Liquid Biopsy in NSCLC

Molecular profiling & Research Use

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Disclosures:

Dr. Tuz Zahra has no conflicts to disclose

Dr. Pellini discloses:

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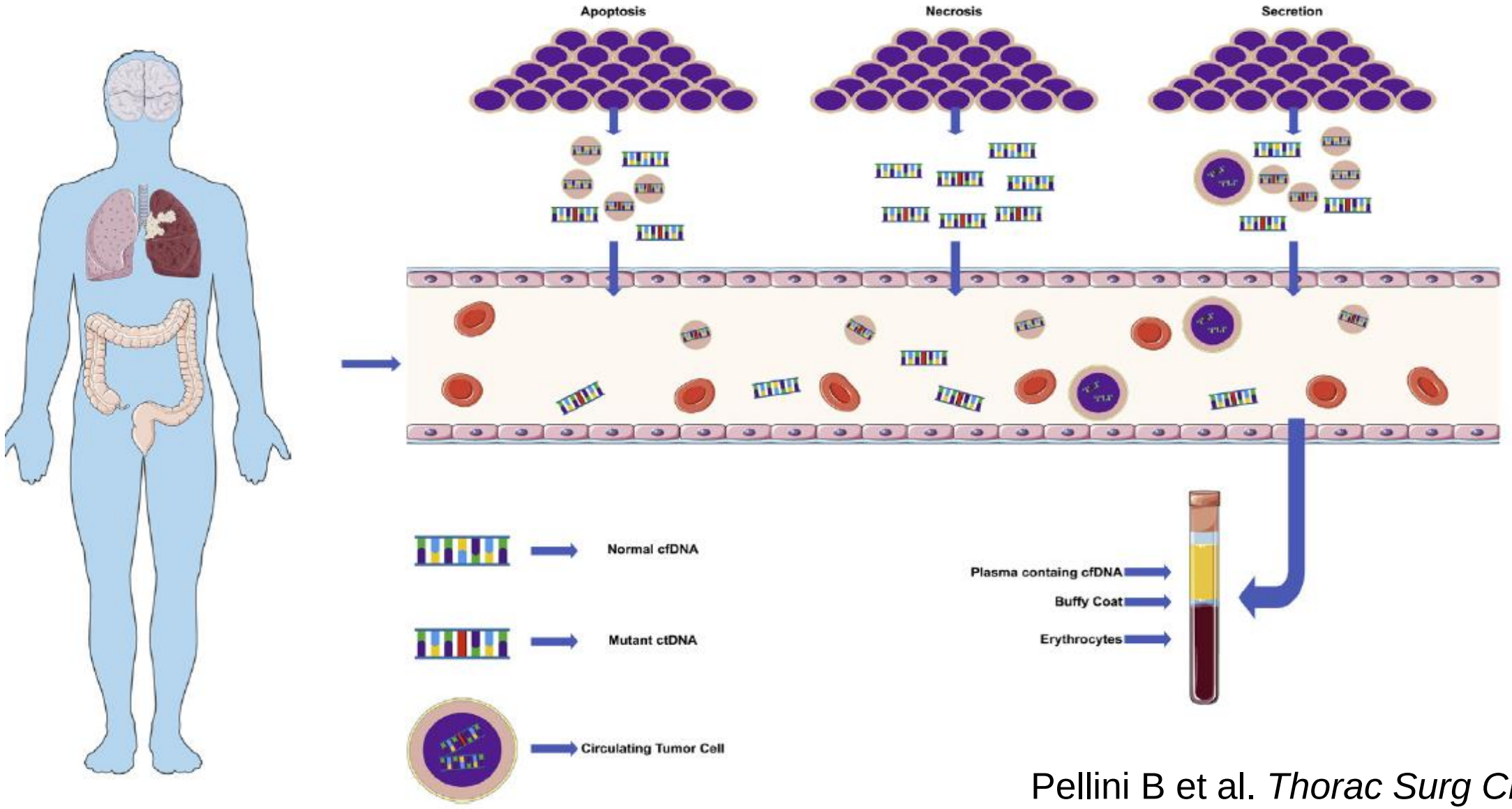
Outline

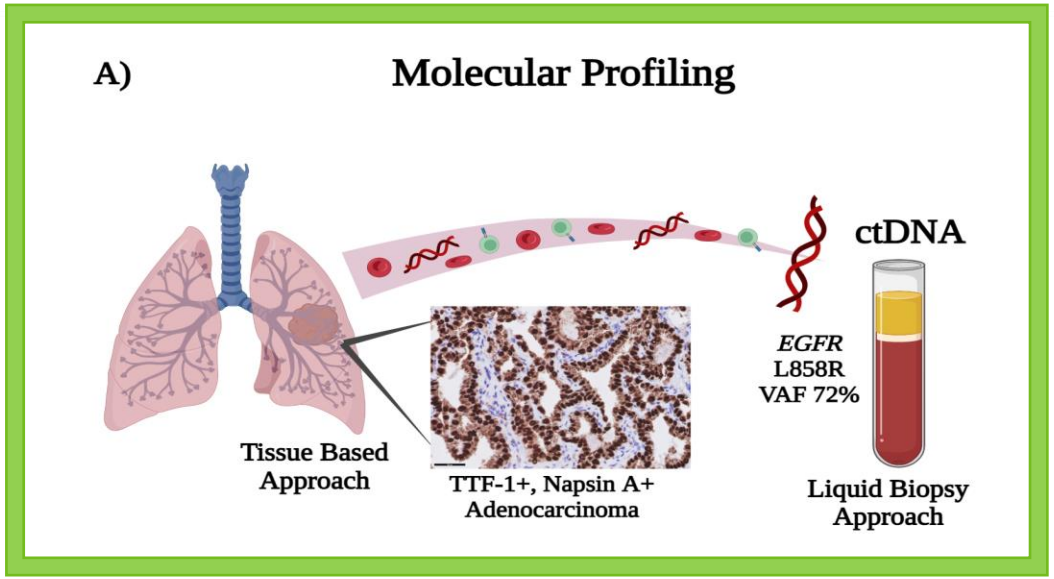
- ctDNA definition & sources of ctDNA
- ctDNA applications in oncology:
  - Molecular profiling
    - Case 1 & 2 presentation
  - Treatment Monitoring
    - 2023 ASCO updates

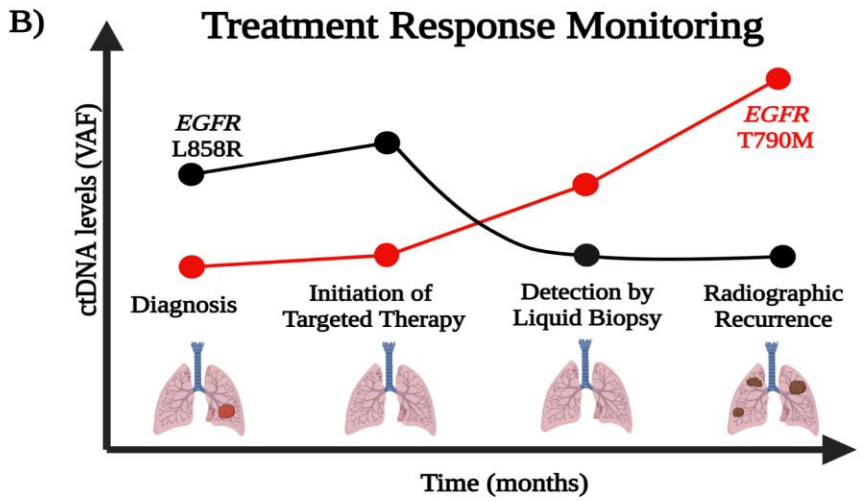
Tumor-derived fragments of nucleic acids identified in the blood are called circulating tumor DNA (ctDNA)

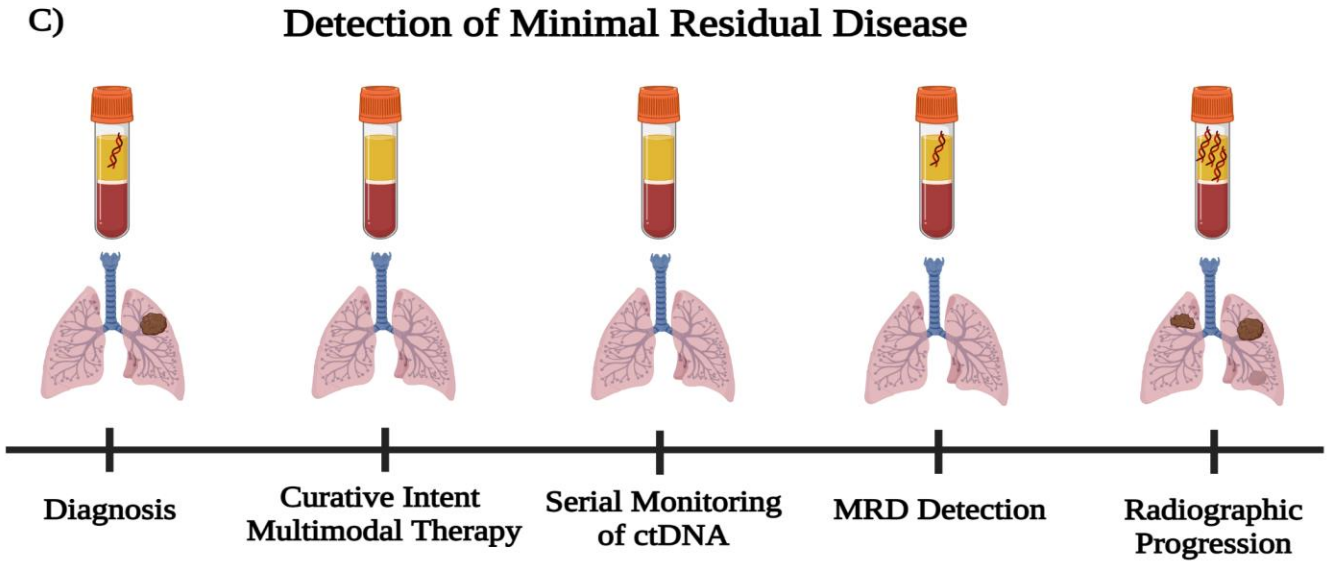


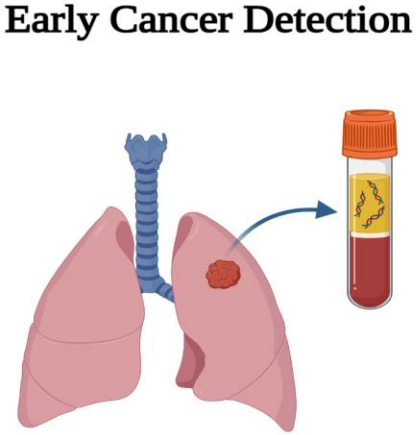
Pellini B et al. *Thorac Surg Clin*. 2020

ctDNA Applications in Oncology









Shields M, Chen K…Pellini B. *Int J Mol Sci*. 2022

ctDNA sequencing has high sensitivity and specificity to identify actionable genomic alterations

Table 3. Comparison of tissue versus cfDNA results for the guideline-recommended biomarkers in newly diagnosed metastatic NSCLC with FDA-approved therapies, *EGFR* exon 19 deletion and L858R, *ALK* fusion, *ROS1* fusion, and *BRAF* V600E

		Tissue+	Tissue−	Tissue not assessed	Tissue QNS	Total		
EGFR exon 19 del	cfDNA+	18	0	0	1	19	Sensitivity	81.8%
	cfDNA−	4	201	19	25	249	PPV	100.0%
	cfDNA TND	0	11	1	1	13	Specificity	100.0%
	cfDNA cancelled	0	0	1	0	1	NPV	98.0%
	Total	22	212	21	27	282	Concordance	98.2%
EGFR L858R	cfDNA+	9	0	0	2	11	Sensitivity	90.0%
	cfDNA−	1	213	19	24	257	PPV	100.0%
	cfDNA TND	0	11	1	1	13	Specificity	100.0%
	cfDNA cancelled	0	0	1	0	1	NPV	99.5%
	Total	10	224	21	27	282	Concordance	99.6%
ALK fusion (original)	cfDNA+	5	0	0	1	6	Sensitivity	62.5%
	cfDNA−	3	207	27	25	262	PPV	100.0%
	cfDNA TND	1	10	2	0	13	Specificity	100.0%
	cfDNA cancelled	0	1	0	0	0	NPV	98.6%
	Total	9	218	29	26	282	Concordance	98.6%
ALK fusion (reanalysis)	cfDNA+	6	0	0	1	7	Sensitivity	75.0%
	cfDNA−	2	207	27	25	261	PPV	100.0%
	cfDNA TND	1	10	2	0	13	Specificity	100.0%
	cfDNA cancelled	0	1	0	0	1	NPV	99.0%
	Total	9	218	29	26	282	Concordance	99.1%
ROS1 fusion	cfDNA+	0	0	0	0	0	Sensitivity	-
	cfDNA−	2	151	85	30	268	PPV	-
	cfDNA TND	0	7	5	1	13	Specificity	100.0%
	cfDNA cancelled	0	1	0	0	1	NPV	98.7%
	Total	2	159	90	31	282	Concordance	98.7%
BRAF V600E mutation	cfDNA+	2	0	0	0	2	Sensitivity	100.0%
	cfDNA−	0	90	158	18	266	PPV	100.0%
	cfDNA TND	0	5	8	0	13	Specificity	100.0%
	cfDNA cancelled	0	0	1	0	1	NPV	100.0%
	Total	2	95	167	18	282	Concordance	100.0%

NOTE: Overall concordance across all four genes was greater than 98.2%, with a PPV of 100%. With continuous assay improvements, one cfDNA result originally reported as a false-negative for *ALK* fusion was identified as positive.

Stage IV NSCLC

(Guardant 360) Liquid biopsy NGS assay that offers comprehensive testing for 74 genes most relevant to solid tumors.

Leighl N et al. *Clin Cancer Res*. 2019

Case 1

- **08/03/2022: 79-year-old, never smoker male, left pleural effusion + consolidation on CT Chest.**
- **Bronchoscopy and Thoracentesis: Adenocarcinoma of Lung Primary. Negative Brain MRI.**
- **PD-L1 (IHC): Performed on pleural fluid = TPS 70 %.**

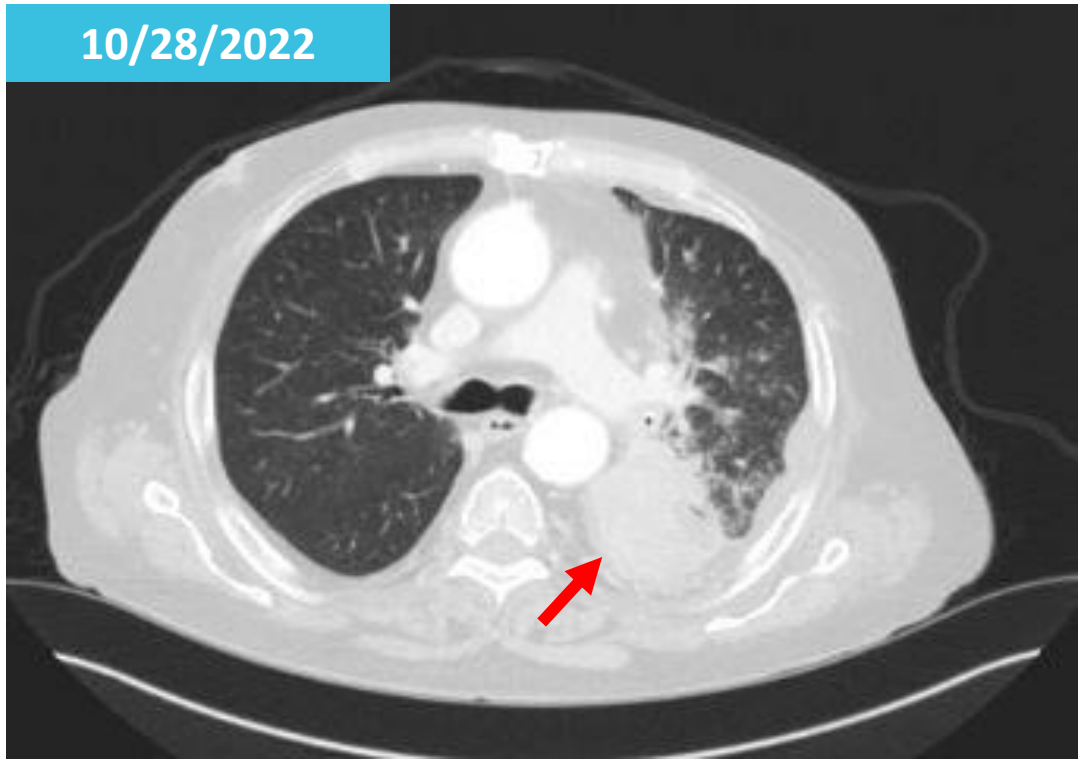
08/26/2022: Liquid Biopsy (NGS testing) = No actionable mutations.

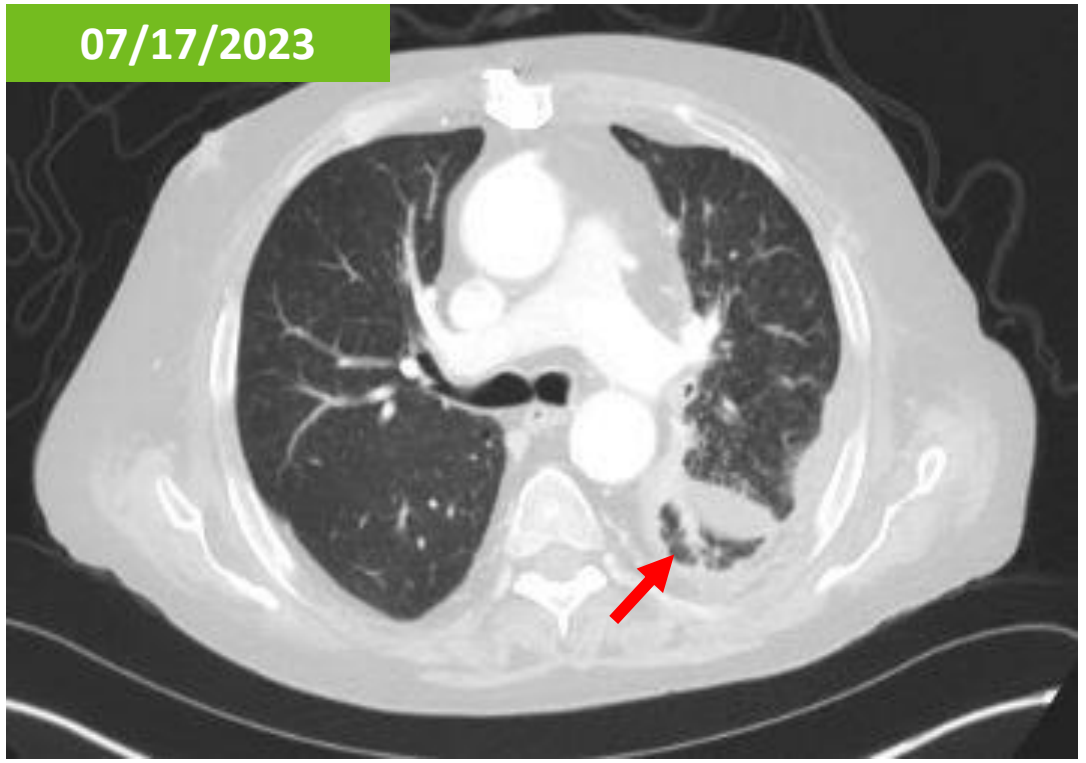
- **(08/23/2022 – 10/02/2022)**: Patient was treated with **single agent Pembrolizumab x 3 cycles.**
- **F/U CT TAP**: Increased lung mass + pleural effusion = **Disease progression.**
- **Patient referred to MCC for** second opinion/clinical trial consideration.

09/20/2022: Pleural Fluid NGS testing. ERBB2/Her-2 Exon 20 insertion identified, GOF - oncogenic.

Case 1

- Patient was started on **Fam-trastuzumab deruxtecan on 11/10/2022**.
- **07/17/2023 - CT-TAP: Left lung scarring without** measurable tumor. **Improved left lower lobe aeration** with **decreased loculated effusion and no new metastases.**





Case 2

- **06/29/2022**: 62-year-old woman presented with R hilar mass + R pleural effusion.
- Thoracentesis: Cytology = **adenocarcinoma of lung.**
- **07/25/2022: CARIS testing on pleural fluid but limited tissue. PD-L1 = 1% TPS**

- Treated with Carboplatin + Pemetrexed + Pembrolizumab and then maintenance Pembrolizumab+Pemetrexed
- **03/14/2023 - CT TAP**: Worsening R pleural effusion. Concern for new hilar mets = ***Progressive disease***

- **04/06/2023 - Liquid Biopsy : NGS testing : EGFR exon 20 insertion identified**.

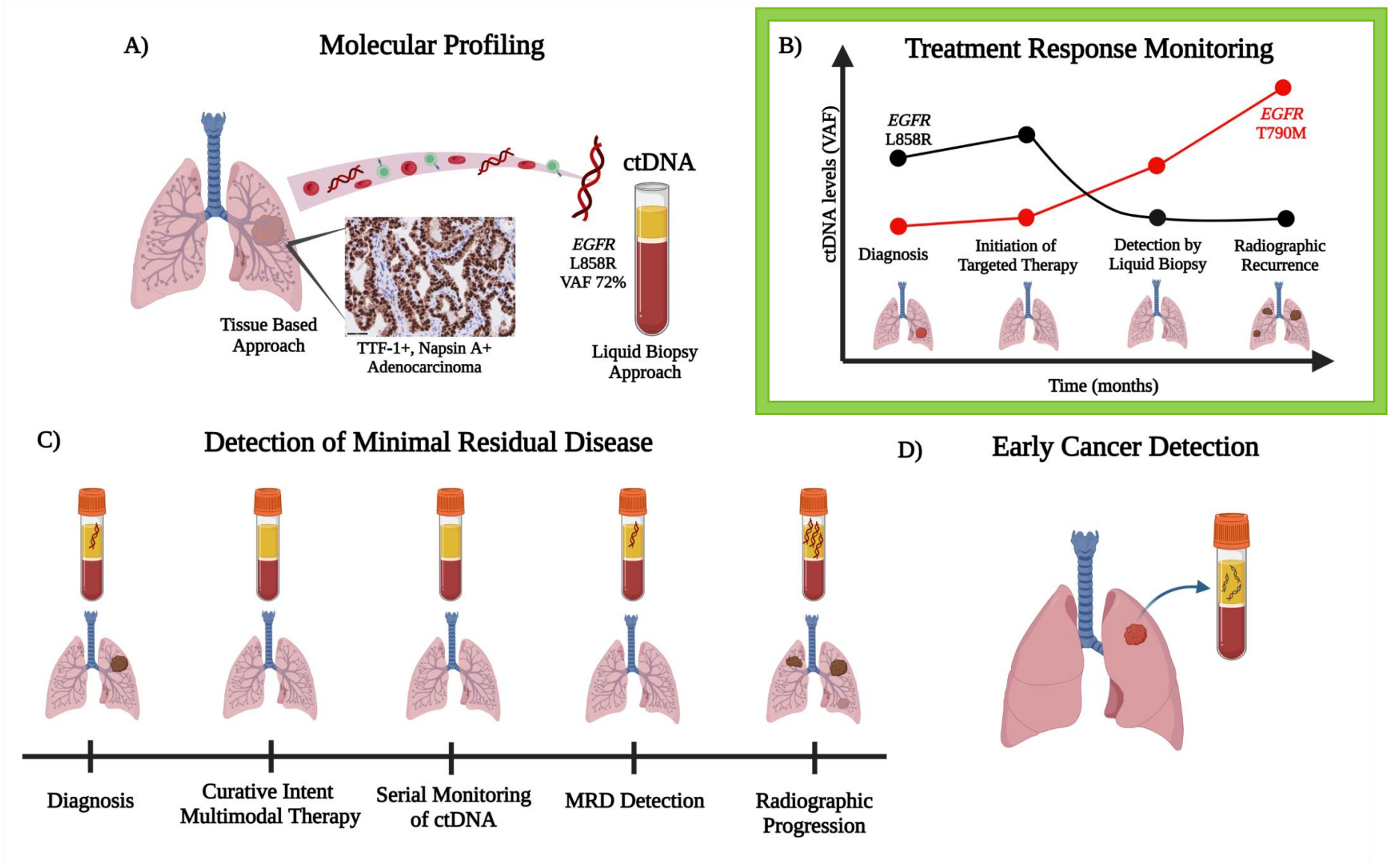
- MCC referral for 2nd line Tx with Amivantamab or Mobocertinib vs Clinical trial.
- **Pre- Clinical trial work up = Repeat LN biopsy + (EGFR gene mutational analysis + solid tissue NGS)**

- **Idylla EGFR Mutation Assay**: No EGFR mutations detected.

- **Comprehensive NGS testing on same core biopsy: POSITIVE for EGFR exon 20 insertion.**

- Patient enrolled in Clinical Trial MCC 20409 - 06/05/2023.
- **07/17/2023 - CT-TAP** : Progressive disease
- Discontinued from the trial and recommended to discuss next-line amivantamab vs. mobocertinib with her local oncologist.

ctDNA applications in oncology

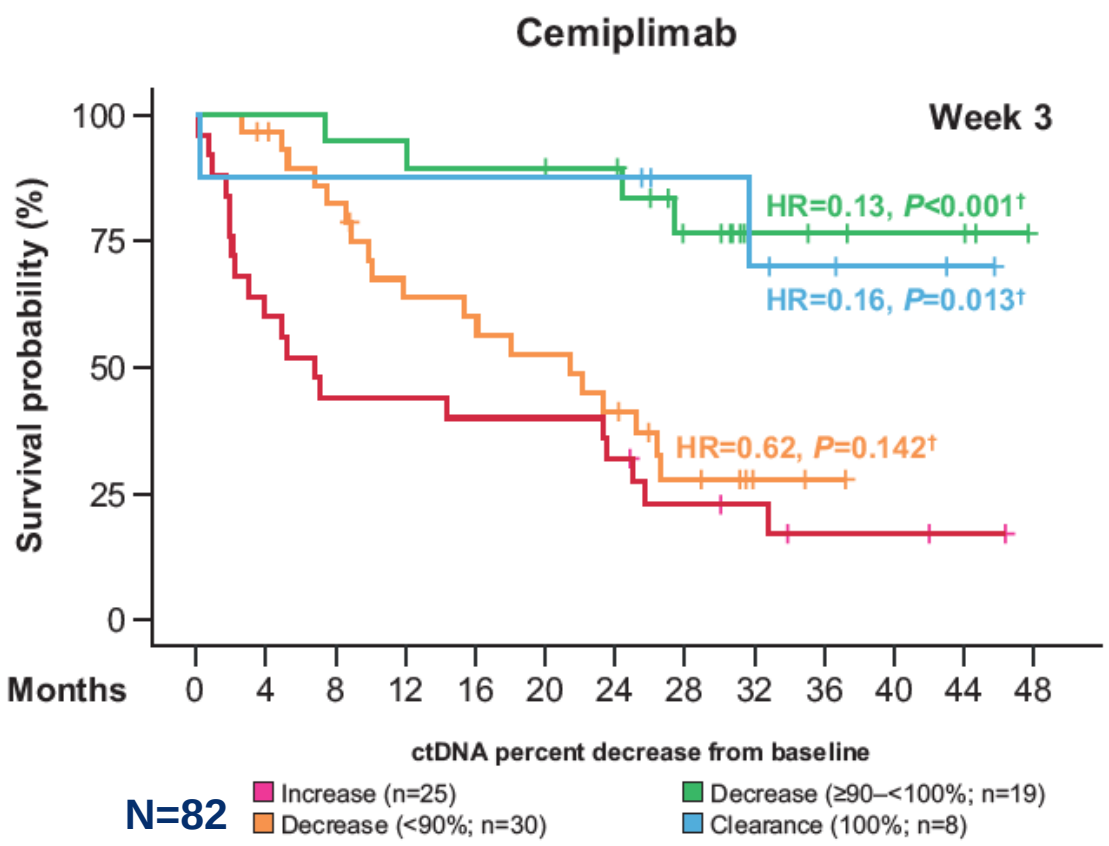


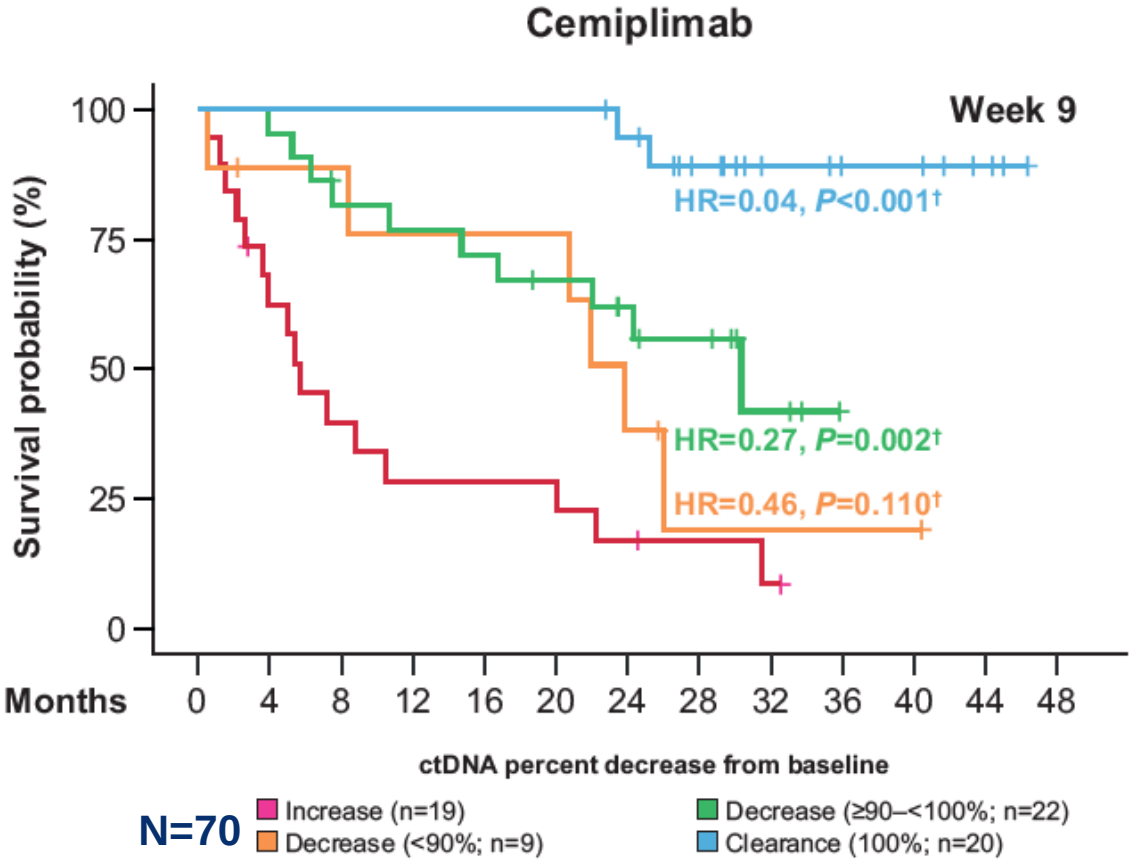
Shields M, Chen K…Pellini B. *Int J Mol Sci*. 2022

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

Advanced NSCLC

Tumor-informed assay (Signatera™ & FoundationOne Tracker)

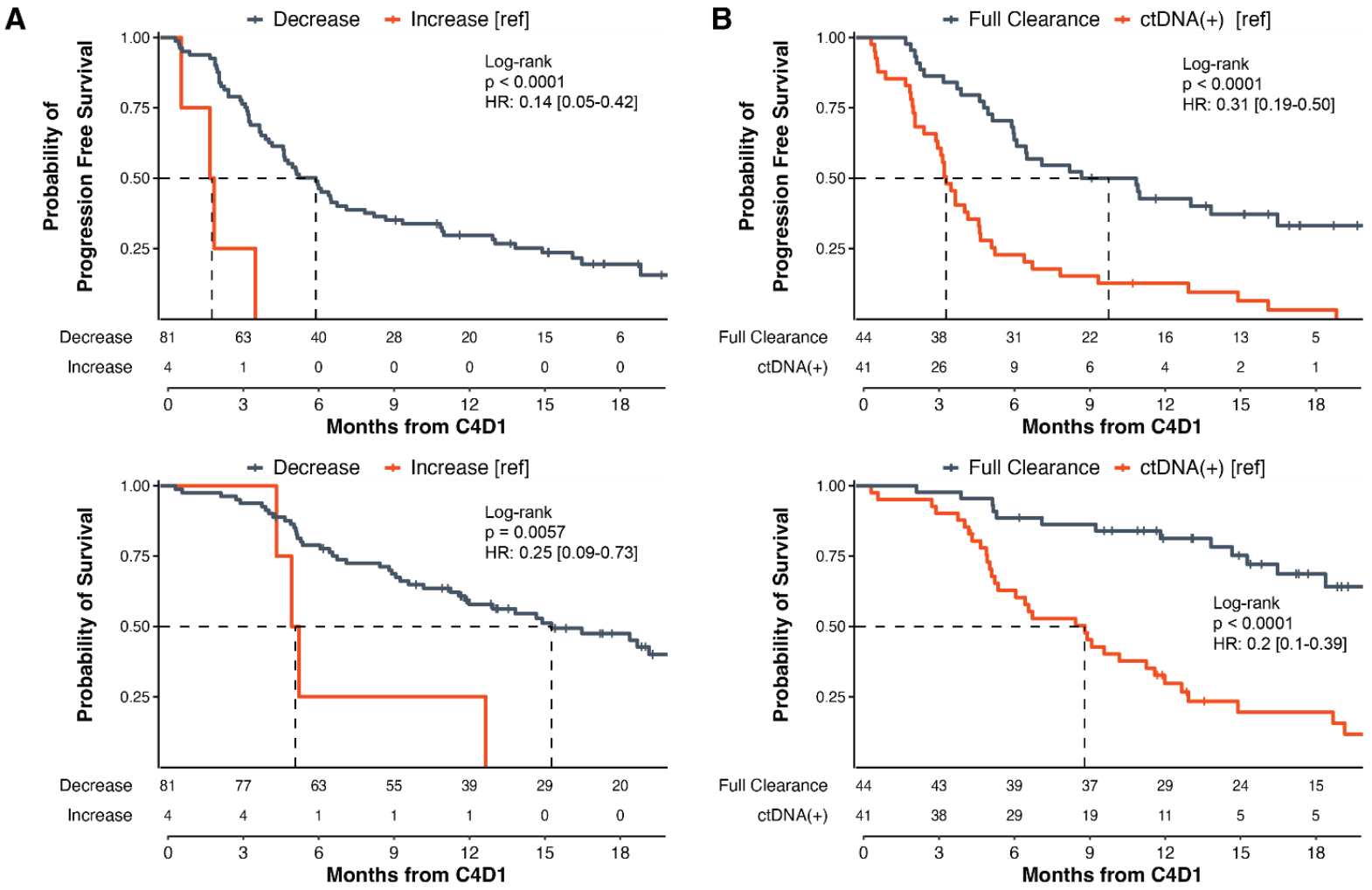




Vokes N et al. 2023 ASCO Annual Meeting.

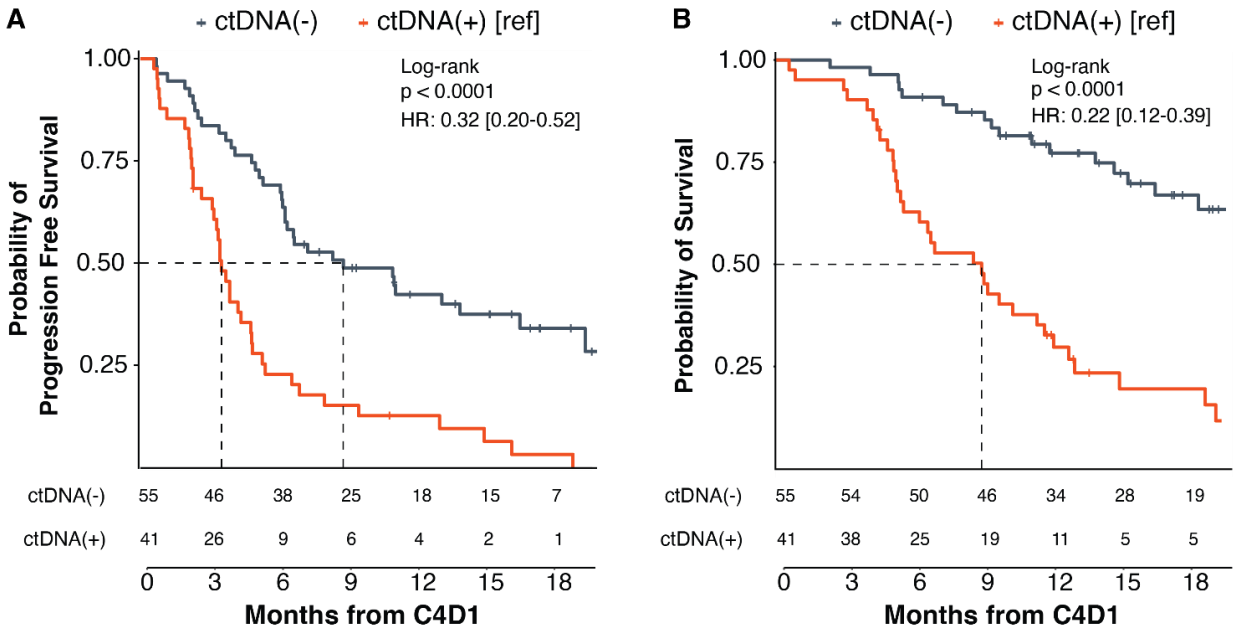
Circulating Tumor DNA Monitoring on Chemo-immunotherapy Informs Outcomes in Advanced Non-Small Cell Lung Cancer

Tumor-informed assay (FoundationOne Tracker)



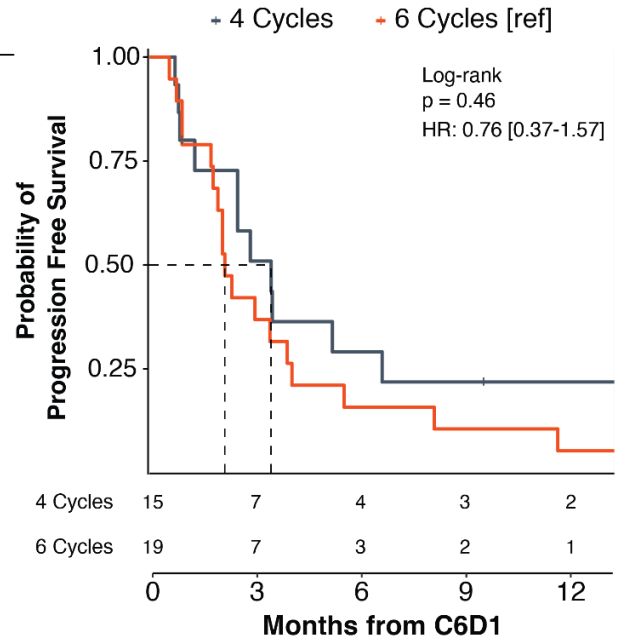
Pellini B et al. *Clin Cancer Res*. 2023

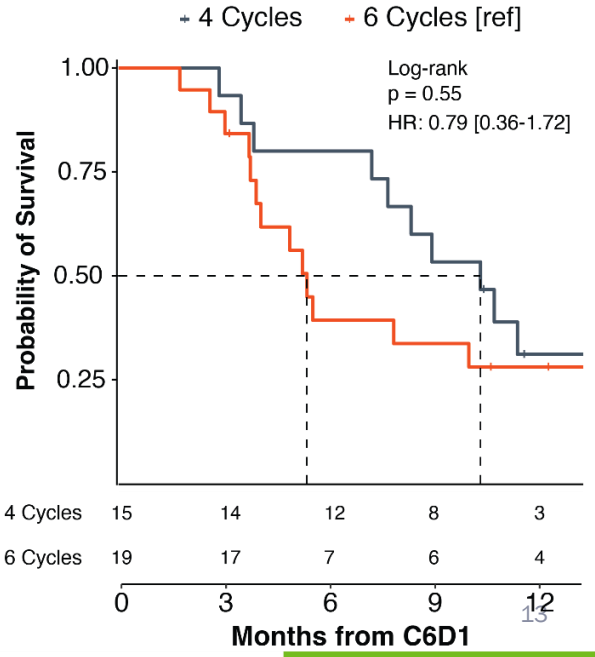
ctDNA detection on chemoIO can inform subsequent outcomes on IO maintenance, even without baseline ctDNA analysis



Tumor-informed assay (FoundationOne Tracker)

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

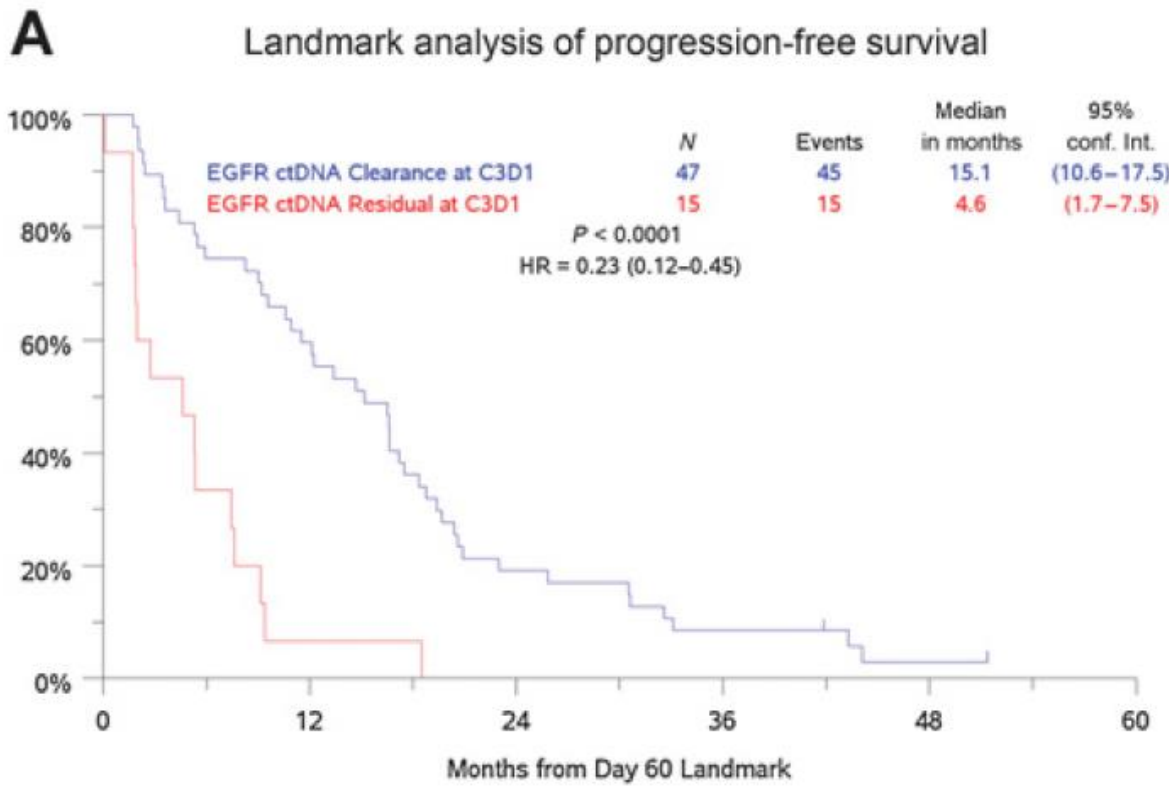


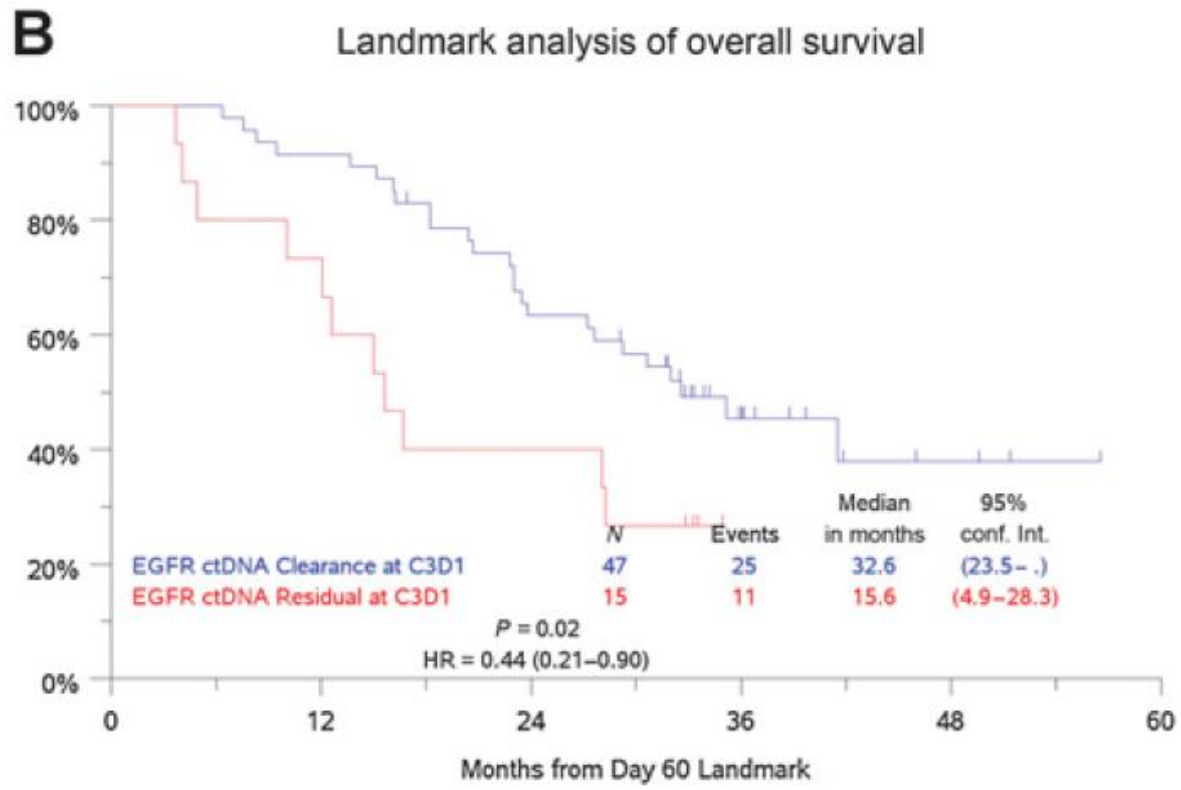


Pellini B et al. *Clin Cancer Res*. 2023

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

Stage IV NSCLC
Tumor-naïve assay
(Guardant 360)



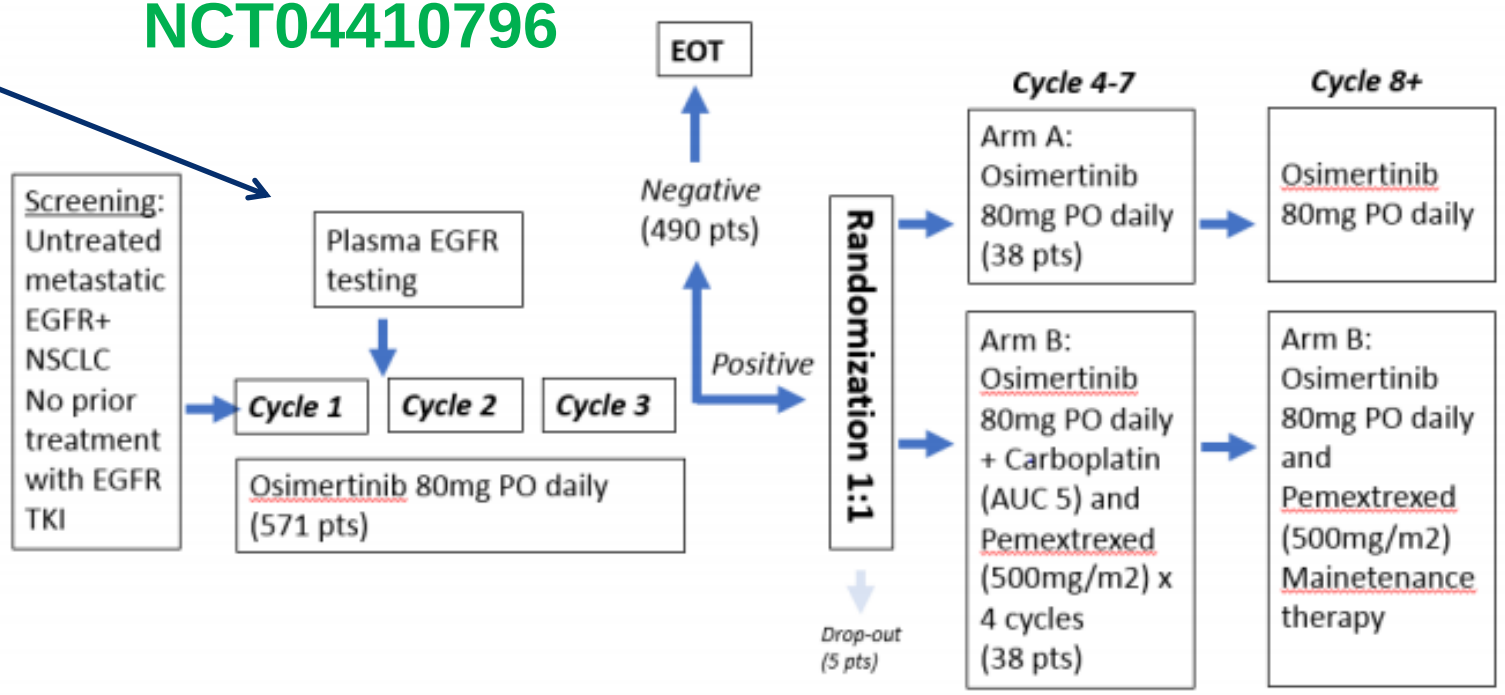


Mack PC et al. *Clin Cancer Res*. 2022

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

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
- Ongoing trials will inform if clinical decision-making can be guided by ctDNA and if that improves patients' outcomes

Questions?

www.moffitt.org

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