

P2.200: ctDNA-based Molecular Residual Disease as a Predictive Biomarker for Treatment Stratification in Unresectable Stage III NSCLC



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Seohee Shim^{1,2}, Sumedha Sudhaman³, Hyemin Kim², Eunjoo Oh², Naeun Lee², Subin Kim², Jinyong Kim², Hyun Ae Jung², Jong-Mu Sun², Jin Seok Ahn², Samantha Cheung³, Sharlene Velichko³, J. Bryce Ortiz³, Caitlin A. Schonewolf³, Sehhoon Park^{1,2*}, Se-Hoon Lee^{1,2,*}

¹Department of Health Sciences and Technology, Samsung Advanced Institute of Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea, ²Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, ³Natera, Inc., Austin, Texas, USA

Correspondence: sehhoon.lee119@gmail.com

INTRODUCTION

- Unresectable stage III non-small cell lung cancer (NSCLC) accounts for approximately 30% of diagnosed patients with NSCLC. For these patients, platinum-based concurrent chemoradiotherapy (CCRT) followed by durvalumab consolidation is the standard of care as established by the PACIFIC trial.
- Not all patients benefit from consolidation immune checkpoint inhibitors (ICI), and unnecessary exposure carries significant costs and toxicities. Reliable biomarkers to identify patients most likely to benefit from ICI remain unestablished.
- This study aimed to evaluate circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) assessment for patient selection and clinical outcomes in this setting.

METHODS & STUDY DESIGN

- We have prospectively enrolled patients with unresectable stage III NSCLC receiving definitive CCRT followed by physician's choice of ICI or CCRT only at Samsung Medical Center since 2021 (IRB No. 2020-10-026, current N=119).
- Personalized, tumor-informed ctDNA analysis based on whole-exome sequencing of tumor and matched normal tissue was performed using the 16-plex PCR NGS SignateraTM assay (Natera, Inc., Austin, TX, USA). Clinically archived specimens from diagnostic biopsies served as the source of tumor tissue. Whole blood was specifically collected at serial timepoints from baseline through completion of durvalumab or CCRT only for ctDNA testing, with a landmark assessment at 2–6 weeks post-CCRT.

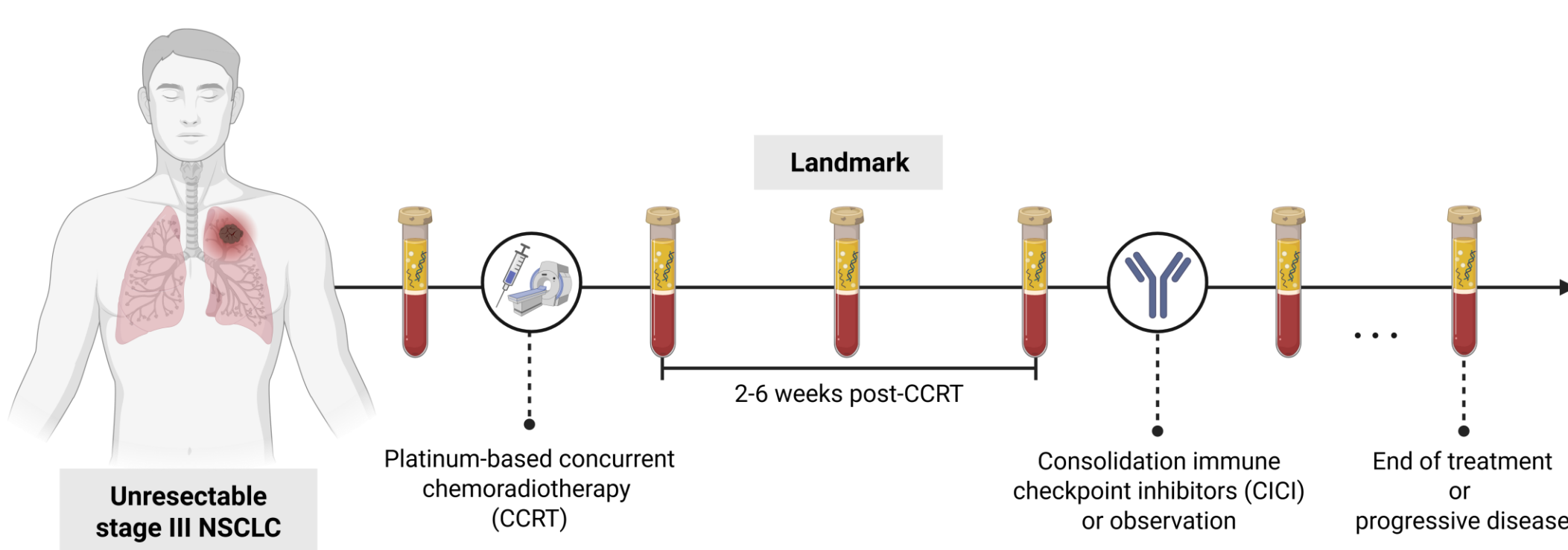


Figure 1. Study design and blood sampling timeline

- Survival analyses including disease-free survival (DFS) and overall survival (OS) were conducted using the Kaplan-Meier method with log-rank test.
- Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using the Cox proportional hazards model.

PATIENT COHORT

- A total of 16 patients with available longitudinal ctDNA data were included in this analysis, comprising CICI (N=6) and CCRT-only (N=10) groups.
- At the pre-CCRT baseline, ctDNA positivity was detected in 15 of 16 patients (93.8%), indicating that ctDNA was detectable in nearly all patients prior to treatment. Following CCRT, ctDNA clearance was achieved in 11 of 15 evaluable patients (73.3%) at the landmark timepoint.
- Disease progression occurred in 12 patients (75%), including 10 deaths (62.5%).

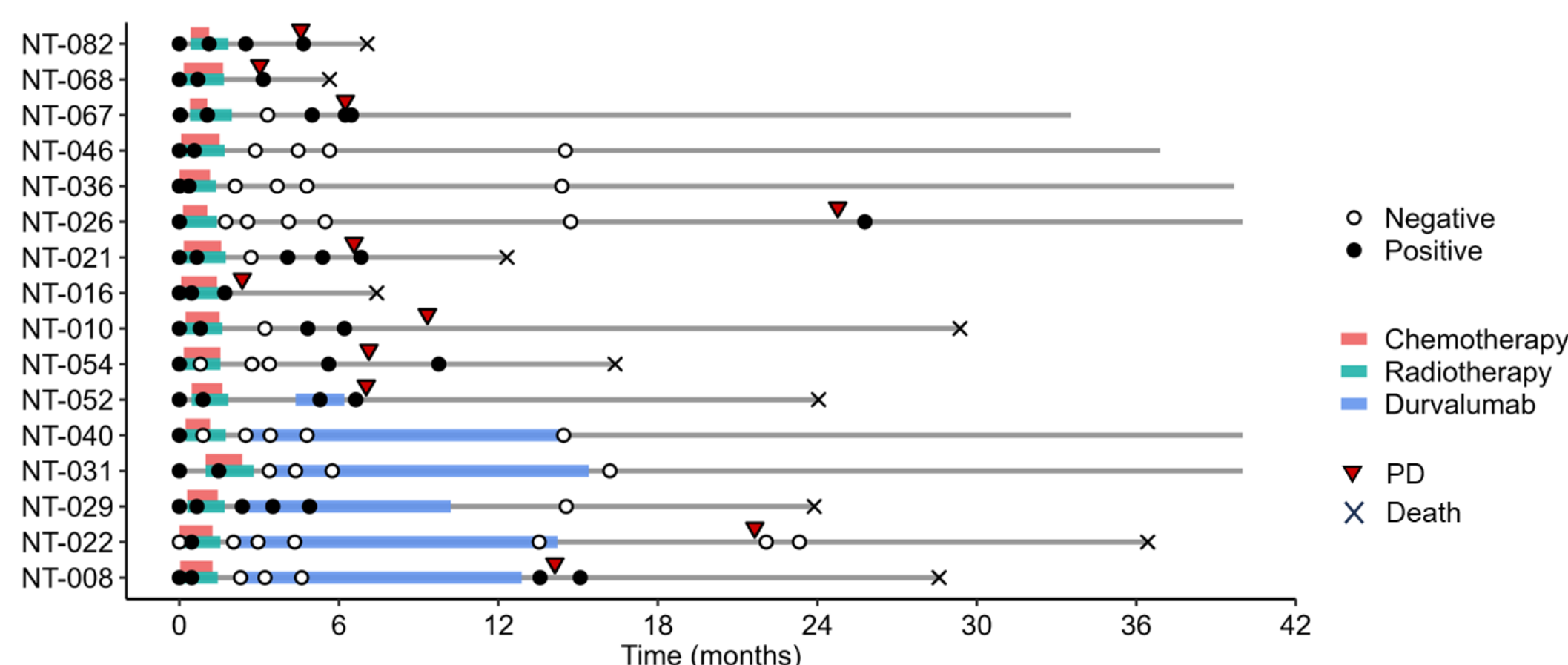


Figure 2. Individual patient treatment course and ctDNA dynamics

DISCUSSION AND CONCLUSION

Conclusion

Our findings demonstrate that tumor-informed ctDNA-based MRD assessment has strong prognostic and potential predictive value in patients with unresectable stage III NSCLC in the post-CCRT setting. Landmark ctDNA status accurately predicted DFS and OS, and exploratory evidence suggested potential ICI benefit in patients with detectable residual disease. Longitudinal ctDNA dynamics further stratified clinical outcomes into three distinct patterns.

Actionable Take Away Message

ctDNA status post-CCRT (pre-IO) is a strong, statistically significant predictor of relapse and survival after CCRT, and can be used today to identify high-risk patients who may warrant closer surveillance or consideration for clinical trial enrollment. These findings provide a rationale for more selective, ctDNA-guided use of ICI in clinical practice.

Future Direction for Research

These findings support ctDNA-based MRD as a clinically actionable biomarker for treatment stratification. Further validation is ongoing in this prospectively enrolling cohort to better define the patient subset most likely to benefit from ICI. This work aims to establish ctDNA-guided treatment selection for future clinical use in unresectable stage III NSCLC.

RESULTS

1. Baseline characteristics

Table 1. Baseline Characteristics				
Variable	Total (N = 16)	CICI (N = 6)	CCRT only (N = 10)	P value
Median age (range)	64 (48-75)	64 (54-75)	64 (48-74)	0.8
Sex				0.6
Male	10 (62.5)	3 (50.0)	7 (70.0)	
Female	6 (37.5)	3 (50.0)	3 (30.0)	
Smoking status				0.6
Ever	12 (75.0)	4 (66.7)	8 (80.0)	
Never	4 (25.0)	2 (33.3)	2 (20.0)	
Histology				>0.9
LUAD	6 (37.5)	2 (33.3)	4 (40.0)	
LUSC	9 (56.3)	4 (66.7)	5 (50.0)	
Others	1 (6.3)	0 (0.0)	1 (10.0)	
EGFR				>0.9
Wild-type	14 (93.3)	5 (100.0)	9 (90.0)	
Mutation	1 (6.7)	0 (0.0)	1 (10.0)	
Missing	1	1	0	
ALK				0.7
Wild-type	15 (100.0)	5 (100.0)	10 (100.0)	
Missing	1	1	0	
PD-L1 (22C3)				
< 1%	8 (53.3)	2 (40.0)	6 (60.0)	
1 - 49%	1 (6.7)	0 (0.0)	1 (10.0)	
≥ 50%	6 (40.0)	3 (50.0)	3 (30.0)	
Missing	1	1	0	

Data are presented as No. (%) or Median (range).
P values from Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.
CICI: Consolidation Immune Checkpoint Inhibitor (Durvalumab); LUAD: Lung Adenocarcinoma; LUSC: Lung Squamous Cell Carcinoma.

2. ctDNA status post-CCRT (pre-IO) predicts DFS and OS

Post-CCRT (pre-IO) ctDNA positivity was significantly associated with inferior DFS (median 2.0 vs 20.1 months; HR 4.11; 95% CI 1.13-14.97; $P=0.021$) and OS (median 7.0 months vs not reached; HR 12.94; 95% CI 2.26-74.06; $P=0.0003$) compared to ctDNA-negative patients.

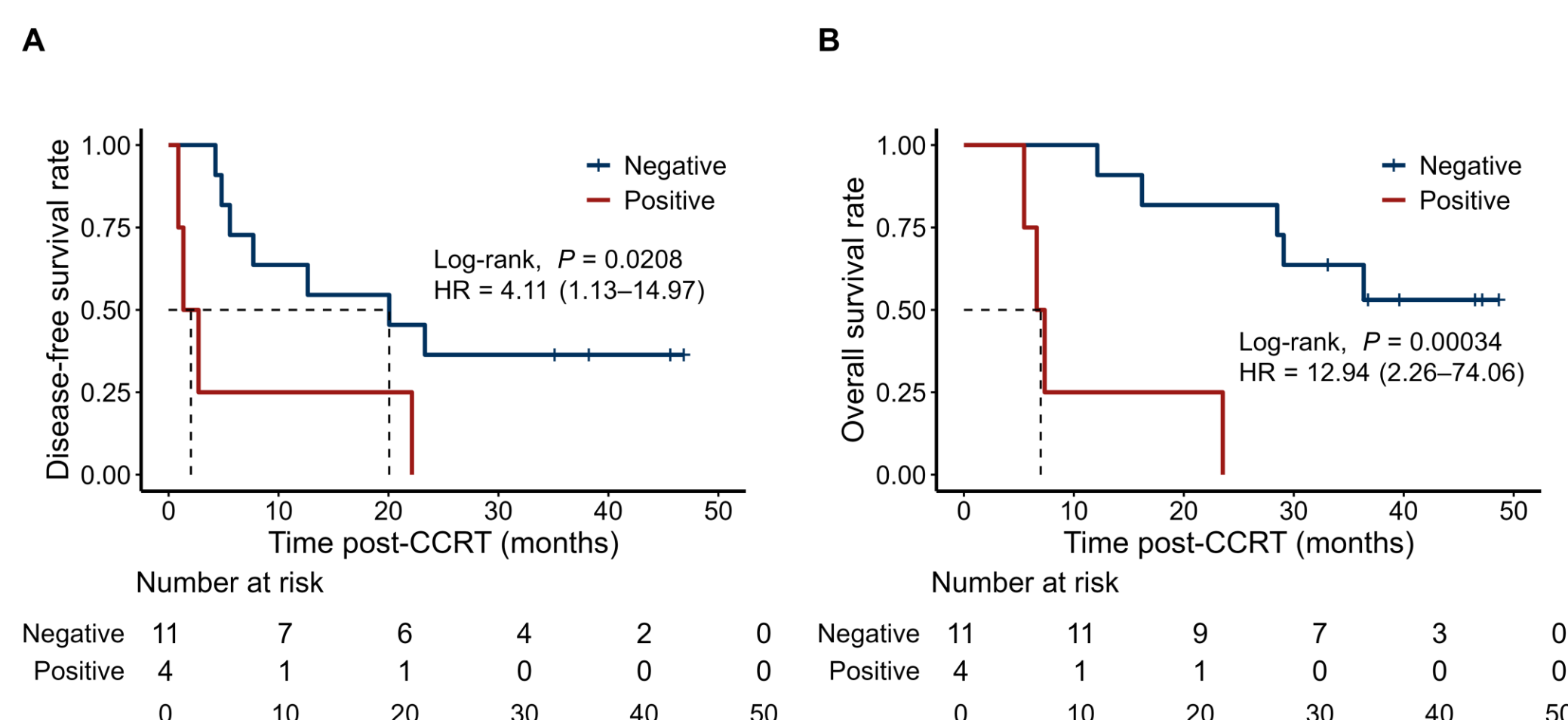


Figure 3. Kaplan-Meier curves for DFS and OS by post-CCRT ctDNA status in evaluable patients (N=15)

3. ICI benefit in landmark ctDNA-positive patients

In the post-CCRT (pre-IO) ctDNA-positive subgroup (N=4), ICI-treated patients demonstrated numerically longer DFS compared to CCRT only (22.1 vs 0.9-2.7 months; $P=0.182$). Given the limited subgroup size, this difference did not reach statistical significance; however, these findings suggest a potential clinical benefit of ICI in post-CCRT (pre-IO) ctDNA-positive patients that warrants validation in larger, prospective cohort.

Table 2. Outcomes in post-CCRT (pre-IO) ctDNA-positive patients by treatment group			
Patient ID	Group	DFS (months)	OS (months)
NT-029	CICI	22.1	22.2
NT-016	CCRT only	0.9	5.9
NT-068	CCRT only	1.3	4.0
NT-082	CCRT only	2.7	5.2

4. Longitudinal ctDNA dynamics define three risk groups

Longitudinal ctDNA analysis identified three distinct dynamic patterns: ctDNA clearance (N=6, positive then negative), ctDNA rebound (N=6, negative then positive), and persistently positive (N=4), significantly associated with DFS (NR vs 6.6 vs 2.0 months, respectively; $P<0.0001$) and OS (NR vs 28.8 vs 7.0 months; $P=0.001$).

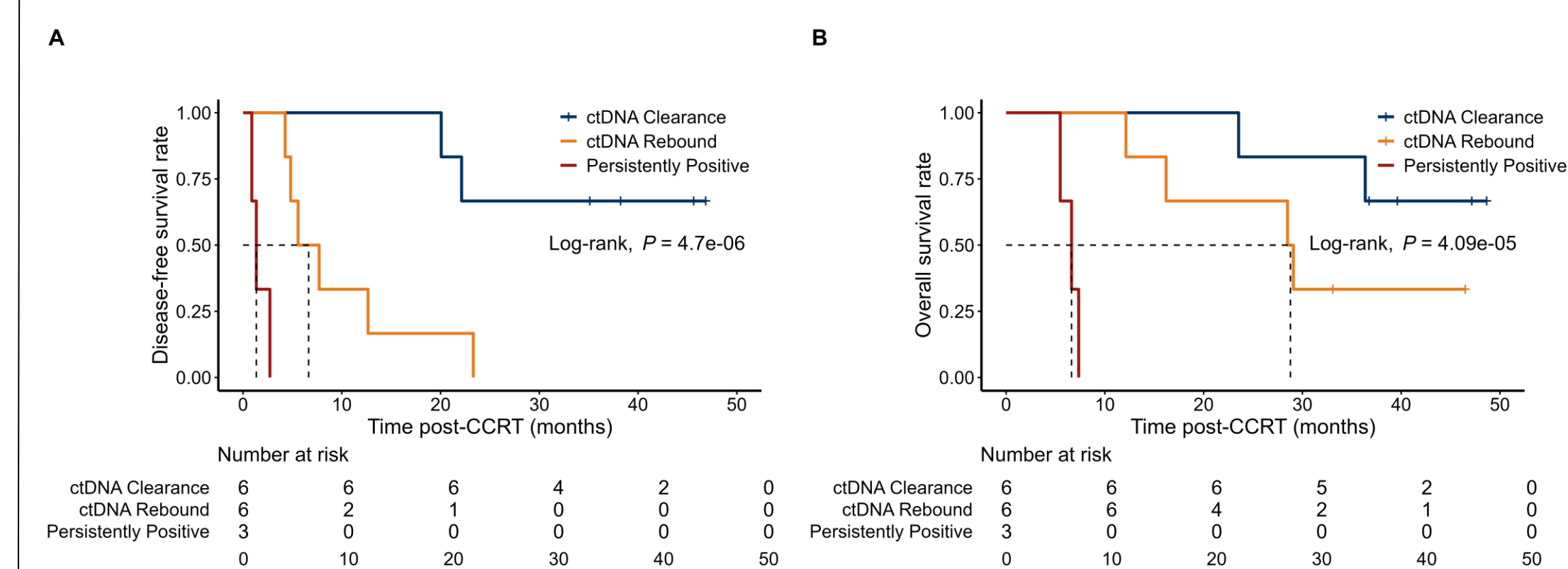


Figure 5. Kaplan-Meier curves for DFS and OS based on longitudinal ctDNA dynamic group

5. Pattern-specific outcomes across the three risk groups

Persistently positive patients had the poorest outcomes, with all experiencing relapse. Rebound cases had intermediate outcomes, with 5 of 6 becoming ctDNA-positive prior to clinical relapse and 1 shortly after. In contrast, ctDNA clearance was associated with the most favorable outcomes, with 4 of 6 remaining event-free; the 2 patients who relapsed after initial clearance did so later, following discontinuation of ICI.

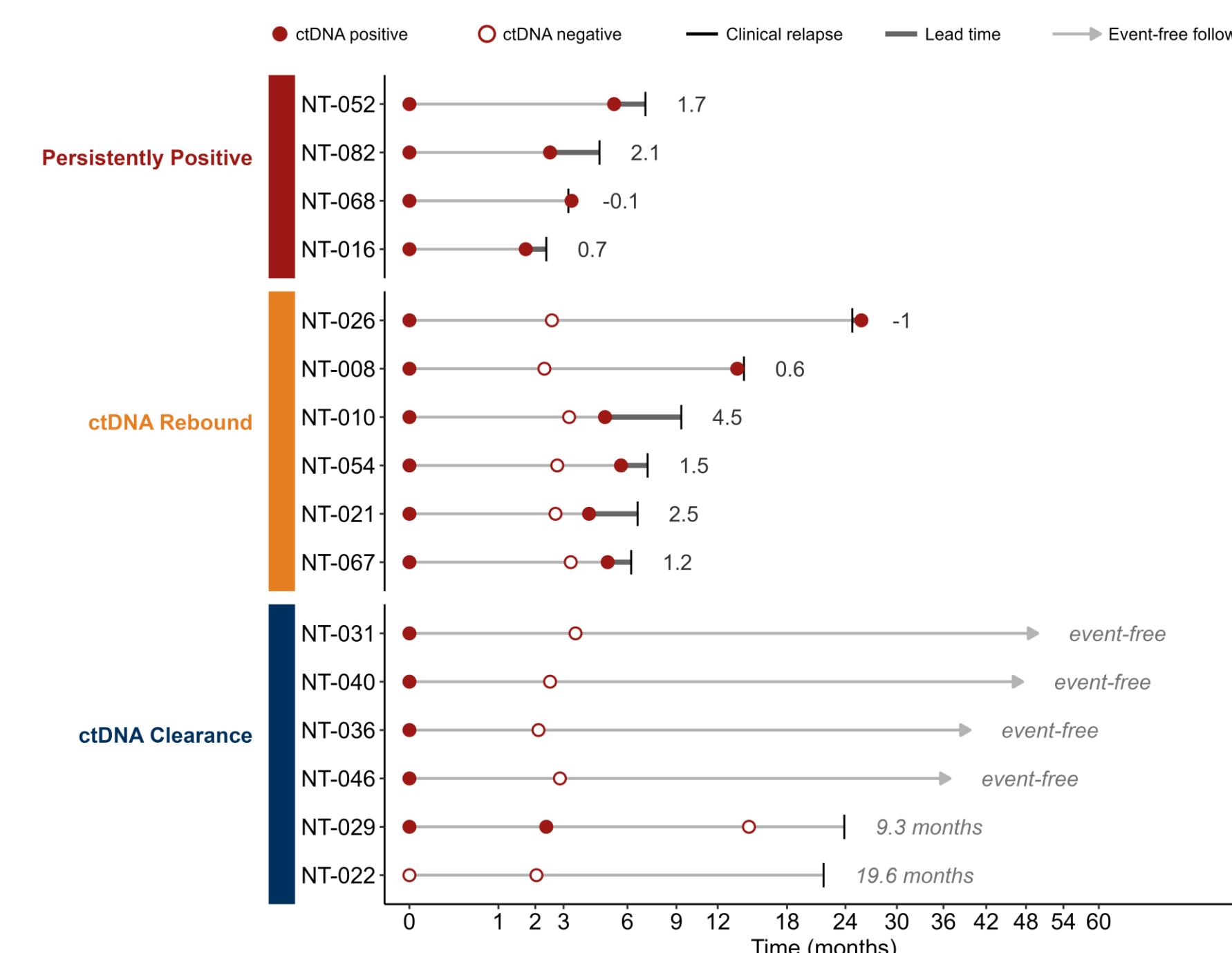


Figure 6. ctDNA dynamics and lead time to clinical relapse across the three risk groups

6. Treatment distribution across the three risk groups

