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GECP lung cancer research

Circulating Tumor DNA as a Prognostic and Dynamic Biomarker in Unresectable Stage III NSCLC

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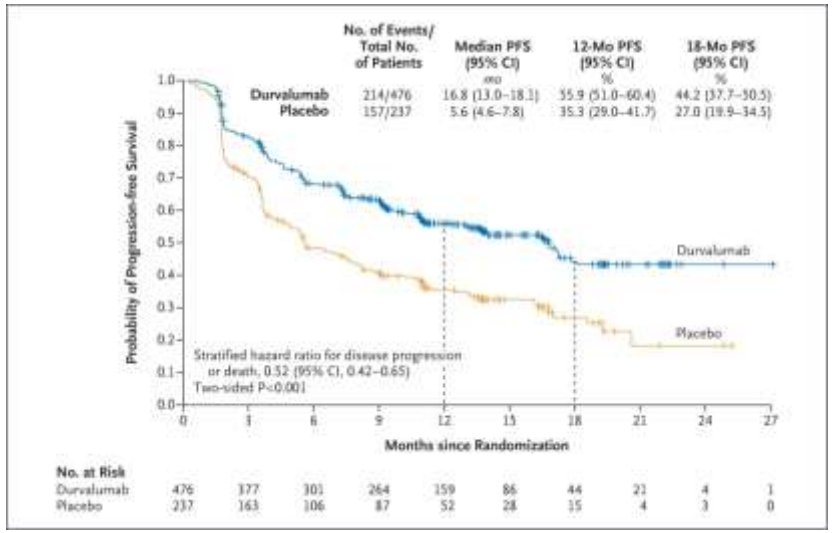
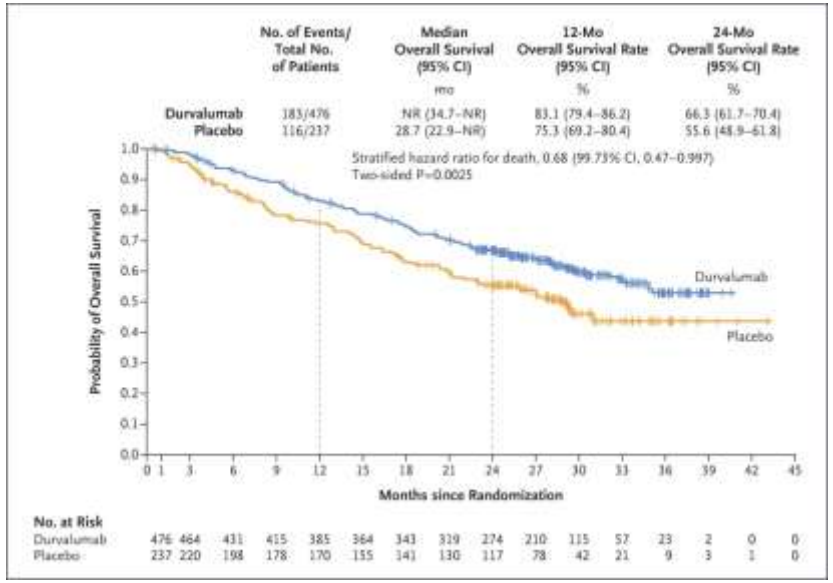
Introduction

Clinical background

- The **PACIFIC trial** established **durvalumab consolidation** therapy as standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) following concurrent chemoradiotherapy (cCRT)
- Significant **heterogeneity** exists in patient outcomes, and **prognostic biomarkers** are needed to identify patients at higher risk of progression
- **Circulating tumor DNA** (ctDNA) is a promising non-invasive tool for monitoring minimal residual disease (MRD) and predicting recurrence risk across multiple cancer types
- In pts with locally advanced NSCLC, ctDNA detection following definitive cCRT may identify patients with **micrometastatic or high-risk disease** who are most likely to experience disease progression





Antonia SJ, et al. NEJM 2017 & 2018

Introduction

Study overview

- This report presents a comprehensive analysis of **ctDNA detection** and its **prognostic value** in patients with stage III NSCLC treated with cCRT in the PACIFIC trial setting
- We aimed to evaluate ctDNA status at multiple timepoints (pre-cCRT, post-cCRT, on durvalumab, and follow-up/post-treatment) and the **association between ctDNA detection and survival outcomes**

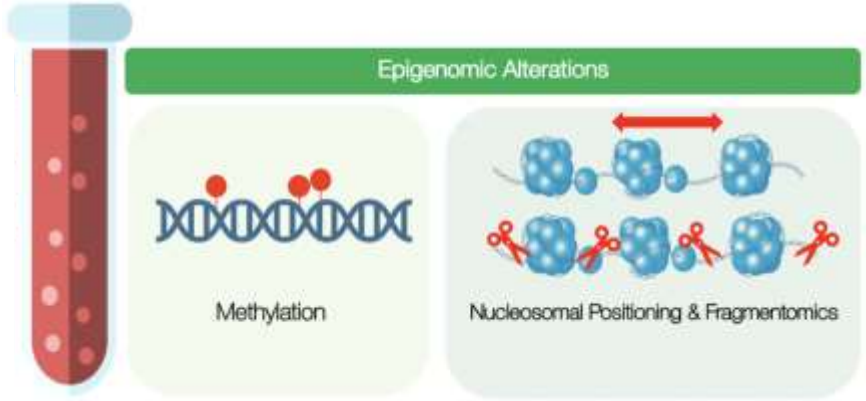
Key objectives include:

1. Characterizing ctDNA **detection rates** across treatment timepoints
2. Evaluating the prognostic impact of **post-cCRT** ctDNA status on survival outcomes
3. Assessing the combined effect of ctDNA status and **durvalumab** consolidation therapy
4. Analyzing ctDNA **dynamics** (clearance, persistence, re-emergence) and their clinical implications

Methods

Study design

- Patients with **stage III NSCLC treated with cCRT**, with or without durvalumab consolidation per local practice guidelines, were included
- ctDNA was analyzed using **Guardant Reveal®** a tissue-free epigenomic assay designed for detection and quantification of ctDNA
- Samples were collected **pre-cCRT**, **post-cCRT**, and subsequently **every 3 months** during durvalumab treatment or the surveillance period
- Associations between ctDNA status across timepoints and **survival outcomes** were evaluated using Kaplan-Meier and log-rank analyses



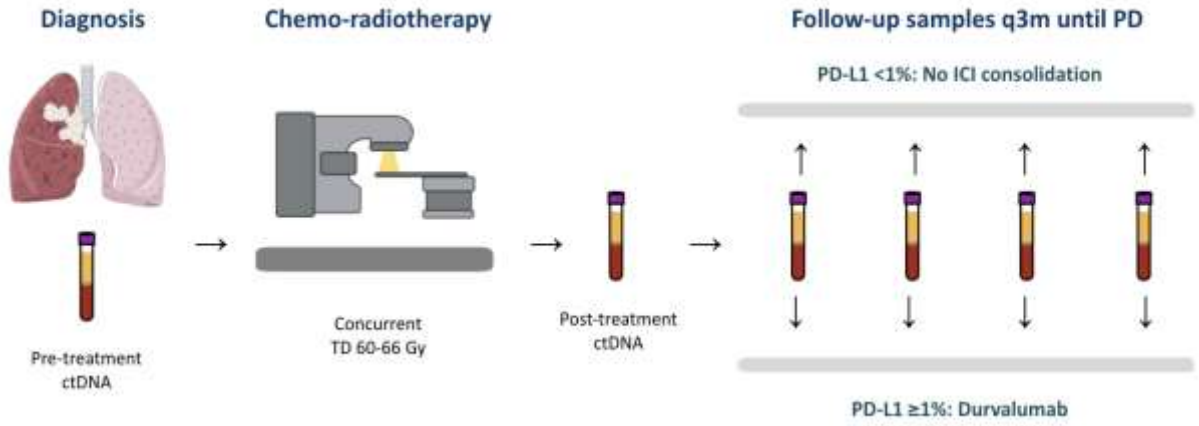
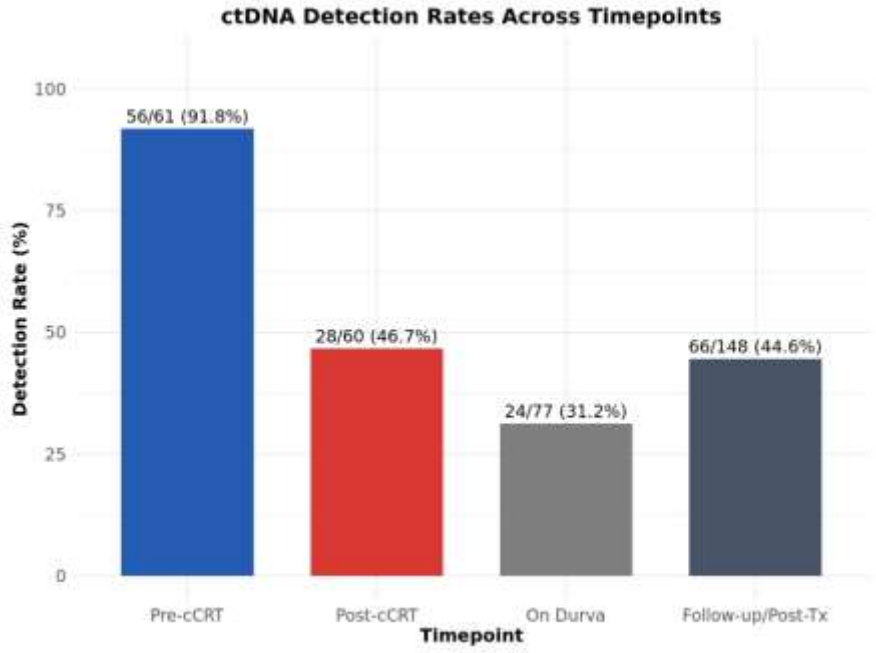


Figure adapted from Moding EJ, et al. Nat Cancer 2021

Results

Patient and sample disposition

- Between January 2021 and June 2024, **82 patients** diagnosed with unresectable stage III NSCLC and treated cCRT were prospectively enrolled in this study
- Patients with confirmed stage IV disease at diagnosis, small-cell histology, actionable driver alterations, incomplete cCRT, or withdrawal of consent were **excluded** after review
- A total of **71 patients** (88%) were fully evaluable for ctDNA analysis and conformed the **final cohort**



- **348 samples** from different timepoints were collected for ctDNA analysis
- **Baseline** (pre-cCRT) plasma samples were available for 61 patients (86%) and **post-cCRT** samples for 60 (85%), conforming the **most robust** subgroups of this study

Results

Baseline patient characteristics

Table 1. Patient characteristics (N=71)	
Age, median (range)	69 (53-86)
Gender	
Male	58 (81.7%)
Female	13 (18.3%)
Clinical stage	
IIIA	27 (38.0%)
IIIB	23 (32.4%)
IIIC	21 (29.6%)
Smoking status	
Active	35 (49.3%)
Former	35 (49.3%)
Never	1 (1.4%)
Histology	
Adenocarcinoma	30 (42.3%)
Squamous Cell Carcinoma	28 (39.4%)
Not Otherwise Specified	13 (18.3%)
PD-L1 status	
<1%	31 (43.7%)
≥1%	40 (56.3%)

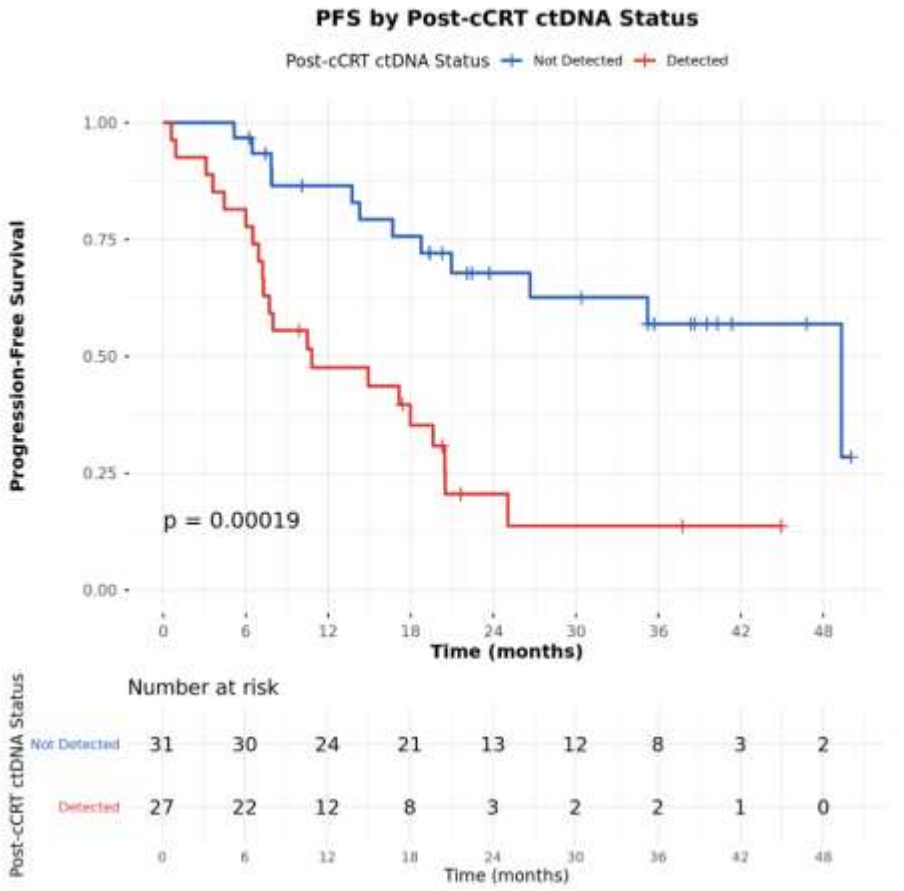
Treatment details and regimens	
Chemotherapy regimen	
Carboplatin-based	48 (67.6%)
Cisplatin-based	23 (32.4%)
Radiation dose	
<60 Gy	8 (11.3%)
≥60 Gy	63 (88.7%)
Durvalumab consolidation	
Yes	33 (46.5%)
No	38 (53.5%)

Genomic profiling of available tissue samples and ctDNA matched analysis is expected in the future

Results

Survival outcomes by post-cCRT ctDNA status

- With a median follow up of 21.4 months, **post-cCRT ctDNA** status was **strongly** associated with survival outcomes
- Patients who were **ctDNA-positive after cCRT** experienced significantly **shorter** progression-free survival (PFS) compared with ctDNA-negative patients



ctDNA post-cCRT	Median PFS	HR (95% CI)	p
Not Detected	**49 m** (27–NR)	**3.80 (1.8–8.01)**	**<0.001**
Detected	**11 m** (7.3–20)		

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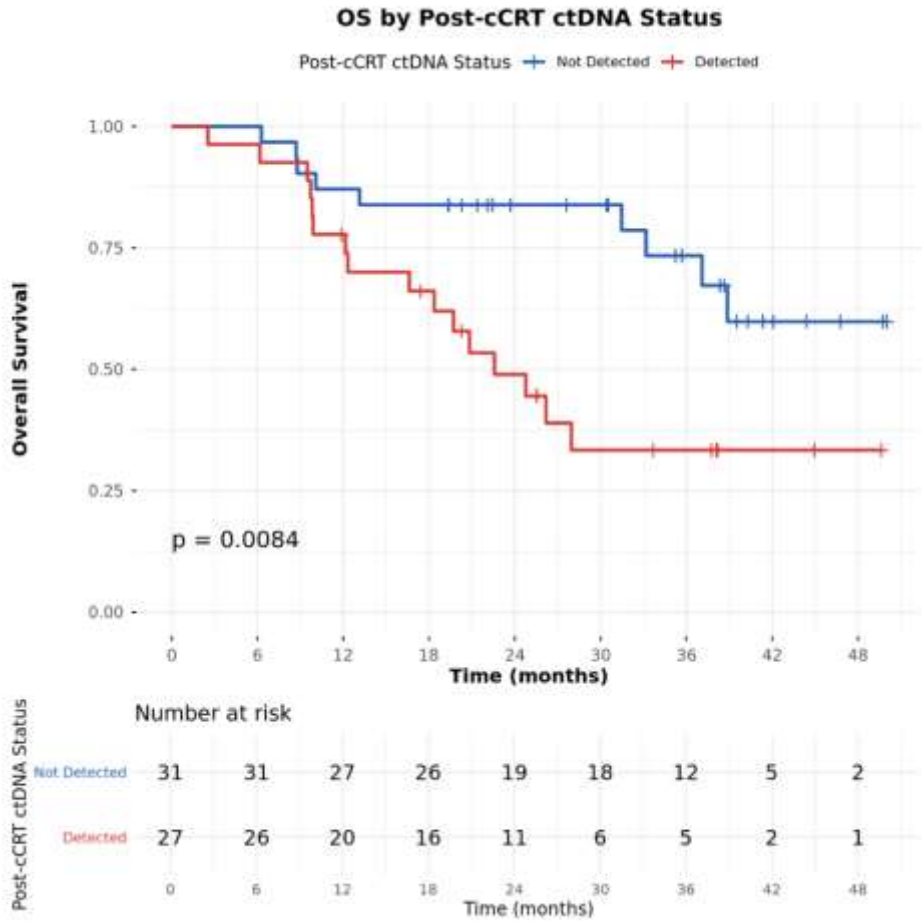
- Overall survival (OS) followed a similar pattern, again reaching **statistical significance**



ctDNA post-cCRT	Median OS	HR (95% CI)	p
Not Detected	**NR** (39—NR)	**2.90 (1.27–6.65)**	**0.009**
Detected	**23 m** (18—NR)		

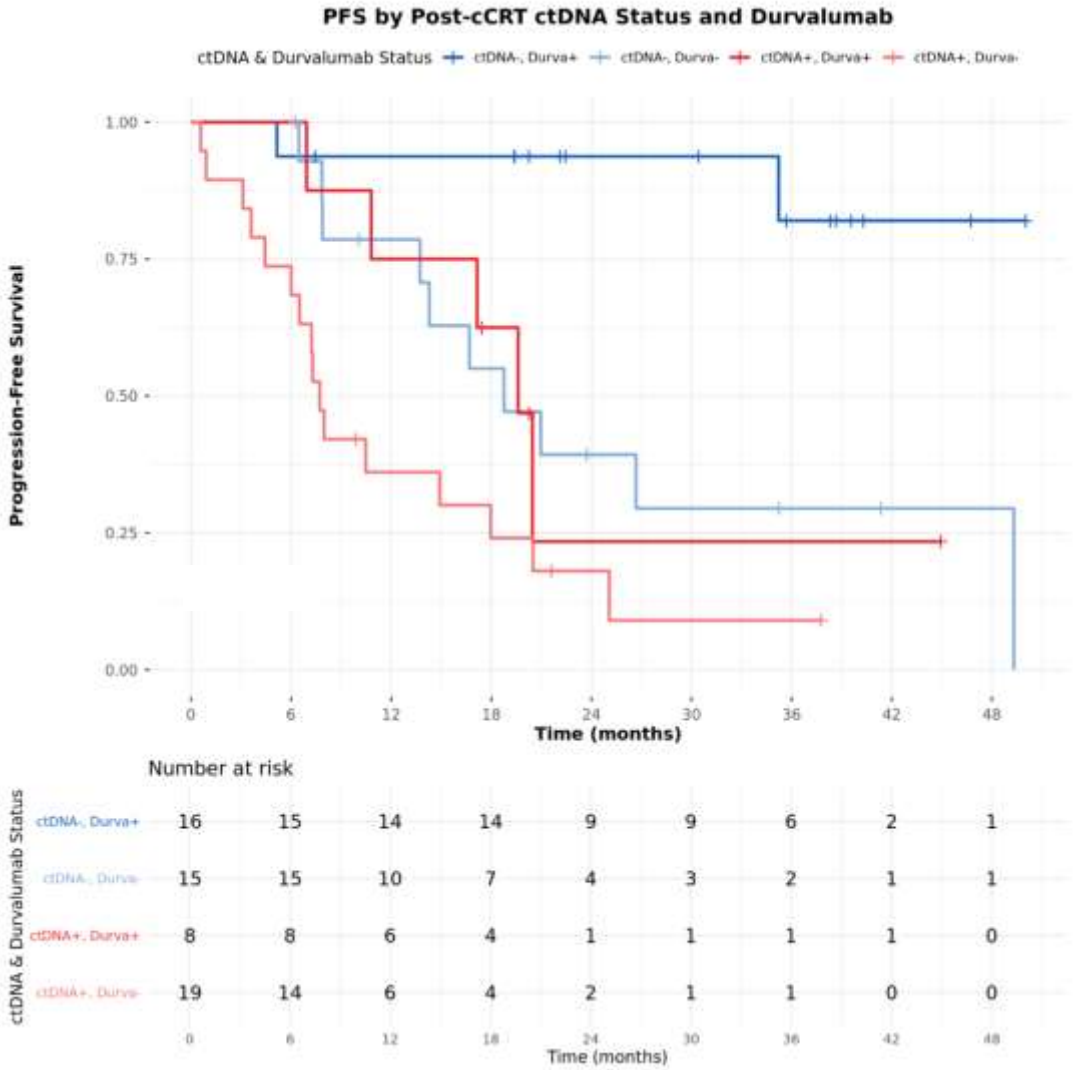
Results

Survival outcomes by post-cCRT ctDNA status AND durvalumab treatment

- Survival outcomes were also evaluated according to post-cCRT ctDNA status and **durvalumab** consolidation treatment
- Patients who achieved **ctDNA clearance after cCRT and received durvalumab** showed the most favorable outcomes
- Durvalumab appeared to **mitigate** the prognostic impact of ctDNA positivity after cCRT

Subgroup	Median PFS, months
ctDNA– / Durva+	**NR** (–)
ctDNA– / Durva–	**19** (14 – NR)
ctDNA+ / Durva+	**20** (17 – NR)
ctDNA+ / Durva–	**7.7** (6.5 – 25)

Prognostic factors	HR	95% CI	p-value
ctDNA detectable (post-cCRT)	**3.10**	1.47 – 6.57	0.003
No Durvalumab	**3.59**	1.54 – 8.41	0.004



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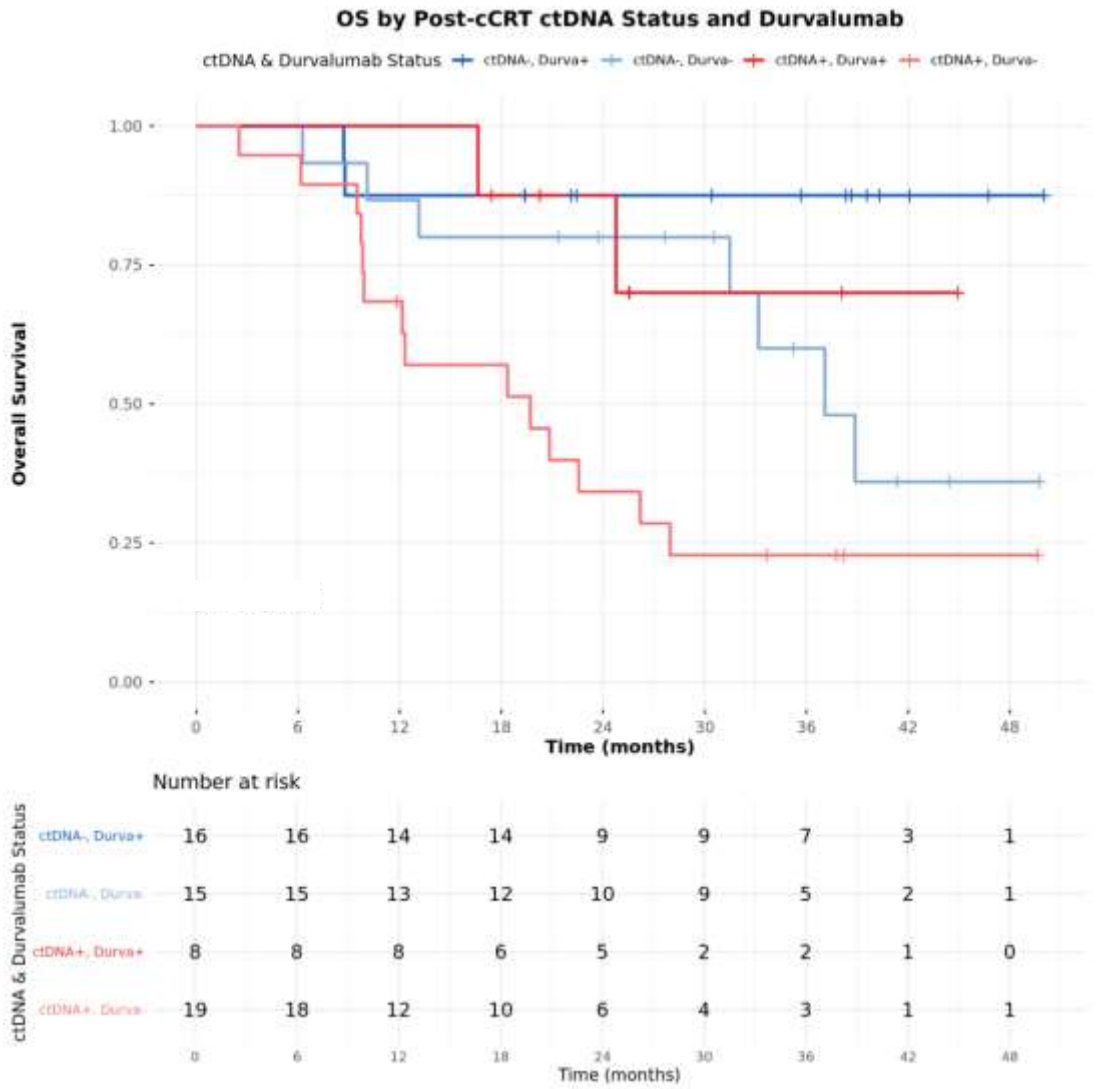
Subgroup	Median OS, months
ctDNA– / Durva+	**NR** (–)
ctDNA– / Durva–	**37** (31 – NR)
ctDNA+ / Durva+	**NR** (25 – NR)
ctDNA+ / Durva–	**20** (12 – NR)

Prognostic factors	HR	95% CI	p-value
ctDNA detectable (post-cCRT)	**2.48**	1.08 – 5.71	0.033
No Durvalumab	**3.88**	1.32 – 11.4	0.014

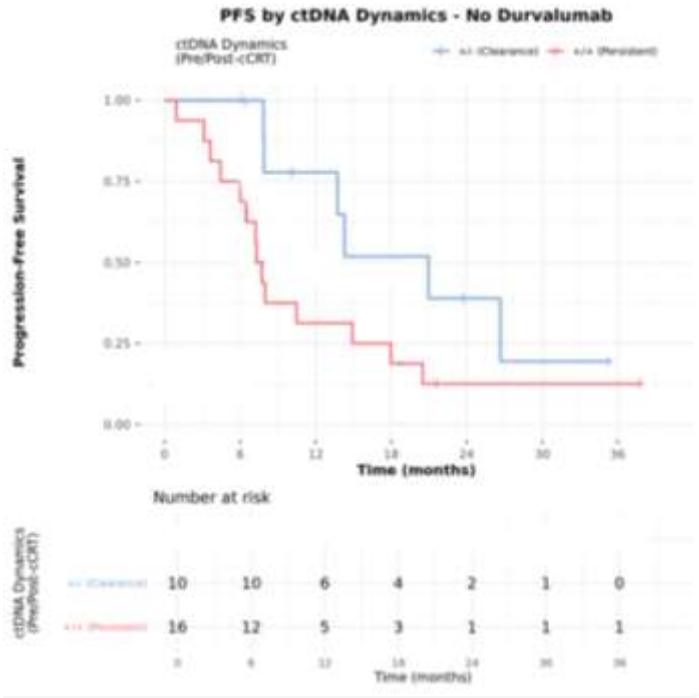


Results

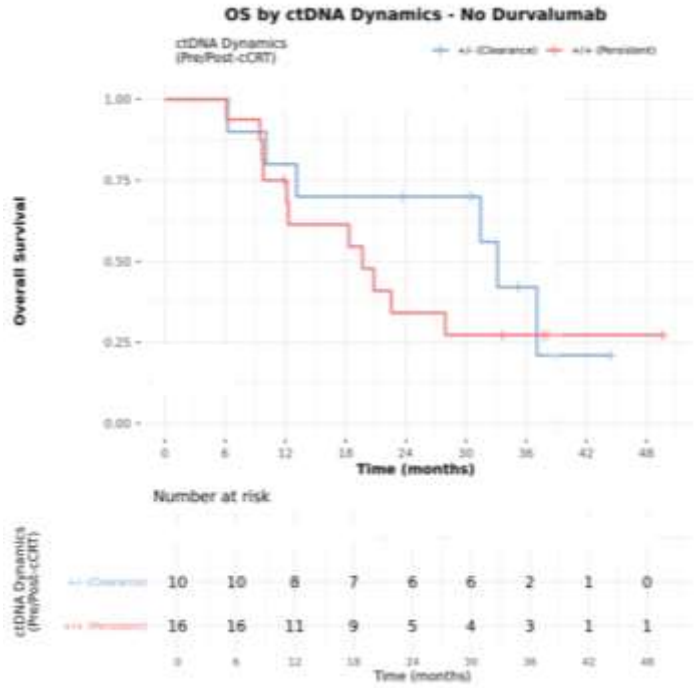
Survival outcomes by pre- and post-cCRT ctDNA dynamics

Surveillance cohort

Patients were classified according to ctDNA dynamics before and after cCRT in **different subgroups**: (−/−) consistently negative, (+/−) achieved ctDNA clearance, (+/+) persistently positive, and (−/+) ctDNA re-emergence



ctDNA dynamics	MedianaPFS (months)	HR	95% CI	p-value
+/− (clearance)	**21** (14, NR)	2.40	0.60–9.50	0.017
+/+ (persistance)	**7.5** (6.0–20)			



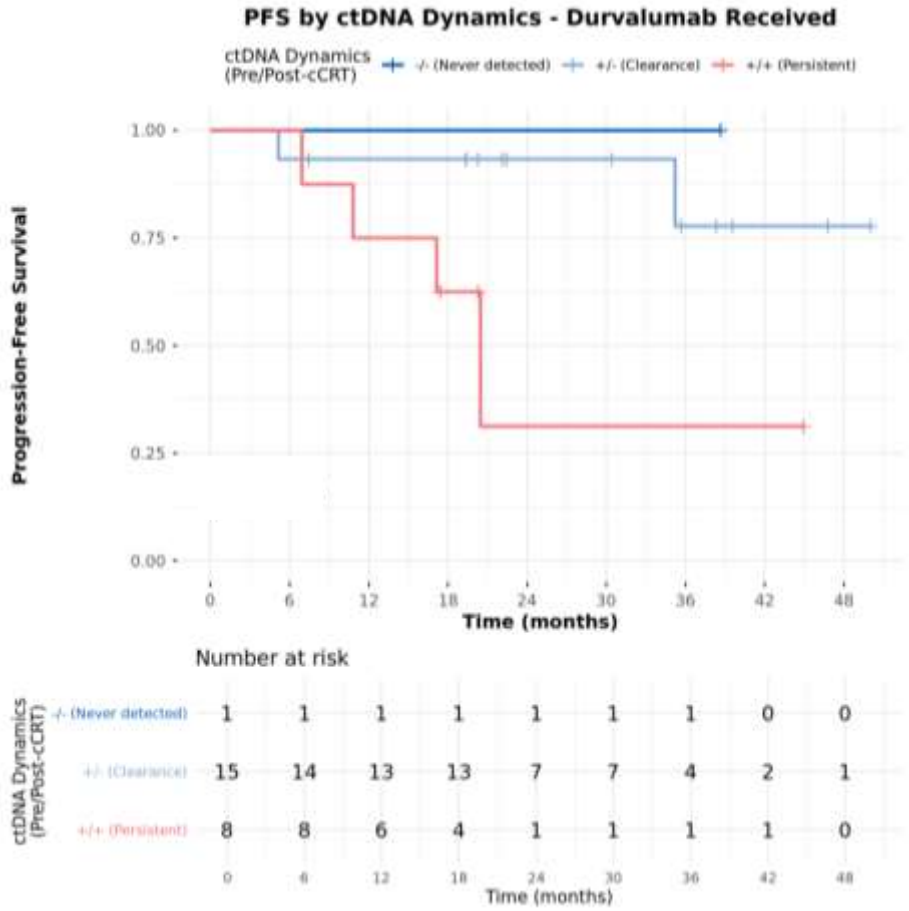
ctDNA dynamics	Median OS (months)	HR	95% CI	p-value
+/− (clearance)	**33** (13, NR)	1.80	0.45–7.60	0.39
+/+ (persistance)	**20** (12, NR)			

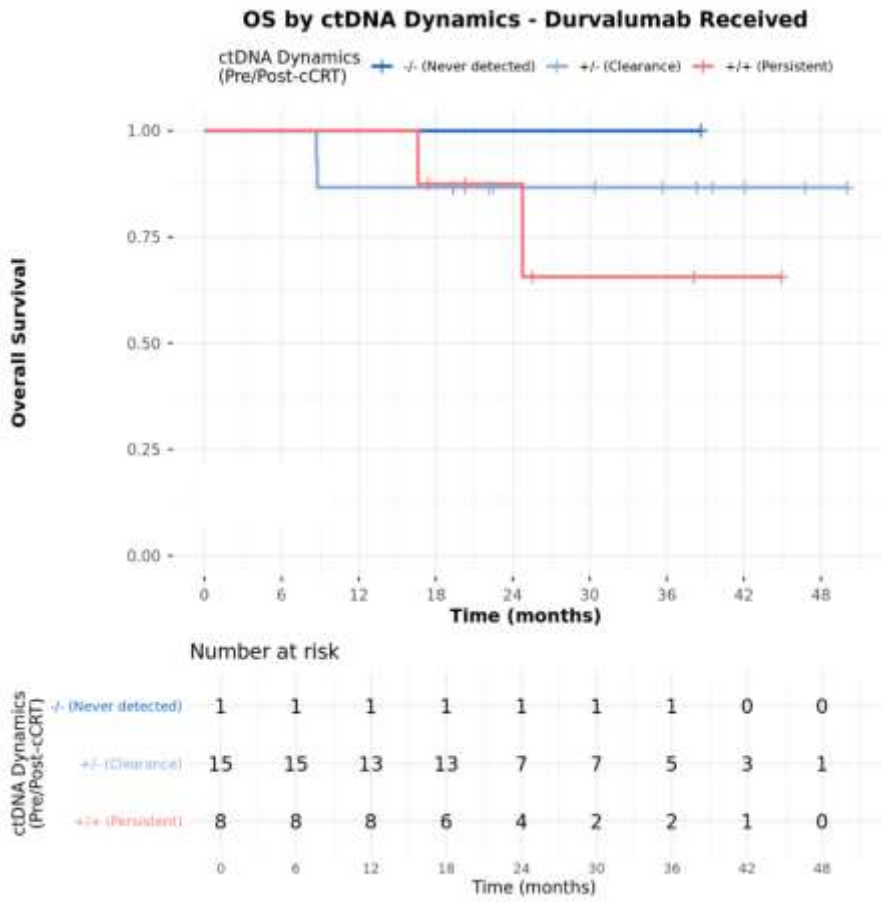
Results

Survival outcomes by pre- and post-cCRT ctDNA dynamics

Durvalumab treatment

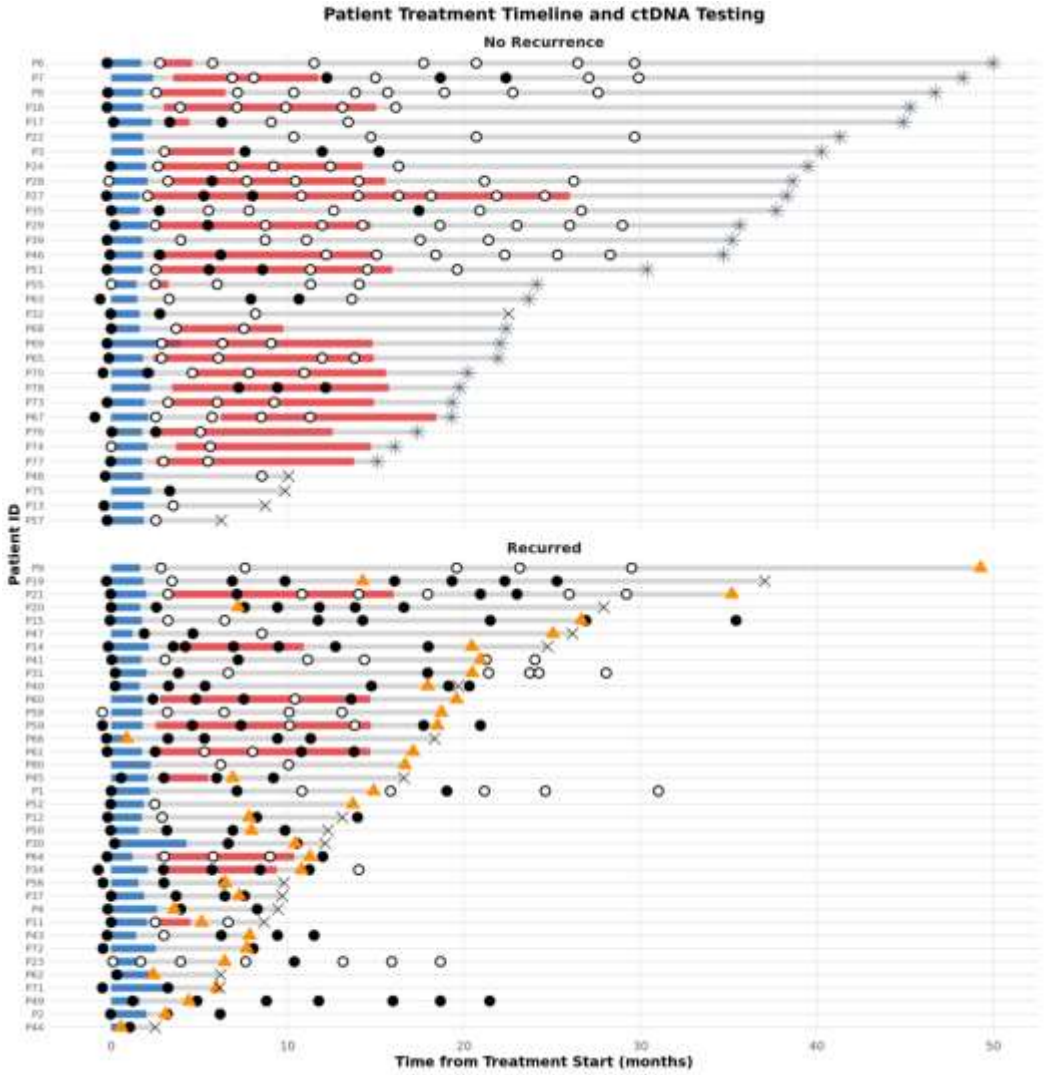
The **low event rate** of this cohort precluded meaningful statistical comparisons and survival estimates can not be reliably interpreted





Results

Longitudinal assessment of ctDNA

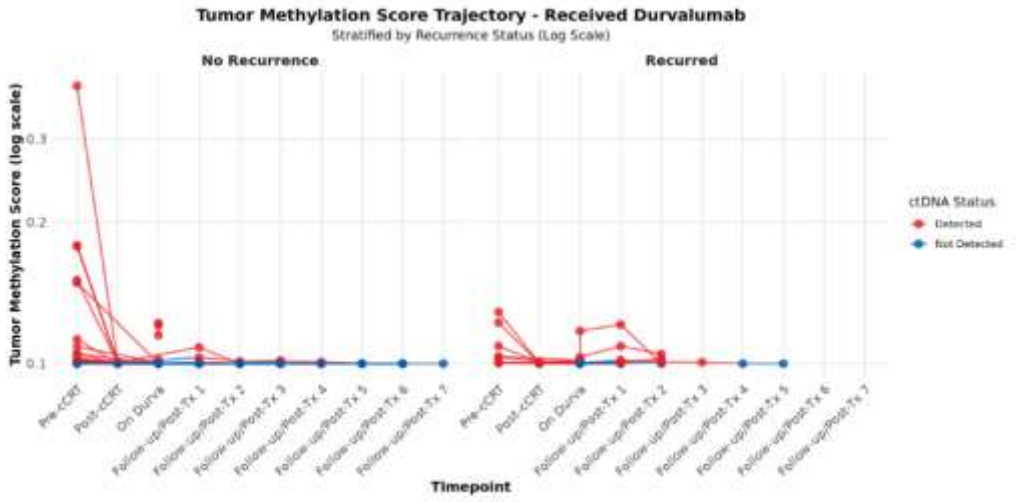


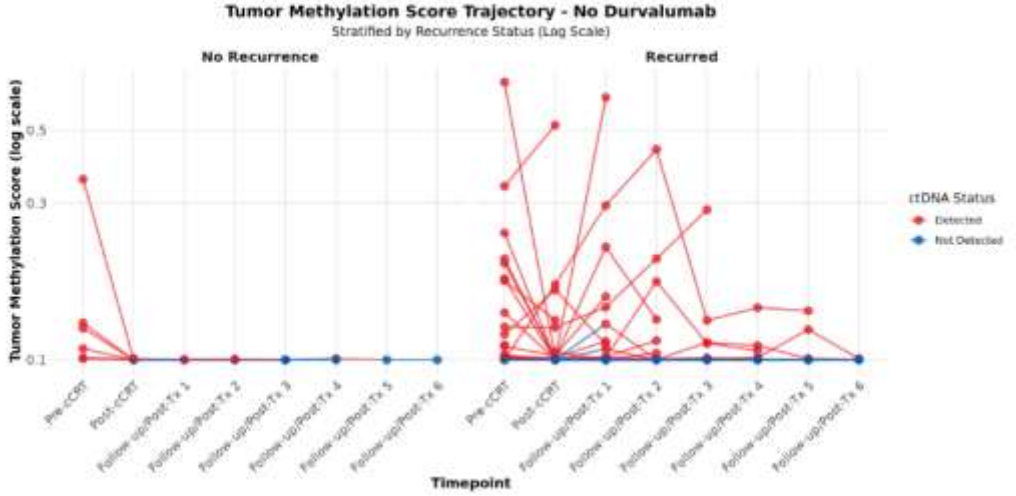
- The swimmer plot illustrates **individual patient trajectories**, integrating ctDNA detection and radiologic outcomes across follow-up
- ctDNA-defined **molecular progression consistently anticipated radiologic relapse**, with a median lead time of 3.8 months (95% CI 1.8–7.2)
- Further analyses will explore **follow-up timepoints** to refine the temporal relationship between ctDNA dynamics and clinical progression

Category	Symbol	Meaning
Treatment	Blue / **Red** / Grey	CRT / **Durvalumab** / Follow-up
ctDNA	● / ○	Detected / Not detected
Events	X / * / ▲	**Death** / Last follow-up / **Recurrence**

Results

Longitudinal assessment of ctDNA





- **Preliminary analyses** of longitudinal samples show **distinct progression patterns** between patients that received durvalumab vs those who underwent surveillance
- Higher **tumor methylation scores** were seen in patients that did not receive durvalumab and recurred
- This results were consistent and align with our previously reported outcomes and the potential protective effect of durvalumab consolidation

Conclusions

...and next steps

- In patients with unresectable stage III NSCLC treated with cCRT ± durvalumab, ctDNA negativity after cCRT was strongly associated with **improved PFS and OS**
- **Durvalumab consolidation enhanced outcomes** among both ctDNA-negative and -positive patients, and even mitigate the prognosis impact of ctDNA positivity after cCRT
- Longitudinal ctDNA assessment provided **early signals of progression**, often preceding imaging evaluation, highlighting its **potential as a dynamic biomarker** for response monitoring, risk-adapted surveillance or treatment intensification

- Ongoing work will analyze all follow-up samples to refine ctDNA dynamics and better define the timing and patterns of recurrence and its implications in survival outcomes
- Upcoming analysis will include longer follow-up and broader genomic profiling and tissue-ctDNA correlation

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THANK YOU

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