

ctDNA in Lung Cancer: Current State and Future Perspective

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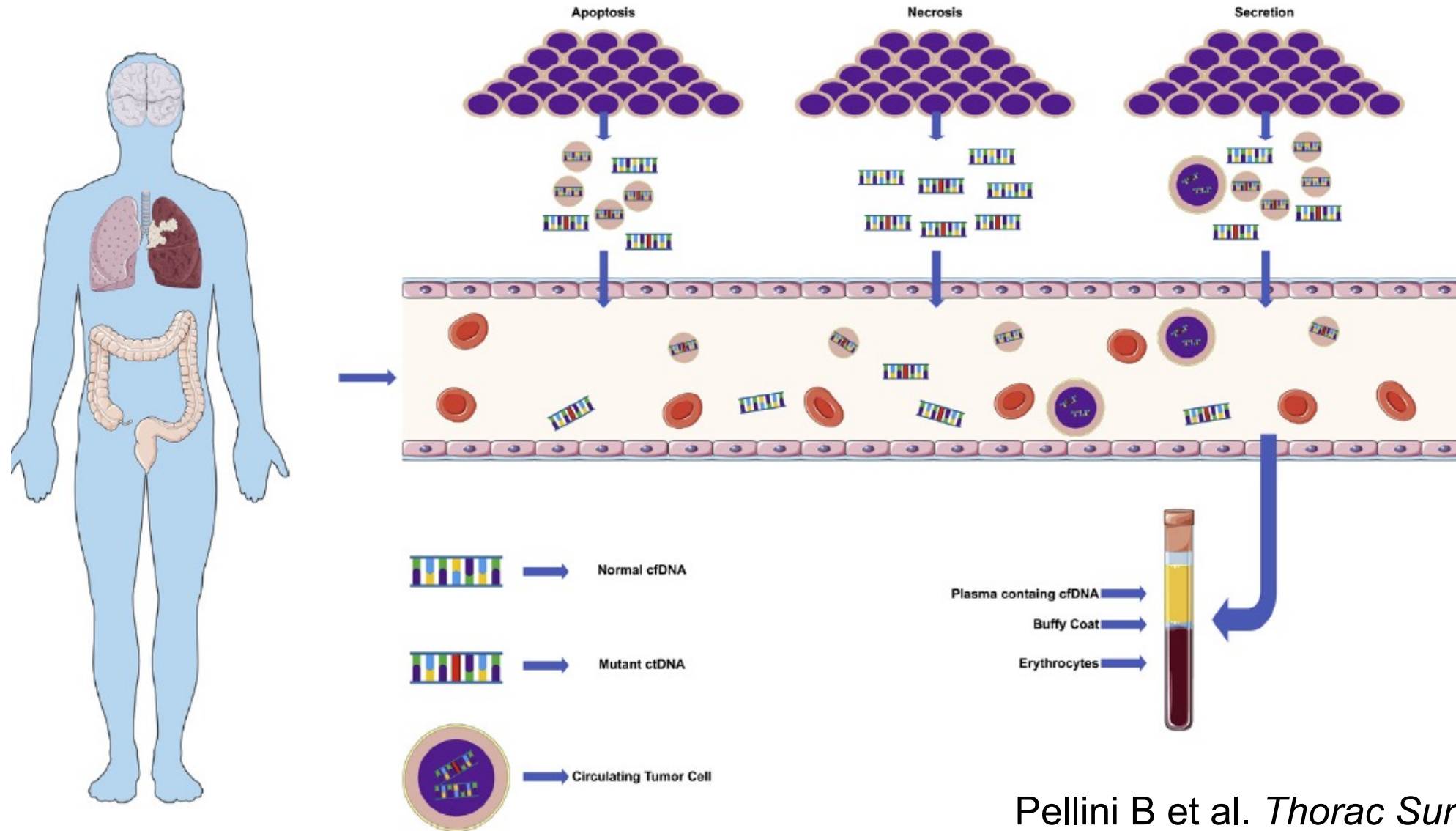


Outline



- ctDNA definition
- Tumor-informed vs. tumor-naïve assays
- ctDNA applications in oncology:
 - Treatment Monitoring
 - Minimal residual disease (MRD) detection

Tumor-derived fragments of nucleic acids identified in the blood are called circulating tumor DNA (ctDNA)



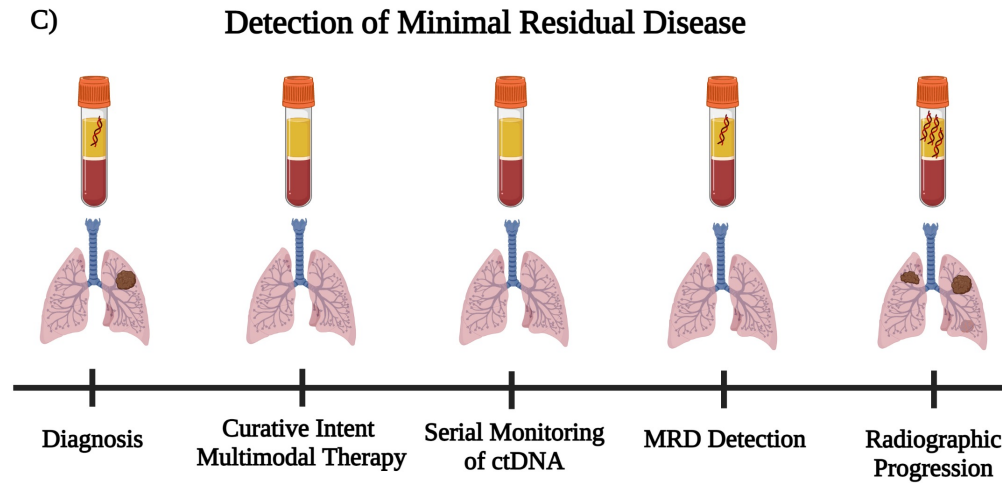
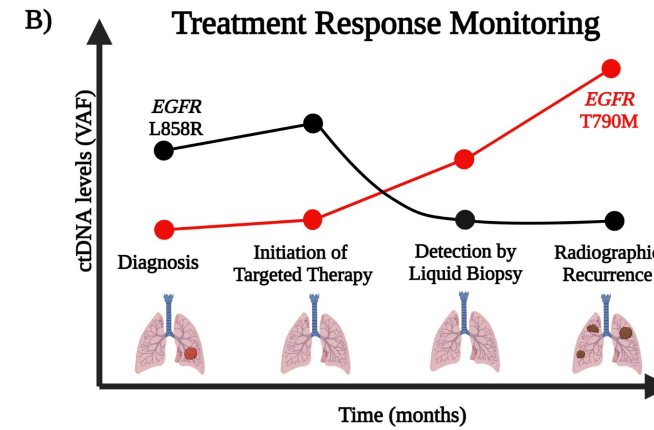
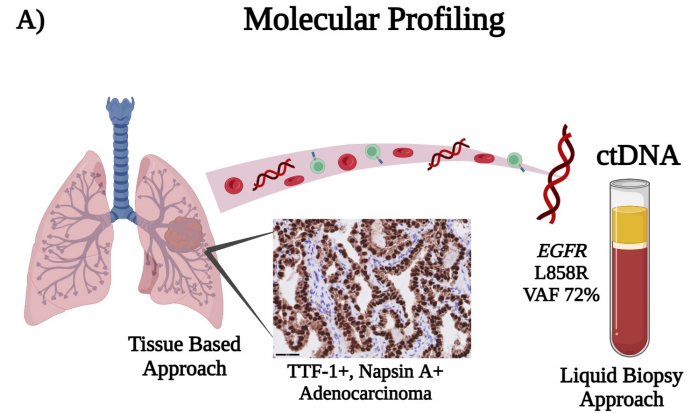
Pellini B et al. *Thorac Surg Clin.* 2020



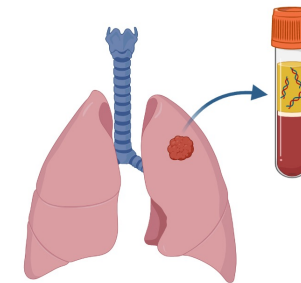
Tumor-informed vs. tumor-naïve assays

Tumor-Informed	Tumor-naïve
Requires tissue biopsy	No need for biopsy
Personalized assay	Off the shelf assay
Longer turnaround time	Shorter turnaround time
Does not account for tumor heterogeneity	Can detect clonal variants that emerge during follow-up
Potential for better sensitivity and specificity	Variable sensitivity and specificity

ctDNA applications in oncology



D) Early Cancer Detection



Outline



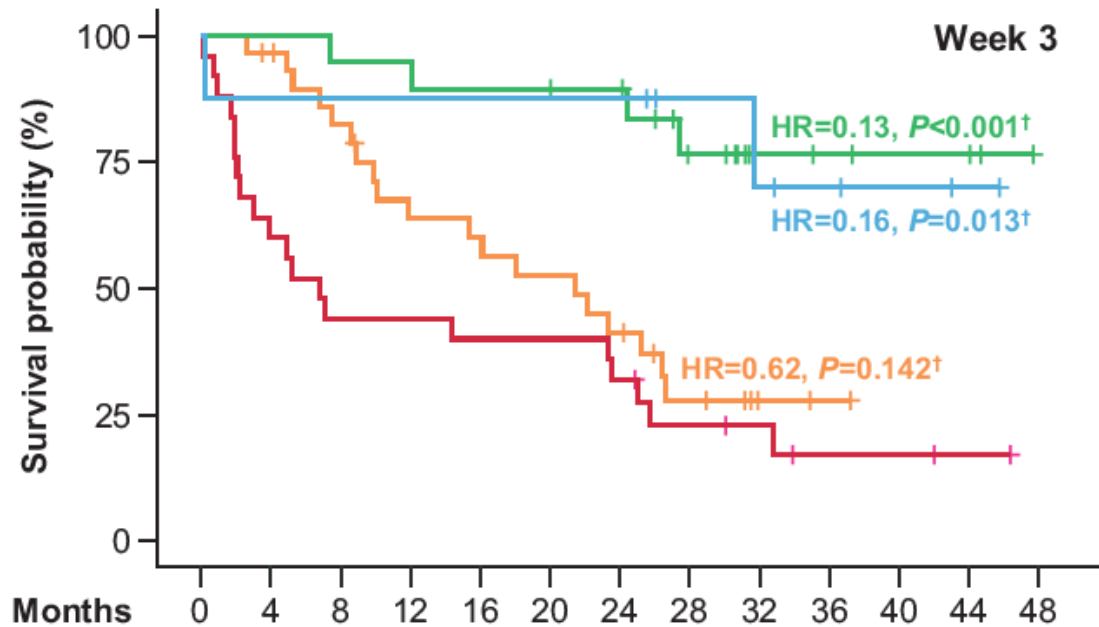
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ctDNA decrease $\geq 90\%$ at week 3 or 9 during cemiplimab treatment is associated with improved OS

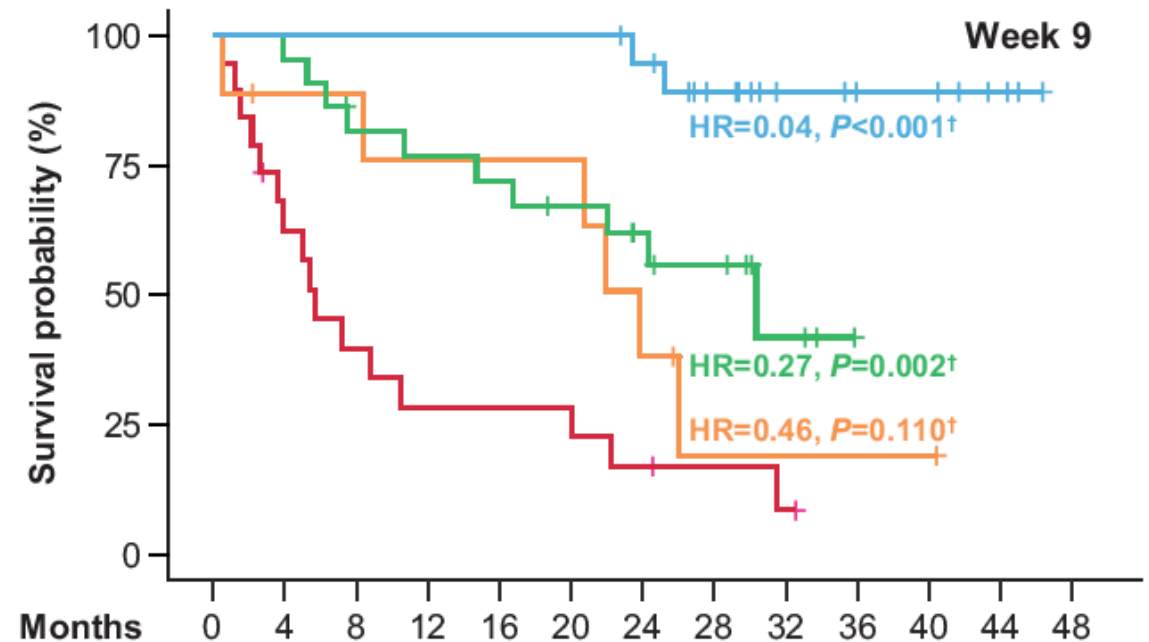


Advanced NSCLC
Tumor-informed assay (Signatera™ & FoundationOne Tracker)

Cemiplimab



Cemiplimab



N=82

ctDNA percent decrease from baseline

- Increase (n=25)
- Decrease ($< 90\%$; n=30)
- Decrease ($\geq 90\%$ – $< 100\%$; n=19)
- Clearance (100%; n=8)

N=70

ctDNA percent decrease from baseline

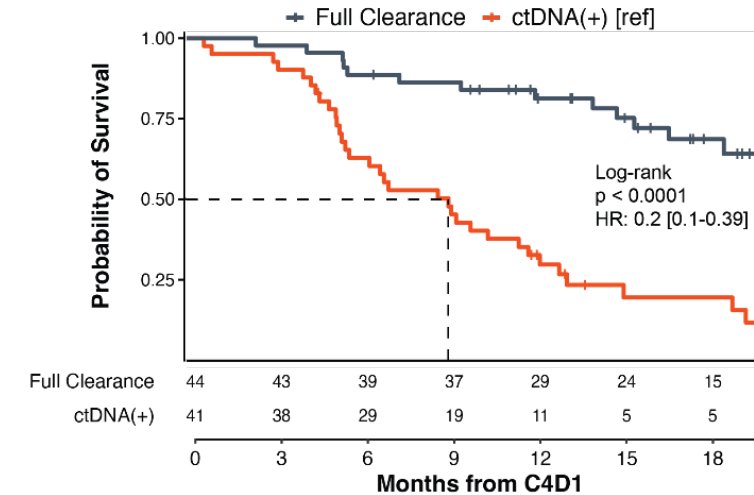
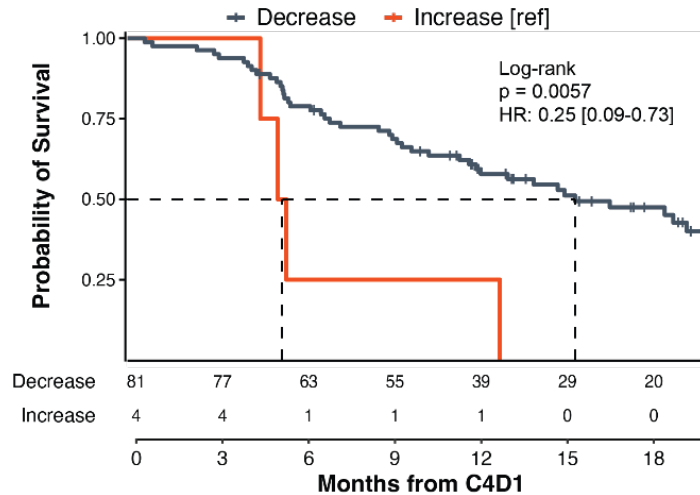
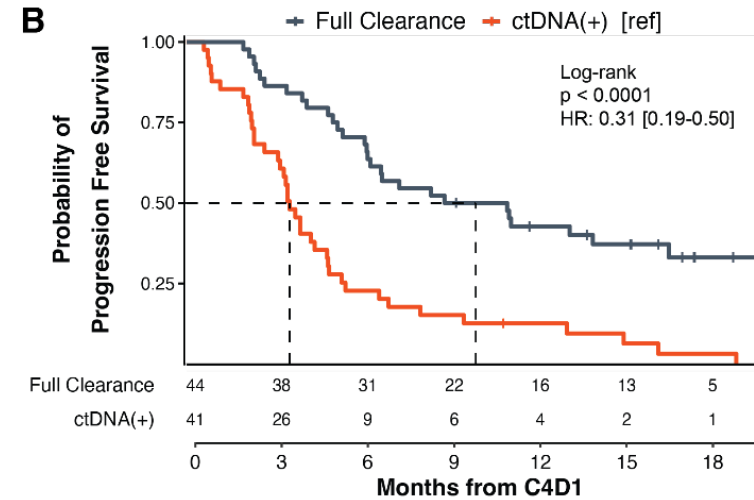
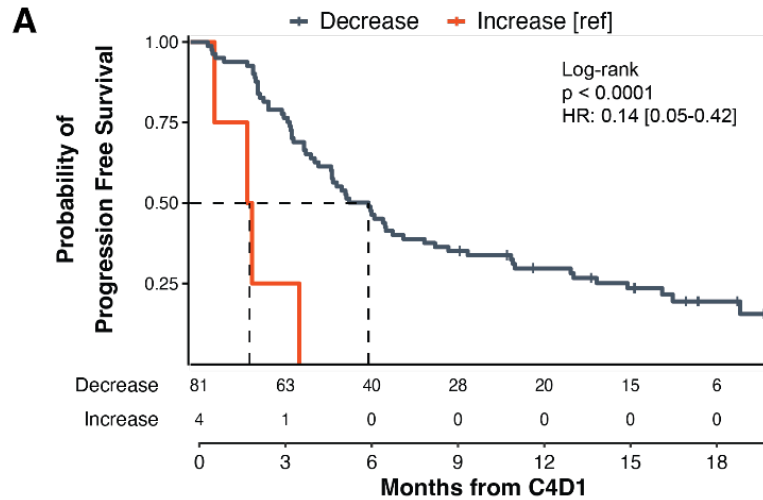
- Increase (n=19)
- Decrease ($< 90\%$; n=9)
- Decrease ($\geq 90\%$ – $< 100\%$; n=22)
- Clearance (100%; n=20)

Vokes N et al. 2023 ASCO Annual Meeting.

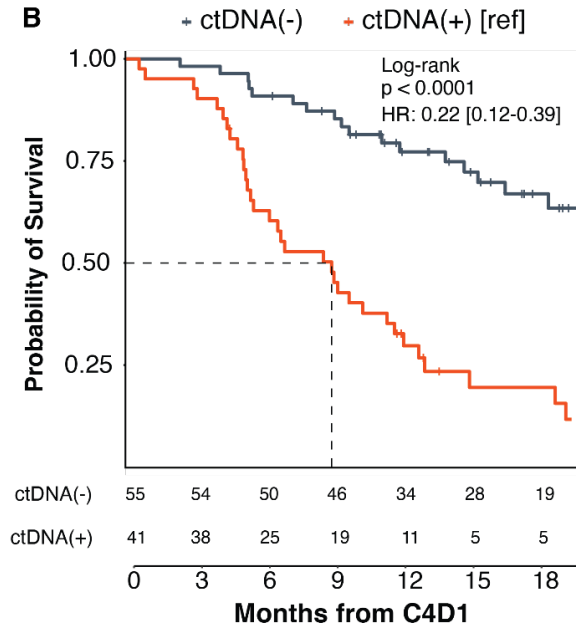
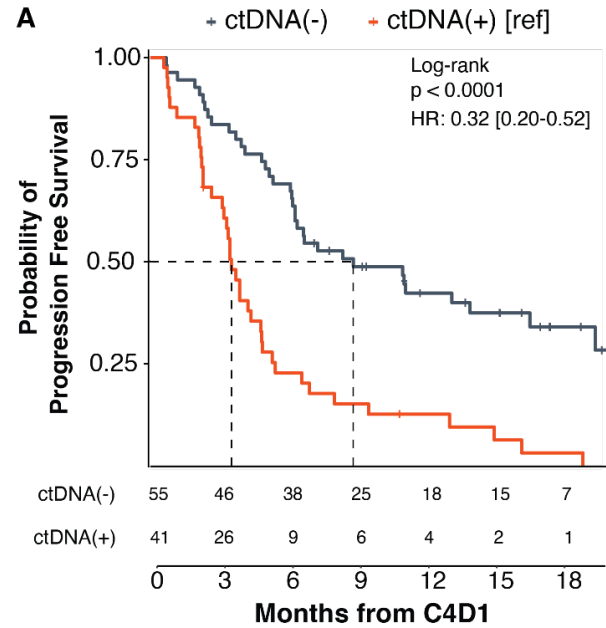
Circulating Tumor DNA Monitoring on Chemo-immunotherapy Informs Outcomes in Advanced Non-Small Cell Lung Cancer



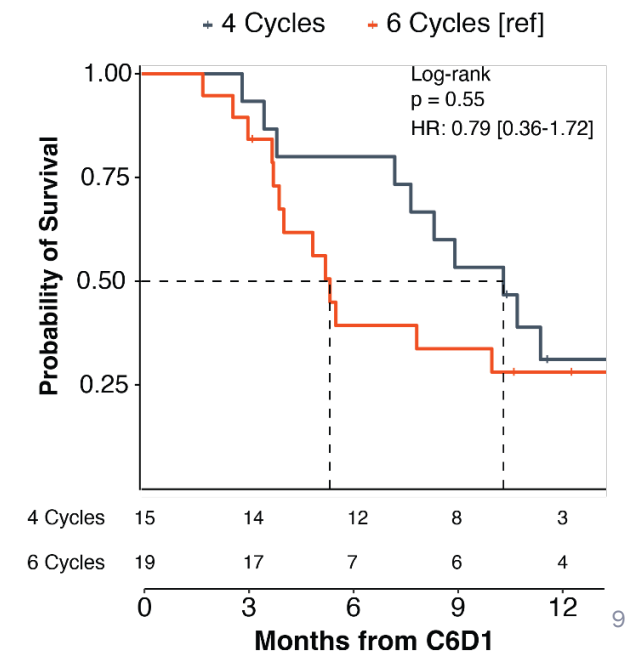
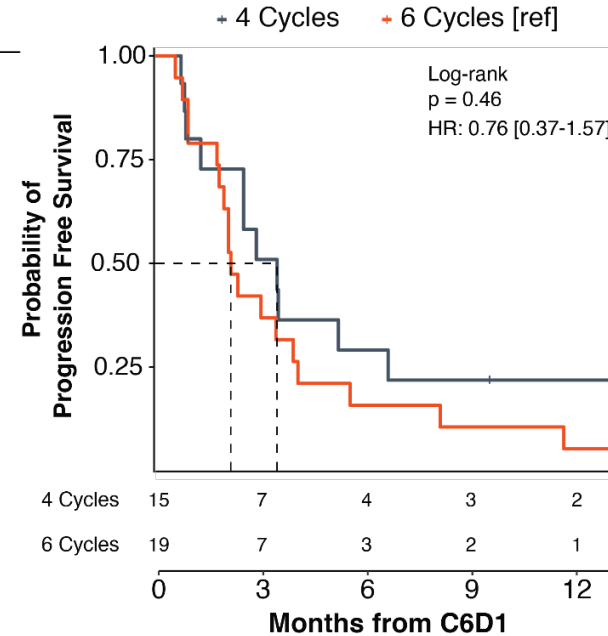
Tumor-informed assay
(FoundationOne Tracker)



ctDNA detection on chemolO can inform subsequent outcomes on IO maintenance, even without baseline ctDNA analysis



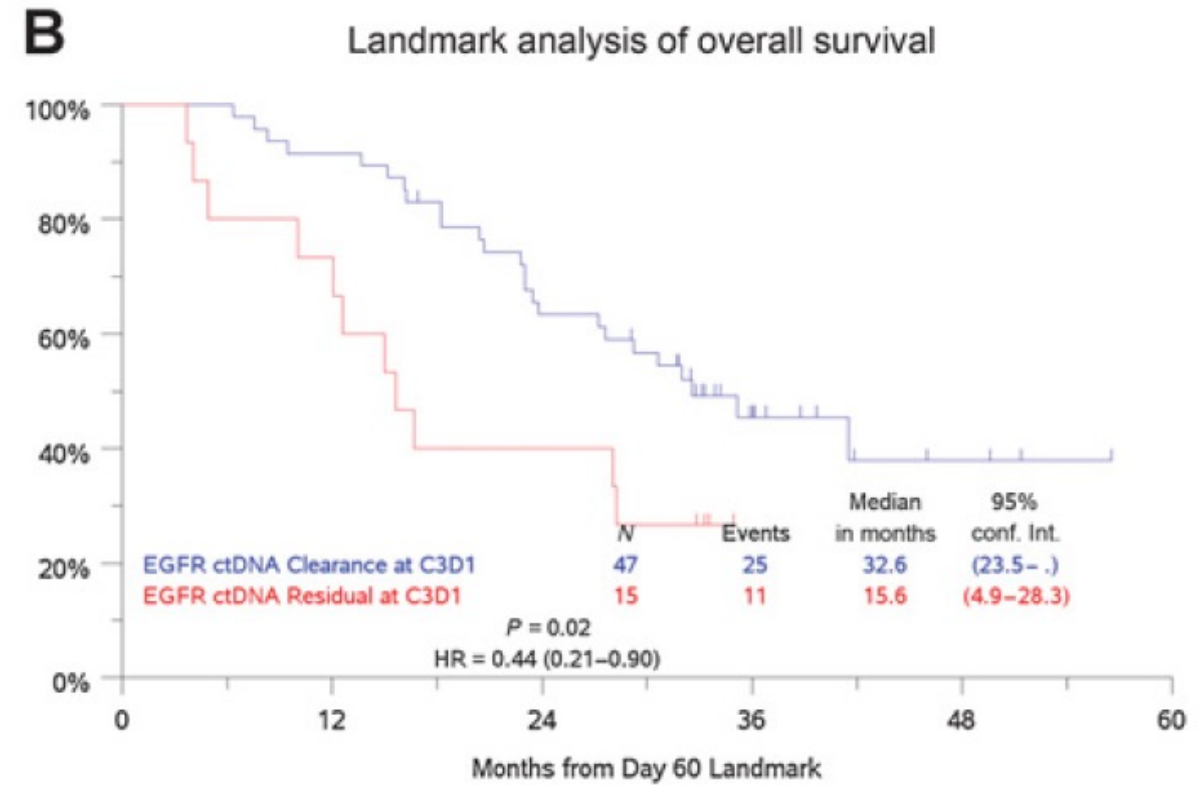
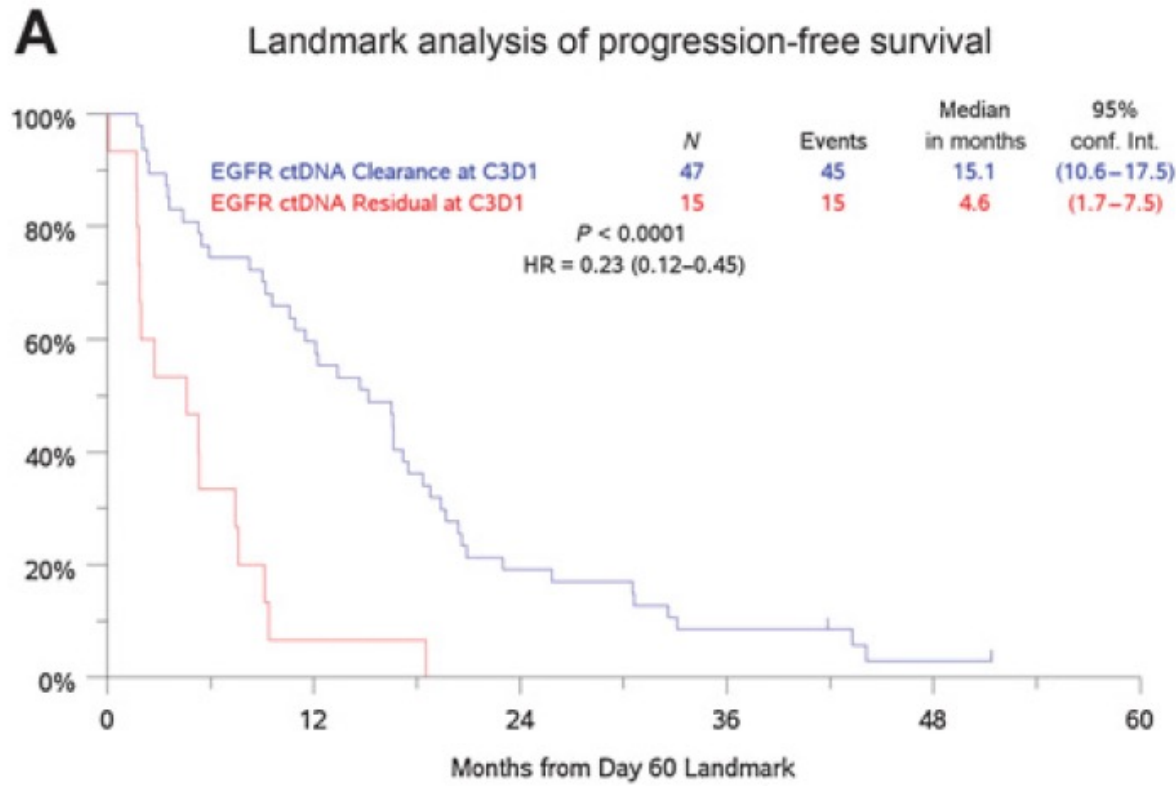
Additional cycles of induction therapy are not associated with improved outcomes in patients with ctDNA detection at C4D1



Patients with undetectable *EGFR* 8 weeks after treatment start had better PFS and OS



Stage IV NSCLC
Tumor-naïve assay
(Guardant 360)

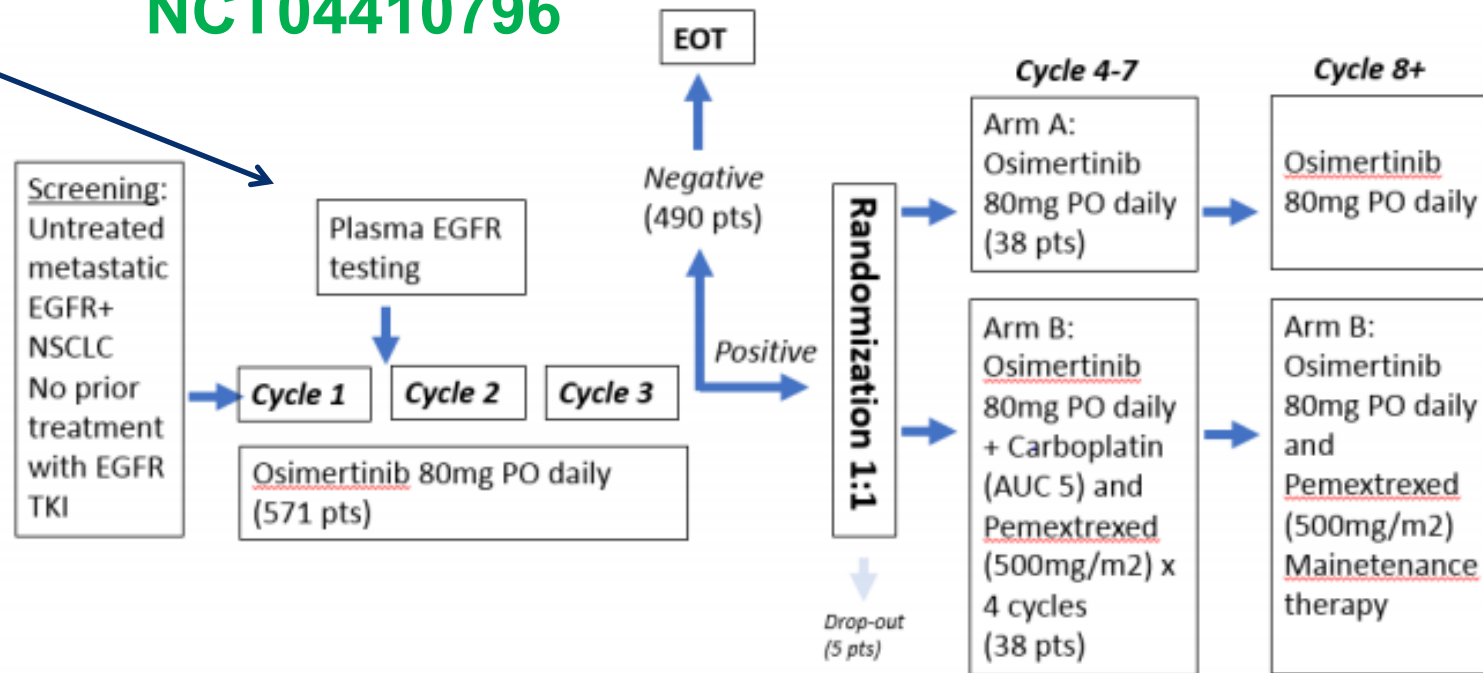




Treatment escalation based on ctDNA detection is under investigation for patients with *EGFR* mutations

3 weeks into therapy

NCT04410796



Treatment plan: All patients will receive osimertinib 80mg orally daily. Patients enrolled in Arm B will receive Carboplatin (AUC 5 IV q 3 weeks) and Pemetrexed (500mg/m² IV q 3 weeks) for a total of 4 cycles followed by pemetrexed maintenance from cycle 8 onwards.

Total enrollment: Approximately 571 patients will be screened. 80 will be eligible for randomization and treatment consent. 76 will be randomized.

Time to completion: 5 years

National Study PI: Helena Yu, MD (MSKCC); Moffitt PI: Bruna Pellini, MD

Outline



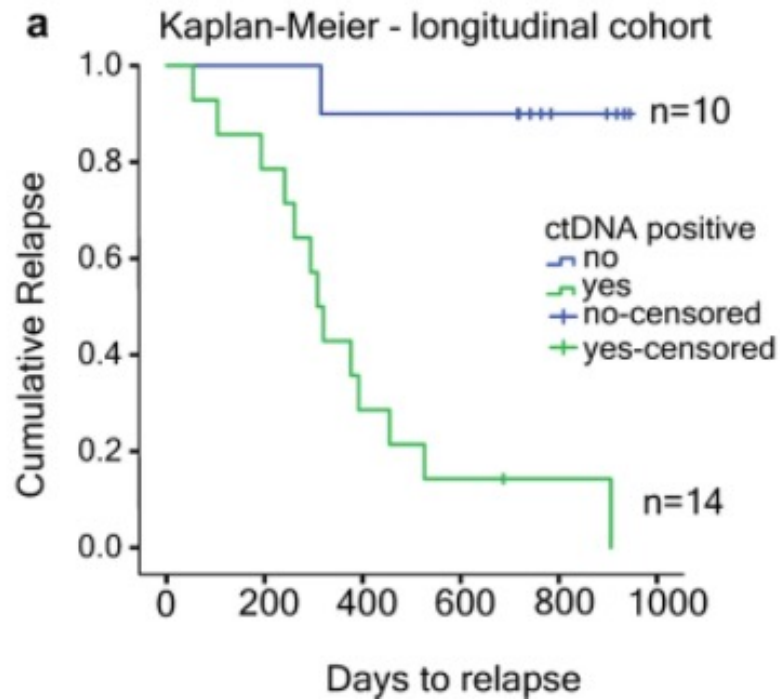
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ctDNA can detect minimal residual disease (MRD) and it is a prognostic biomarker



Stages I-III NSCLC

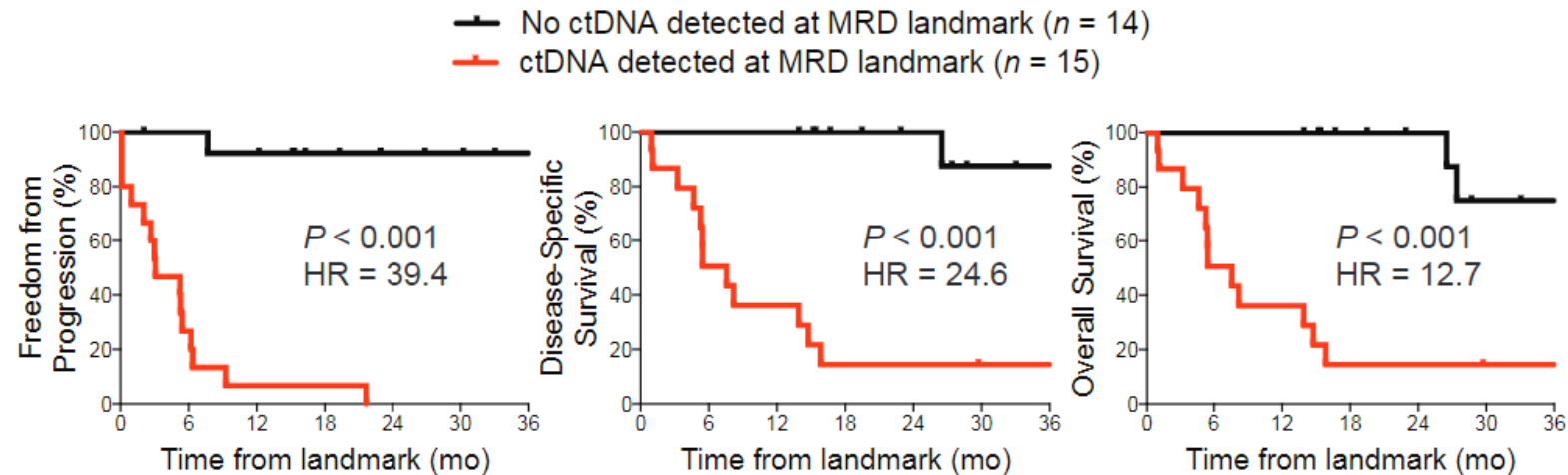
Tumor-informed assay
(Signatera™)



Stages I-III NSCLC

Tumor-naïve assay
(CAPP-Seq)

NSCLC patients analyzed at the MRD landmark



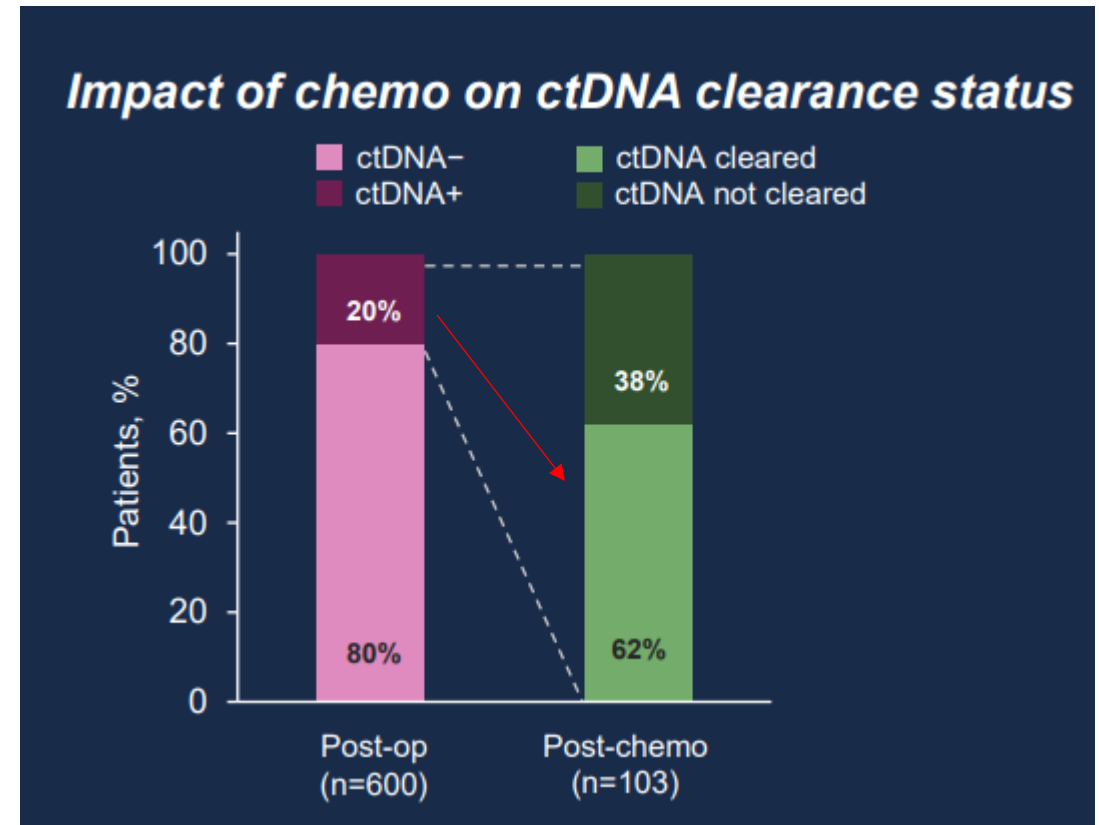
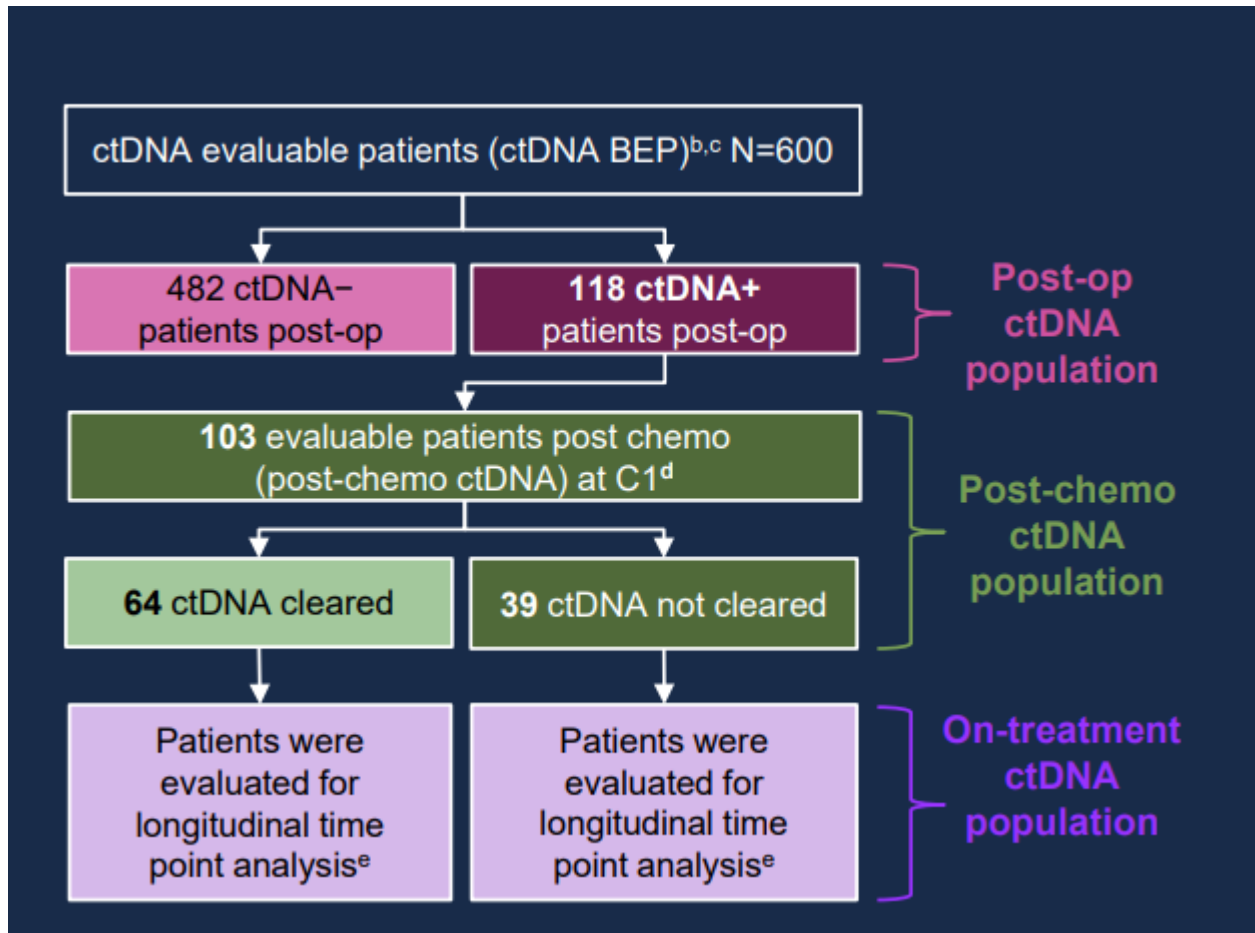
Abbosh C et al. *Nature*. 2017

Chaudhuri A et al. *Cancer Discov*. 2017

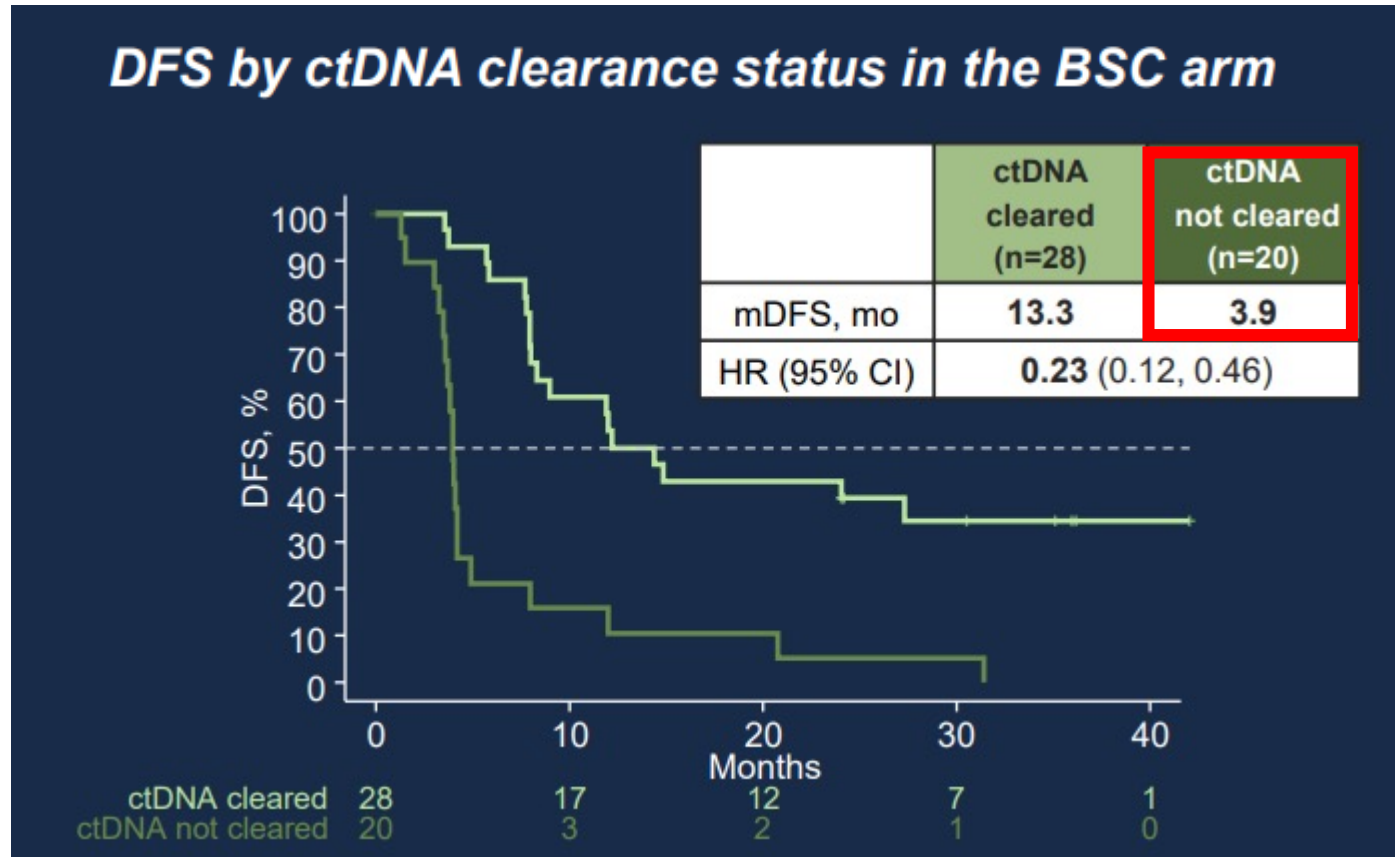
IMpower010: ctDNA Status in Patients With Resected NSCLC Who Received Adjuvant Chemotherapy Followed by Atezolizumab or Best Supportive Care



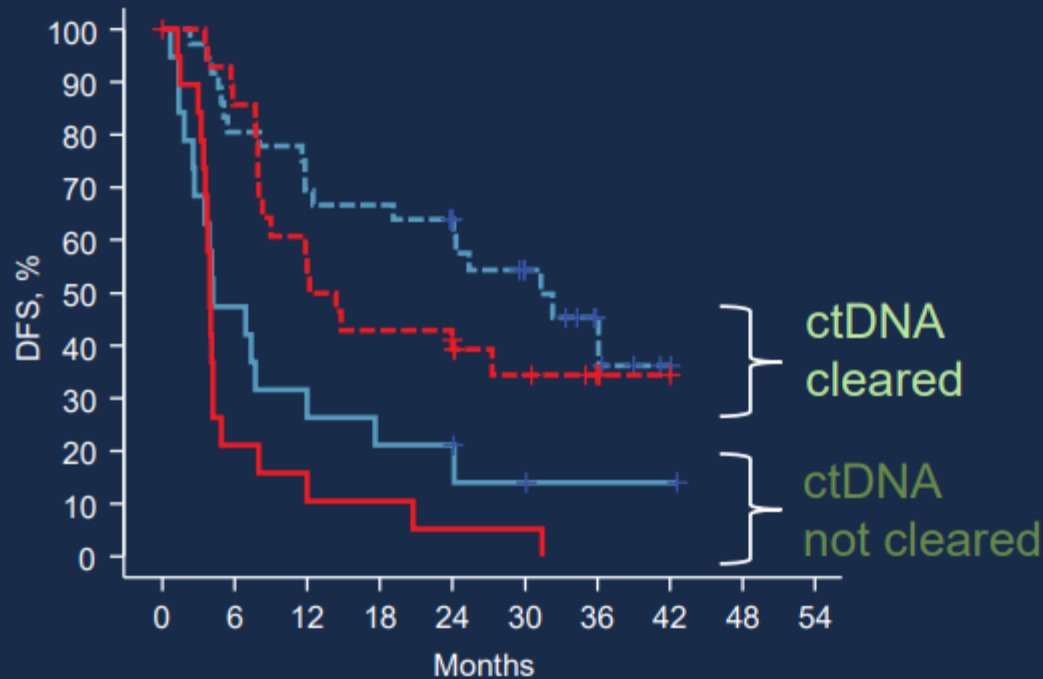
Adjuvant chemotherapy cleared ctDNA in ~62% of patients



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



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



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

Post-Chemo
clearance
status

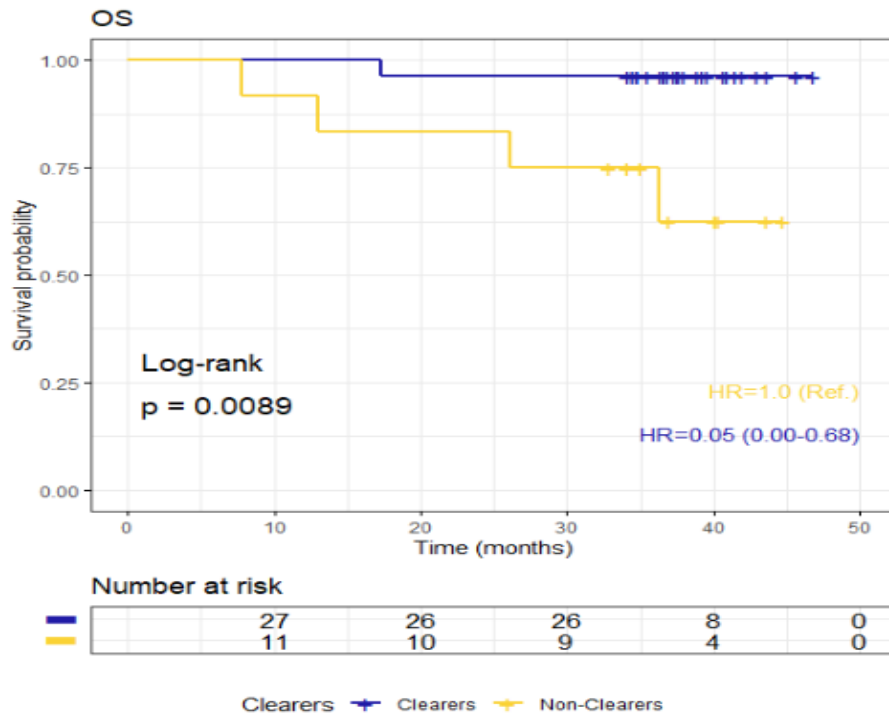
ctDNA cleared	Atezo (n=36)	BSC (n=28)
mDFS, mo	31.3	13.3
HR (95% CI)	0.7 (0.37, 1.34)	

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

ctDNA clearance after neoadjuvant chemIO correlates with clinical outcomes

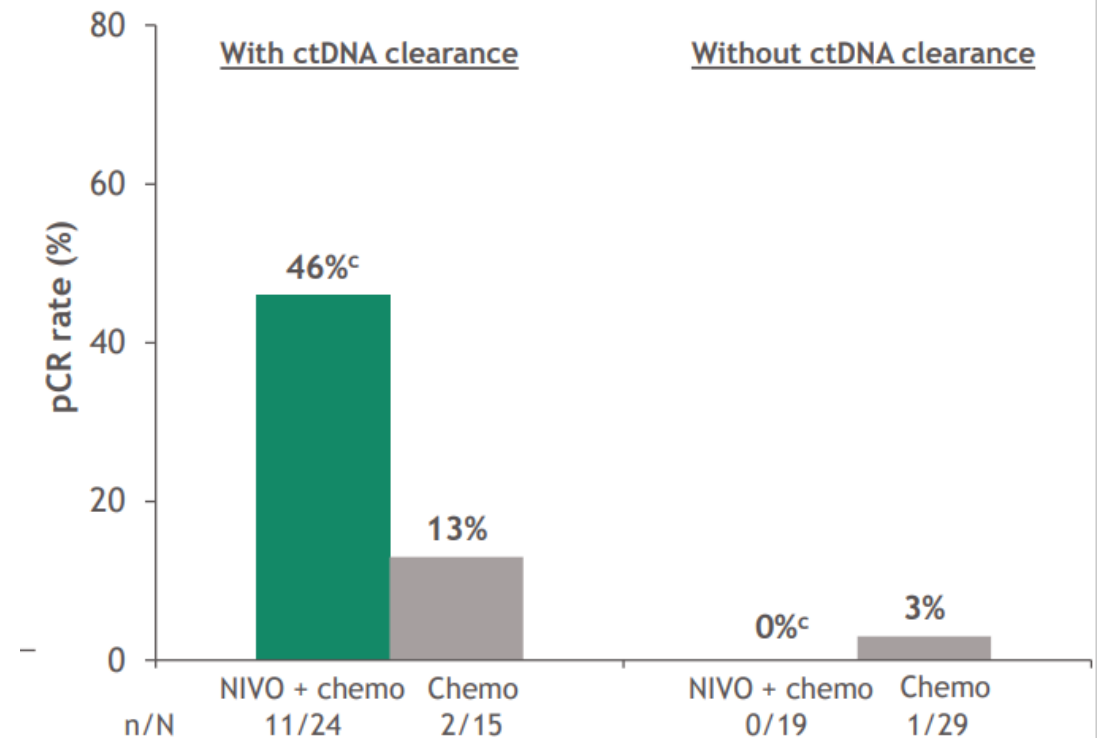


NADIM



CM816

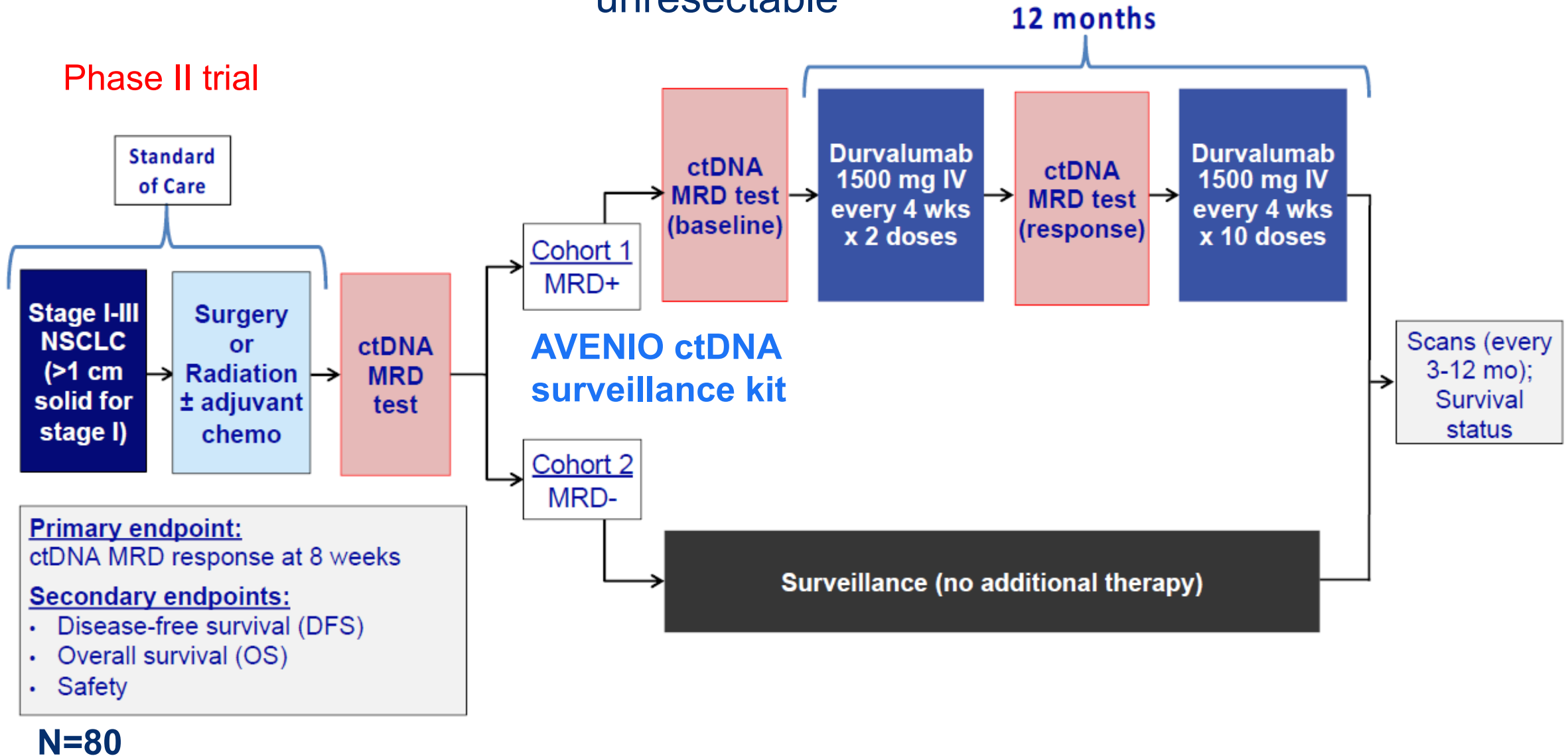
ctDNA clearance and pCR rates



ctDNA clearance at the end of neoadjuvant treatment was associated with improved OS

Romero A et al. *J Thorac Oncol.* 2021:OA20.02
Forde P et al. *Cancer Res.* 2021: CT003

Prospective ctDNA MRD trial for patients with NSCLC stages I-III resectable & unresectable

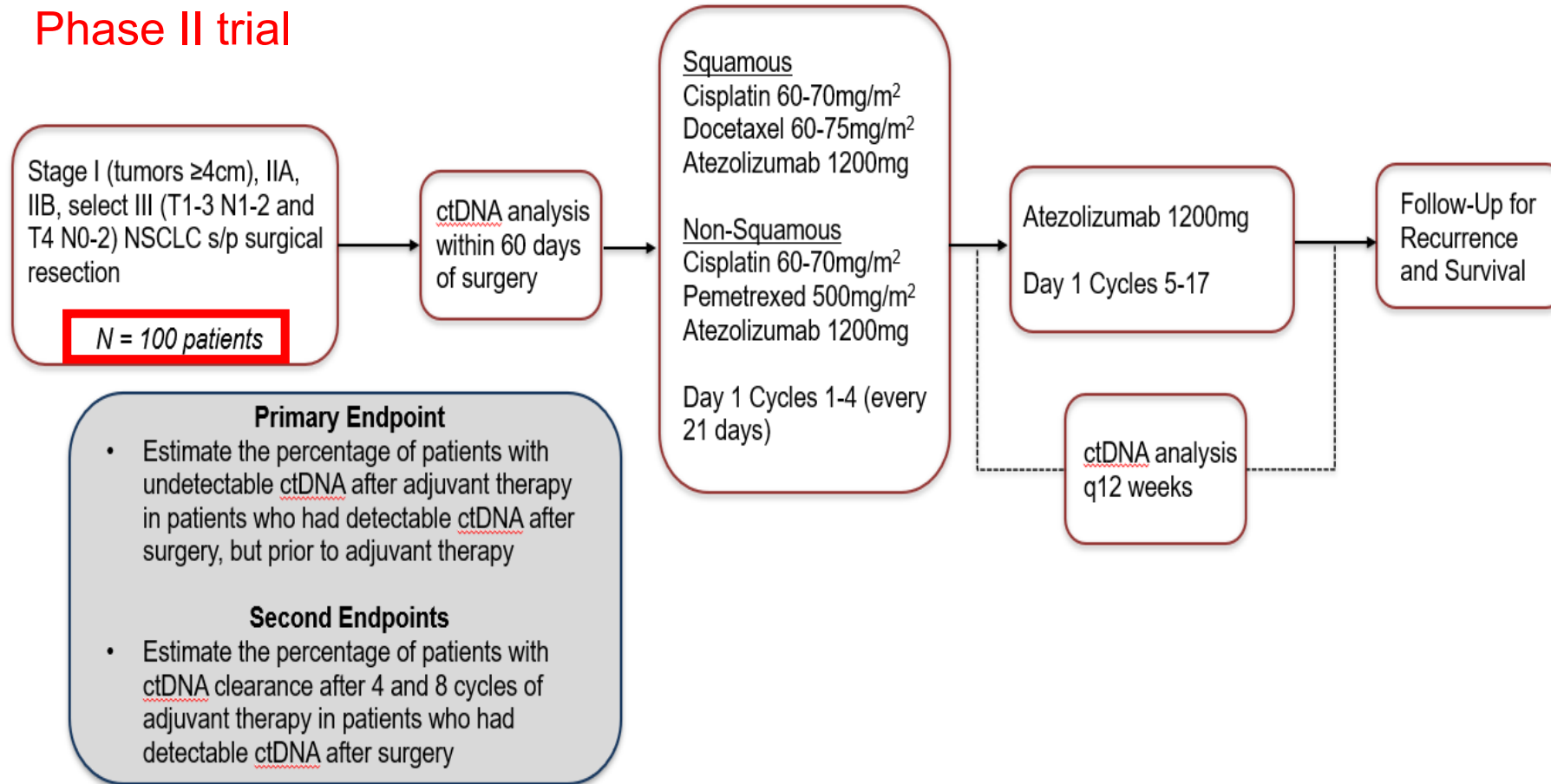


Prospective ctDNA MRD trial for patients with resectable NSCLC stages I-III



BTCRC LUN19-396

Phase II trial



Slide adapted from G. Durm at 2023 Hawaii Lung Cancer Summit.



Take home points

- Multiple technologies are available for plasma genotyping with variable sensitivity and specificity
- ctDNA can identify patients with advanced NSCLC who are responding to therapy (molecular response) at an early timepoint
- ctDNA can detect MRD and it is a strong prognostic biomarker
- Ongoing trials will inform if clinical decision-making can be guided by ctDNA and if that improves patients' outcomes

Thank you



www.moffitt.org

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