

Tumor-Informed ctDNA for Disease Monitoring Across Stages I–IV NSCLC: A Real-World Analysis

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BACKGROUND

- Tumor-informed circulating tumor DNA (ctDNA) enables molecular residual disease (MRD) detection and treatment-response monitoring in non-small cell lung cancer (NSCLC).
- Real-world data characterizing its diagnostic performance and prognostic utility across all disease stages remain limited.
- This study assesses ctDNA-radiographic concordance in a stage I-IV NSCLC cohort and evaluates the prognostic impact of ctDNA kinetics in the metastatic setting.

OBJECTIVES

- Evaluate ctDNA–radiographic concordance (SE, SP, PPV, NPV) across stage I–IV NSCLC using a 90-day paired event-level methodology
- Assess the prognostic impact of ctDNA kinetics (≥2 consecutive ctDNA-positive results) on PFS and OS in the metastatic setting

METHODS

- Design: Multi-center retrospective analysis between 2022–2026
- Setting: Memorial Cancer Institute, Pembroke Pines, FL
- Assay: Signatera™, personalized 16-variant tumor-informed ctDNA panel
- Cohort: 120 patients with stage I–IV NSCLC and serial ctDNA testing
 - 75 early-stage / locally advanced (stages I–III)
 - 45 metastatic (stage IV)
- Primary endpoint: ctDNA–imaging concordance (542 paired events, ±90-day window)
- Secondary endpoints (stage IV): PFS and OS stratified by ≥2 consecutive ctDNA-positive vs. <2, via Kaplan–Meier analysis and Cox proportional hazards models
- ctDNA lead time was assessed as the interval in days between first ctDNA-positive result and the subsequent imaging-confirmed progression in the cohort.
- ctDNA completion rate was defined as the proportion of ordered ctDNA tests that yielded a reported result, assessed from institutional ordering records.

BASELINE PATIENT CHARACTERISTICS

Characteristic	Overall (n=120)	Early Stage/LA (n=75)	Stage IV (n=45)
Demographics			
Age, median (range), yr	69 (43-88)	70 (47-88)	65 (43-80)
Male sex, n (%)	53 (44.2%)	32 (42.7%)	21 (46.7%)
Female sex, n (%)	67 (55.8%)	43 (57.3%)	24 (53.3%)
Histology			
Adenocarcinoma	100 (83.3%)	63 (84.0%)	37 (82.2%)
Squamous cell carcinoma	11 (9.2%)	9 (12.0%)	2 (4.4%)
Other	9 (7.5%)	3 (4.0%)	6 (13.4%)
Disease Stage			
Stage I	37 (30.8%)	37 (49.3%)	—
Stage II	18 (15.0%)	18 (24.0%)	—
Stage III	20 (16.7%)	20 (26.7%)	—
Stage IV	45 (37.5%)	—	45 (100%)
Genomic profile			
EGFR mutation	32 (26.7%)	18 (24.0%)	14 (31.1%)
KRAS mutation	22 (18.3%)	15 (20.0%)	7 (15.6%)
RET fusion	7 (5.8%)	1 (1.3%)	6 (13.3%)
MET amplification / exon 14	5 (4.2%)	2 (2.7%)	3 (6.7%)
ALK fusion	2 (1.7%)	0 (0.0%)	2 (4.4%)
ROS1 fusion	1 (0.8%)	1 (1.3%)	0 (0.0%)
TMB-high (≥10 mut/Mb)	13 (10.8%)	10 (13.3%)	3 (6.7%)
PD-L1 ≥50%	13 (10.8%)	12 (16.0%)	1 (2.2%)
Stage IV metastatic sites			
CNS / brain metastases	—	—	21 (46.7%)
Bone metastases	—	—	18 (40.0%)
Liver metastases	—	—	9 (20.0%)
Pleural metastases	—	—	10 (22.2%)
Adrenal metastases	—	—	7 (15.6%)

Data shown as n (%) unless stated. LA = locally advanced. NGS = next-generation sequencing. Patients may have >1 mutation or metastatic site recorded.

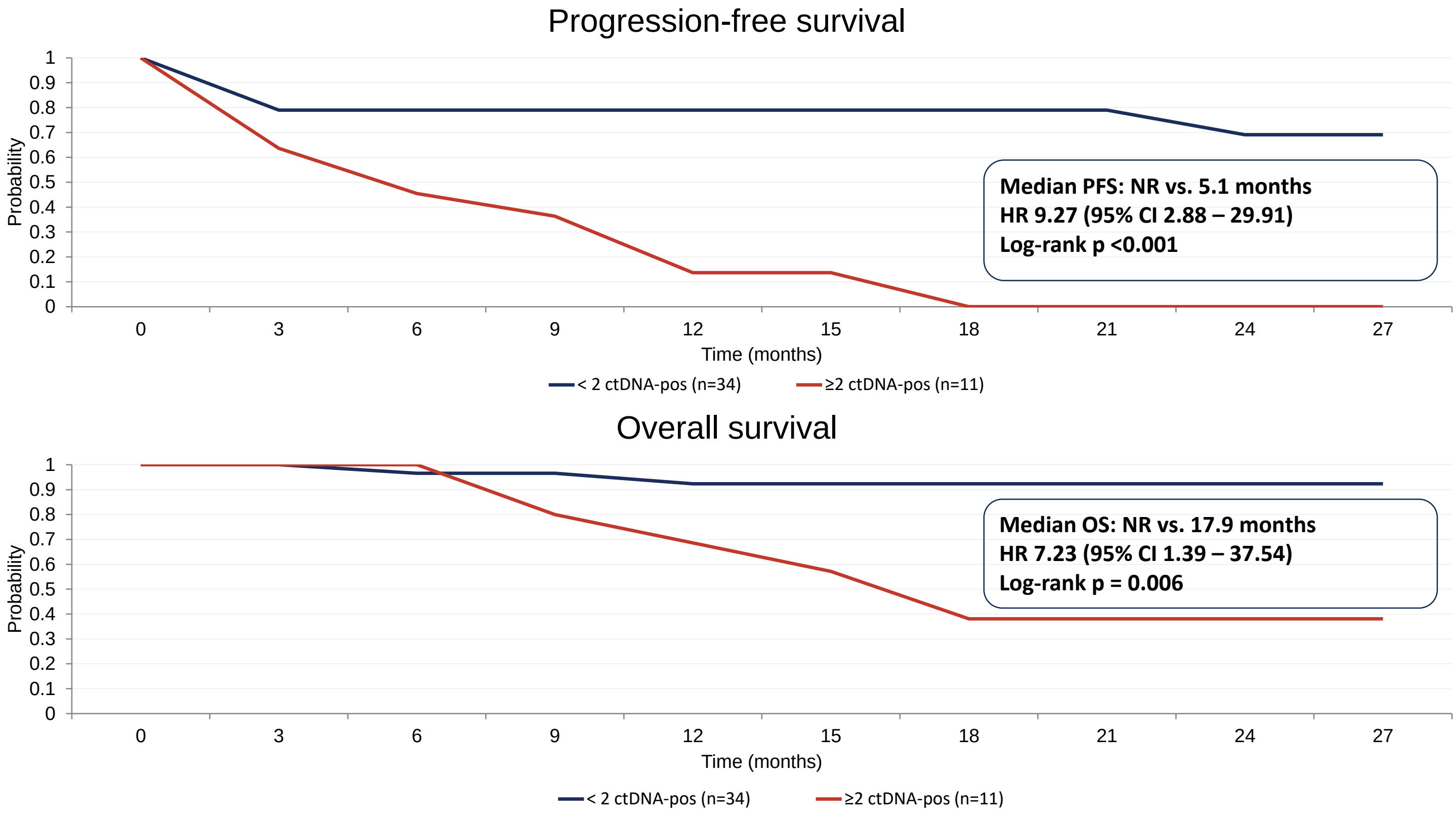
DIAGNOSTIC PERFORMANCE

	Imaging +	Imaging -	58.7% Sensitivity
ctDNA +	27	44	91.1% Specificity
ctDNA -	19	452	38.0% Positive Predictive Value
Total	46	496	96.0% Negative Predictive Value

Early stage (I–III): SE 37.5% SP 96.5% PPV 23.1% NPV 98.2%

Stage IV: SE 63.2% SP 84.0% PPV 41.4% NPV 92.7%

STAGE IV: ctDNA KINETICS AND OUTCOMES



ctDNA LEAD TIME

- ctDNA positivity preceded radiographic progression by a median of **24.5 days**

EARLY-STAGE / LOCALLY ADVANCED RESULTS (N = 75)

- 87.3% (62/71) of resected patients were serially ctDNA-negative with no evidence of disease (NED) at last follow-up
- 100% concordance between ctDNA negativity and imaging NED in all 4 unresectable stage III patients during and after systemic therapy
- NPV 98.2% in early stage supports that ctDNA negativity reliably confirms disease-free status after resection

CONCLUSIONS

- ctDNA demonstrated high specificity (91.1%) and NPV (96.0%), supporting tumor-informed ctDNA as a reliable complementary surveillance tool in NSCLC
- ≥2 consecutive ctDNA-positive results are strongly associated with inferior PFS (5.1 months vs. NR; HR 9.27, p<0.001) and OS (17.9 months vs. NR; HR 7.23, p=0.006) in stage IV NSCLC
- ctDNA provided 24.5-day median lead time in our cohort, representing a clinically actionable window for earlier treatment decisions
- ctDNA negativity is highly associated with disease-free status in resected stage I–III disease
- Real-world ctDNA completion rate of 74.5% highlights implementation barriers, warranting further study for optimization