

Prognostic, Not Yet Predictive: What ctDNA / MRD Can — and Cannot — Decide in Resectable NSCLC

Daniel E. Rosas, MD · Luis E. Raez, MD · Memorial Cancer Institute, Memorial Healthcare System · Hollywood, Florida, USA · drosas@mhs.net

BACKGROUND & QUESTION

- Perioperative chemo–immunotherapy has transformed resectable NSCLC; ctDNA / MRD gives a non-invasive read on treatment response and residual disease.
- The clinical goal is decision-making: escalate therapy when MRD-positive, de-escalate when MRD-negative.
- Prognostic, surrogate, and predictive roles are distinct — and only predictive validation justifies changing therapy.
- **Question — which of these roles does the current NSCLC evidence actually support, and which does it not?**

THE EVIDENCE LADDER — THREE ROLES

PROGNOSTIC (risk)

Robust in NSCLC. CheckMate 816: 5-yr OS 75% vs 53% by presurgical ctDNA clearance. NADIM: low pretreatment ctDNA — PFS HR 0.20, out-predicting PD-L1, TMB and imaging.

SURROGATE (response)

Credible candidate. Post-induction ctDNA clearance tracks pathologic response (AEGEAN). Formal trial-level surrogacy is not yet established.

PREDICTIVE (treatment-guiding)

Not validated in NSCLC — IMpower010 showed adjuvant benefit regardless of post-operative ctDNA. Prospective predictive proof exists only cross-cancer.

Scope & method. Narrative synthesis of perioperative trials plus cross-cancer predictive benchmarks; populations, endpoints, assays and sampling timing differ. No pooling — the hazard ratios shown are from separate trials and are not directly comparable head-to-head.

NSCLC EVIDENCE: PROGNOSTIC — ROBUST

CheckMate 816 Forde, NEJM 2025 · NADIM Provencio, JCO 2022

- CheckMate 816: by presurgical ctDNA clearance, 5-yr OS 75% (cleared) vs 53% (not cleared); clearance was more frequent with nivolumab + chemo (56% vs 35%).
- NADIM: low pretreatment ctDNA → PFS HR 0.20, OS HR 0.07; ctDNA out-predicted PD-L1, TMB and RECIST (C-index 0.82 vs 0.72 for OS).
- **Across trials, ctDNA / MRD status separates outcome more sharply than standard pathologic or molecular markers.**

75% v 53%

CheckMate 816 5-yr OS by ctDNA clearance

HR 0.20

NADIM PFS low pretreatment ctDNA

0.82 v 0.72

ctDNA vs RECIST C-index (OS)

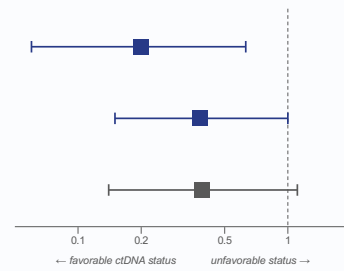
PROGNOSTIC SIGNAL — ACROSS TRIALS

ctDNA / MRD status is strongly prognostic across NSCLC trials

NADIM · low vs high pretreatment ctDNA — PFS
HR 0.20 (0.06–0.63) · JCO 2022

CheckMate 816 · clearance vs none — OS (N+C)
HR 0.38 (0.15–1.00) · NEJM 2025

CheckMate 816 · clearance vs none — OS (chemo)
HR 0.39 (0.14–1.11) · NEJM 2025



Surrogate signal — AEGEAN. Pre-surgical ctDNA clearance was higher with durvalumab (66% vs 41%); early (C2D1) clearance tracked pathologic response (pCR 50% vs 15%). Post-surgical MRD-positivity was powerfully prognostic for relapse (DFS HR ≈ 21 durvalumab, ≈ 14 placebo). Clearance is a plausible early-response surrogate; trial-level surrogacy remains unproven.

THE PREDICTIVE GAP — READ CAREFULLY

- IMpower010 ctDNA substudy: adjuvant atezolizumab improved DFS across PD-L1–positive subgroups irrespective of post-operative ctDNA status.
- Investigators cautioned this ‘calls into question the sensitivity and negative predictive value’ of ctDNA as a selection tool.
- **Prognostic ≠ predictive. Only a marker-stratified randomized design proves who benefits — and none is yet positive in NSCLC.**

PREDICTIVE PROOF: CROSS-CANCER ONLY

IMvigor011 bladder · Powles, NEJM 2025

ctDNA-positive, MRD-guided adjuvant atezolizumab: DFS 9.9 vs 4.8 mo, HR 0.64 (0.47–0.87). ctDNA-negative patients spared therapy kept excellent outcomes (2-yr OS 97%). First prospective validation of ctDNA-guided adjuvant IO selection.

DYNAMIC stage II colon · Tie, NEJM 2022

ctDNA-guided de-escalation was non-inferior: 2-yr RFS 93.5% vs 92.4% while halving adjuvant chemotherapy use (5-yr RFS 88% vs 87%). Proof that MRD can safely subtract therapy — the de-escalation arm of the NSCLC question.

CONCLUSIONS & NEXT STEPS

- In NSCLC, ctDNA / MRD is robustly prognostic and a credible surrogate candidate — but formal trial-level surrogacy is not yet established.
- Treatment-guiding (predictive) validation exists only cross-cancer: IMvigor011 (DFS HR 0.64) and DYNAMIC (non-inferior de-escalation).
- Caveats: lower ctDNA shedding in squamous histology; assay timing, design and sensitivity vary; no FDA companion diagnostic for this indication.
- Priority — prospective MRD-guided NSCLC trials: escalate MRD-positive, de-escalate MRD-negative, with regulatory engagement from inception.

EVIDENCE AT A GLANCE

Trial (source)	Setting	ctDNA / MRD role	Key published result	Role
CheckMate 816 (NEJM 2025)	Resectable NSCLC, neoadj	Presurgical clearance	5-yr OS 75% vs 53% by clearance; overall 65% vs 55%	Prognostic
NADIM (JCO 2022)	Resectable NSCLC, neoadj	Pretreatment + post-neoadj	Low ctDNA PFS HR 0.20; out-predicts PD-L1 / TMB / RECIST	Prognostic
AEGEAN (JCO 2025)	Perioperative NSCLC	Induction clearance / MRD	Clearance 66% vs 41%; post-op MRD DFS HR ≈ 21 / ≈ 14	Surrogate candidate
IMpower010 (ESMO IO 2022)	Adjuvant NSCLC	Post-op selection	Benefit regardless of ctDNA — NPV questioned	NOT predictive
IMvigor011 (NEJM 2025)	Adjuvant bladder	ctDNA-guided selection	DFS HR 0.64; ctDNA-negative safely spared	Predictive (cross-cancer)
DYNAMIC (NEJM 2022)	Adjuvant stage II colon	ctDNA-guided de-escalation	Non-inferior RFS; adjuvant chemo use halved	Predictive (cross-cancer)

References. 1. Forde PM, NEJM 2025 (CheckMate 816, 5-yr OS). 2. Provencio M, JCO 2022 (NADIM ctDNA). 3. Heymach JV / AEGEAN, Ann Oncol 2023; JCO 2025 (abstr 8009). 4. Zhou C, ESMO IO 2022 (IMpower010 ctDNA substudy, abstr 10). 5. Powles T, NEJM 2025 (IMvigor011). 6. Tie J, NEJM 2022 (DYNAMIC).

Disclosures. No external funding. D. Rosas: consulting / advisory boards — AstraZeneca, Nuvation Bio. All values reported as published; no pooled estimates were computed. ‘Prognostic / surrogate / predictive’ used in the biomarker-qualification sense. Generative AI (Claude, Anthropic) was used in the development of this poster; the authors reviewed all content and take full responsibility for its accuracy.