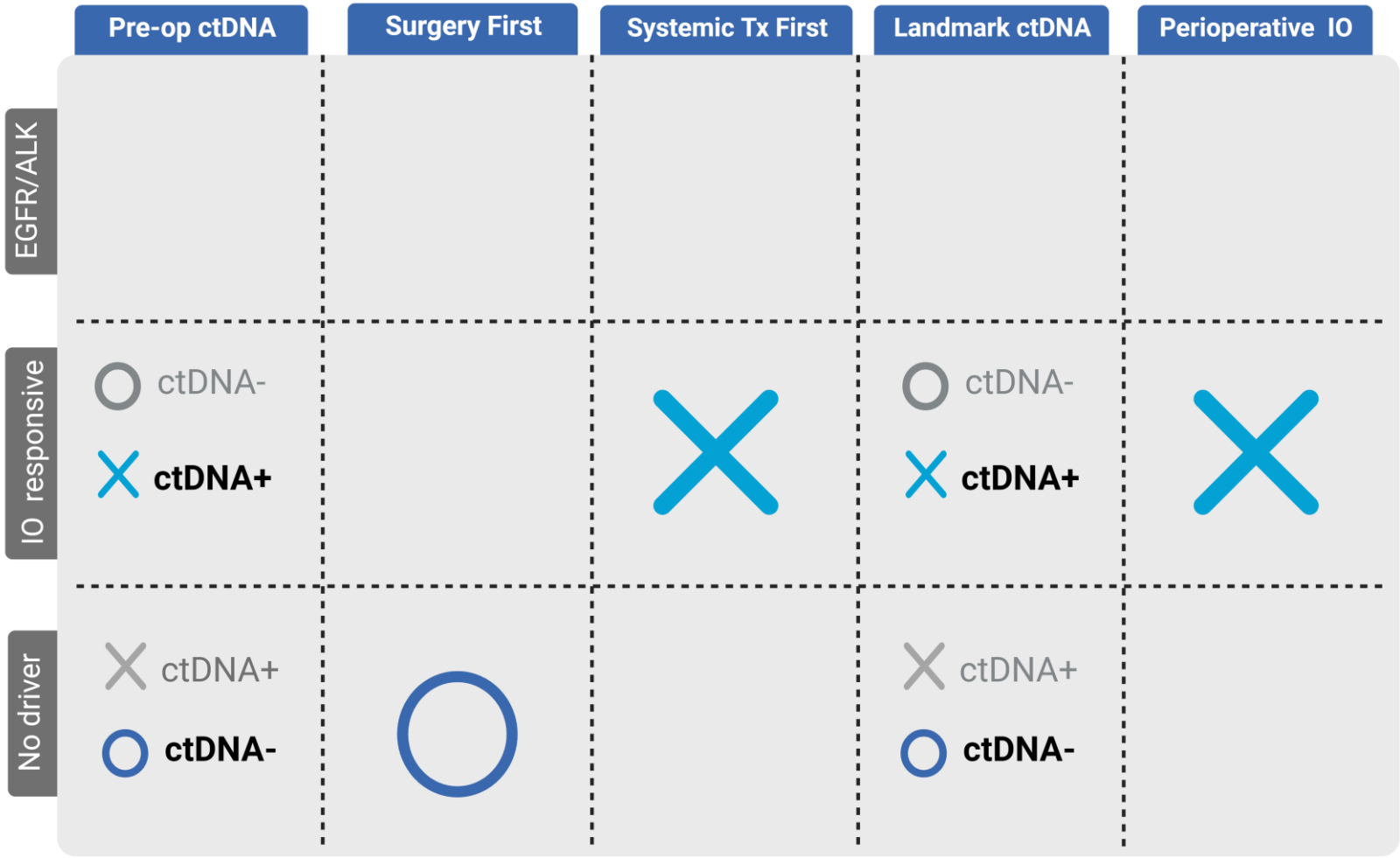






Landon et al., *presented at 2023 AACR Annual Meeting, manuscript under review*

The evolving therapeutic landscape of early stage NSCLC



Acknowledgements

Sidney Kimmel Cancer Center

Thoracic Oncology

Julie Brahmer
Patrick Forde
Christine Hann
Kristen Marrone
Ben Levy
Joy Feliciano
David Ettinger
Vincent Lam
Joe Murray
Susie Scott
Michael Conroy

Cancer Biology

Victor Velculescu
Steve Baylin

Cancer Immunology

Drew Pardoll
Kellie Smith

Molecular Oncology Lab

Noushin Niknafs
Gavin Pereira
Lavanya Sivapalan
Blair Landon
Archana Balan
Jenna Canzoniero
Maria Fatteh
Nisha Rao
Chris Cherry
Jinny Huang
Jaime Wehr
Mimi Najjar
Shreshtha Jolly
Kavya Velliangiri
Katerina Karaindrou
Justin Huang
Mohamed Sherief

Bioinformatics

Rob Scharpf
James White
Rachel Karchin

Cancer Genomics Lab

Vilmos Adleff
Jill Phallen
Stephen Christiano
Daniel Bruhm
Nic Vulpescu
Carlie Hruban
Jamie Medina
Zach Foda
Akshaya Annapragada

Lung cancer PMCOE

Vasan Yegnasubramanian
Lei Zheng
Sharon Penttinen
Durrant Barasa

Pathology

Ed Gabrielson
Peter Illei
Janis Taube
Kay Li

Thoracic Surgery

Malcolm Brock
Richard Battafarano
Stephen Yang
Kristen Rodgers

Johns Hopkins MTB

ECOG-ACRIN

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Jill Curran

FDA OCE

PJ Vellanki
Julie Schneider
Preeti Narayan

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Kim Monkhorst
Karlijin Hummerlink
Willemijn Theelen

Our patients and their families

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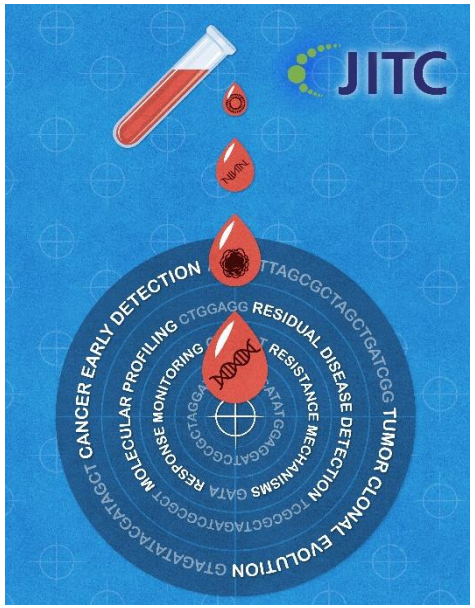
Funding Sources: NIH, FDA OCE, Department of Defense, Maryland Department of Health and Mental Hygiene, EA Thoracic ITSC, Johns Hopkins ICTR, Johns Hopkins Catalyst Award, Cancer Research Institute, LUNGevity, V Foundation, Swim Across America, Emerson Collective, The Mark Foundation, The Elsa U. Pardee Foundation, BMS, Astra Zeneca, Delfi Diagnostics, Labcorp



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cfDNA biology
ctDNA ultrasensitive technologies
Early detection and MRD
ctDNA as an early endpoint of IO response
CTCs and other blood analytes
Clinical Implementation & Regulatory Implications
https://jitc.bmj.com/content/11/1/e006367

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