Circulating Tumor DNA (ctDNA) as a Biomarker to Guide Treatment Escalation and De-Escalation in Non-Small Cell Lung Cancer (NSCLC): A Review of the Current Evidence

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Background

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for 85% of lung cancers. While treatment for NSCLC has advanced, there remains a need for reliable tools to identify which patients need additional therapy versus who can safely de-escalate. Standard imaging often misses minimal residual disease (MRD), and fixed treatment durations fail to account for individual response. Circulating tumor DNA (ctDNA) offers a minimally invasive approach for real-time assessment of molecular response and residual disease, potentially overcoming limitations of radiographic monitoring and tissue-based testing.

Objective(s)

Summarize current evidence and limitations regarding the use of ctDNA to inform treatment escalation, de-escalation, and surveillance strategies in non-small cell lung cancer (NSCLC).

Supplemental Table

Methods

A targeted literature search was conducted using PubMed and EMBASE, to identify studies evaluating ctDNA in NSCLC. Search terms included "circulating tumor DNA", "non-small cell lung cancer", "treatment escalation," and "de-escalation."

Discussion

ctDNA clearance may identify candidates for de-escalation, while persistence may identify patients needing escalation or closer monitoring. Ongoing trials (CTONG 2105, 2201) will help determine whether ctDNA can safely guide treatment personalization in clinical practice.

Study	Population / Setting	ctDNA Use	Key findings
Gale et al., 2022 – LUCID	88 early-stage NSCLC, I,II, IIIA/B	Detect molecular residual disease (MRD) and recurrence after treatment	Residual ctDNA predicted early relapse, supporting ctDNA as an early marker of recurrence
Abbosh et al., 2017 – TRACERx	Early-stage resectable NSCLC, stage I–III	Track tumor evolution and relapse	ctDNA detected 93% (13/14) of relapses, with a median 70-day lead time before clinical/radiographic recurrence
Dong et al., 2024 – JAMA Oncology	Advanced NSCLC, stage IIIA/IIIB or IV	Guide Tyrosine Kinase Inhibitor (TKI) de-escalation/restart	ctDNA-guided treatment pauses provided meaningful treatment-free intervals without compromising outcomes; restarting treatment based on ctDNA positivity was better than waiting for imaging-confirmed relapse.
Anagnostou et al., 2023 – BR.36	Advanced/metastatic NSCLC	Assess response to pembrolizumab	ctDNA response provided an early indicator of benefit from immunotherapy and was used to guide treatment intensification vs continued pembrolizumab.
Gray et al., 2024 – FLAURA/AURA3	EGFR-mutated advanced NSCLC	Monitor progression during osimertinib	ctDNA progression occurred at or before imaging in 64% of FLAURA and 56% of AURA3 patients, detecting progression ~2.6–3.4 months earlier.
Hellmann et al., 2020	Stage IV NSCLC with durable response to PD-(L)1 therapy	Predict risk of relapse	27 patients had undetectable ctDNA and 25 (93%) remained progression-free; all 4 patients with detectable ctDNA eventually progressed
Dong et al., 2025	Resected EGFR-mutated stage I–III NSCLC	Longitudinal MRD monitoring to guide adjuvant TKI duration	ctDNA-MRD detected molecular recurrence early and showed potential for safely shortening/de-escalating adjuvant TKI therapy, but larger prospective trials are needed
Zhang JT et al, 2024 - CTONG 2201 (Ongoing trial)	Resected stage IB–IIIA NSCLC	Identify patients with persistently undetectable MRD who may avoid adjuvant therapy	Evaluates whether patients with 2 consecutive undetectable MRD tests can safely omit adjuvant therapy; primary endpoint is 2-year DFS (Disease-free survival)

Results / Conclusion

In resectable disease, postoperative ctDNA clearance predicts excellent outcomes (TRACERx, LUCID), while persistent MRD identifies patients undertreated by adjuvant EGFR Tyrosine Kinase Inhibitor (TKI) therapy. In metastatic disease, Dong et al. showed feasibility of ctDNA-guided TKI discontinuation in selected patients (median PFS off-therapy 18.4 months; 96% re-clearance), supporting de-escalation strategies. In contrast, persistent ctDNA during treatment is associated with poor outcomes with both pembrolizumab (BR.36) and osimertinib (FLAURA, AURA3), highlighting its potential to identify patients needing escalation or closer monitoring. Current evidence supports ctDNA as a powerful prognostic biomarker, but prospective randomized trials are needed to establish its role in guiding treatment escalation and de-escalation in NSCLC.

Reference(s) and Disclosure

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