The importance of using ctDNA to detect minimal residual disease (MRD)

Natasha Leighl MD MMSc FRCPC FASCO

Lung Medical Oncology Site Lead

Princess Margaret Cancer Centre, Toronto, Canada

Professor of Medicine, University of Toronto

Adjunct Professor, Institute of Health Policy, Management and Evaluation

Dalla Lana School of Public Health

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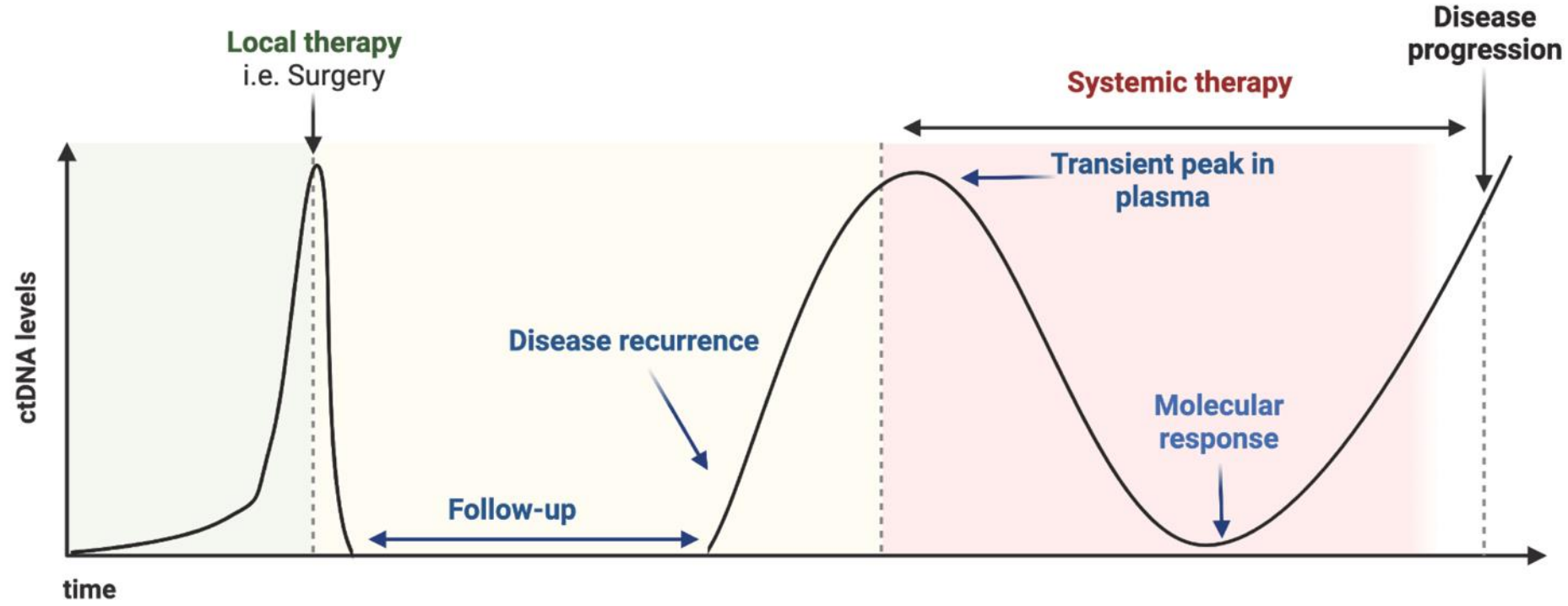
Objectives

- To review recent data on the prognostic impact of MRD in lung cancer
- To highlight recent data on the role of MRD detection in early lung cancer treatment
- To discuss some challenges and ongoing studies in this area

Potential uses of liquid biopsy throughout the lung journey



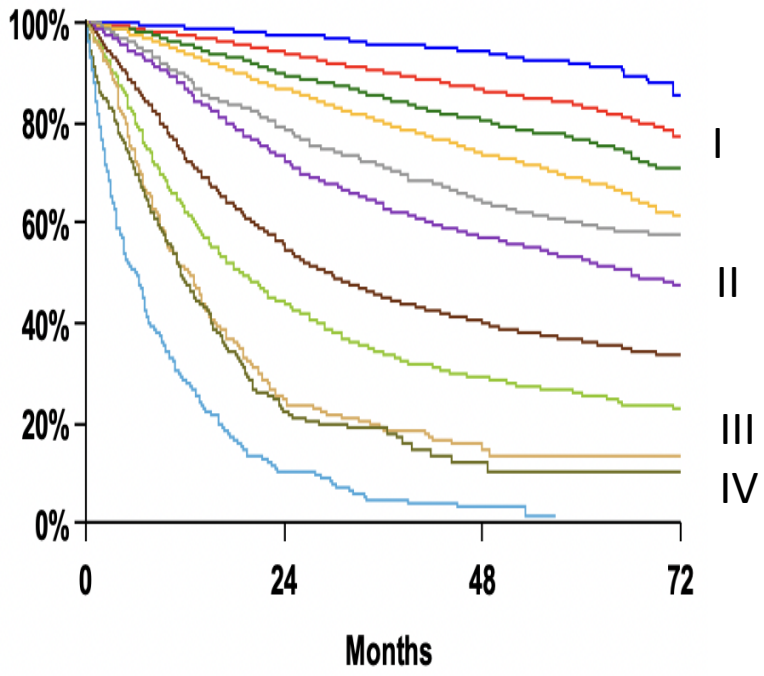
Applications of ctDNA analyses	Screening and Early detection	MRD monitoring	Tumor genotyping for therapy selection	Treatment monitoring	Tumor genotyping for the identification of resistance mechanisms

Small volume of tumor cells remaining after treatment in patients who have no clinical evidence of disease

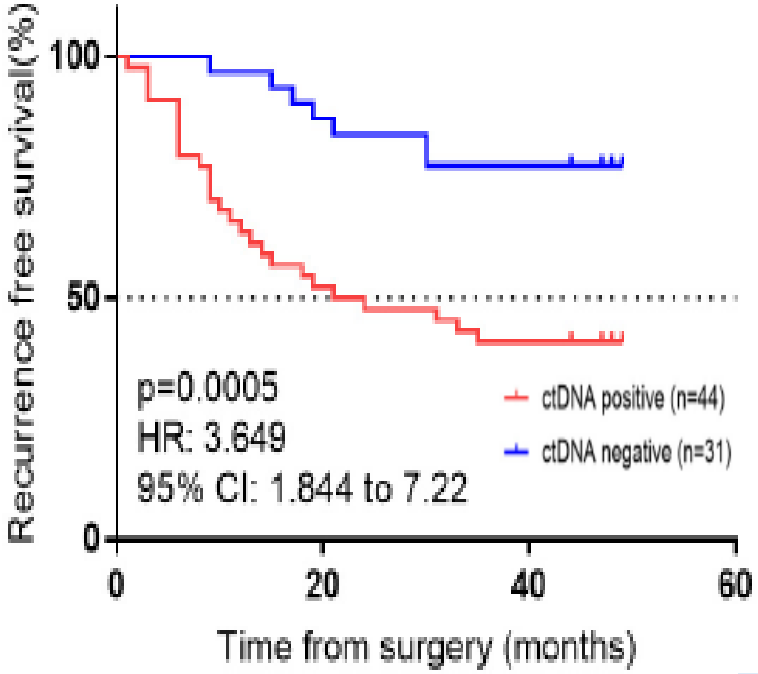
Malapelle et al Lung Cancer 2022

Plasma ctDNA: a powerful prognostic marker in early (and late) stage cancer

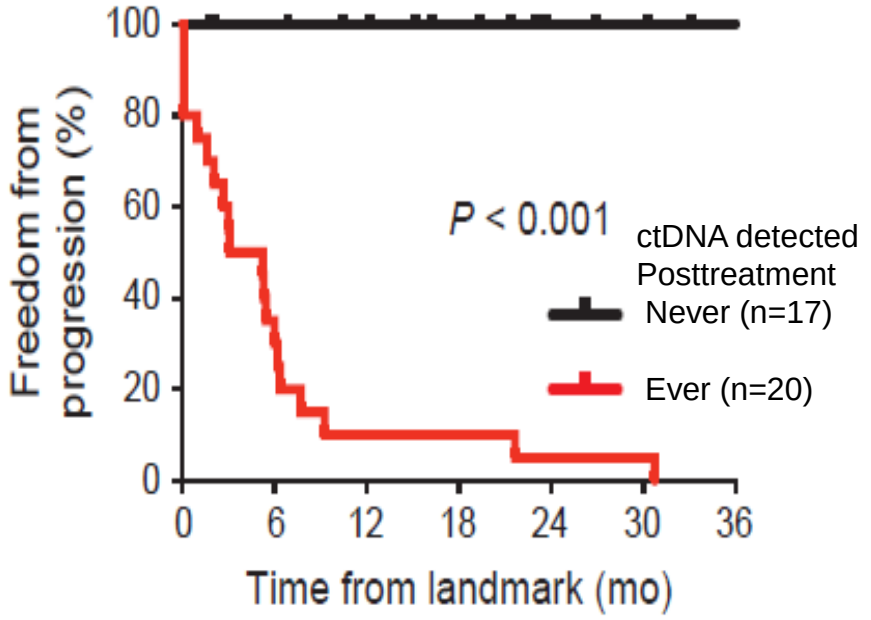
IASLC 8th edition TNM staging
11 prognostic groupings



Preoperative ctDNA levels in patients with stage I-III NSCLC (N=75)



Post-treatment ctDNA levels in patients with stage I-III NSCLC (N=40)



ctDNA precedes radiographic progression in 72% by median 5.4 months

Goldstraw P, et al. *J Thorac Oncol*. 2016;11(1):39-51. Peng M, et al. *Front Oncol*. 2020;10:561598; Chaudhuri AA, et al. *Cancer Discov*. 2017;7(12):1394-1403

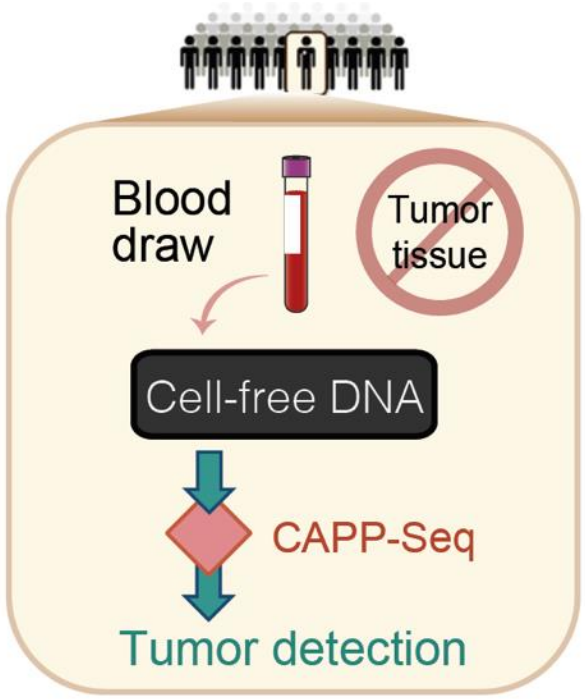
Retrospective Data From ~900 NSCLC Patients: Pre- and Post-treatment MRD strongly prognostic

Study	N	Stage	Treatment(s)	ctDNA assay
Chaudhuri *Cancer Discov* 2017	37	IB-IIIB	RT and/or surgery +/- chemo	CAPP-Seq
Abbosh *Nature* 2017	24	IA-IIIB	Surgery +/- chemo	Natera
Chen *CCR* 2019	25	I-III	Surgery +/- chemo	cSMART
Moding *Cancer Discov* 2020	48	IIB-IIIB	chemoRT +/- IO	CAPP-Seq
Abbosh *AACR* 2020	88	I-III	Surgery +/- chemo	ArcherDx
Zviran *Nat Med* 2020	22	I-III	Surgery +/- chemo	MRDetect
Waldeck *Mol Oncol* 2021	16	IA-IIIB	Surgery +/- chemo, RT	Custom NGS
Xia *CCR* 2021	329	I-III	Surgery +/- chemo	Custom NGS
Gale *Ann Oncol* 2022	59	I-III	RT and/or surgery +/- chemo	Inivata
Zhang *Cancer Discov* 2022	245	I-III	Surgery +/- chemo, IO, TKI	Custom NGS

Courtesy Dr. Max Diehn

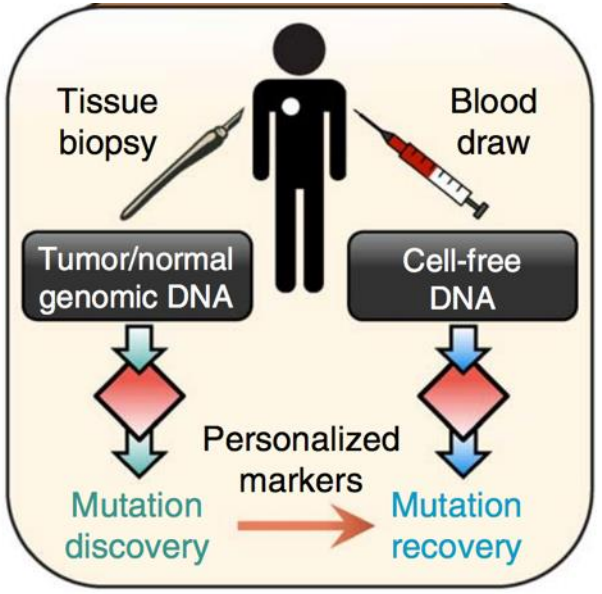
Different types of ctDNA MRD Assays

Tumor-naive



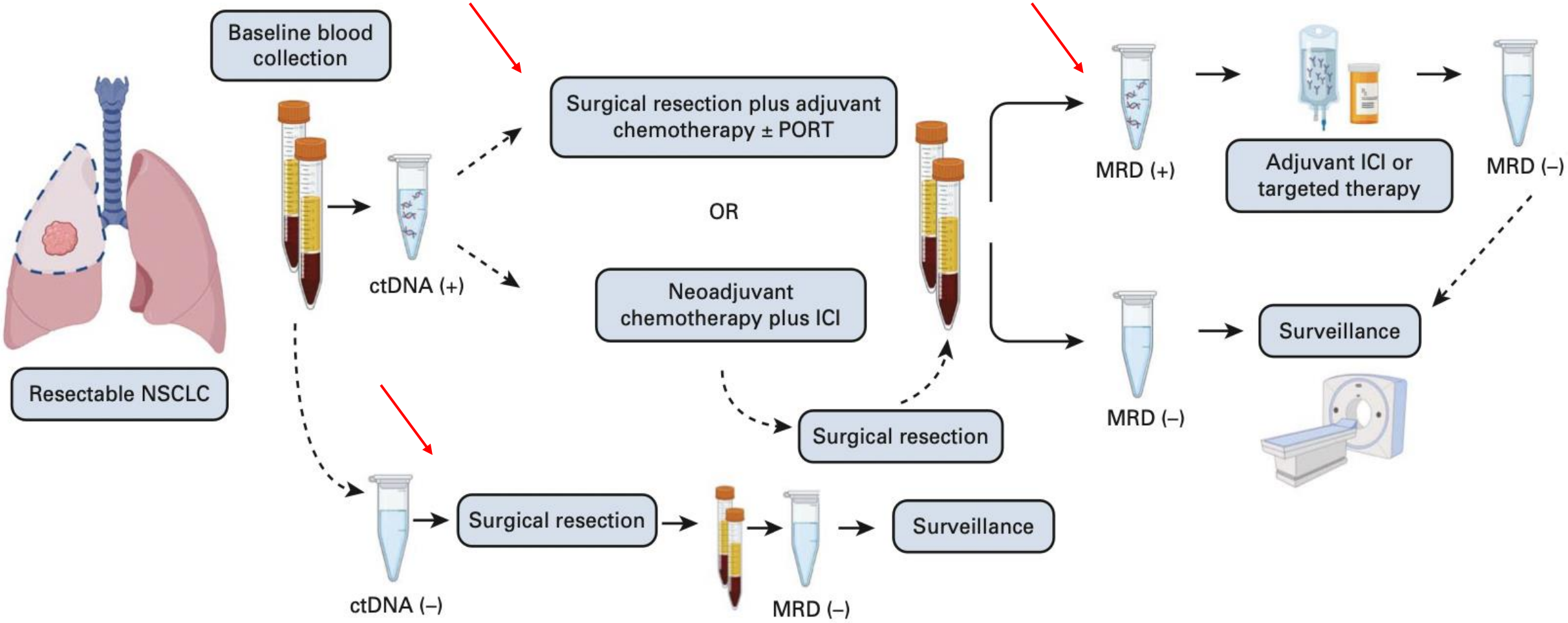
- Genotyping with no knowledge of tumor mutations (“off the shelf”)
- Faster, less expensive
- Limit of detection ~0.1%

Tumor-informed



- Tracking multiple known mutations (bespoke or personalized)
- Requires tumor tissue, time, $$
- Limit of detection ~0.01%

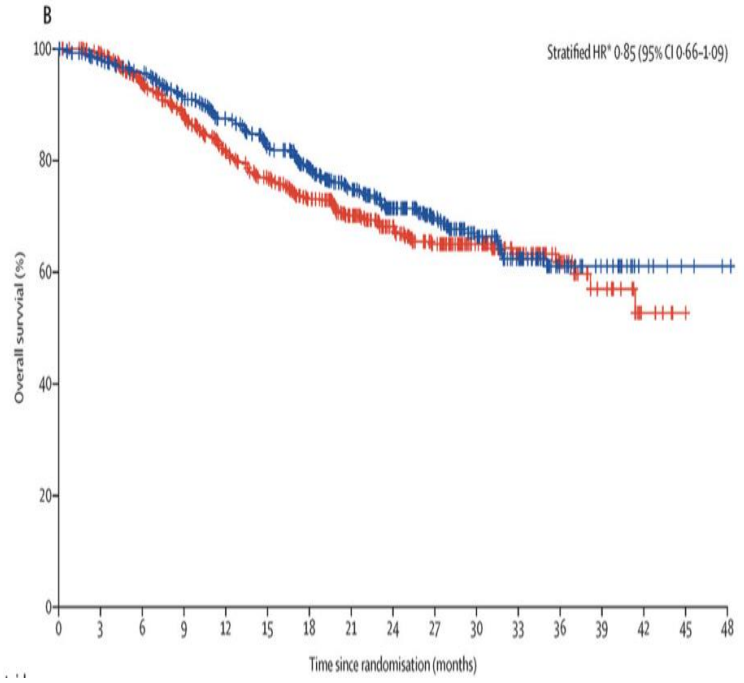
Plasma ctDNA for treatment selection – need trials to show clinical utility



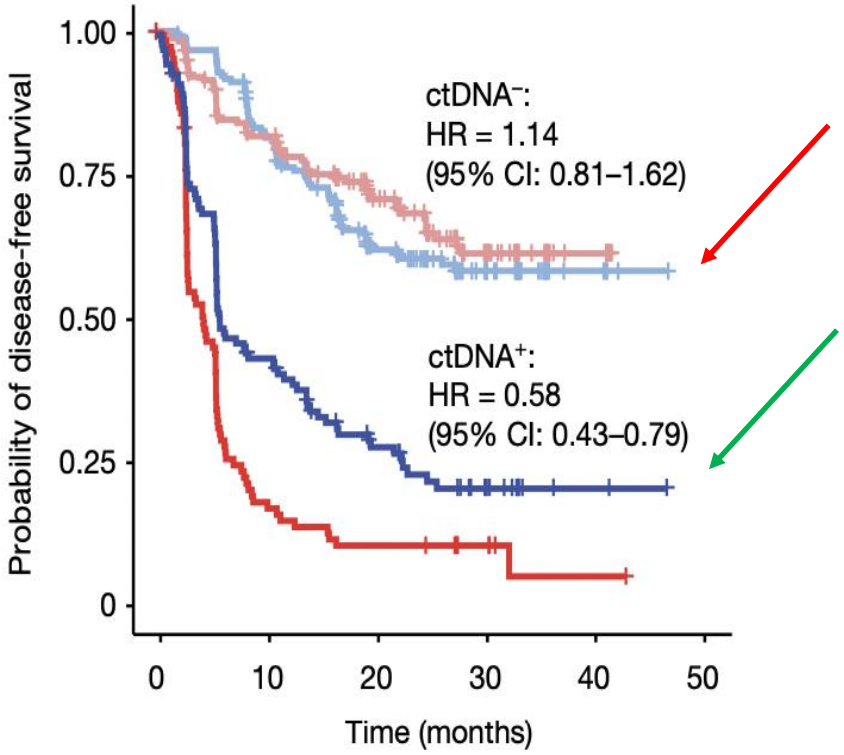
Pellini B, Chaudhuri AA. J Clin Oncol. 2022 Feb 20;40(6):567-575.

ImVIGOR 010 – adjuvant atezolizumab in patients with muscle invasive bladder cancer

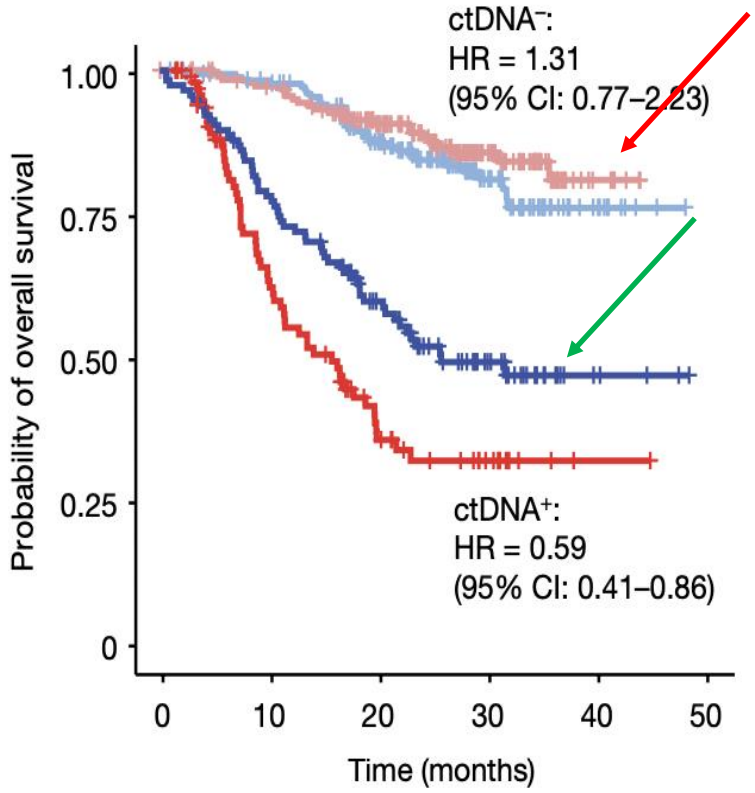
Overall OS – ITT



PFS by post-op baseline ctDNA (day 1 cycle 1)



OS by post-op baseline ctDNA (day 1 cycle 1)

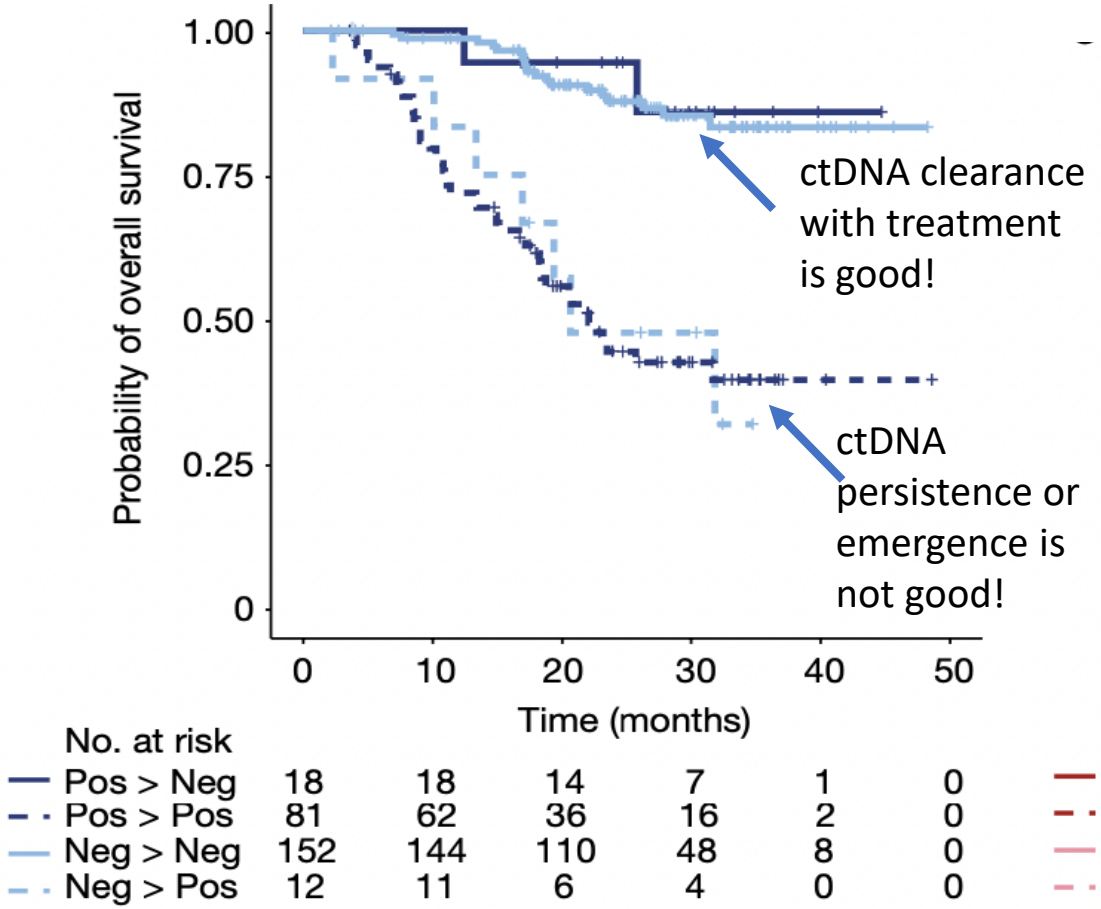


Signatera tumor informed assay
95% Limit of Detection 0.01%

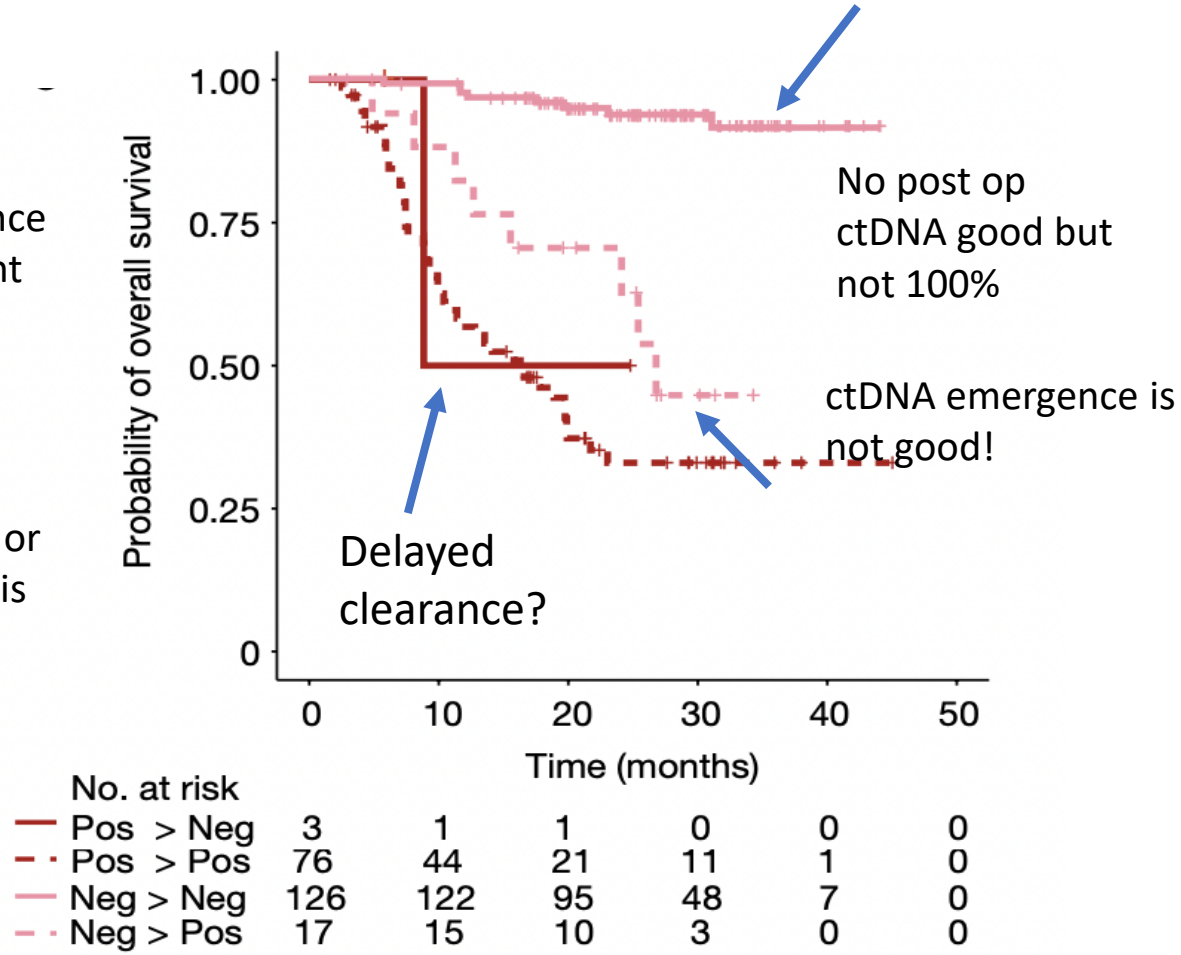
Bellmunt J, et al. Lancet Oncol. 2021 Apr;22(4):525-537.;Powles T, et al. Nature. 2021; 595(7867):432-437.

ImVIGOR010: ctDNA changes over time also important
Pre- (C1) or On-treatment (C3) ctDNA clearance

Adjuvant Atezolizumab

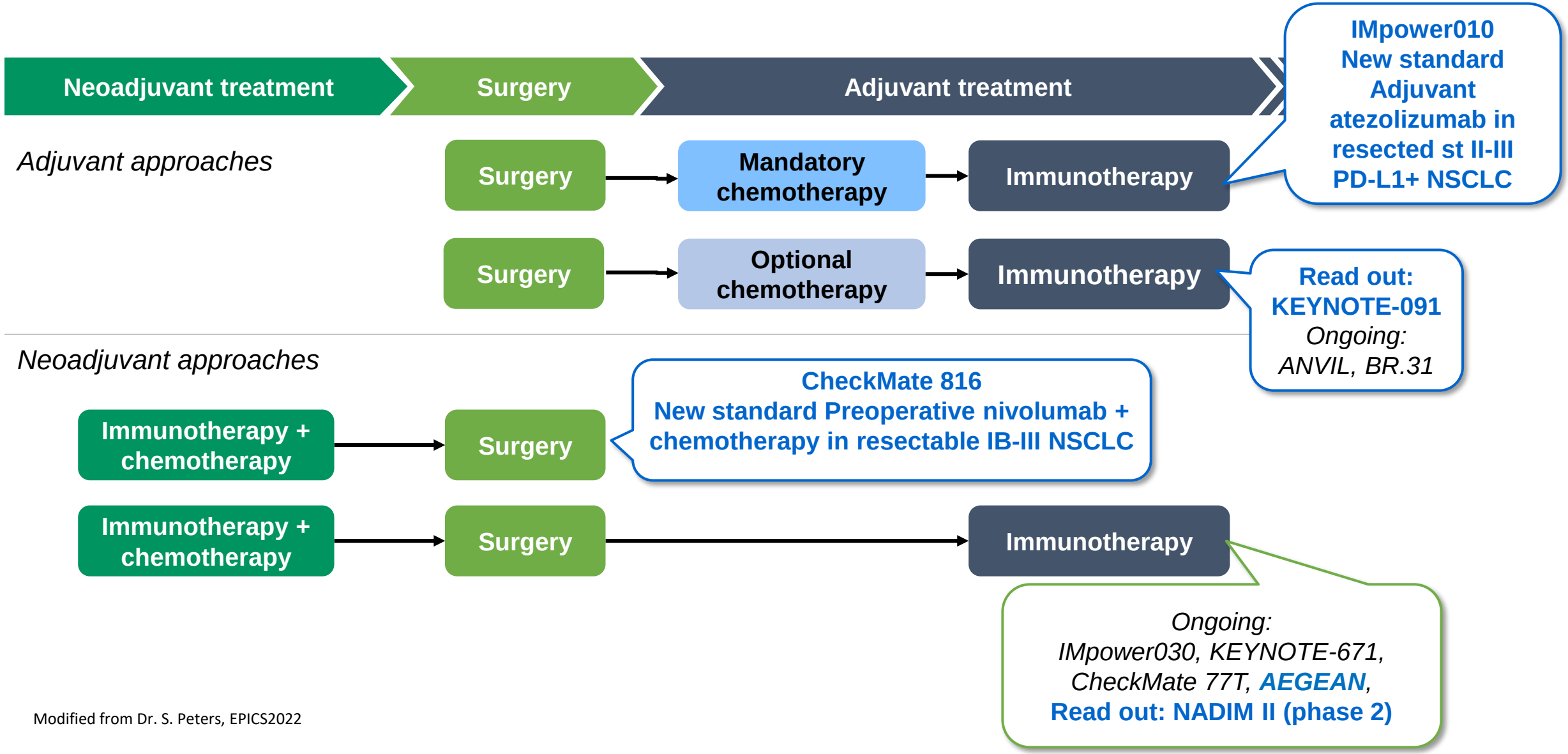


Observation post resection



Powles T, et al. Nature. 2021; 595(7867):432-437

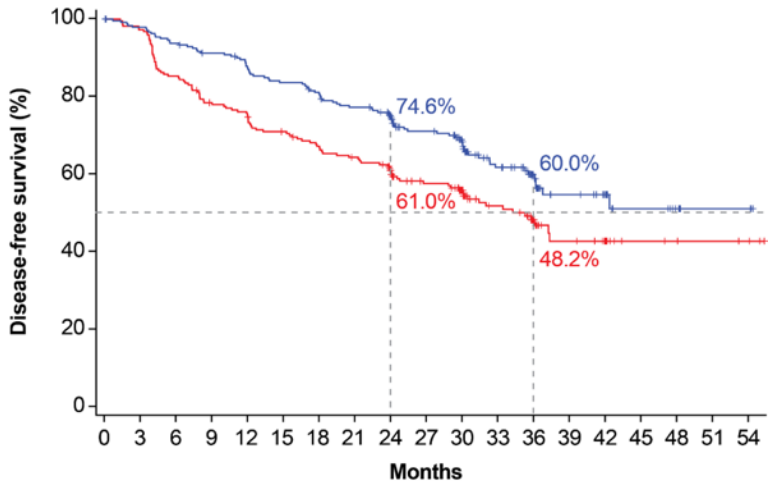
Phase III studies in resectable NSCLC



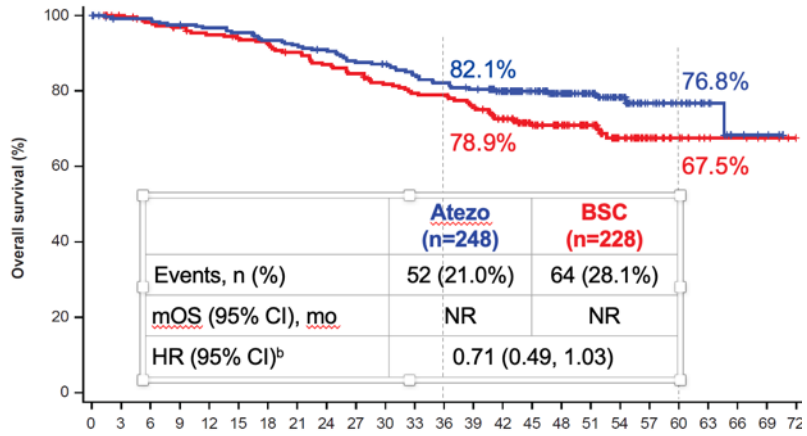
Modified from Dr. S. Peters, EPICS2022

ImPOWER010: Adjuvant atezolizumab in resected NSCLC

IMpower010[1] Stage II, III, PD-L1>=1%



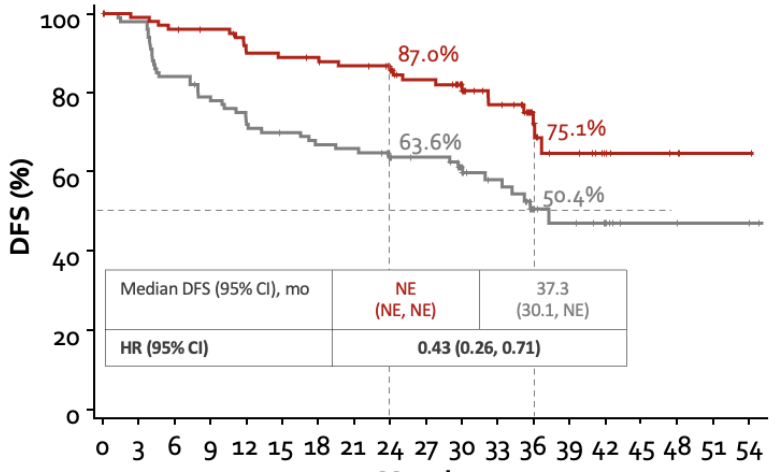
DFS HR 0.66



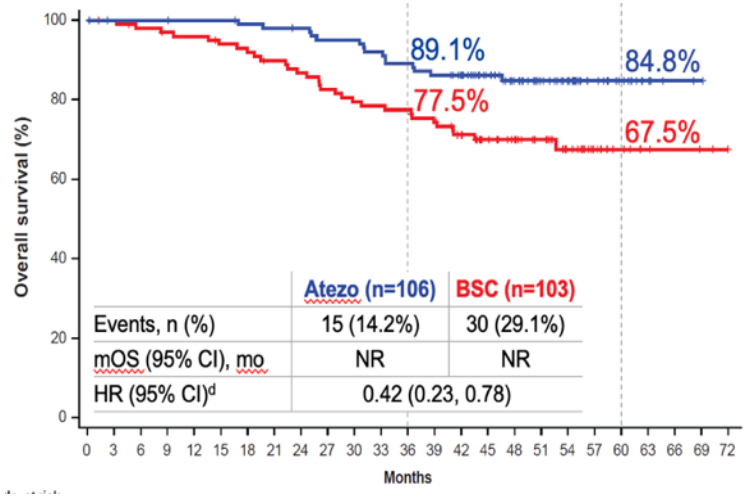
	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[b]	0.71 (0.49, 1.03)	

Interim OS HR 0.71

IMpower010 Stage II, III, PD-L1>=50%



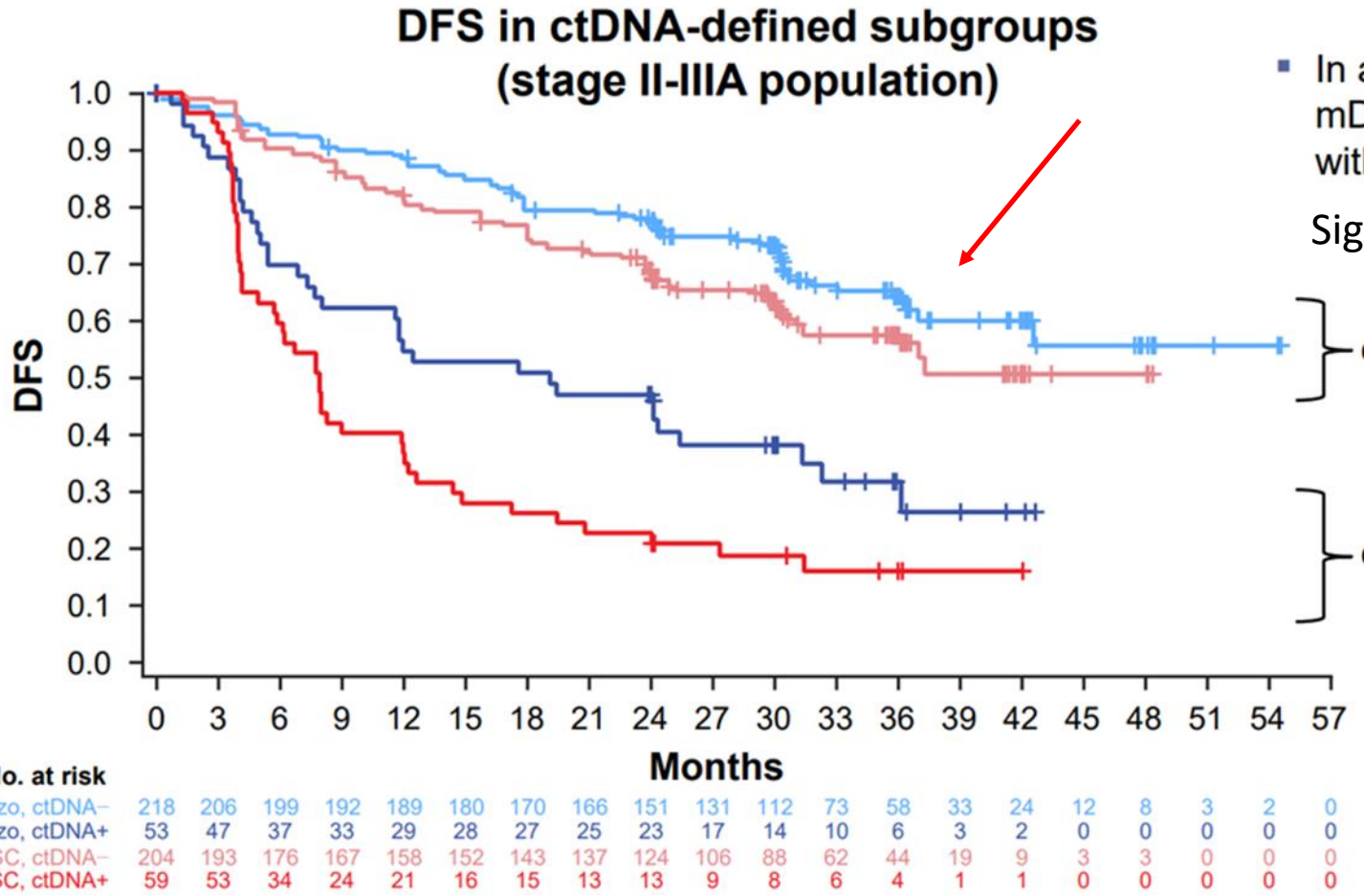
Median DFS (95% CI), mo	NE (NE, NE)	37.3 (30.1, NE)
HR (95% CI)	0.43 (0.26, 0.71)	



	Atezo (n=106)	BSC (n=103)
Events, n (%)	15 (14.2%)	30 (29.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)[d]	0.42 (0.23, 0.78)	

Felip E, et al. Lancet 2021;398:1344–57; Felip E et al WCLC2022 Presidential Symposium

IMpower-010: post op ctDNA is prognostic but does not help select therapy
Need greater sensitivity in our current MRD assays



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

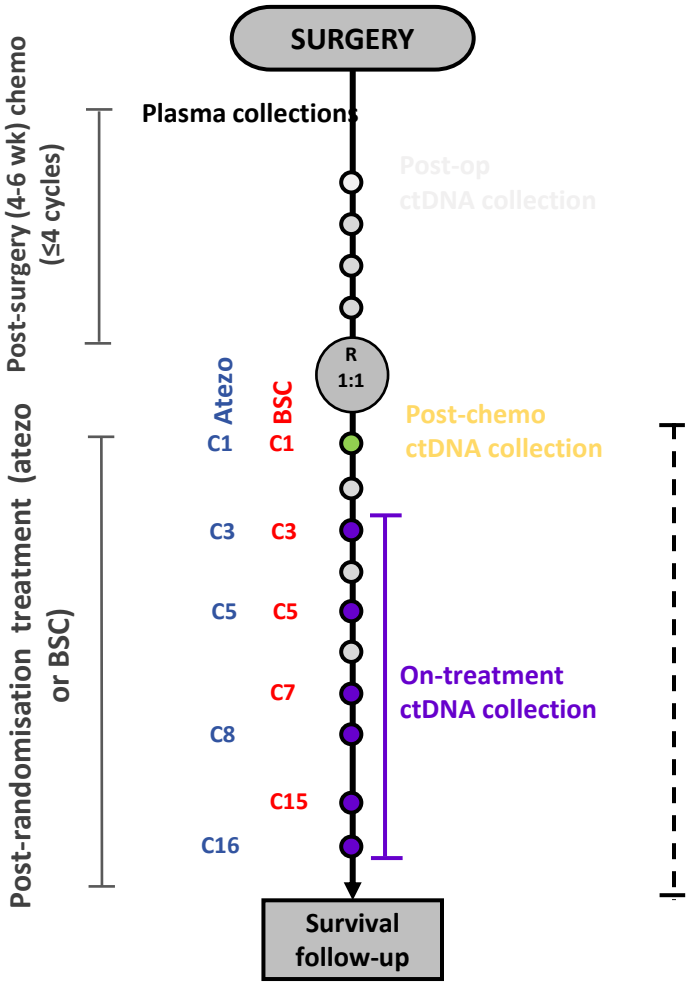
Signatera tumor informed approach

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

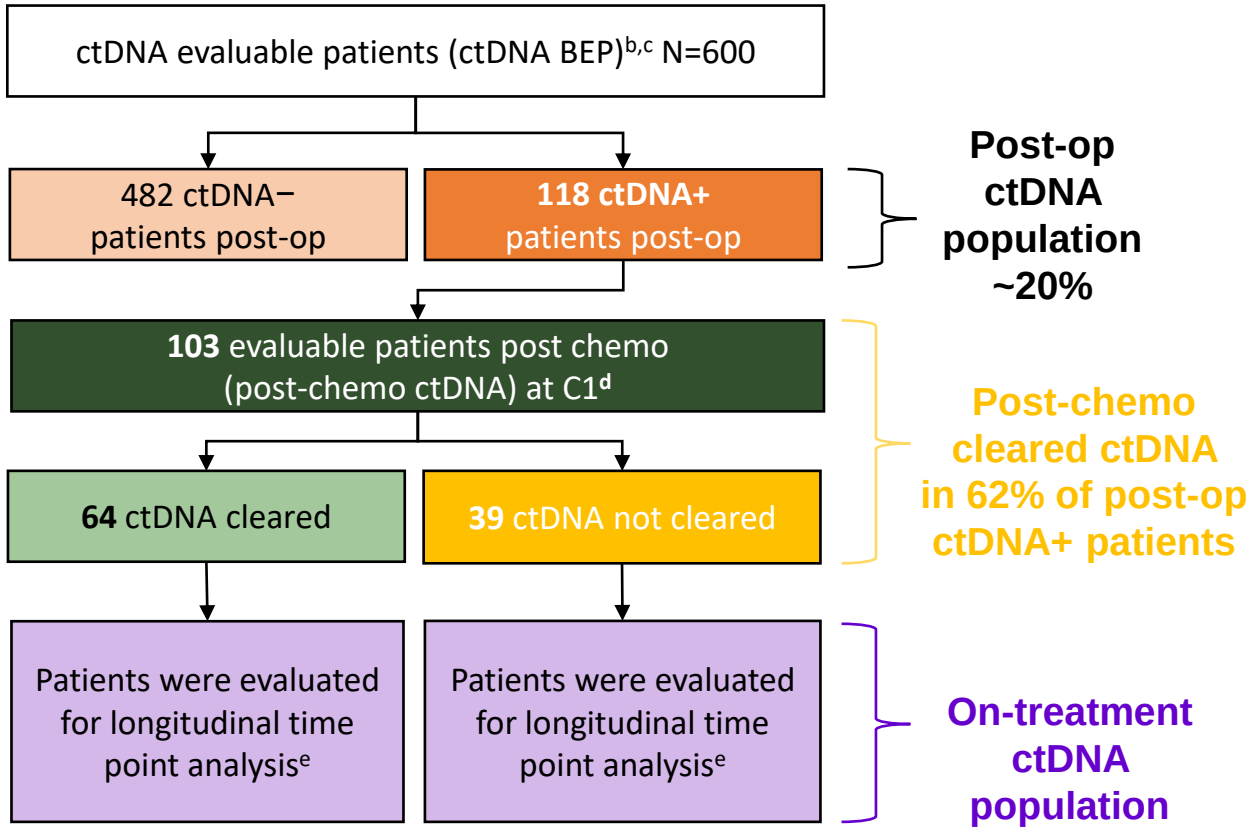
ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Reck et al. ESMO IO 2021

Baseline and longitudinal plasma collection for ctDNA testing[a]



Longitudinal sample analysis only performed in post-op ctDNA+ patients

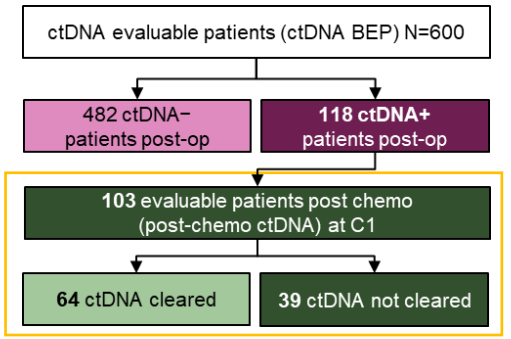


Chemo, chemotherapy; C, cycle. Clinical cutoff: 21 January 2021. [a] Using the Signatera (Natera) RUO test. [b] Treatment arms in the ctDNA BEP were balanced and comparable to the ITT population. [c] PD-L1 subgroup analyses conducted in the stage II-IIIA ctDNA BEP (n=532). [d] Samples in 15 patients were missing due to lack of consent or 4 mL plasma. [e] Patients with ≥1 on-treatment sample at C3, C5, C7/8 and C15/16. On-treatment analyses are shown on slides 9 (ctDNA cleared) and 10 (ctDNA not cleared) .

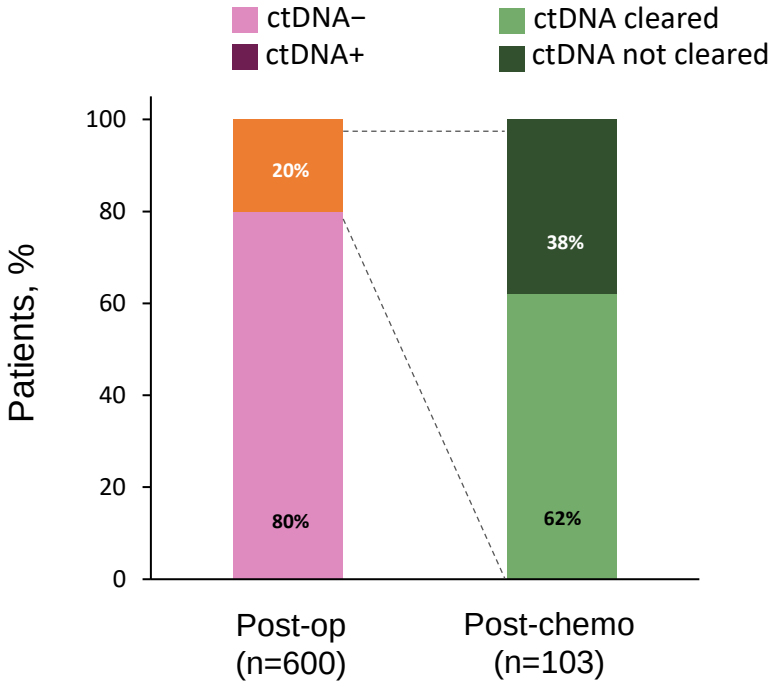
Modified from Dr. Felip, ESMO IO 2022

ctDNA clearance with adjuvant chemo in post-op ctDNA+ patients

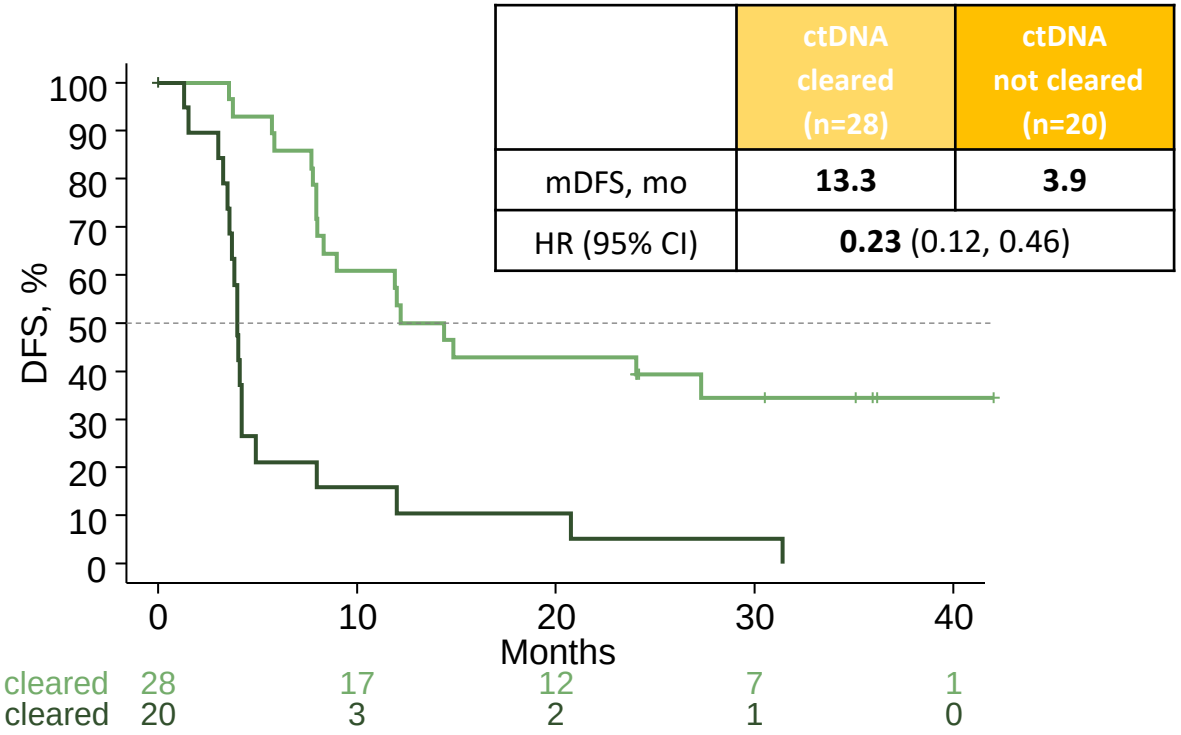
- Adjuvant chemo was effective in clearing ctDNA in ≈62% of post-op ctDNA+ patients
- Post-chemo ctDNA positivity was linked to poor DFS outcome



Impact of chemo on ctDNA clearance status



DFS by ctDNA clearance status in the BSC arm

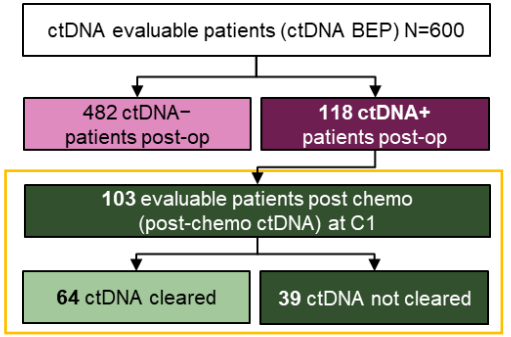


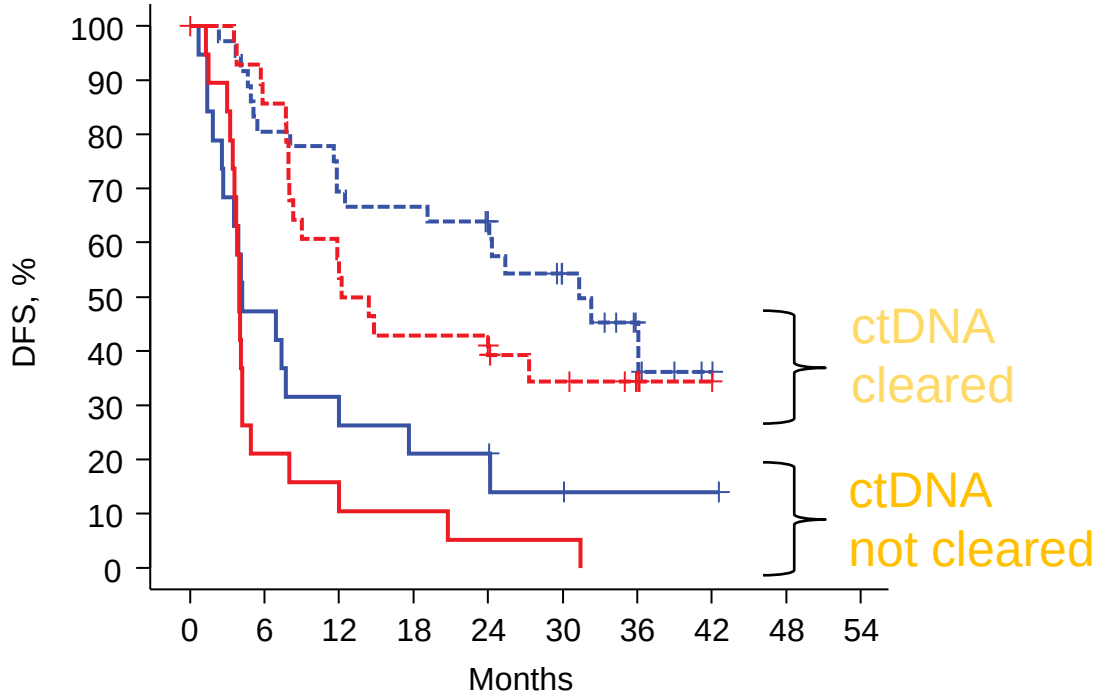
	ctDNA cleared (n=28)	ctDNA not cleared (n=20)
mDFS, mo	**13.3**	**3.9**
HR (95% CI)	**0.23** (0.12, 0.46)	

Clinical cutoff: 21 January 2021. Unstratified HRs are reported.

Courtesy Dr. Felip, ESMO IO 2022

DFS by treatment and post-chemo ctDNA clearance - all groups still appear to benefit from atezolizumab





Atezo, ctDNA cleared	36	35	29	28	25	24	24	23	21	17	12	10	5	2	1	0	0	0	0
Atezo, ctDNA not cleared	19	13	9	6	5	5	4	4	4	2	2	1	1	1	1	0	0	0	0
BSC, ctDNA cleared	28	28	24	18	15	12	12	12	12	8	7	6	4	1	1	0	0	0	0
BSC, ctDNA not cleared	20	16	4	3	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0

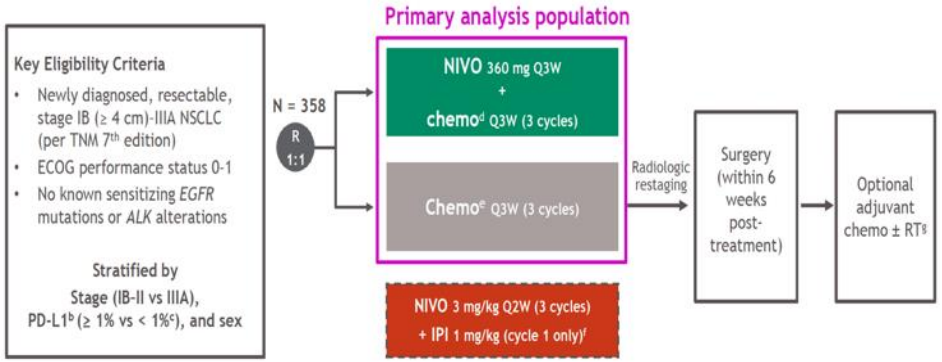
ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	**0.7** (0.37, 1.34)	

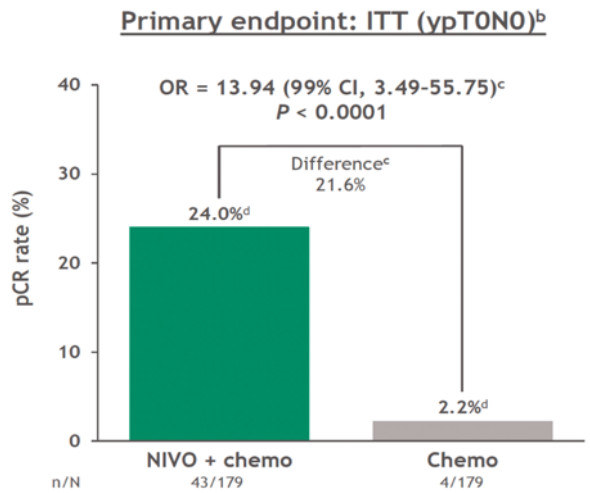
ctDNA not cleared	Atezo (n=19)	BSC (n=20)
mDFS, mo	4.2	3.9
HR (95% CI)	**0.67** (0.34, 1.32)	

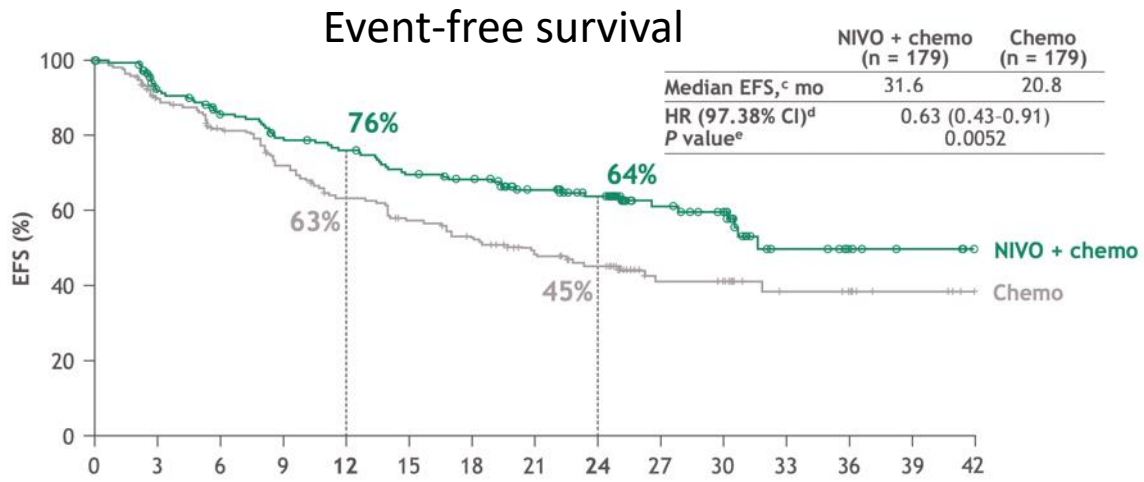
Clinical cutoff: 21 January 2021.
Data are hypothesis generating and should be interpreted with caution due to the exploratory nature of the analysis and small sample size.

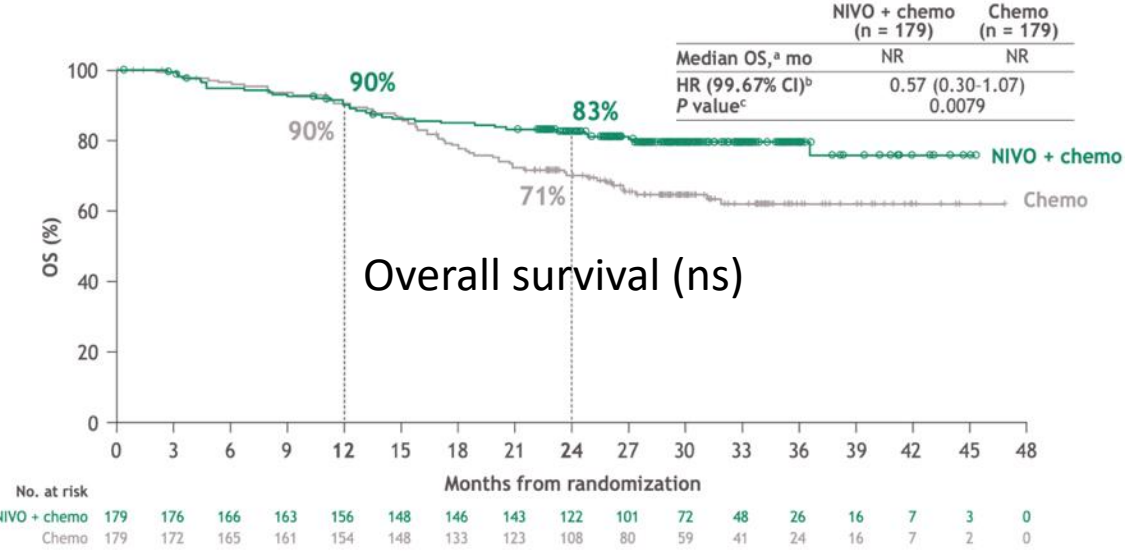
Modified from Dr. Felip, ESMO IO 2022

CheckMate 816: Preoperative Nivolumab + Chemotherapy improves path CR, event-free survival versus Chemotherapy in resectable NSCLC





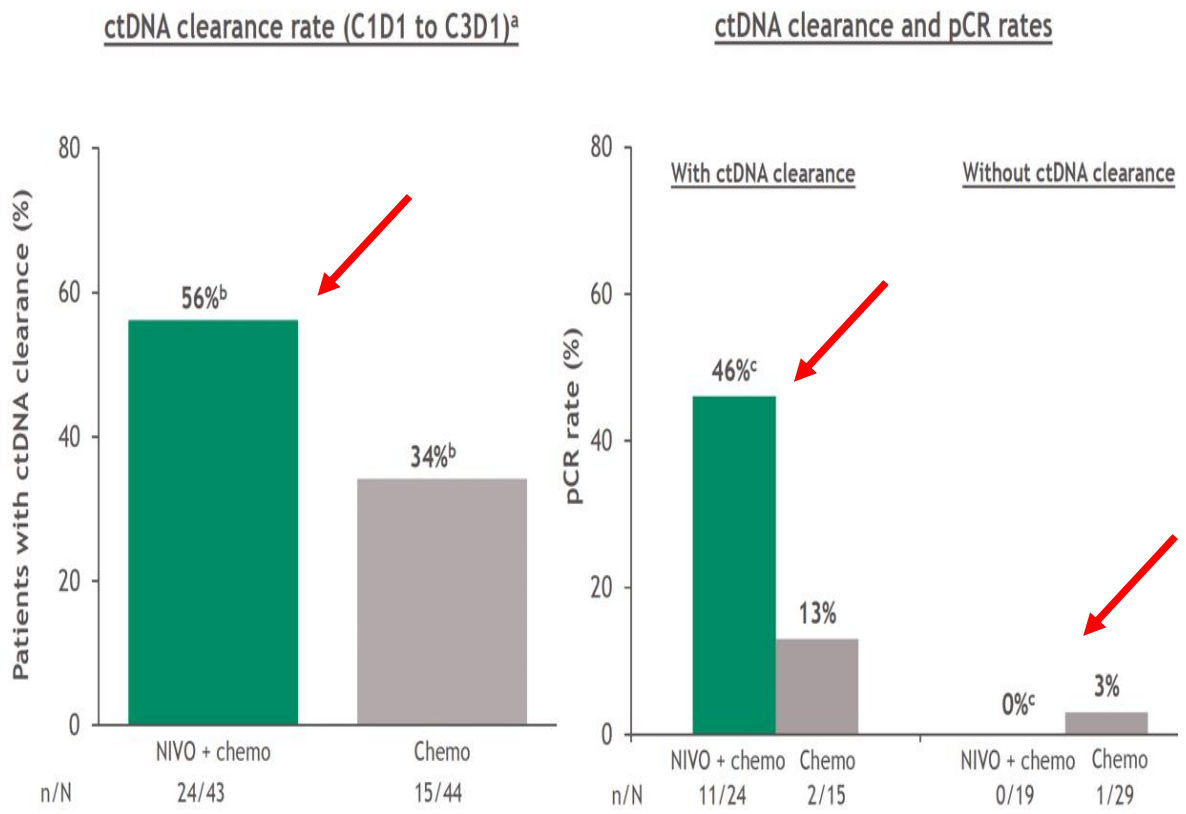




Overall survival (ns)

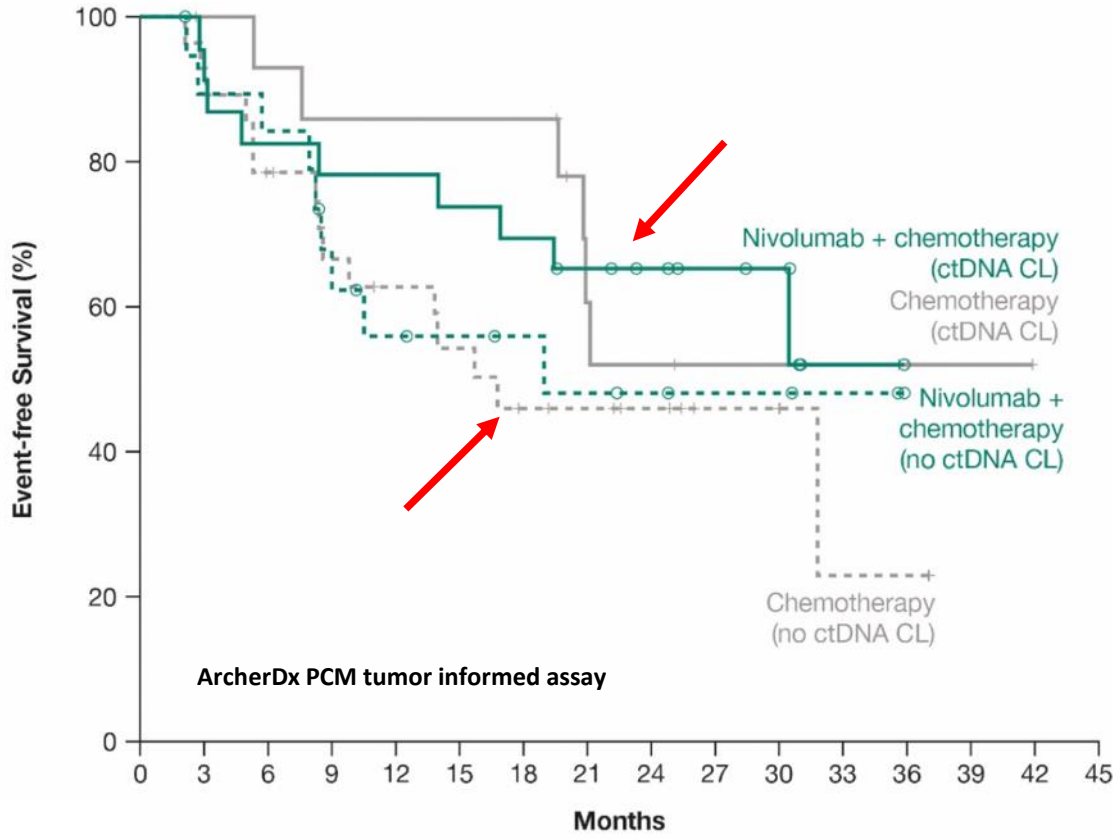
Girard N, Spicer J, et al. AACR 2022 Abstr CT012; Forde PM, Spicer J, et al New Engl J Med 2022

CheckMate 816: Plasma ctDNA clearance associated with pCR, Event-Free Survival



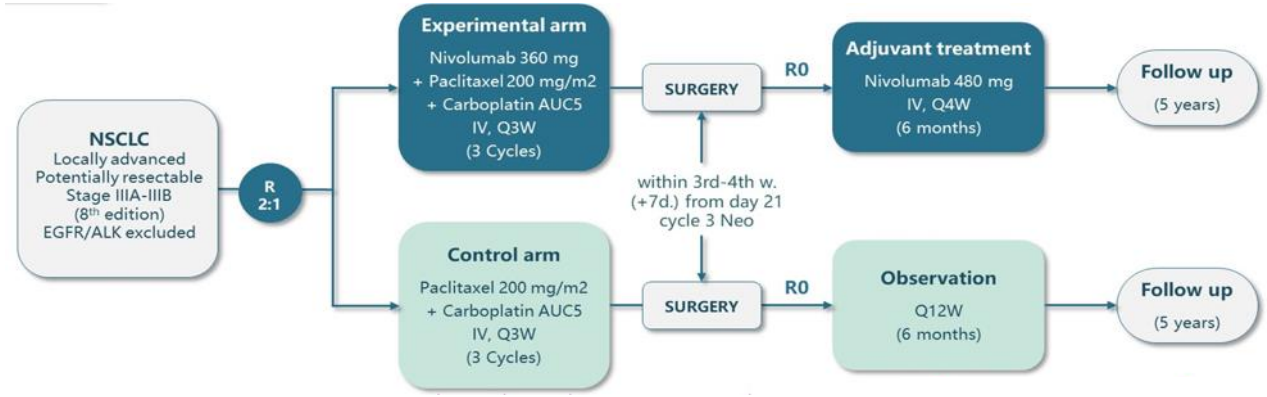
[a]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring); 90 patients were ctDNA evaluable and 87 had detectable ctDNA at C1D1; main reason for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma; [b]ctDNA clearance 95% CI: NIVO + chemo, 40-71; chemo, 20-50; [c]pCR rates 95% CI for NIVO + chemo: with ctDNA clearance, 26-67; without ctDNA clearance, 0-18.

	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)	

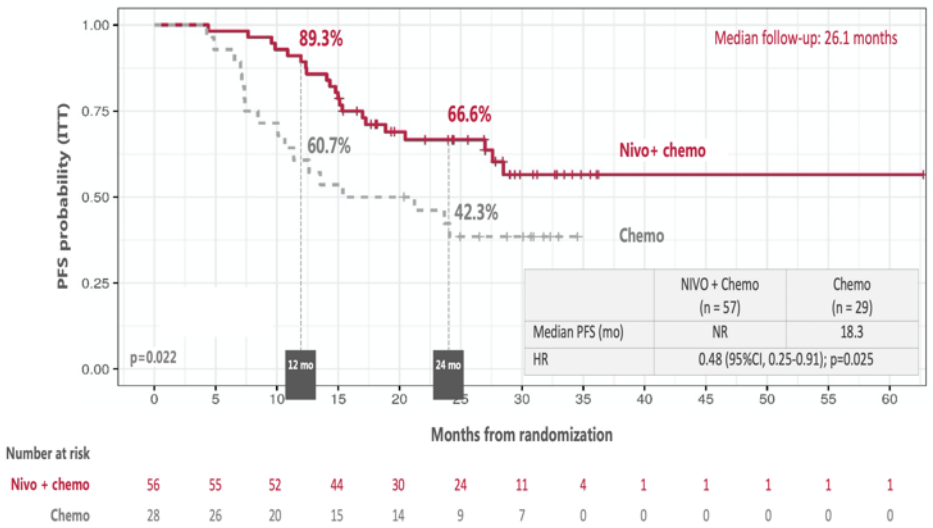


Forde et al. AACR 2021; Abstract CT003; Forde et al N Engl J Med in press

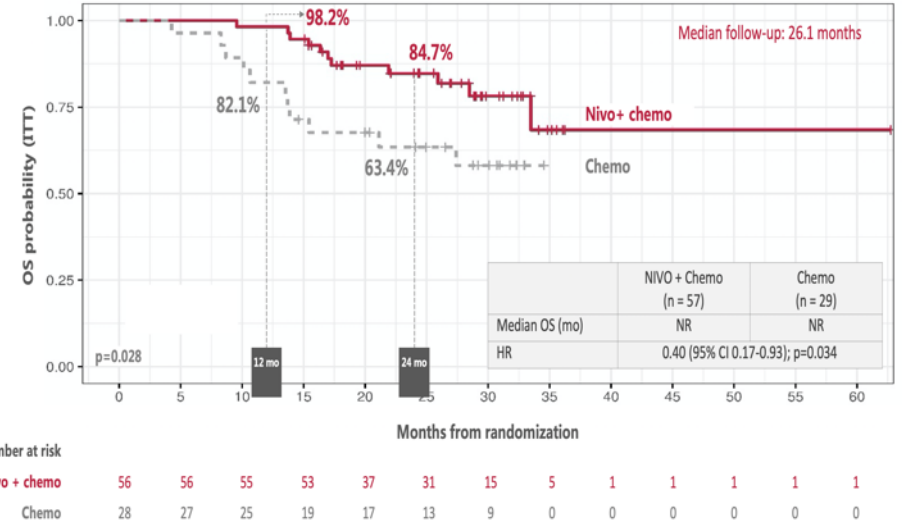
NADIM II: Preoperative Nivolumab + Chemotherapy improves pathologic CR, PFS, OS in patients with resectable stage III NSCLC



SECONDARY ENDPOINTS – Progression-free survival



SECONDARY ENDPOINTS – Overall survival



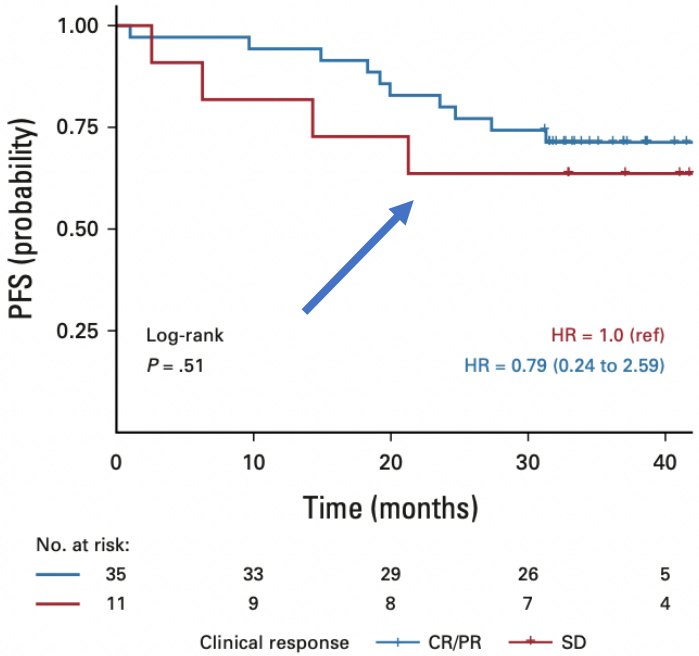
Provencio et al WCLC2022 Presidential Symposium

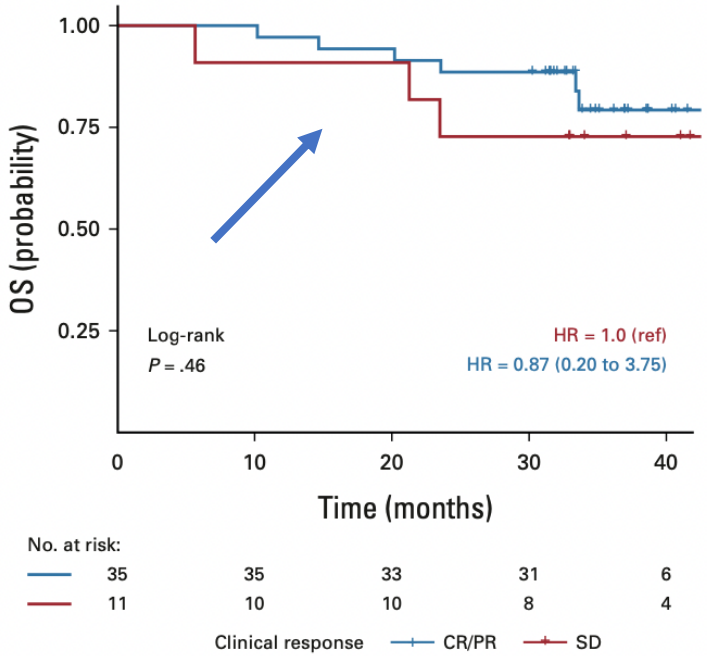
NADIM I: preoperative nivolumab + chemotherapy

ctDNA clearance associated with RFS but not OS (top panel)

ctDNA clearance + response improves signal of benefit (bottom panel)

i.e. composite endpoint better predictor of RFS, OS benefit





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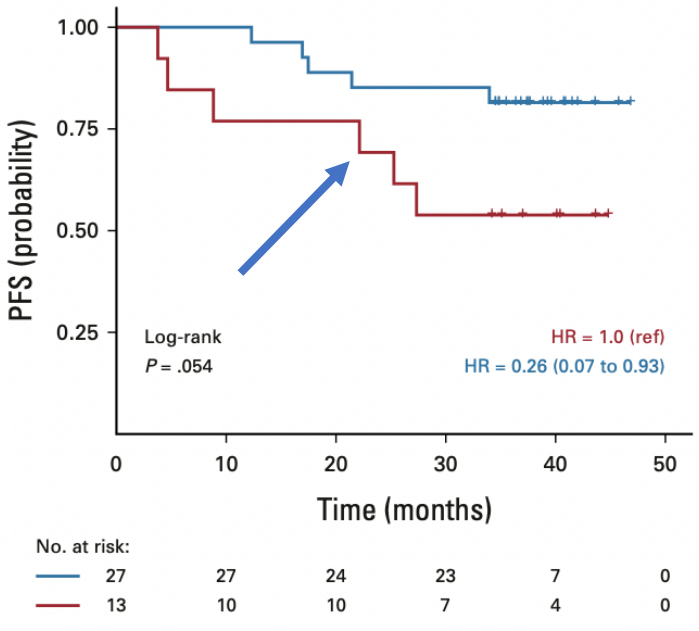

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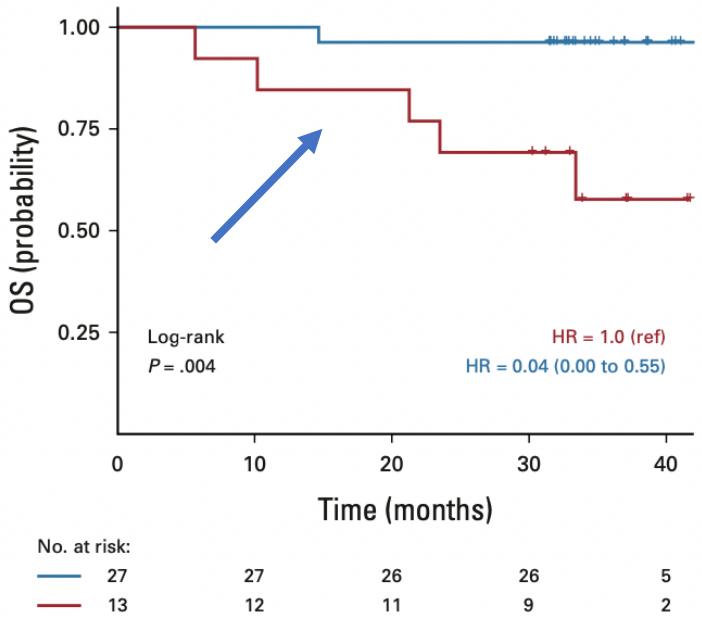
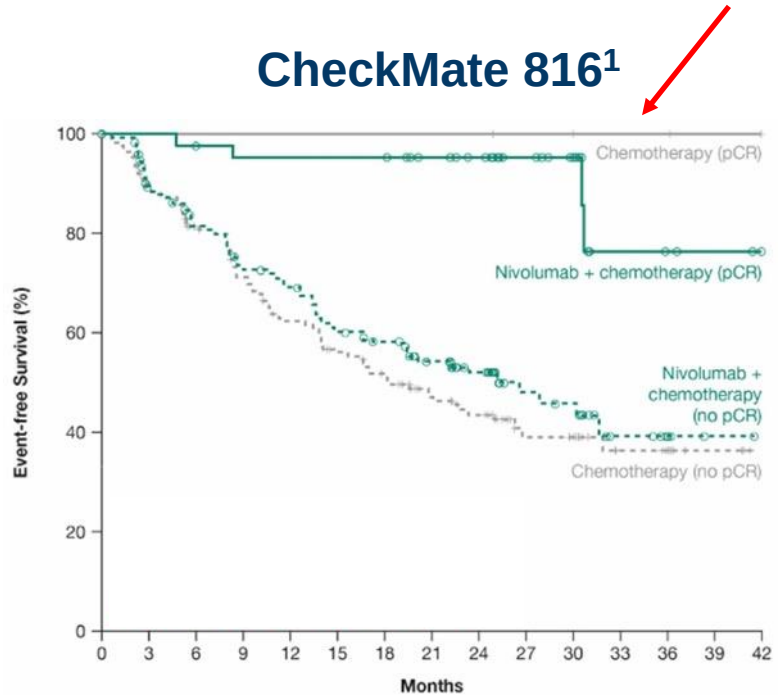


Provencio et al J Clin Oncol 2022

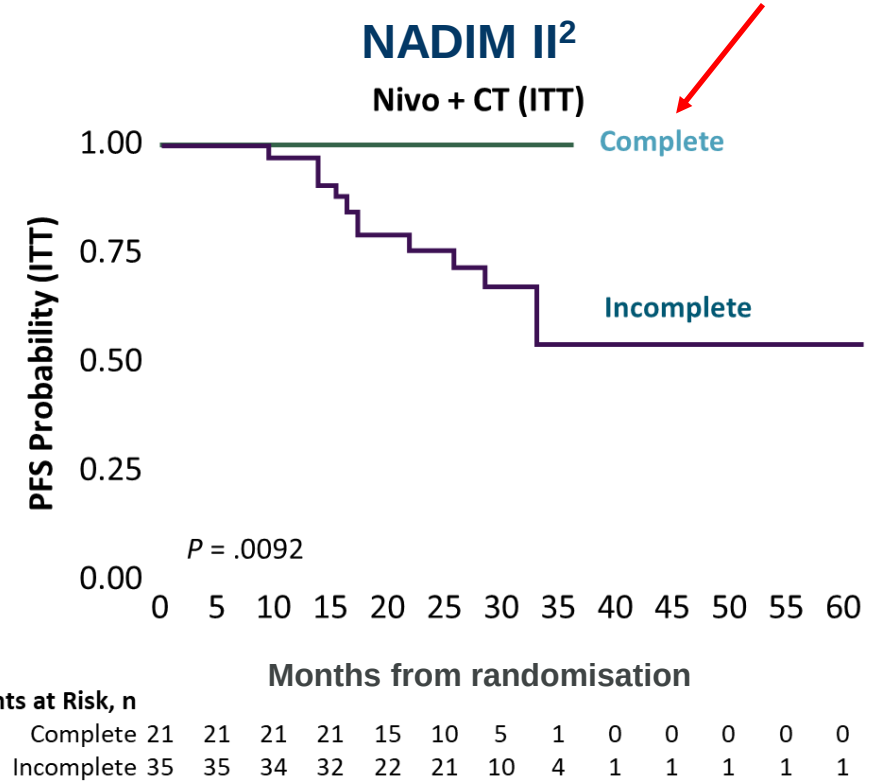
Pathologic complete response - a more promising surrogate endpoint

CheckMate 816[1]



	Nivo + CT		CT	
	pCR	No pCR	pCR	No pCR
mEFS, months	NR	26.6	NR	18.4
HR (95% CI)	0.13 (0.05, 0.37)		Not computed*	

NADIM II[2]



Courtesy of Dr. David Planchard, IGR, France

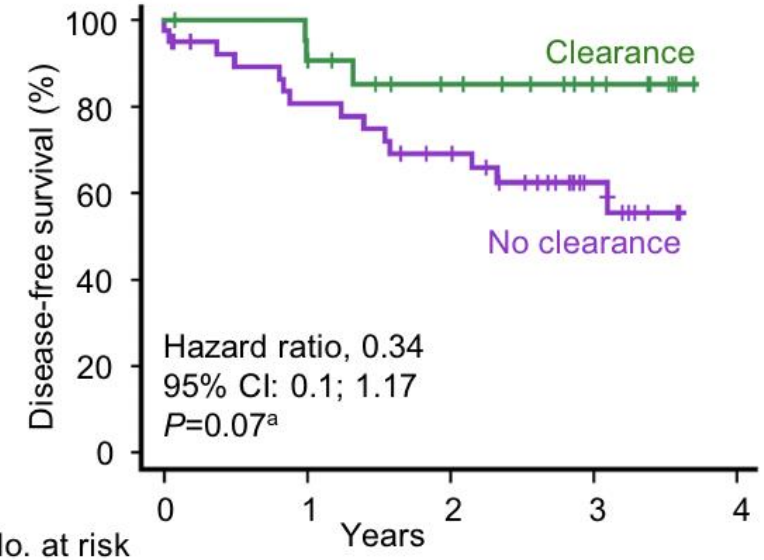
*HR was not computed for the chemotherapy arm due to only 4 patients having a pCR

CI, confidence interval; CT, chemotherapy; (m)EFS, (median) event-free survival; HR, hazard ratio; ITT, intent to treat; nivo, nivolumab; NSCLC, non-small cell lung cancer; NR, not reached; pCR, pathological complete response; PD-1, programmed cell death-1; PFS, progression-free survival

1. Forde PM, et al. N Engl J Med 2022;386:1973–85; 2. Provencio M, et al. Presented at WCLC 2022 (Abstract PL03.12)

ctDNA as part of a composite endpoint rather than standalone: LCMC3 study

Disease-free survival by baseline to post-atezo clearance

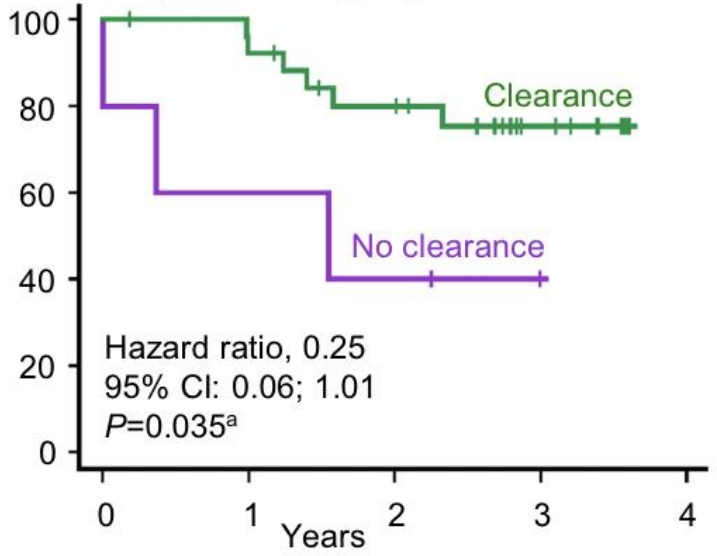


No. at risk

Clearance	22	19	13	7	0
No clearance	39	28	22	9	0

Years	Clearance		No clearance	
	DFS rate, %	At risk, n	DFS rate, %	At risk, n
1	91	19	81	28
2	85	13	69	22
3	85	7	62	9

Disease-free survival by baseline to post-surgery clearance

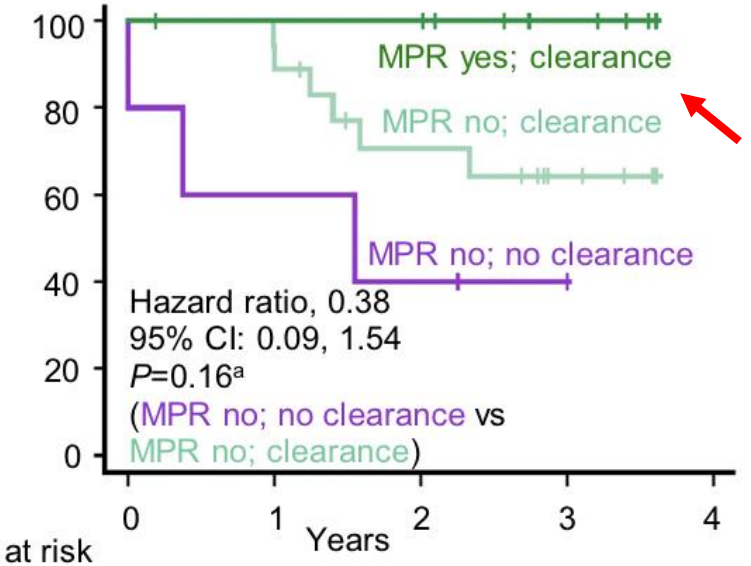


Clearance	27	24	19	10	0
No clearance	5	3	2	0	0

Years	Clearance		No clearance	
	DFS rate, %	At risk, n	DFS rate, %	At risk, n
1	92	24	60	3
2	80	19	40	2
3	75	10	–	–

Stratify by MPR

Disease-free survival by baseline to post-surgery clearance and MPR

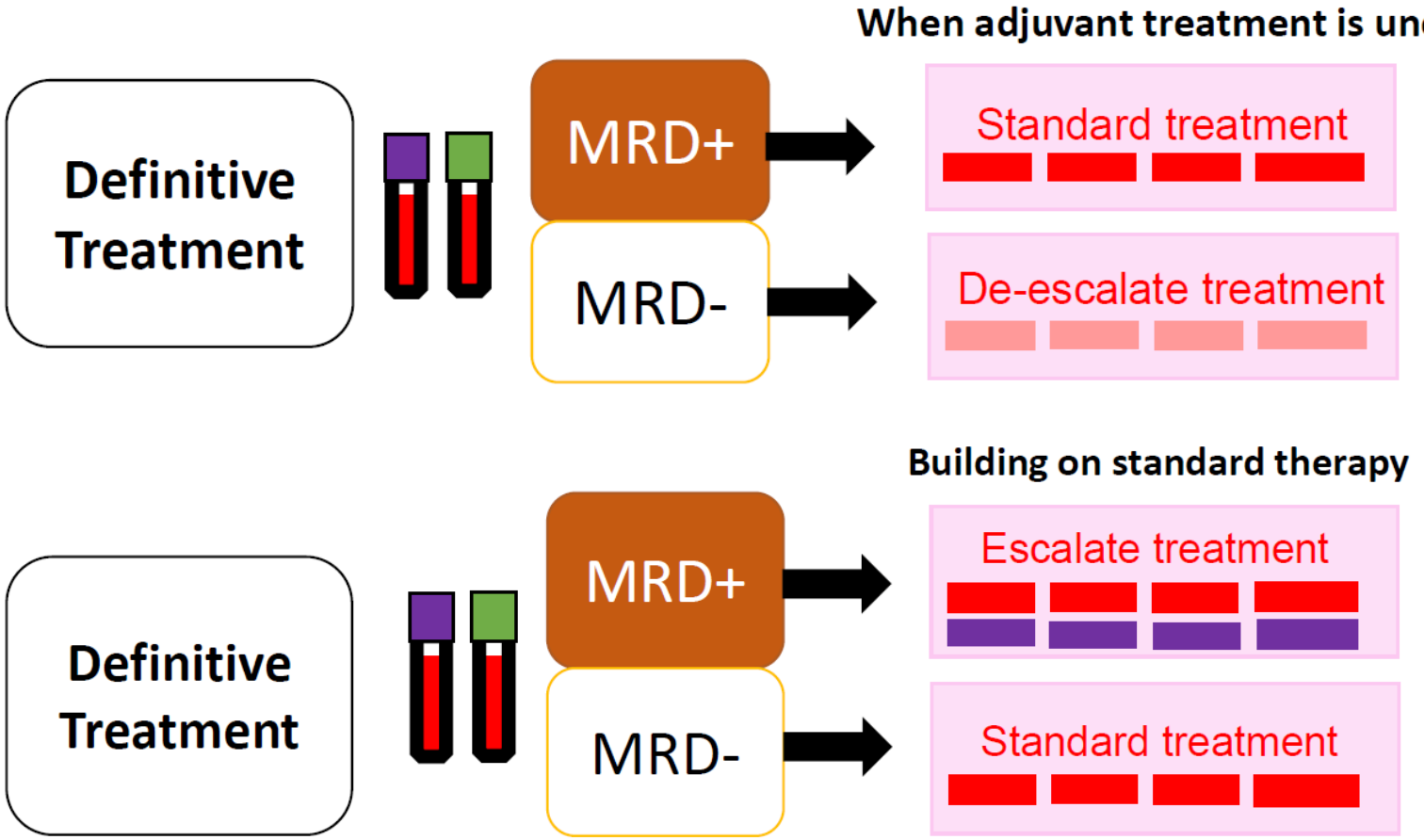


MPR yes; clearance	8	8	8	4	0
MPR no; clearance	19	16	11	6	0
MPR no; no clearance	5	3	2	0	0

Years	MPR yes; clearance		MPR no; clearance		MPR no; no clearance	
	DFS rate, %	At risk, n	DFS rate, %	At risk, n	DFS rate, %	At risk, n
1	100	8	89	16	60	3
2	100	8	71	11	40	2
3	100	4	64	6	–	–

Kris et al ESMO IO 2019

Ongoing trials to demonstrate clinical utility



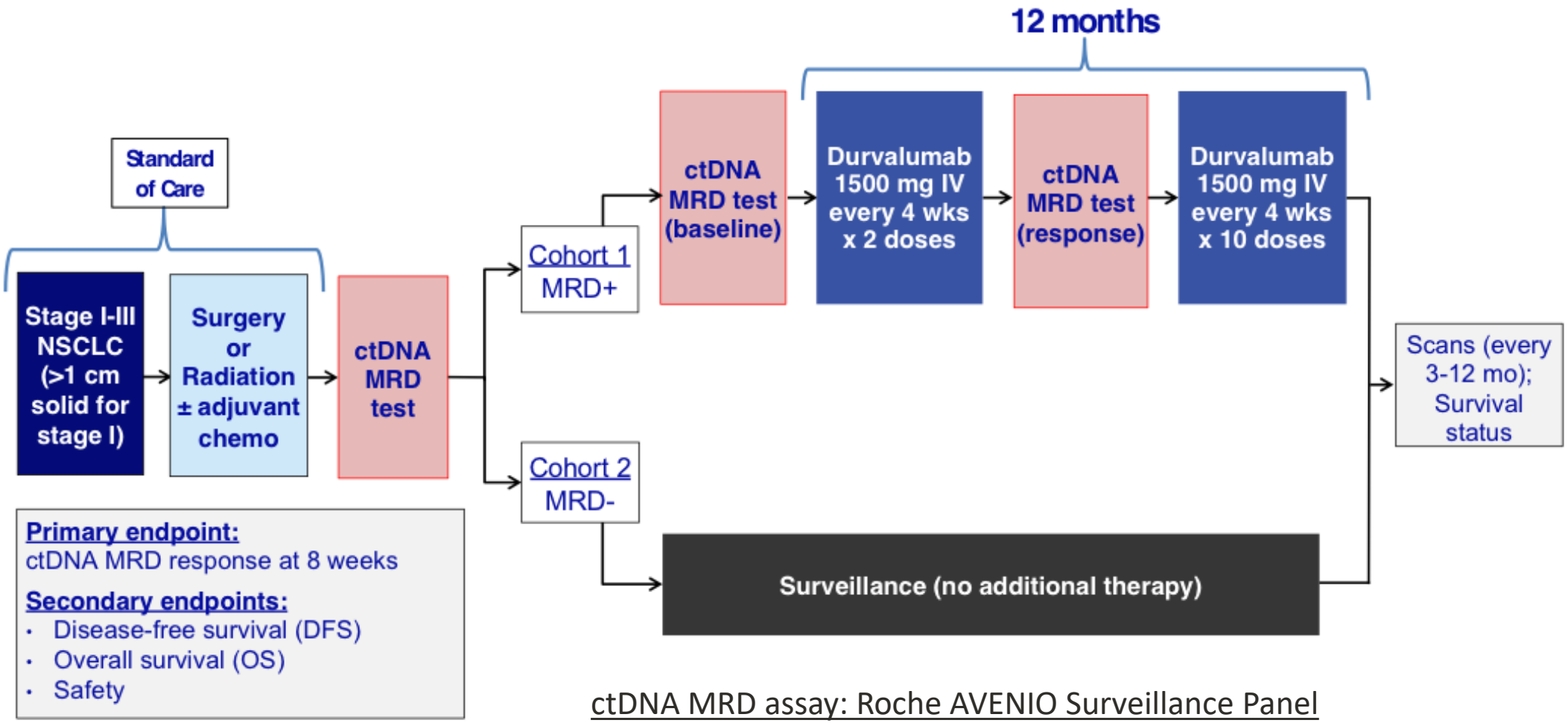
Assays not sensitive Enough yet?
(despite promising data in colorectal cancer)

ctDNA, circulating tumour DNA; MRD, minimal residual disease

Current prospective interventional trials in early stage lung cancer

Number	Prior tx	Stage	N	ctDNA-positive intervention	ctDNA-negative intervention	Phase	Primary Endpoint	Site(s)
NCT04585477	Surgery or RT +/- chemo	I-III	80	Durvalumab	None	II	ctDNA change	Stanford
NCT04585490	chemoRT + several cycles durvalumab	III	48	Durvalumab + chemo	None	II	ctDNA change	Stanford
NCT04966663	Surgery	I	66	Nivolumab + chemo vs. No treatment	None	II	RFS	Toronto

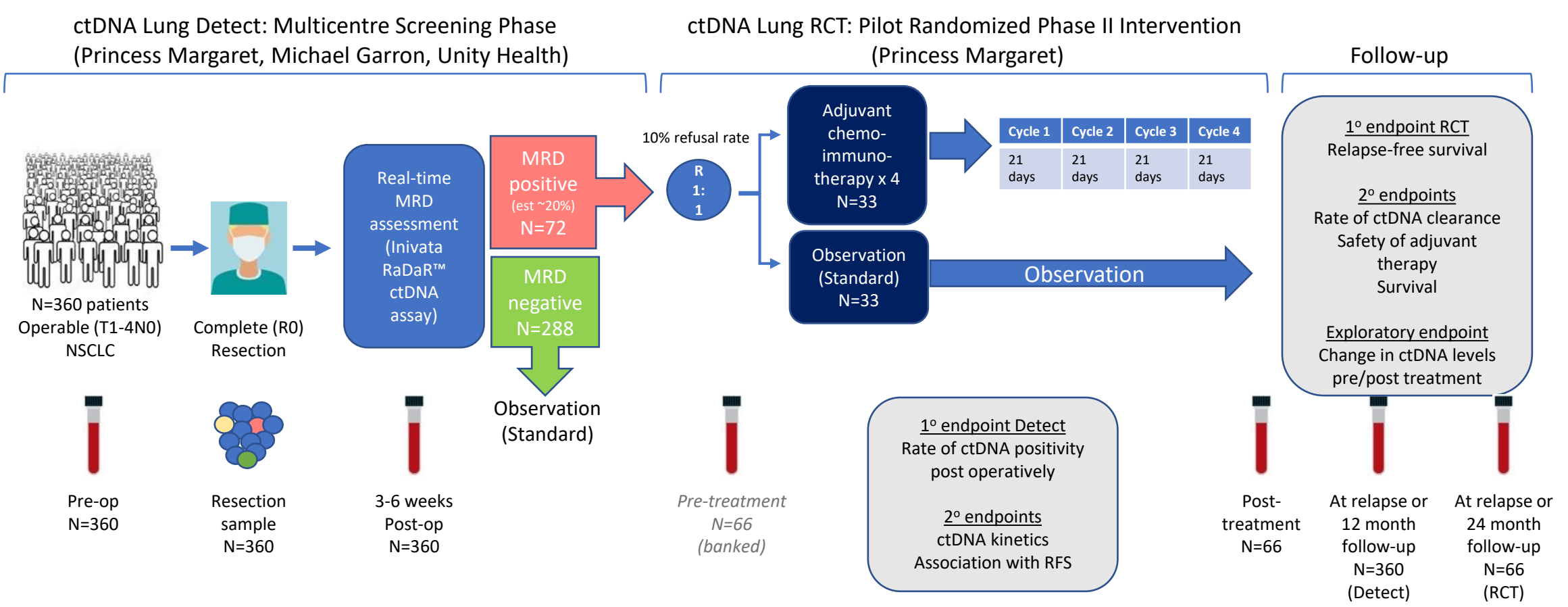
Adjuvant ctDNA-Adapted Personalized Treatment in Early Stage NSCLC (ADAPT-E) Trial



ctDNA MRD assay: Roche AVENIO Surveillance Panel

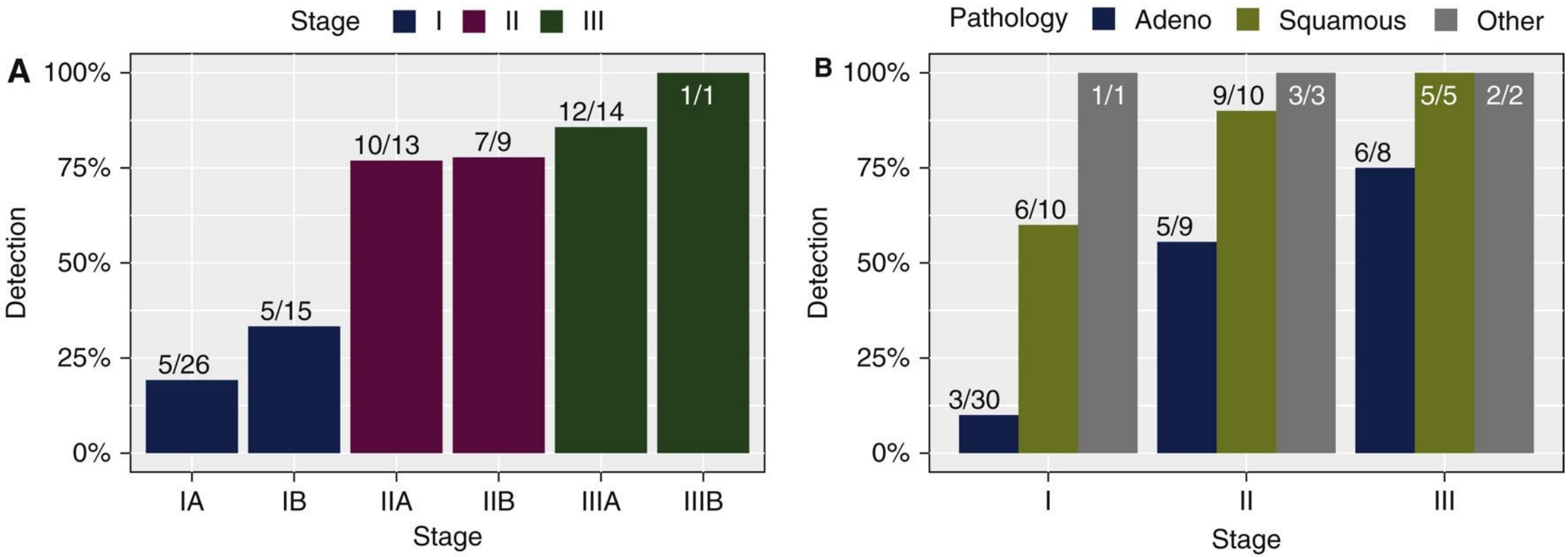
PIs: J. Neal & M. Diehn (NCT04585477)

Ongoing study in resected Stage I, multifocal (<4cm) N0
ctDNA Lung Detect and RCT: PI – Leighl
Surgical Leads: Tom Waddell, Najib Safieddine, Michael Ko



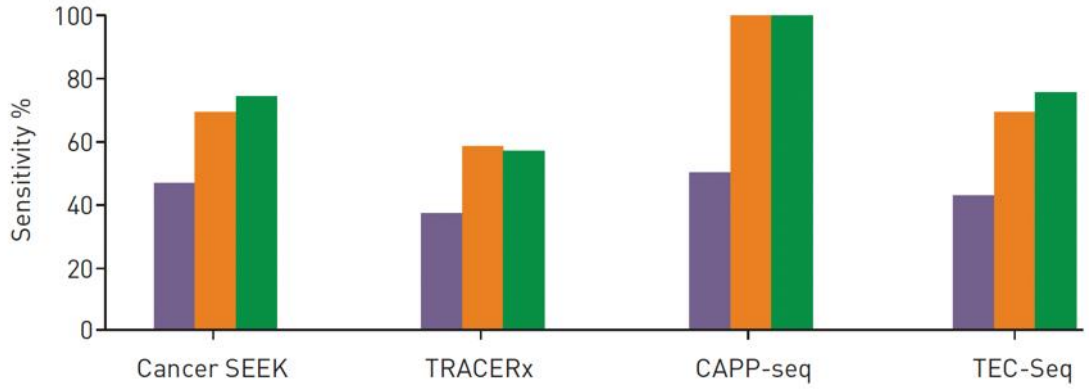
NCT05254782; NCT04966663

MRD detection T size, stage and histology dependent



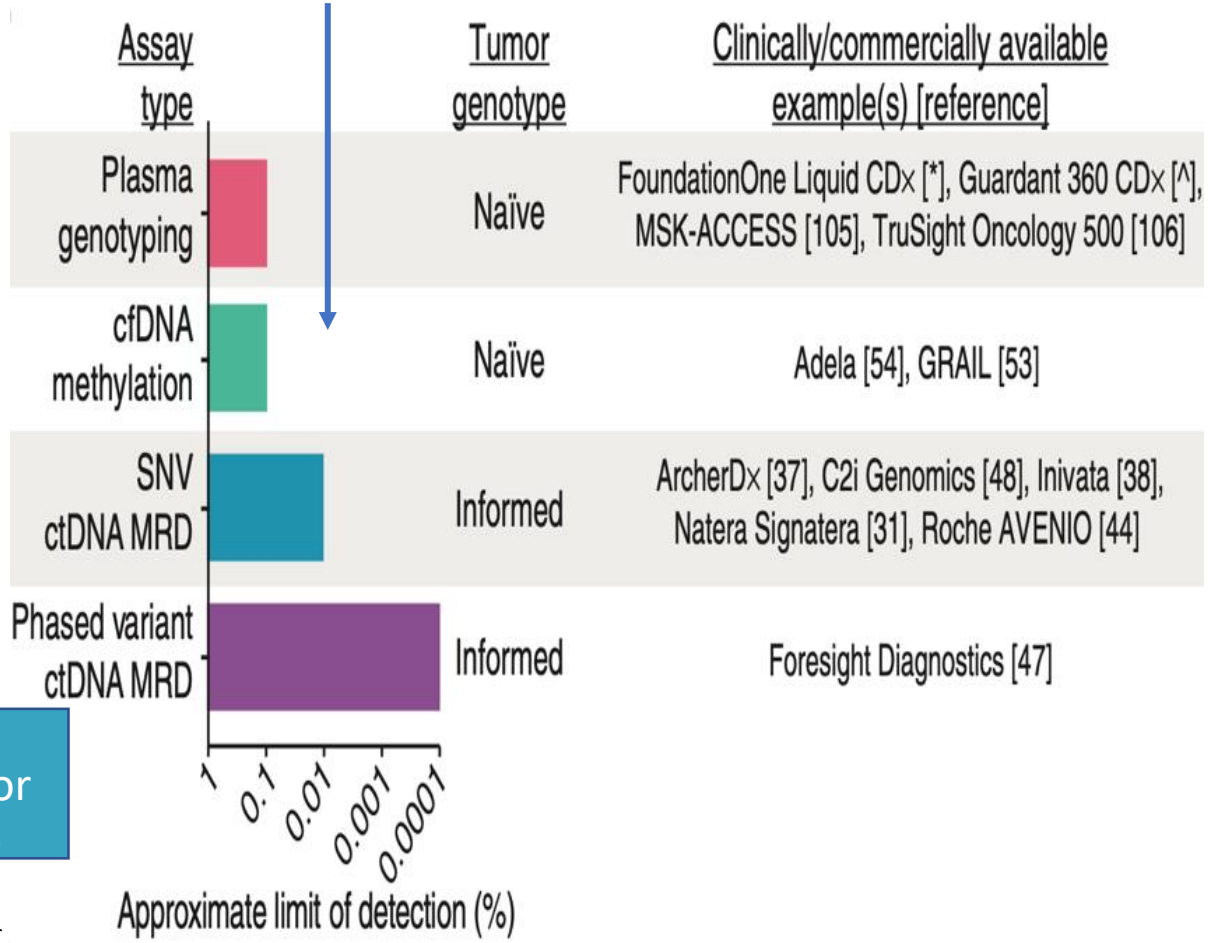
Gale et al Ann Oncol 2022

Key challenge of ctDNA assays in screening, minimal residual disease identification is the limit of detection



	Cancer SEEK#	TRACERx¶	CAPP-seq+	TEC-Seq§
Stage I	43	37	50	45
Stage II	69	59	100	72
Stage III	74	57	100	75

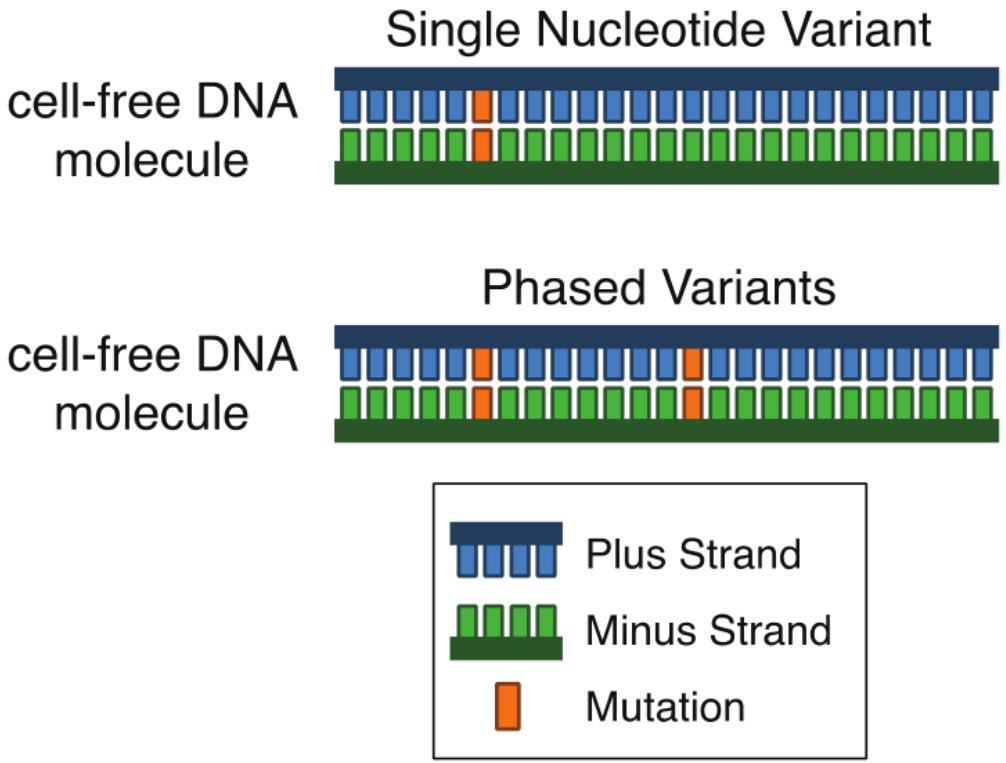
0.01% 95% lower limit of detection not enough!



Important to understand limitations of assay: pre-analytical, analytical (coverage, limit of detection (LOD), variant calling, error correction, reporting of clonal hematopoiesis (WBC correction)

Guibert et al Eur Resp Rev 2020; Dr. Max Diehn, ESMO Applications of Liquid Biopsy Series – Lung Cancer, October
Chin et al Mol Diagn Ther; Moding et al Canc Discov 2021

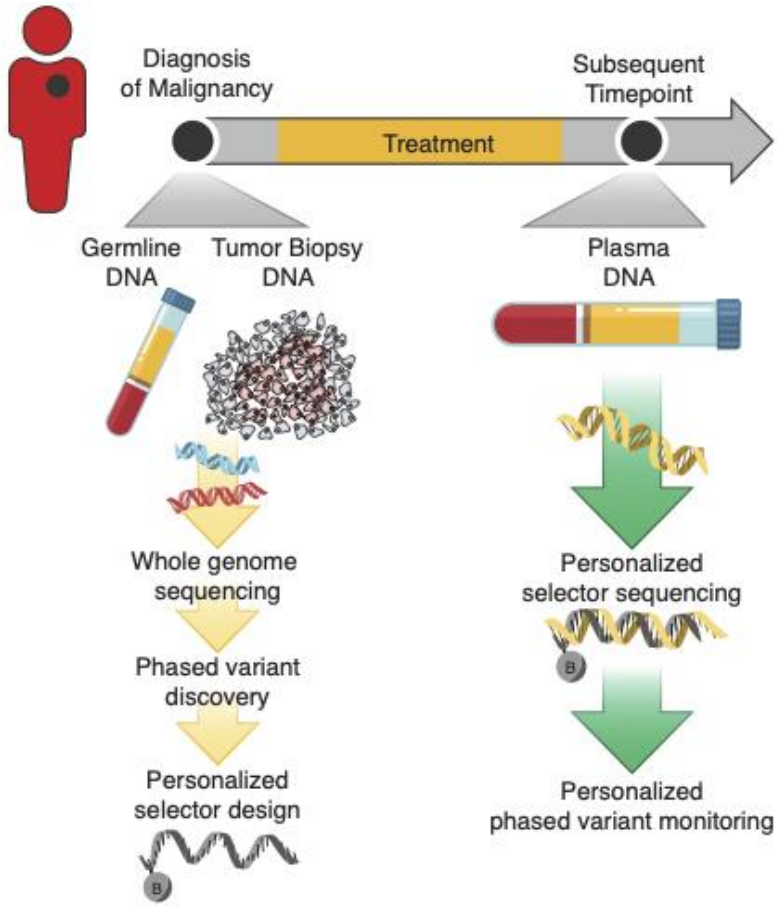
Novel ways to improve LOD: Phased Variants



Limit of Detection

~0.01%

0.01% * 0.01% ≤ 1e-6

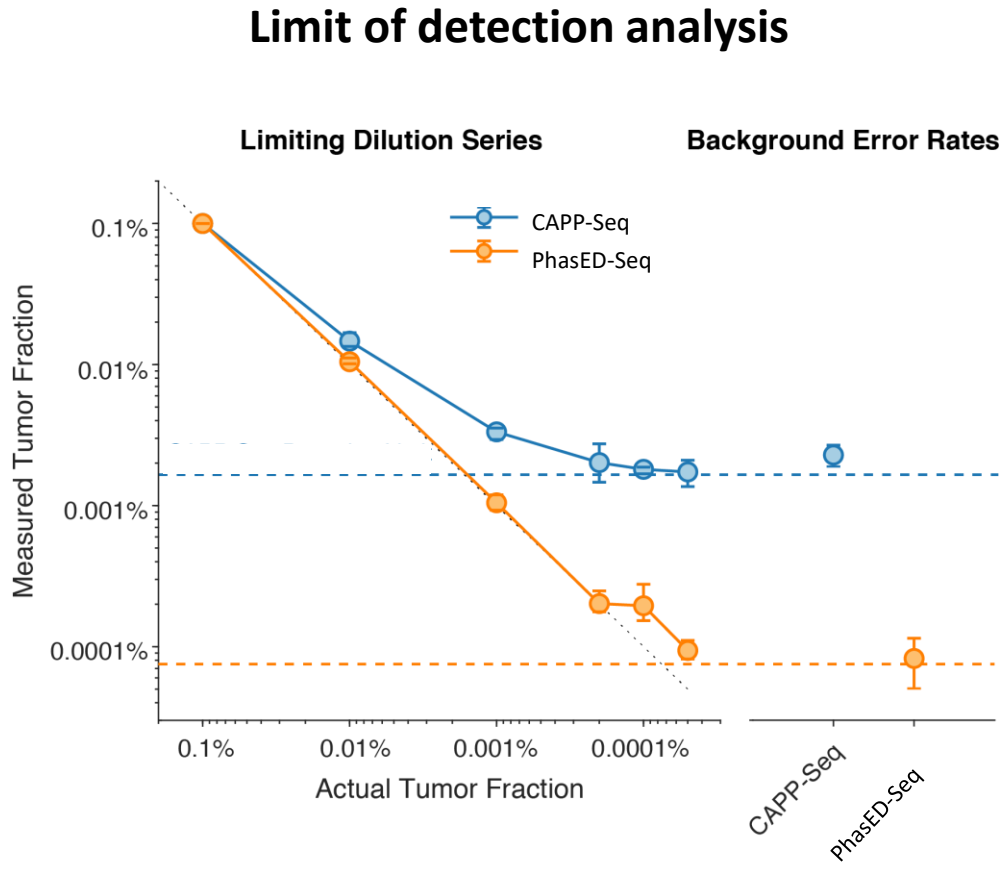


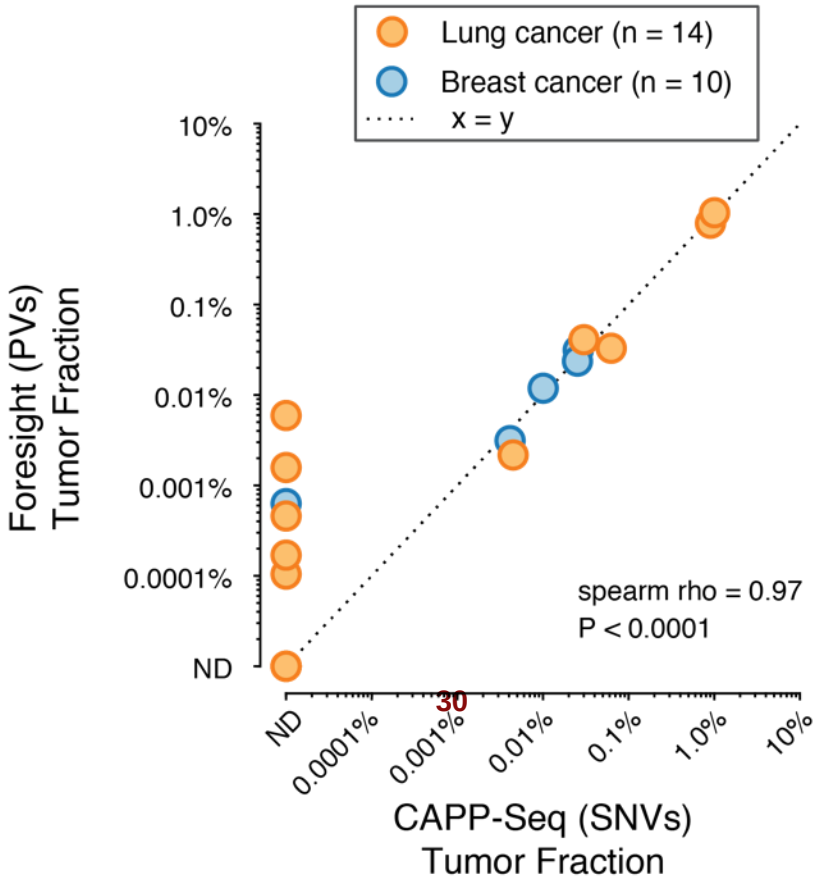
Median of ~1,000 PVs per NSCLC

Kurtz et al. *Nature Biotechnology* 2021; courtesy Dr. Max Diehn

More sensitive ctDNA Detection in Lung and Breast Cancers

Minimize risk of false negative results – potential to de-esacalate therapy?





Kurtz et al. *Nature Biotechnology* 2021

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

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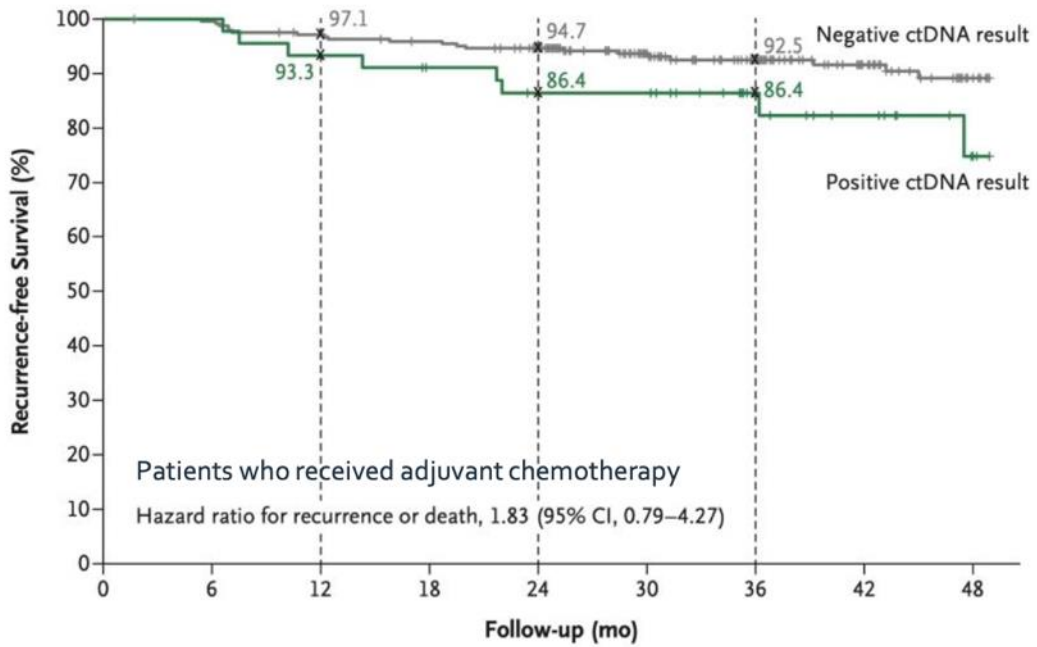
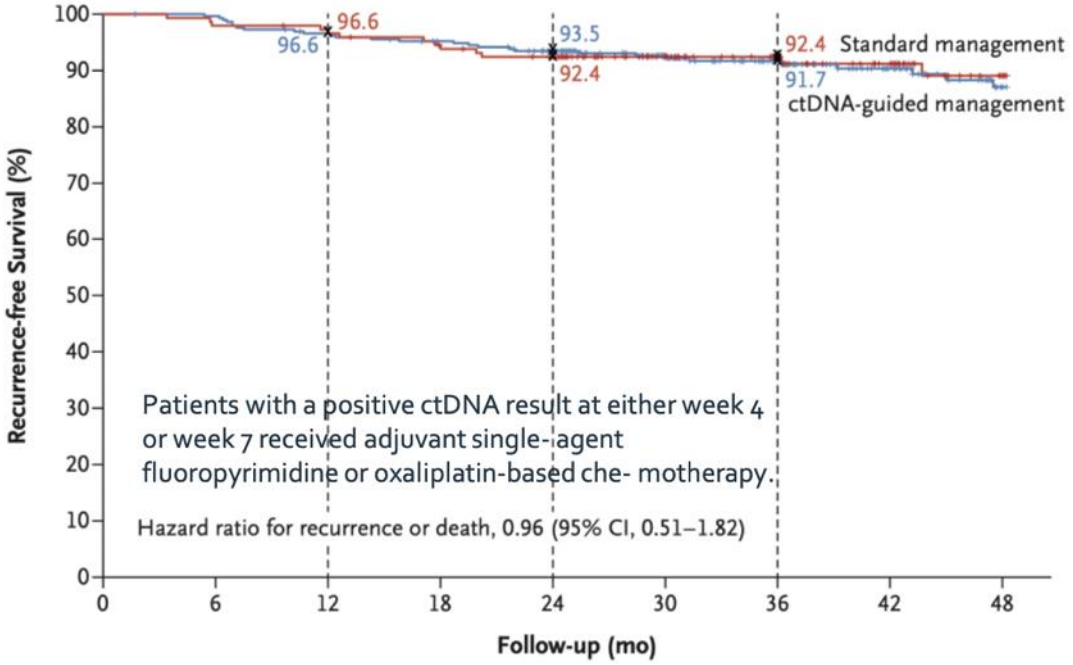
ctDNA-guided adjuvant therapy had similar outcomes to stage-directed treatment



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



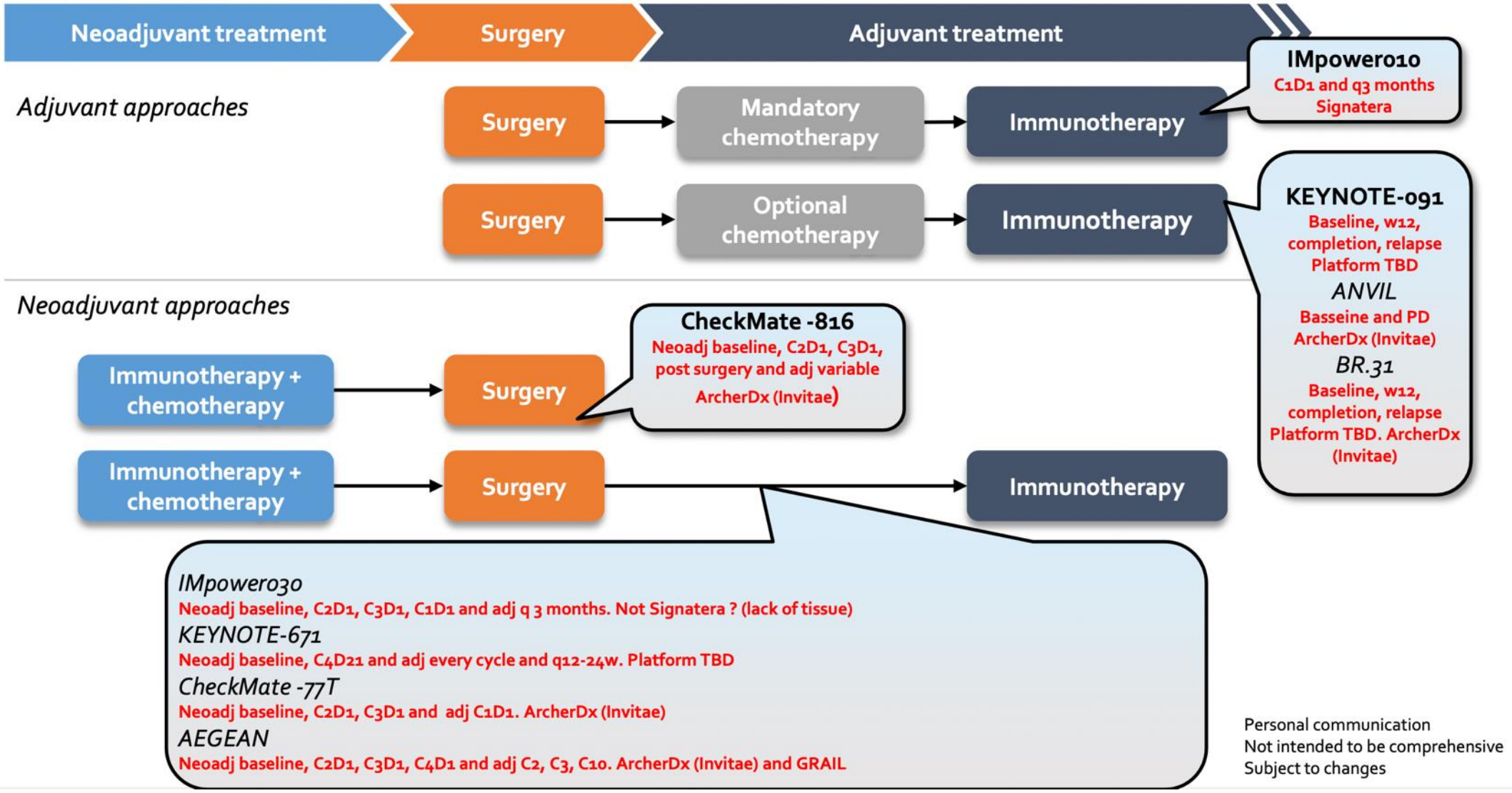
- 455 patients randomized, 302 were assigned to ctDNA-guided management and 153 to standard management
- 15% of patients in the ctDNA-guided group vs 28% in standard-management group received adjuvant chemotherapy
- ctDNA-guided management was noninferior to standard management
- Safe-Sequencing System tumor-informed personalized ctDNA assays (tumor-informed personalized approach)

Tie et al. New Engl J Med 2022; slide courtesy Dr. S. Peters ESMO 2022

Other key challenges

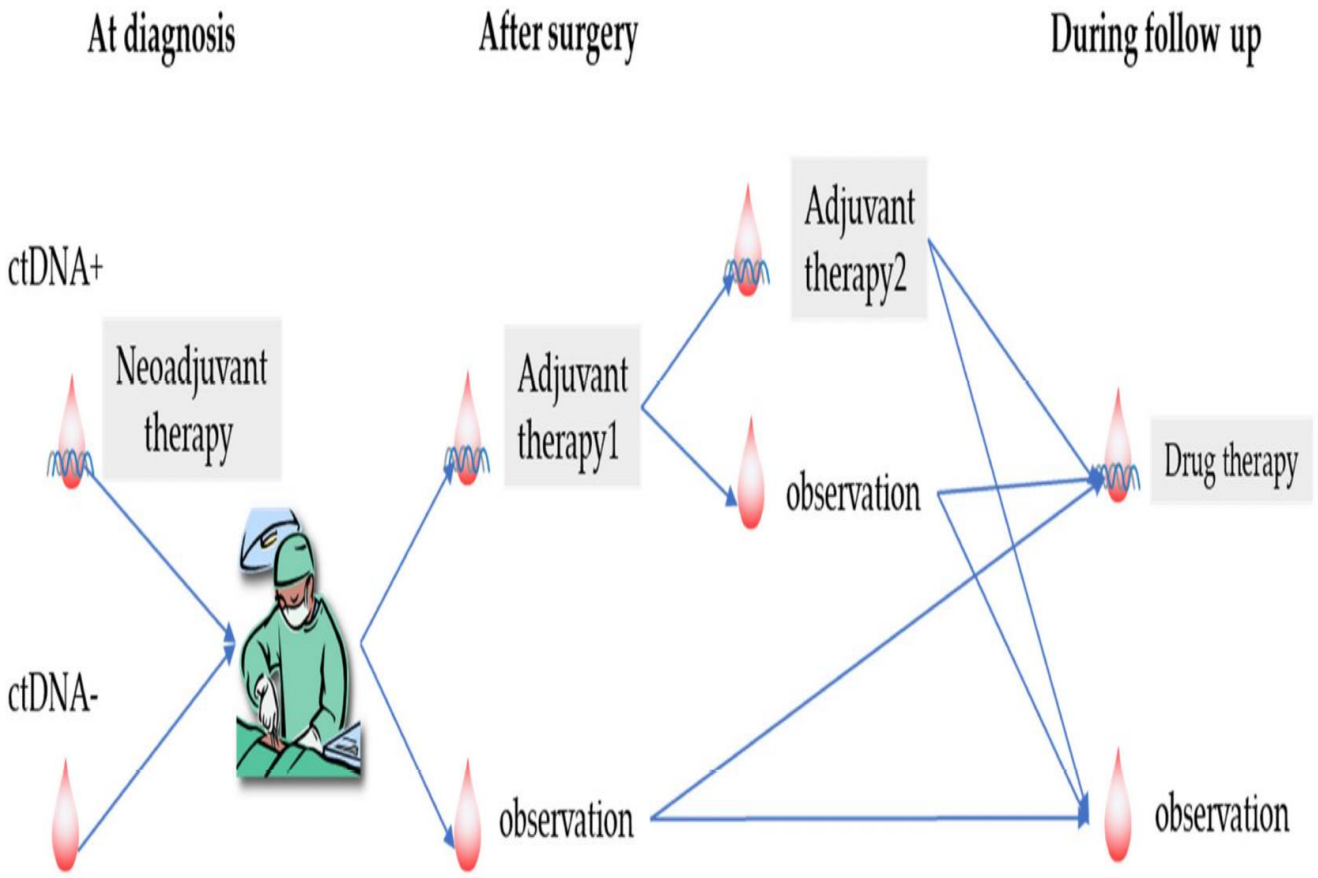
- Assay limit of detection – need lower than 0.01%!
- Need to move beyond ctDNA – TCR, methylation, fragmentomics, others
- False positives?
- Turnaround time; accessing tissue – preop versus post op selection
- When is the optimal MRD landmark time? >2 weeks, less than 12? Or any time?
- Best endpoint?
  - FDA draft guidance (May 2022) ; need multiple RCTs with DFS, EFS, OS to establish ctDNA clearance as a surrogate endpoint

More data are on the way!



Courtesy: Dr. Solange Peters, 2022

The future (but not today…)



- Minimal residual disease is a rapidly emerging biomarker in early stage NSCLC
  - Pre- and Post-treatment ctDNA MRD is strongly prognostic
  - Clinical trials are prospectively testing interventions based on ctDNA MRD
  - Next generation assays needed to improve sensitivity to decrease false negative detection rate
- We need more prospective trials to validate the use of MRD in lung cancer to increase cure

Soh et al. *Cancers*. 2021;13:4035.

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Dr. Richard Lanman
Lesli Kiedrowski
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