The importance to Use ctDNA to Detect Minimal Residual Disease (MRD)

Bruna Pellini, MD

Assistant Member, Department of Thoracic Oncology, H. Lee Moffitt Cancer Center and Research Institute

Assistant Professor, Department of Oncologic Sciences, University of South Florida

Co-Chair, Liquid Biopsies Scientific Interest Group, National Institute of Health

2025 FLASCO Early Lung Cancer Summit
January 25, 2024

MOFFITT CANCER CENTER

@BrunaPellini

Disclosures:

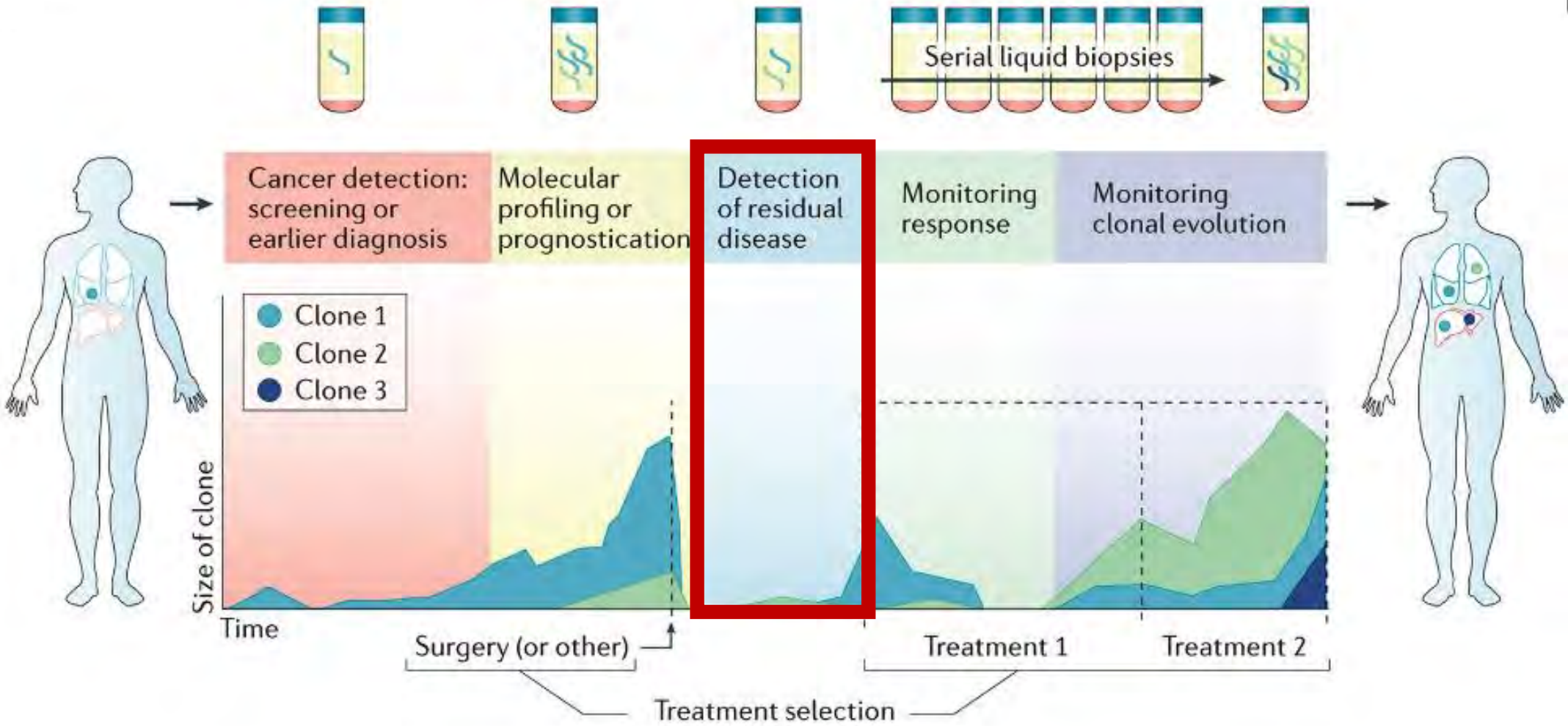
- Research support: George Edgecomb Society at Moffitt Cancer Center, NIH/NCI 4UM1-CA186644-07 (institution), NIH/NCI 1R21CA259215-01A1 (institution), Merck (institution)

- Advisory Board/Consultant: AstraZeneca, Bayer, BMS, Catalyst, Guardant Health, Gilead, Regeneron, Illumina, Foundation Medicine, Merus, OncoHost.

- Speaker Honoraria: Merck/MSD, Foundation Medicine

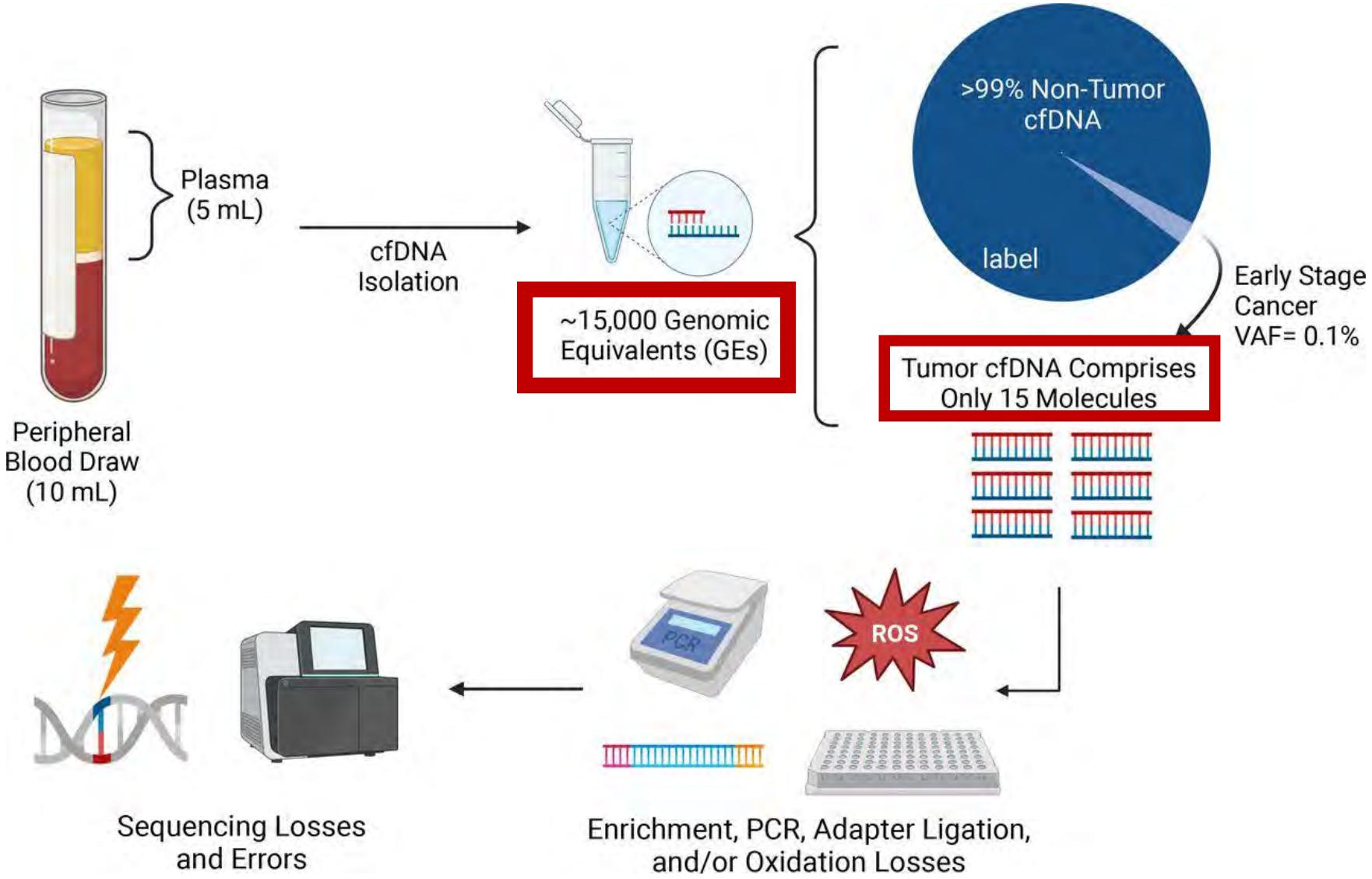
- i3 Health and FLASCO have mitigated all relevant financial relationships

ctDNA applications in thoracic oncology



Wan J et al. *Nat Rev Cancer*. 2017

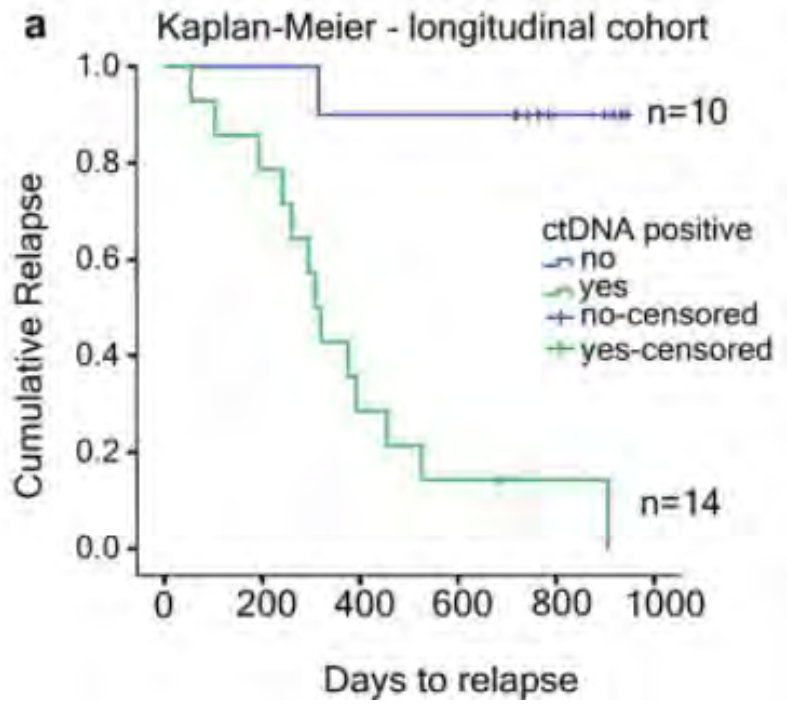
Challenges of ctDNA detection in MRD settings



Semenkovich N et al. *J Immunother Cancer*. 2023

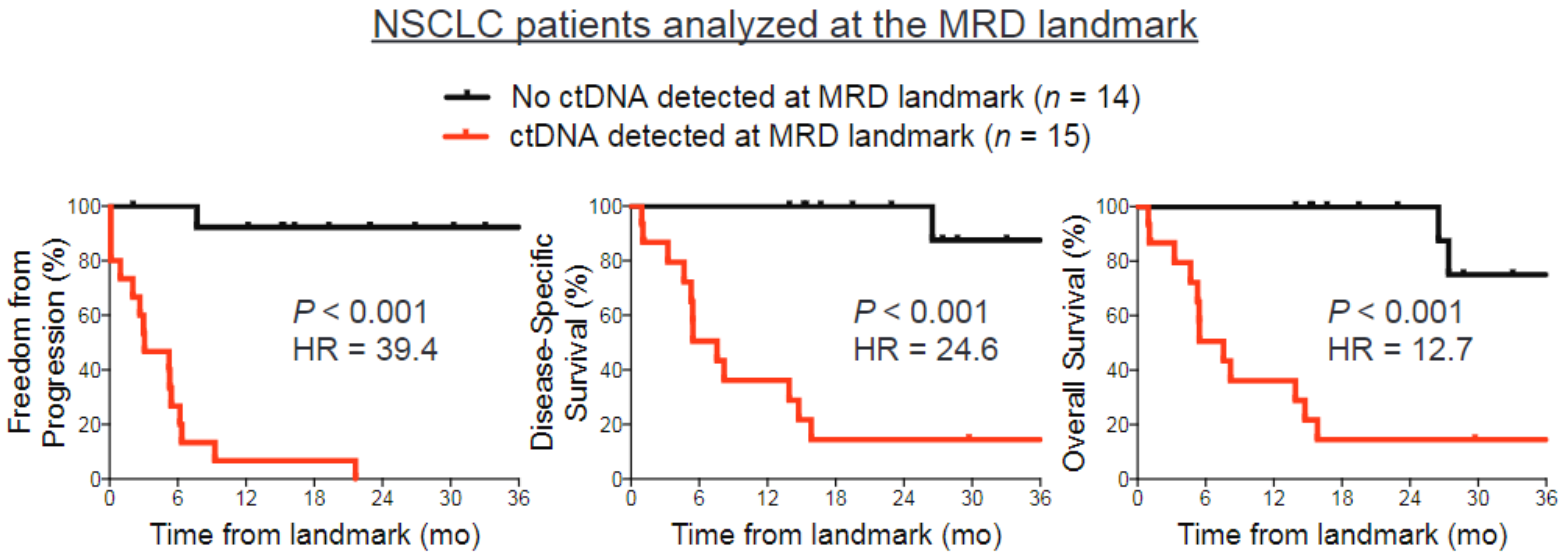
Multiple studies have shown that ctDNA can be used to detect minimal residual disease (MRD) and it is a powerful prognostic biomarker

Stages I-III NSCLC
Tumor-informed assay
(Signatera™)



LOD= 0.01%

Stages I-III NSCLC
Tumor-naïve assay
(CAPP-Seq)

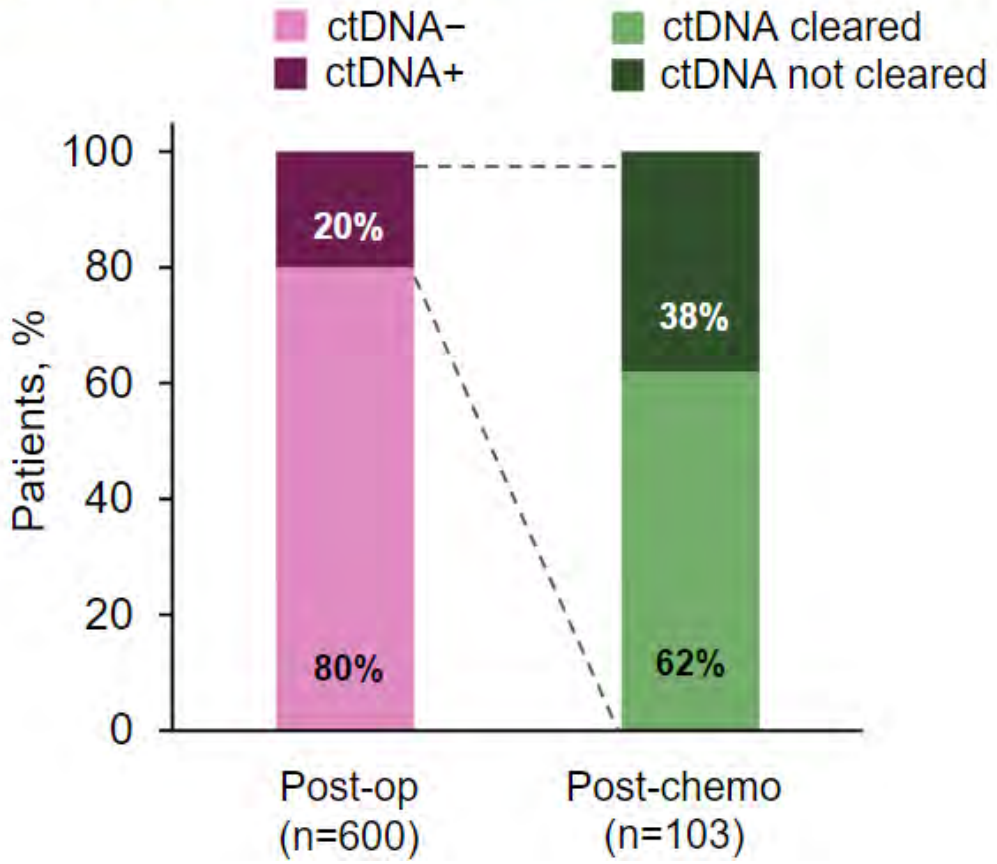


LOD= 0.002%
(0.1%)

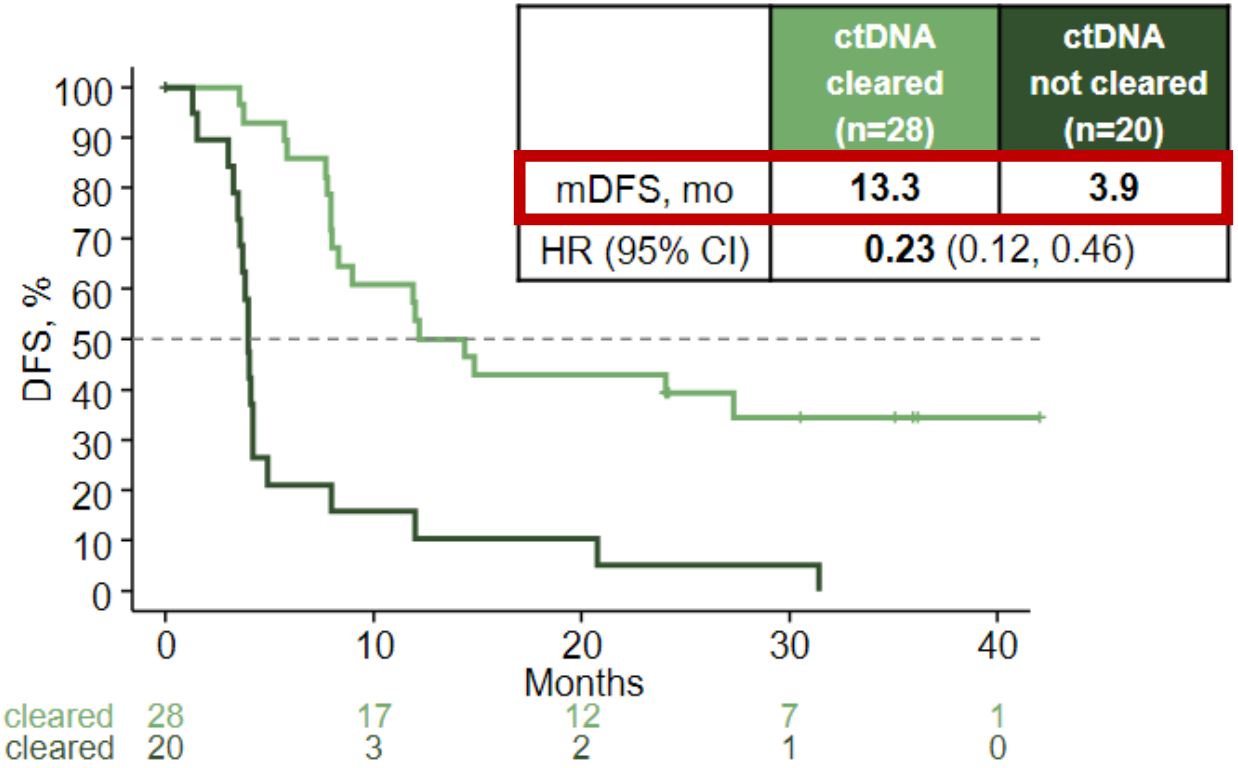
Abbosh C et al. *Nature*. 2017
Chaudhuri A et al. *Cancer Discov*. 2017

IMpower-010: patients with detectable ctDNA MRD after adjuvant chemotherapy have worse prognosis

Impact of chemo on ctDNA clearance status



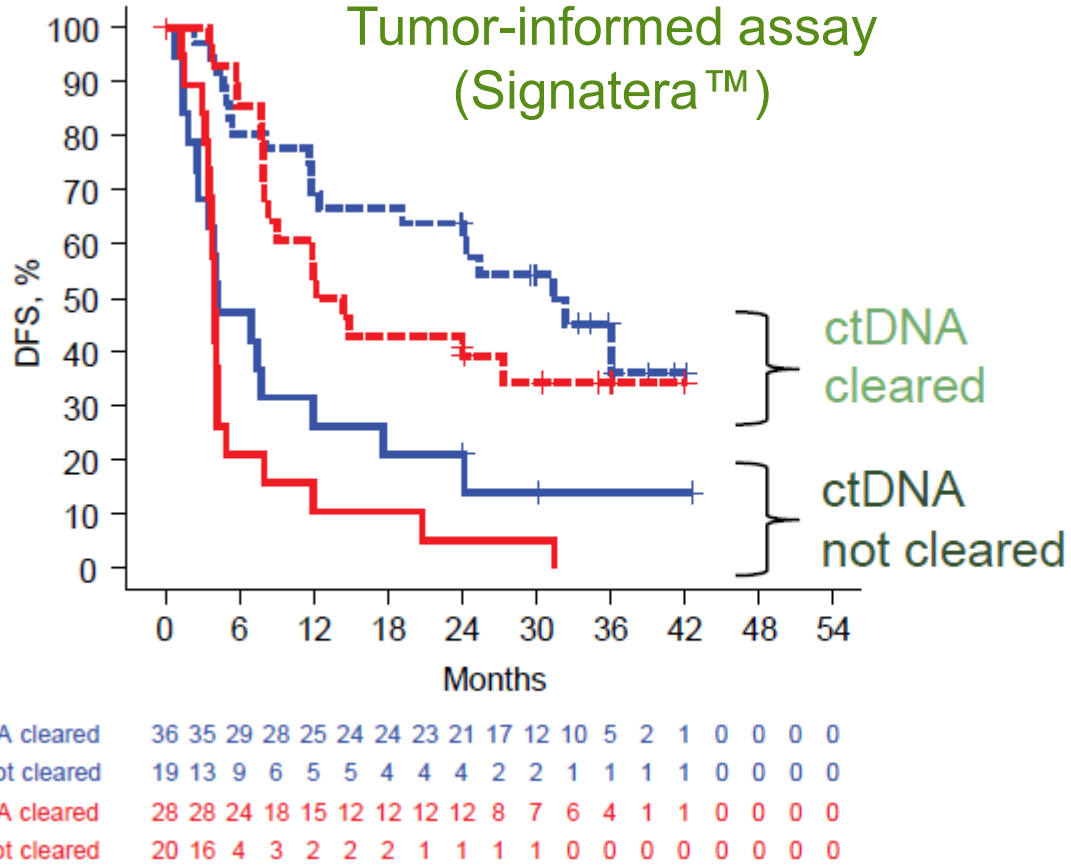
DFS by ctDNA clearance status in the BSC arm



	ctDNA cleared (n=28)	ctDNA not cleared (n=20)
mDFS, mo	**13.3**	**3.9**
HR (95% CI)	**0.23** (0.12, 0.46)	

Presented by Enriquera Felip. ESMO Immuno-Oncology Congress 2022, Abstract 1O (https://bit.ly/3sZVgye)

IMpower-010: data suggests adjuvant atezolizumab delays conversion to ctDNA +



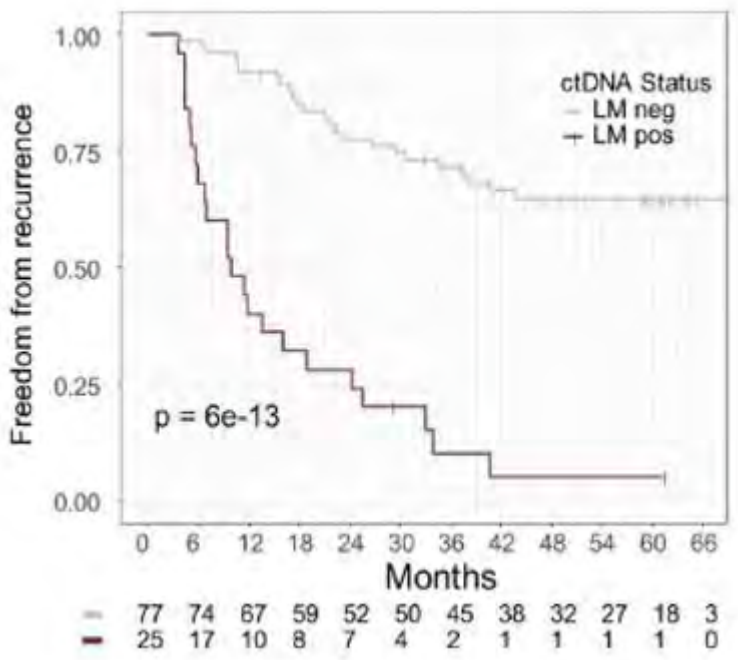
ctDNA status post- adjuvant chemotherapy

ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

Presented by Enriquera Felip. ESMO Immuno-Oncology Congress 2022, Abstract 1O (https://bit.ly/3sZVgye)

Limited clinical sensitivity of current ctDNA assays to detect disease recurrence remains a challenge for clinical practice implementation



TRACERx

LOD= 0.008%

(0.05%)

Stages I-III NSCLC

Invitae PCM™

(Tumor-informed assay)

- Stage I – 50%, stage II – 31%, stage III – 19%
- 25% pts had + ctDNA on post-operative samples
- 51/108 patients (47%) developed disease recurrence
- Clinical Sensitivity = 49% and Clinical Specificity = 96% to detect disease recurrence

Abbosh C et al. *Nature*. 2023

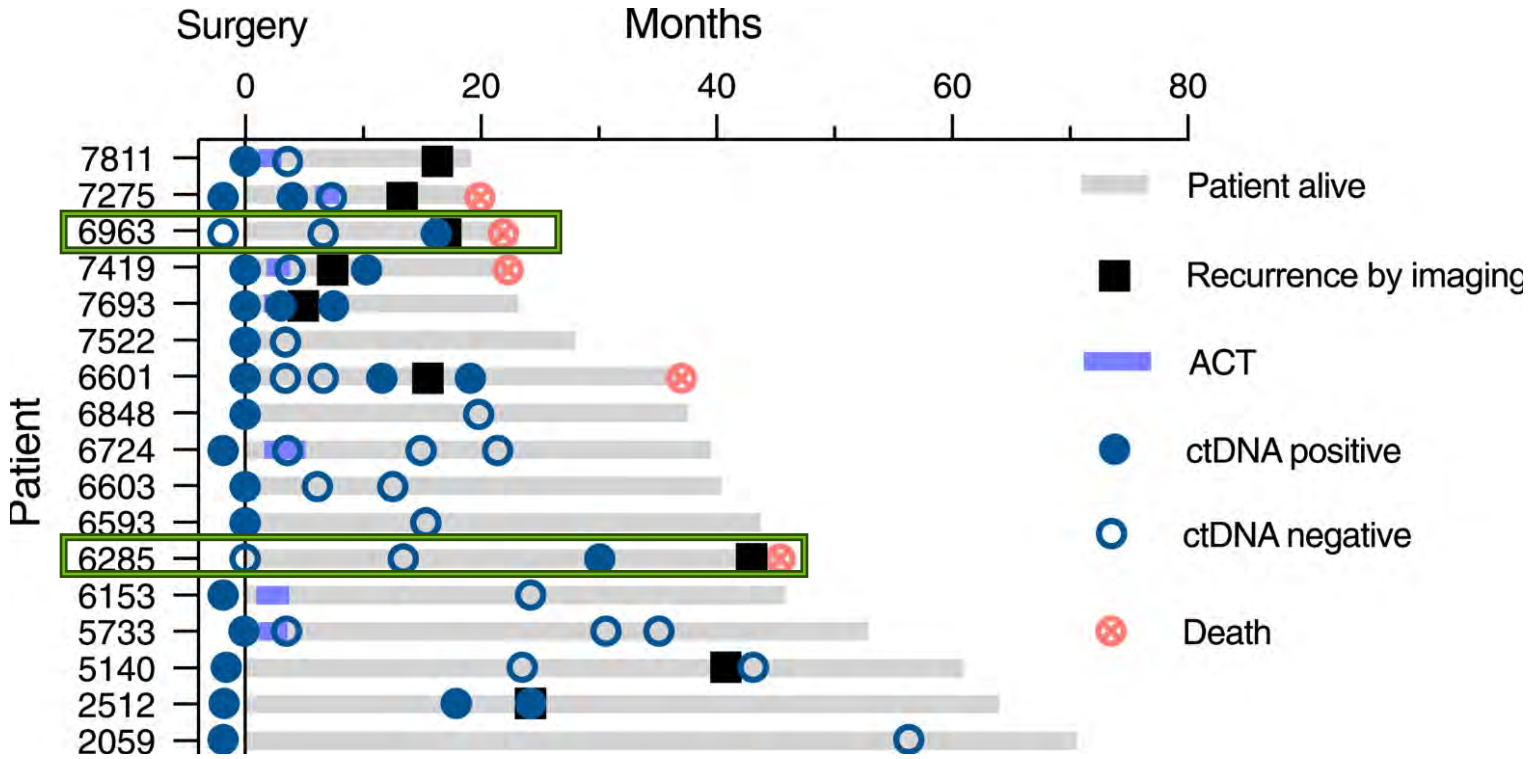
Data suggests one ctDNA MRD timepoint may not be enough to achieve meaningful clinical sensitivity to detect disease recurrence

15 patients developed disease recurrence

Patient	ctDNA positive pre-surgery	ctDNA positive post-surgery	Site(s) of recurrence
5597	No	No	Lung
6285	No	Yes	Lung, nodal
7811	Yes	No	Brain, lung
5944	No	No	Lung, nodal
7246	No	No	Brain
7487	No	No	Lung
7275	Yes	Yes	Bone, liver, pleura
7693	Yes	Yes	Brain, lung, nodal
6963	No	Yes	Liver, lung
5140	Yes	No	Lung, nodal
7419	Yes	Yes	Lung, nodal
6601	Yes	Yes	Lung
5470	No	No	Lung
2512	Yes	Yes	Lung, nodal
2493	No	No	Lung

Clinical sensitivity with one MRD timepoint= 46%
(post-surgery)

Stages I-III NSCLC
Tumor-informed assay
(Signatera™)



Tan AC et al. *Cancer*. 2024

The sensitivity to detect disease recurrence is heterogenous across different platforms and may be too low

Author & Year	No.[a]	Clinical Stage	Treatment	ctDNA Assay	Sensitivity (%)[b]	Specificity (%)[b]
Chaudhuri et al (2017)[c]	32	IB-IIIB	CRT or RT and/or surgery +/- chemo	CAPP-Seq	94	100
Abbosh et al (2017)[d]	24	IA-IIIB	Surgery +/- chemo +/- PORT	Signatera	36	90
Chen et al (2019)[e]	25	IIB-IIIB	Surgery +/- chemo	cSMART	44	88
Zviran et al (2020)[f]	22	IA-III	Surgery +/- chemo and RT	MRDetect	100	71

Pellini B & Chaudhuri A. *J Clin Oncol*. 2022

Interrogating ctDNA in multiple timepoints after curative-intent treatment improves the sensitivity to detect disease recurrence

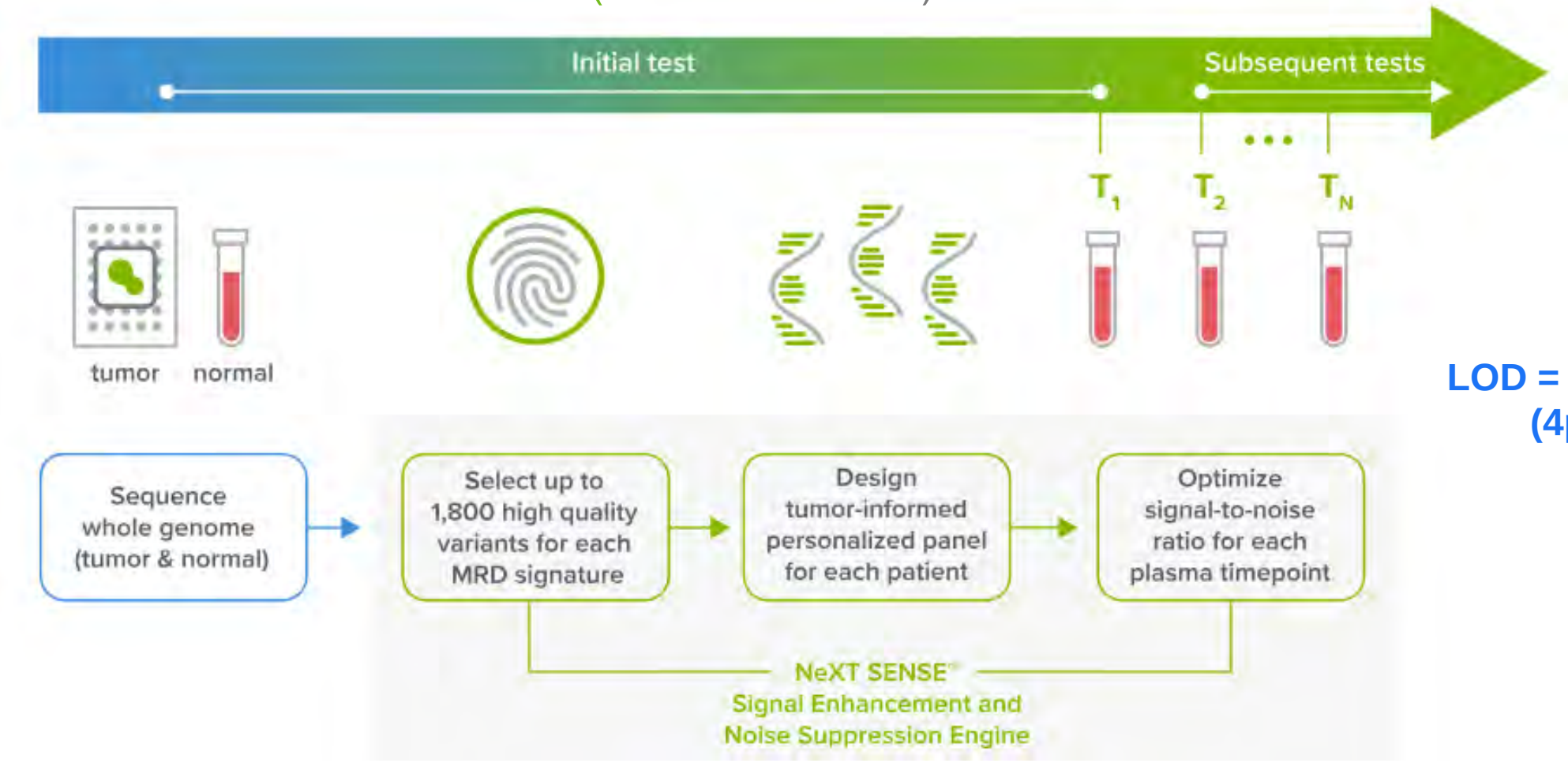
Author & Year	No.[a]	Clinical Stage	Treatment	ctDNA Assay	Sensitivity (%)[b]	Specificity (%)[b]
Chaudhuri et al (2017)[c]	37	IB-IIIB	CRT or RT and/or surgery +/- chemo	CAPP-Seq	100	100
Abbosh et al (2017)[d]	24	IA-IIIB	Surgery +/- chemo	Signatera	93	70
Abbosh et al (2020)[e]	78	I-III	Surgery +/- chemo	ArcherDx	82	96

ctDNA post-treatment surveillance studies in NSCLC

Pellini B & Chaudhuri A. *J Clin Oncol*. 2022

Will WGS solve the issue of clinical sensitivity?

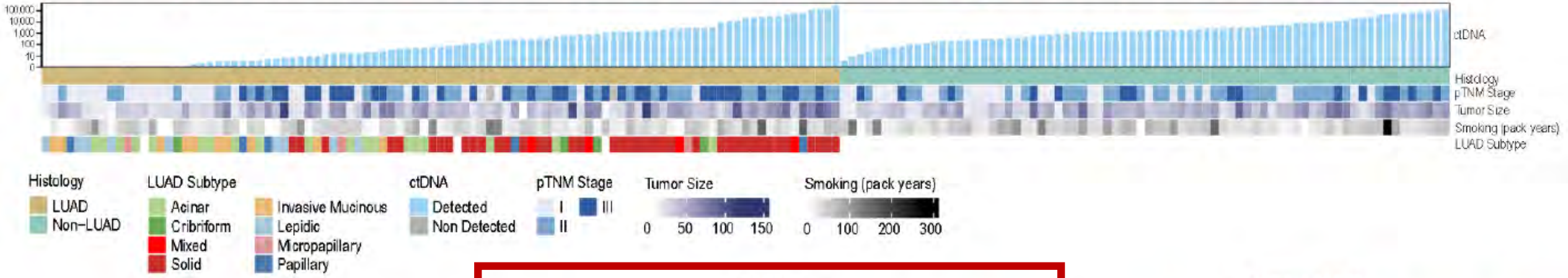
Stages I-III NSCLC
Tumor-informed assay
(NeXT Personal®)



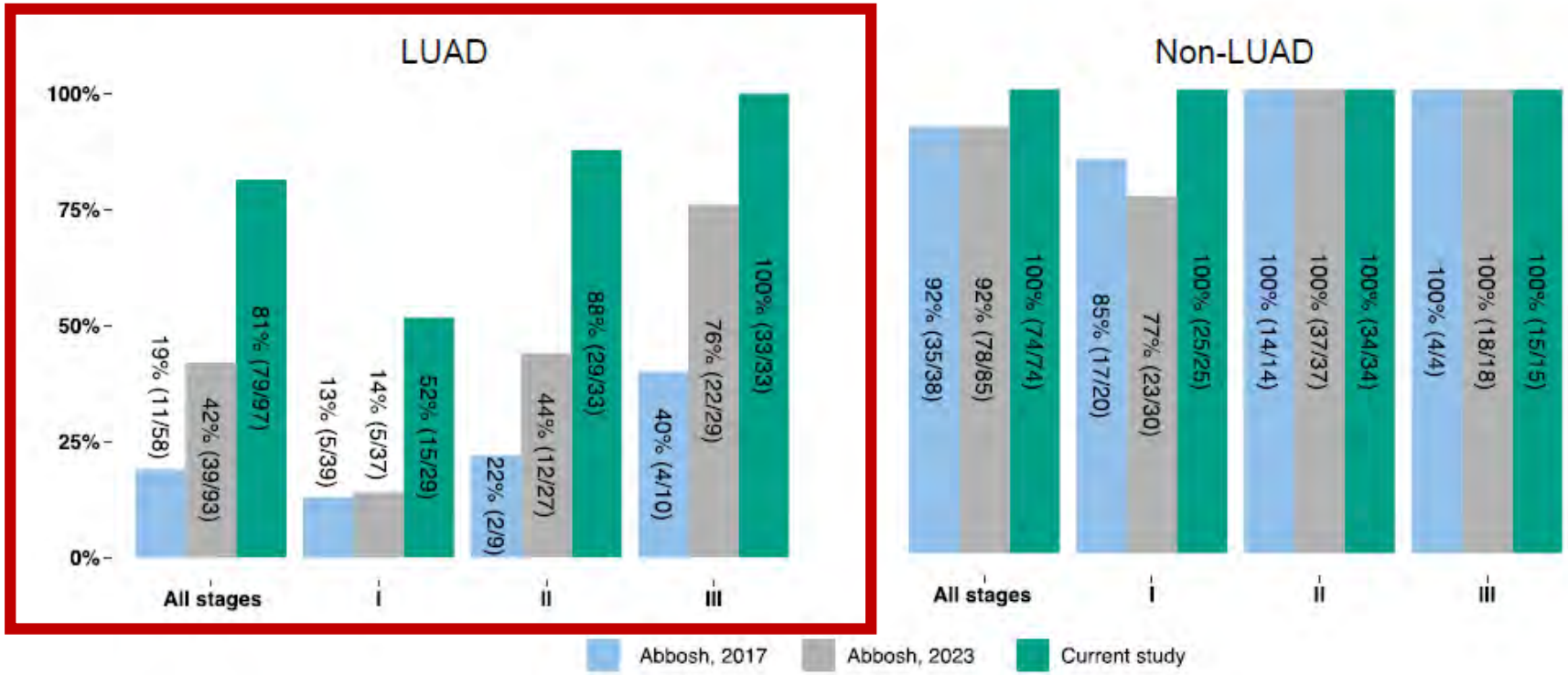
LOD = 0.00037% (4ppm)

Source https://www.personalis.com/products/next-personal/

Pre-operative detection of ctDNA using NeXT Personal



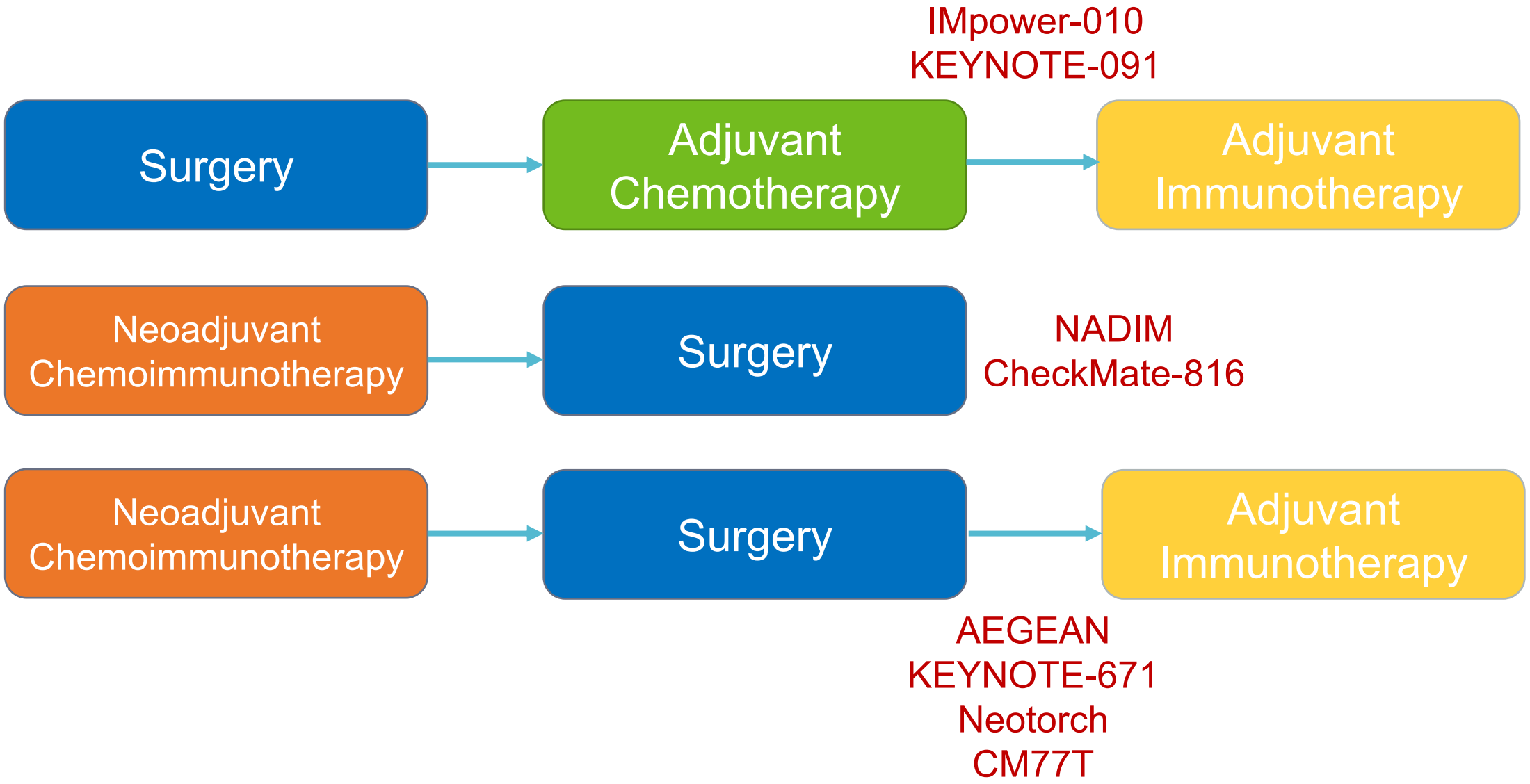
- ctDNA detected from 1.7 to 253,826 PPM
- Pre-operative ctDNA detected in **81%** of LUAD and **100%** of non-LUAD patients
- Includes **52%** of pTNM stage I LUAD patients



MADRID 2023 ESMO congress

Black JRM. 2023 ESMO

Current treatment landscape for resectable NSCLC



Current treatment landscape for resectable NSCLC

IMpower-010
KEYNOTE-091

Surgery → Adjuvant Chemotherapy → Adjuvant Immunotherapy

Neoadjuvant Chemoimmunotherapy → Surgery

NADIM
CheckMate-816

pCR rates= 17.2-24.9%
MPR rates= 30.2-48.5%

Neoadjuvant Chemoimmunotherapy → Surgery → Adjuvant Immunotherapy

AEGEAN
KEYNOTE-671
Neotorch
CM77T

Unanswered questions

- Tumor-informed vs. tumor-naïve assays– which one is better?
- How many timepoints should we use to guide treatment escalation or de-escalation in trials and clinical practice?
- Will treatment de-escalation based on MRD status be equal to SOC?
- Will treatment escalation based MRD status improve DFS and OS?

How do I treat ctDNA positive after a complete resection?

I do not order ctDNA in the MRD setting given assay limitations and lack of proven clinical utility

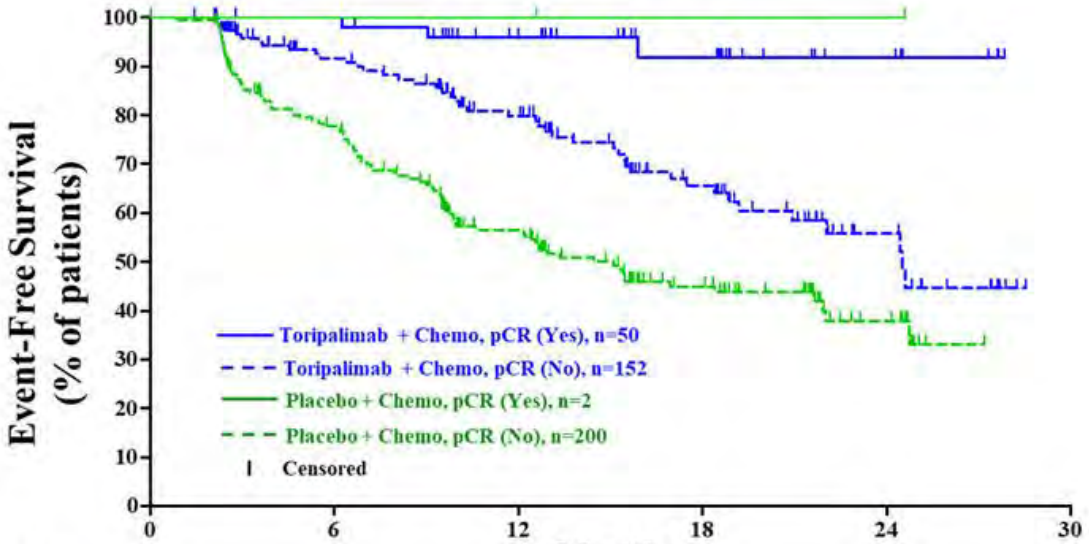
If you choose to order ctDNA in the post-op setting, what would I recommend?

- Obtain a pre-neoadjuvant or pre-surgical blood specimen for ctDNA analysis→ ctDNA dynamics matter for risk stratification
- Assess ctDNA after surgery if you have given neoadjuvant therapy or after chemotherapy if you have opted for the surgery first approach→ your MRD timepoint should be prior to adjuvant immunotherapy selection
- If clinically feasible, obtain blood samples in 2 MRD timepoints→ 2 weeks post-op & 4 weeks post-op
- Analyze your ctDNA MRD results together with your pathological response findings

You need to analyze ctDNA in at least 3 timepoints to increase the odds of obtaining clinically meaningful information

Neotorch: EFS based on pCR and MPR

pCR

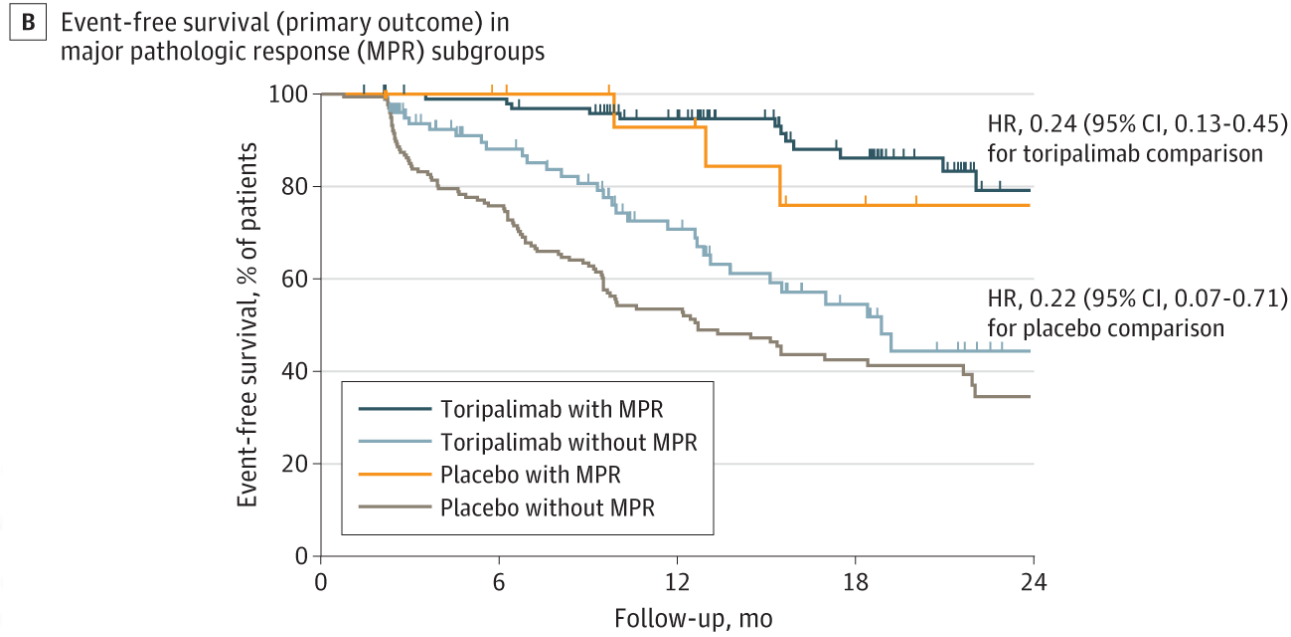


No. at Risk						
Toripalimab + chemo, pCR	Yes	50	49	36	21	7	0
	No	152	107	80	45	16	0
Placebo + chemo, pCR	Yes	2	2	2	1	1	0
	No	200	137	84	42	14	0

Toripalimab arm
- Median EFS NE versus 24.5 months
- HR= 0. 16 (95%CI 0.05-0.51)

Placebo arm
- Median EFS NE versus 15.1 months
- HR= NE

MPR

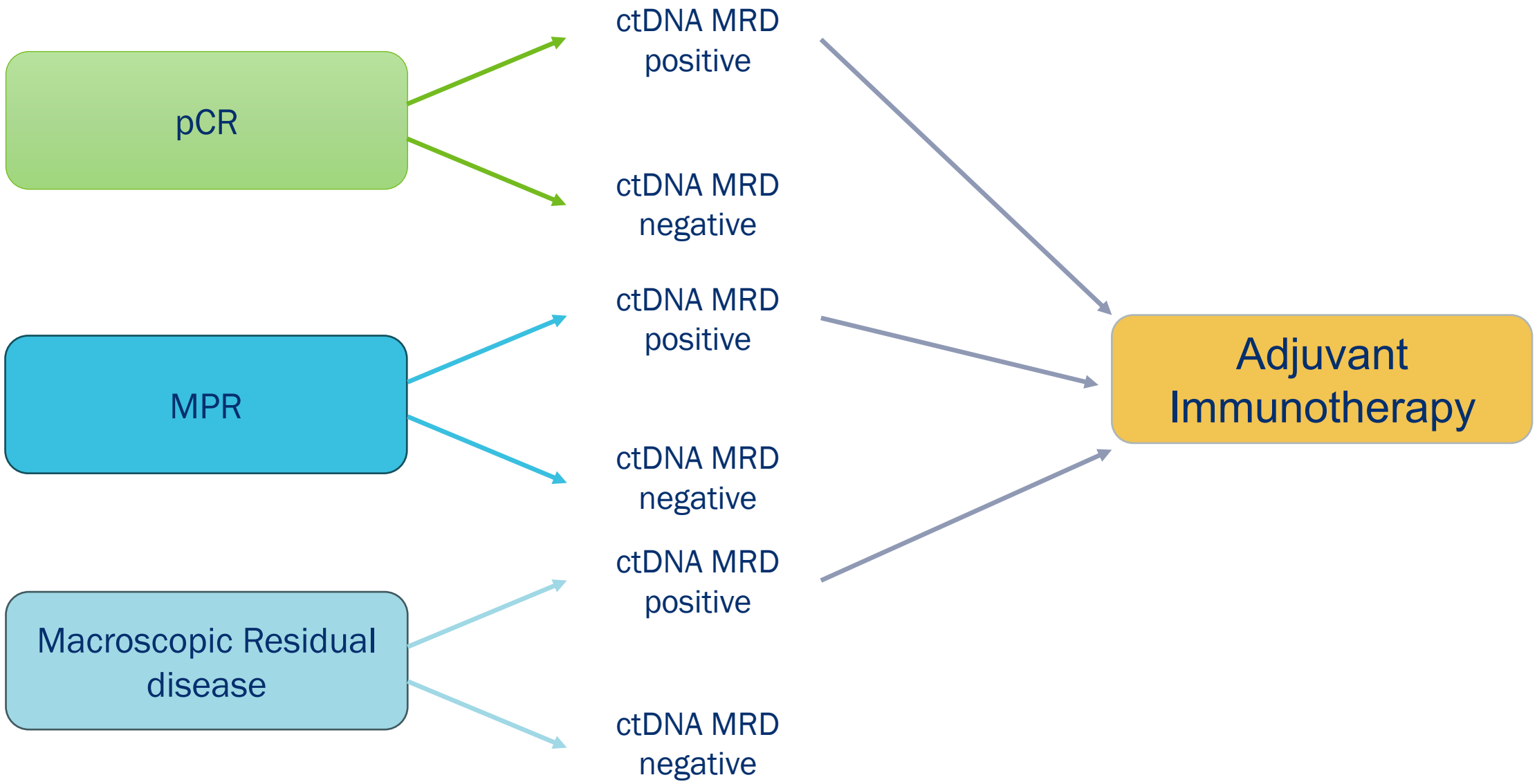


No. at risk					
Toripalimab with MPR	98	95	77	46	17
Toripalimab without MPR	104	61	39	20	6
Placebo with MPR	17	16	13	7	5
Placebo without MPR	185	123	73	36	10

Lu S et al. *JAMA*. 2024

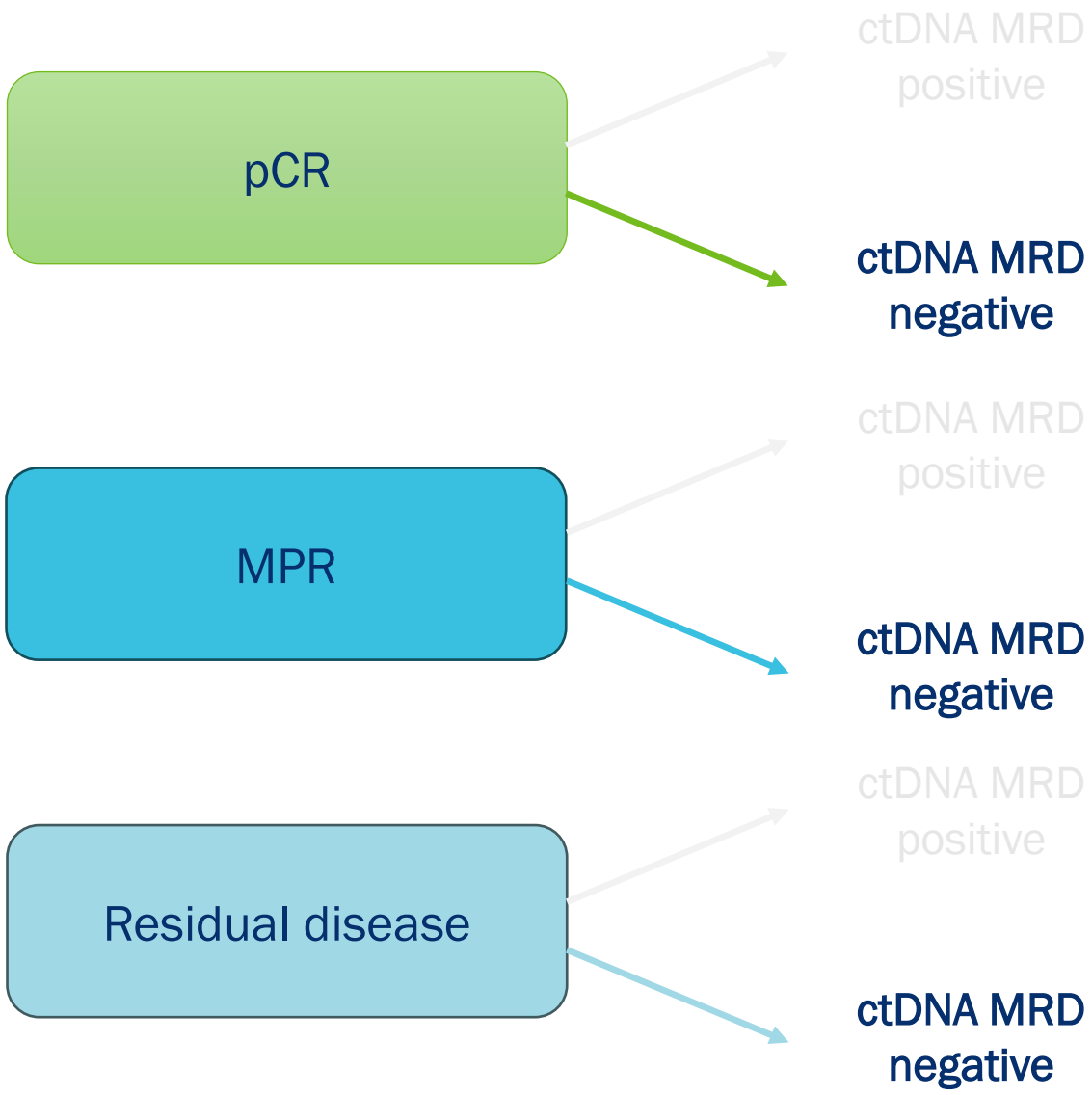
How do I treat ctDNA positive after a complete resection?

My recommended approach as of 01/2025



How do I treat ctDNA positive after a complete resection?

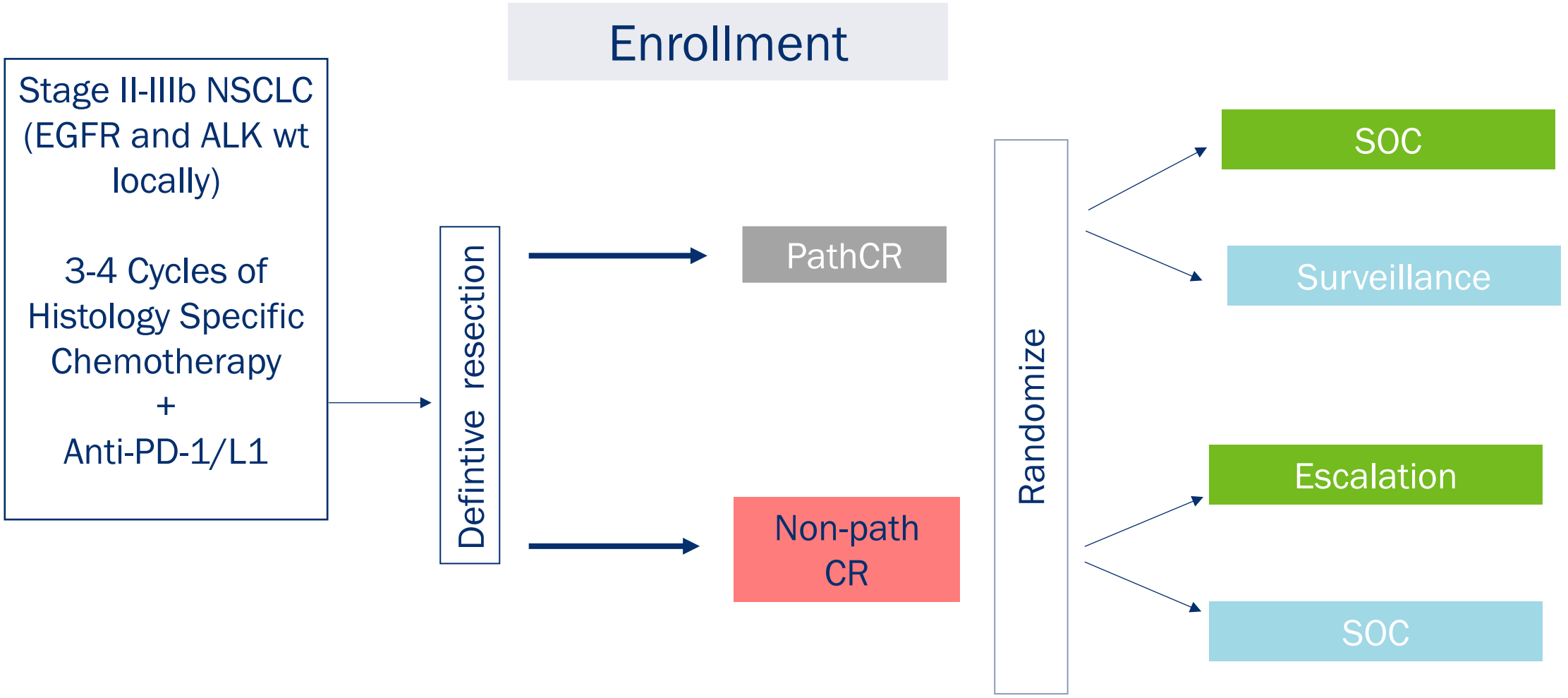
My recommended approach as of 01/2025



It depends…

- If ctDNA undetectable prior to curative-intent treatment start in the setting of pCR and MPR and ctDNA MRD (-), pts **likely do not need additional treatment**
- If ctDNA (+) pre-treatment and cleared (ctDNA MRD -), I would recommend adjuvant immunotherapy

We need clinical trials that will investigate escalation and de-escalation based on MRD status to then change our clinical practice



Take home points

- ctDNA can detect MRD and it is a strong prognostic biomarker
- One timepoint MRD status may not be enough to inform clinical-decision making
- Tumor-informed MRD assays will not be feasible for patients with pCR and MPR
- Ongoing trials will inform if clinical decision-making can be guided by ctDNA and if that improves patients' outcomes

Thank you!

www.moffitt.org

Bruna.Pellini@moffitt.org

@BrunaPellini