

Two Signals, Two Verdicts: ctDNA Dynamics and Blood TMB in Metastatic NSCLC

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BACKGROUND & QUESTION

- ctDNA monitoring in metastatic NSCLC can read treatment response earlier than imaging and flag acquired resistance before radiographic progression.
- Two constructs are routinely conflated: on-treatment VAF dynamics / molecular response (a response surrogate) versus baseline blood TMB (a proposed predictive biomarker).
- They are validated by different designs and carry very different weights of evidence.
- **Question** — what does each construct actually deliver, and where does the evidence stop?

THE EVIDENCE LADDER

ON-TREATMENT → SURROGATE

Credible. VAF dynamics / molecular response correlate with radiographic response and outcome (BR.36; Goldberg 2018).

BASELINE → PROGNOSTIC

Detectable baseline ctDNA forecasts worse outcome (EGFRm PFS HR 1.82). One exploratory signal suggests it may also select for chemo benefit.

PREDICTIVE / bTMB

Not established in metastatic NSCLC. Blood TMB is limited by absent calculation standards and reduced genomic panel coverage.

Scope & method. Narrative synthesis of landmark trials; populations, endpoints, and assay platforms differ across studies. No pooling or meta-analysis was performed — the hazard ratios shown are drawn from separate trials and are not directly comparable head-to-head.

ON-TREATMENT DYNAMICS = SURROGATE

BR.36 stage 1 · Anagnostou, Nat Med 2023 · n = 50, pembrolizumab

- Met primary endpoint — ctDNA molecular response vs RECIST: sensitivity 82% (90% CI 52–97), specificity 75% (90% CI 56.5–88.5).
- Molecular response = maximal VAF clearance by cycle 3; median time to ctDNA response 2.1 months.
- **Molecular responders: PFS 5.0 vs 2.6 mo; OS not reached vs 7.2 mo.**

82% / 75%ctDNA→RECIST
sens / spec**2.1 mo**median time to
ctDNA response**5.0 v 2.6**molecular-responder
PFS (months)

A caution on concordance. In IMpower150 (Nat Commun 2024), post-treatment ctDNA response correlated with imaging but only modestly — a complementary early read, not a drop-in surrogate for RECIST.

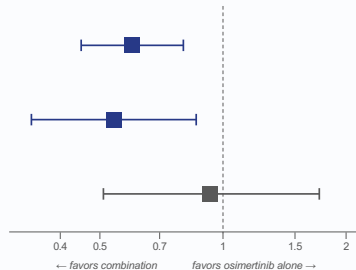
BASELINE EGFRm: PROGNOSTIC + SELECTIVE SIGNAL

Adding chemotherapy to osimertinib — benefit tracks ctDNA status

FLAURA2 — detectable baseline
HR 0.60 (0.45–0.80) · AACR 2024

FLAME — persistent wk-3 ctDNA
HR 0.54 (0.34–0.86) · ASCO 2026, n=80

FLAURA2 — non-detectable baseline
HR 0.93 (0.51–1.72) · AACR 2024



Prognostic anchor. Detectable baseline plasma EGFRm carries **HR 1.82 (1.37–2.38)** for worse PFS, independent of treatment arm. The 0.60-vs-0.93 contrast rests on point estimates — confidence intervals overlap and no interaction test was reported. Read it as hypothesis-generating, not validated prediction.

BLOOD TMB: THE WEAKER CONSTRUCT

- No harmonized TMB calculation standard exists — even in tissue — limiting analytical validity as a threshold biomarker.
- Blood-based panels interrogate fewer genomic regions than tissue, adding measurement noise at the low-ctDNA range.
- Reported bTMB associations are inconsistent across trials and thresholds; no prospective NSCLC trial validates bTMB as treatment-guiding.
- **Bottom line** — bTMB is not ready for treatment selection. On-treatment VAF dynamics carry the stronger, more reproducible signal.

CONCLUSIONS & NEXT STEPS

- On-treatment VAF dynamics / molecular response — not baseline bTMB — should anchor ctDNA monitoring in metastatic NSCLC.
- Baseline ctDNA detectability is prognostic; an exploratory FLAURA2 signal suggests it may also select for chemo benefit (unconfirmed).
- bTMB needs harmonized calculation and broader panel coverage before any treatment-guiding use.
- Priority: prospective ctDNA-directed early-switch / intensification trials — BR.36 stage 2 (IO) and FLAME-type designs (targeted).

EVIDENCE AT A GLANCE

Trial (source)	Setting	ctDNA construct	Key published result	Evidence type
BR.36 stage 1 (Nat Med 2023)	Metastatic, IO	On-treatment molecular response	Sens 82% / spec 75%; mR PFS 5.0 vs 2.6 mo	On-treatment surrogate
FLAURA2 (AACR 2024)	Metastatic EGFRm	Baseline detectability	Detectable PFS HR 1.82; detectable→chemo HR 0.60	Prognostic (+ exploratory)
IMpower150 (Nat Commun 2024)	Metastatic, chemo-IO	On-treatment response	Correlates with imaging; only modest concordance	Complementary, not surrogate
FLAME (ASCO 2026, n=80)	Metastatic EGFRm	ctDNA-guided intensification	Persistent ctDNA: osi+chemo PFS 23.1 vs 12.7 mo	Prospective ctDNA-directed
Blood TMB (multiple)	Metastatic, IO	Baseline predictive	No standard; inconsistent; reduced panel coverage	NOT validated

References. 1. Anagnostou V, Nat Med 2023 (BR.36). 2. Goldberg SB, Clin Cancer Res 2018. 3. Jänne PA, AACR 2024 (FLAURA2 ctDNA, CT017). 4. IMpower150 ctDNA, Nat Commun 2024. 5. Zhong J/Wang J, ASCO 2026 LBA101 (FLAME). 6. Gandara DR, Nat Med 2018 (bTMB).

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