

INTRODUCTION

- Circulating tumor DNA (ctDNA) kinetics is a validated prognostic and predictive biomarker in curative-intent NSCLC, where post-treatment clearance or persistence is strongly associated with recurrence risk.
- In advanced NSCLC, the clinical utility of ctDNA kinetics is less well established.
- Prior studies have largely focused on binary on-treatment ctDNA changes (clearance vs persistence) during the **current** line of therapy, providing limited insight into outcomes after progression.
- Because patients with advanced NSCLC commonly receive multiple sequential lines of treatment, biomarkers that forecast outcomes on the **next** line of therapy could inform treatment selection, clinical trial enrollment, and patient counseling.
- We hypothesized that the rate of ctDNA increase immediately preceding disease progression ("pre-progression ctDNA kinetics") reflects tumor aggressiveness and is associated with progression-free survival (PFS) on subsequent therapy.**

METHODS

- Study design:** Retrospective single-center analysis of patients with advanced NSCLC receiving palliative systemic therapy and serial tumor-informed ctDNA monitoring (Signatera™) at Northwestern Memorial Hospital.
- Pre-progression ctDNA kinetics:** Defined as the slope between the two most recent log-transformed ctDNA measurements (log MTM/mL) obtained within 100 days before documented disease progression. Slopes were expressed as the rate of change per day (×100/day).
- Patient stratification:** Evaluable patient-line cases were dichotomized at the cohort median ctDNA slope into **High-slope** and **Low-slope** groups.
- Cohort derivation:** Among 292 screened patients with advanced NSCLC, 26 met baseline ctDNA-monitoring criteria. Eleven evaluable patient-line cases from 9 patients met all analytic criteria, including ≥2 ctDNA measurements within the 100-day pre-progression window and documented progression-free survival (PFS) on subsequent therapy.
- Endpoints and statistical analysis:** The primary outcome was subsequent-line PFS. Associations between ctDNA kinetics and clinical outcomes were assessed using Pearson and Spearman correlation analyses. PFS was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) were estimated using univariable and multivariable Cox proportional hazards models adjusted for treatment type.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Pre-progression ctDNA kinetics were associated with subsequent-line PFS in advanced NSCLC.
- Faster increases in ctDNA immediately preceding progression were associated with shorter PFS on subsequent therapy.
- Notably, this signal emerged before radiographic confirmation of progression, suggesting a potential opportunity for earlier treatment planning and clinical trial consideration.

Future Direction for Research

- These findings support ctDNA kinetics as a forward-looking biomarker, with prognostic value extending beyond the current line of therapy.
- Assessment of ctDNA trajectory before progression may help identify patients at risk for poor outcomes on subsequent treatment and inform sequencing strategies.

Limitations

- Small, single-center retrospective study with a limited analytic cohort (9 patients; 11 patient-line cases).
- Progression assessments were performed in routine clinical practice and were not protocol-defined.
- Findings should be considered hypothesis-generating and require prospective validation. strategies.

Conclusions

- Pre-progression ctDNA kinetics may provide an early indicator of outcomes on subsequent therapy in advanced NSCLC.**
- If validated prospectively, pre-progression ctDNA dynamics could support real-time treatment planning, clinical trial enrollment, and future biomarker-guided sequencing**

REFERENCES & ACKNOWLEDGEMENTS

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Artificial Intelligence (AI) Use Disclaimer

Claude (Anthropic) was used to (1) refine the language of the manuscript and abstract, and (2) writing code for statistical analysis. All statistical outputs generated with AI-assisted code were independently reviewed and verified by the study authors. AI did not contribute to study design, data interpretation, or scientific conclusions, which remain the sole responsibility of the authors

RESULTS

Table 1. Patient & treatment-line characteristics

Patient Characteristics	No. (%) (N=9)
Age (years)	
Median (range)	69 (57–79)
Sex	
Male	3 (33%)
Female	6 (67%)
Smoking History	
Yes	6 (67%)
No	3 (33%)
ECOG Performance Status	
0-1	8 (89%)
2	1 (11%)
Histology	
Adenocarcinoma	6 (67%)
Squamous cell carcinoma	3 (33%)
Stage at Diagnosis	
Stage I-II	2 (22%)
Stage III-IV	7 (78%)
Treatment Line Characteristics	No. (%) (N=11)
Targeted therapy	5 (45%)
Immunotherapy	2 (18%)
Chemoimmunotherapy	1 (9%)
Immunotherapy + targeted therapy	1 (9%)
Chemotherapy	1 (9%)
Clinical trial ^a	1 (9%)

Figure 2. Forest Plot

Univariable and multivariable Cox regression for pre-progression ctDNA slope (per-unit increase), adjusted for treatment type.

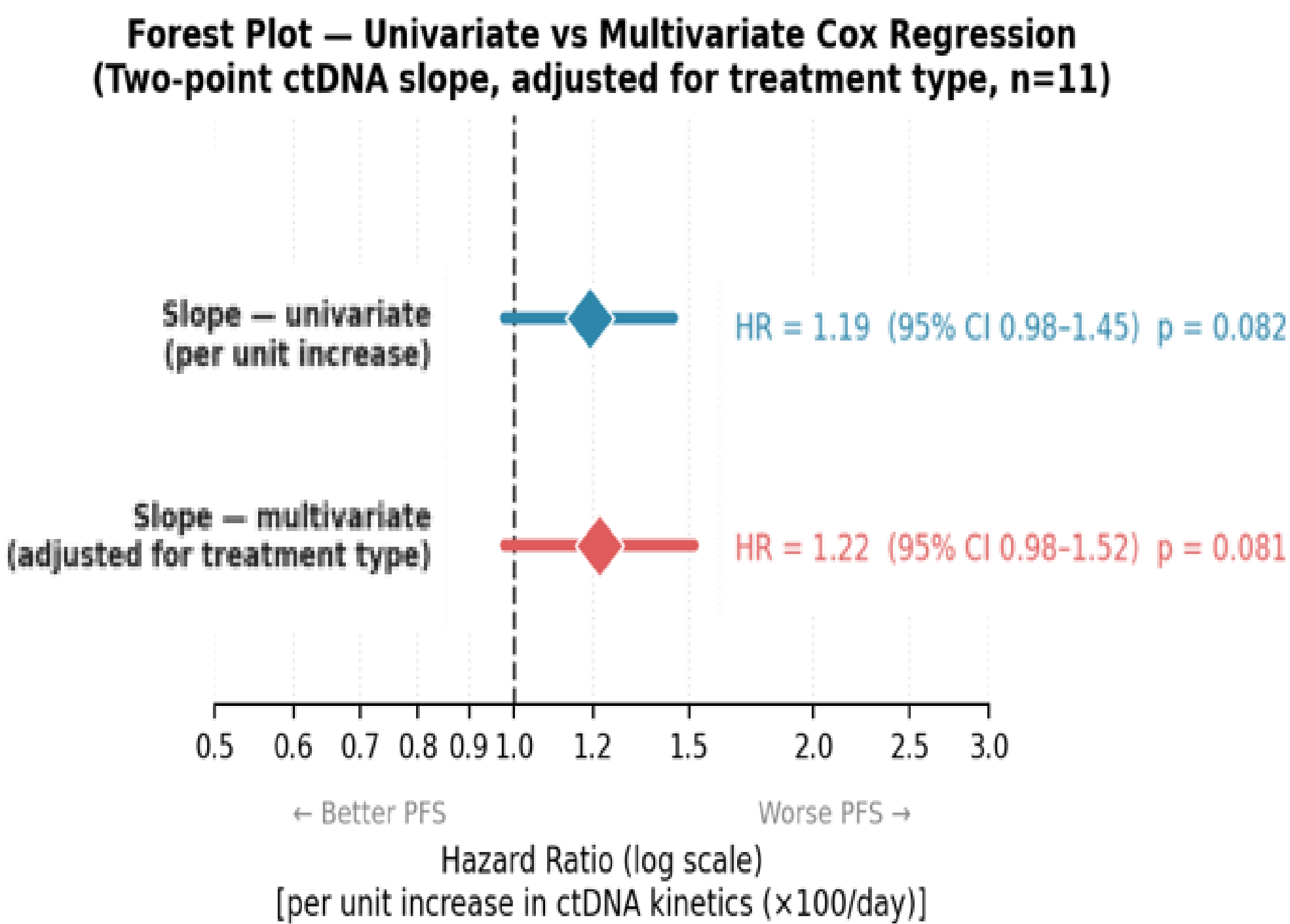


Figure 1a. Scatter Plot

Pre-progression ctDNA kinetics vs. subsequent-line PFS (Pearson $r = -0.81$, $p = 0.003$).

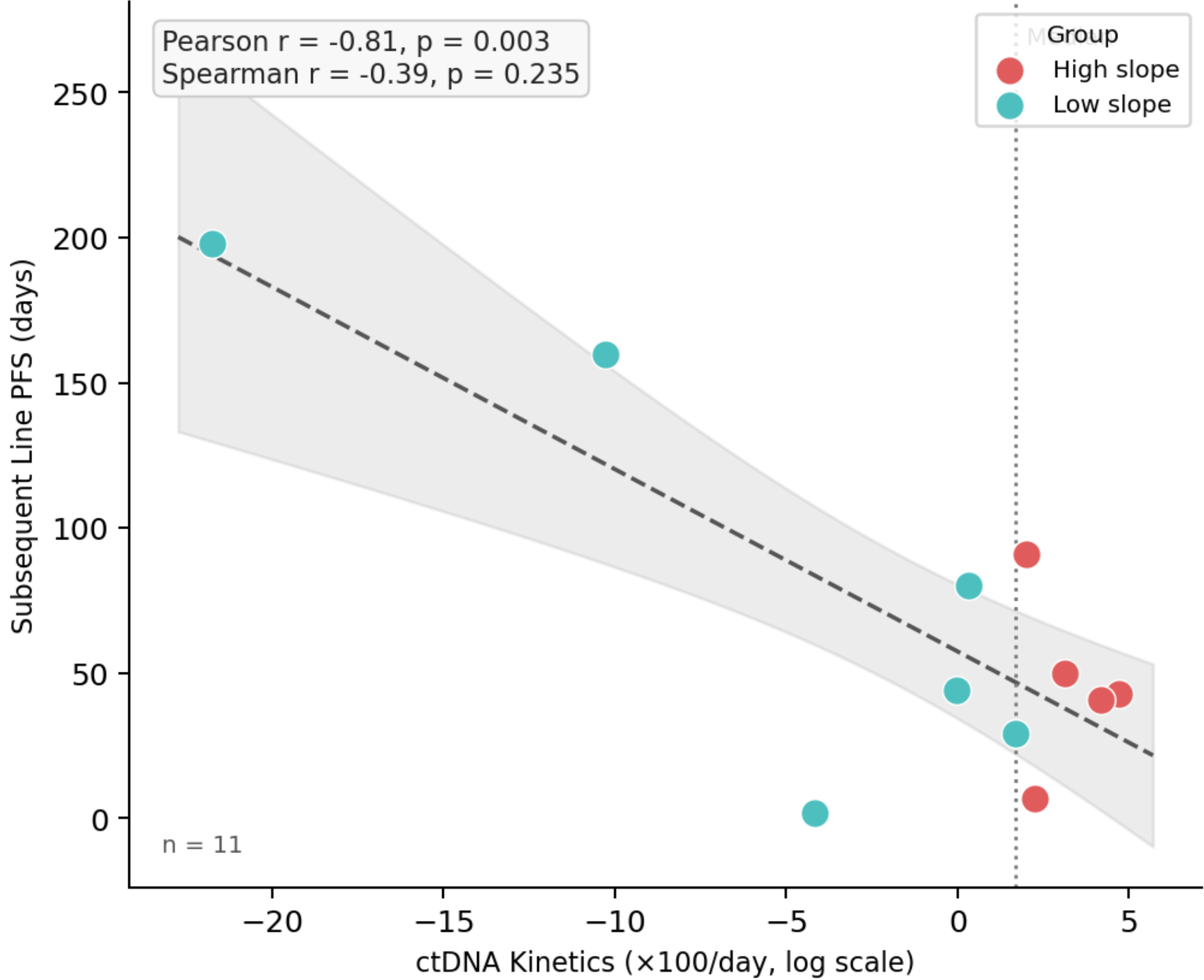


Figure 1b. Kaplan-Meier Curve

subsequent-line PFS by High- vs. Low-slope group, dichotomized at cohort median slope (log-rank $p = 0.351$; HR 1.87, 95% CI 0.49–7.10)

