

CONCORDANCE-2: Concordance of EGFR Mutation Detection by Liquid Versus Tissue Biopsy in Patients With Stage III Non-Small Cell Lung Cancer

Christian Rolfo¹, Melinda C. Power², Jiemin Liao³, Jayati Saha⁴, Sara Wienke⁵, Yanique Rattigan-Brown⁴, Emre Basar⁶, YongJin Kim⁵

¹ Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC–James), Columbus, OH, USA
² Oncology Outcomes Research, AstraZeneca, Gaithersburg, MD, USA
³ Guardant Health, Palo Alto, CA, USA
⁴ US Oncology Medical Affairs, AstraZeneca, Gaithersburg, MD, USA
⁵ Oncology Outcomes Research, AstraZeneca, Mississauga, ON, Canada

Objective

- To evaluate concordance between liquid biopsy (LBx) and tissue biopsy (TBx) for the detection of actionable *EGFR* mutations (*EGFRm*) in patients with stage III non-small cell lung cancer (NSCLC).

Conclusions

- LBx demonstrated high overall concordance and excellent PPV with TBx for detecting actionable *EGFRm* in stage III NSCLC.
- Positive LBx results accurately identified patients with *EGFRm* disease and may facilitate earlier treatment decisions in stage III unresectable NSCLC due to substantially faster turnaround times compared with TBx.
- Negative LBx results should be interpreted with caution and confirmed via TBx testing, particularly in patients with low ctDNA tumor fraction.
- ctDNA tumor fraction is a key determinant of LBx performance and may serve as a valuable indicator to identify patients at greater risk for false-negative results.

Plain language summary



Why did we perform this research?

- EGFR* is a gene / protein that controls how cells grow and divide. Changes, or mutations, in *EGFR* can help doctors choose treatments for patients with NSCLC.
- EGFR* testing is usually done using tissue biopsy (TBx, i.e., pieces of tumor tissue are removed from the body, e.g., through surgery or via a needle), but liquid biopsy (LBx, which tests for tumor DNA or cells in patient blood samples) is a less invasive test.
- To understand LBx utility in this population, we evaluated whether LBx results were consistent with TBx results for detecting *EGFRm* in patients with stage III NSCLC.



How did we perform this research?

- We analyzed real-world data from patients with stage III NSCLC who received both LBx and TBx testing.
- We compared *EGFRm* results from LBx and TBx to see how often they matched.
- We also looked at how quickly results were available and whether the amount of tumor DNA in the blood (ctDNA) affected the results.



What were the findings of this research?

- LBx and TBx matched 97% of the time for identifying *EGFRm* status.
- In our sample, all *EGFRm* identified by LBx were confirmed by TBx. All mismatches were cases of TBx identifying *EGFRm* that LBx did not identify.
- When TBx detected *EGFRm* that LBx did not detect, it occurred mainly in patients who had low levels of ctDNA in their blood.
- LBx results were available substantially sooner than TBx results.



What are the implications of this research?

- LBx provides faster results and serves as a helpful, complementary tool alongside traditional TBx to identify *EGFRm*.
- However, a negative LBx result should be interpreted with caution, and confirmed with a TBx when possible, especially if the tumor releases very little DNA into the blood.

Introduction

- Comprehensive genomic profiling is recommended in non-small cell lung cancer (NSCLC) to identify actionable genomic alterations and guide treatment selection.
- Targeted therapies are available for patients with identified epidermal growth factor receptor mutations (*EGFRm*) across multiple disease stages.
- LBx offers a minimally invasive approach to molecular testing and may provide results more rapidly than TBx.
- Although LBx performance for *EGFRm* detection has been extensively studied in advanced NSCLC, evidence remains limited in stage III disease, where lower ctDNA shedding may affect detection.

Methods

Sample:

- CONCORDANCE-2 was a retrospective observational study using the InfinityAI Data Library, which integrates electronic health record and claims data from ConcertAI Translational360™ with Guardant Health genomic testing data.
- Eligible patients had both LBx and TBx with valid *EGFR* results within 60 days of each other around the time of their stage III NSCLC diagnosis. Full eligibility criteria are detailed in Figure 1.

Endpoints:

- Performance of LBx versus TBx in detecting actionable *EGFRm* (Ex19Del, Ex20ins, L858R, T790M, G719C, S768I, and/or L861Q) overall and by patient characteristics and circulating tumor DNA (ctDNA) levels, including:
 - Overall concordance
 - PPA (i.e., sensitivity), NPA (i.e., specificity), PPV, NPV
- Characteristics of LBx and TBx, including turnaround times and testing methods.

Results and interpretation

Study Population

- A total of 231 patients had paired LBx and TBx with valid *EGFR* results within 60 days of each other around the time of their stage III NSCLC diagnosis and met all eligibility criteria (Figure 1).
- The sample was predominantly comprised of persons with a history of smoking (89%), and had limited Asian representation (4%), and included a substantial proportion of non-adenocarcinoma histology (31% squamous, 29% other/NOS, Table 1).

Table 1. Patient Characteristics

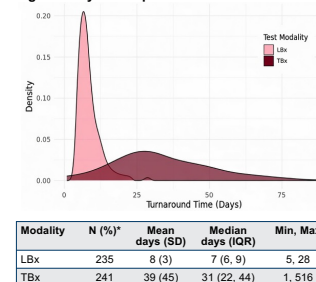
Characteristic*	N (%)
Total Patients	231 (100%)
Median Age, years (range)	71 (38, 80*)
Sex	
• Male	126 (55%)
• Female	105 (45%)
Race	
• Asian	8 (4%)
• White / Caucasian	171 (74%)
• Black / African American	36 (16%)
• Others	5 (2%)
• Unknown	11 (5%)
Histology	
• Adenocarcinoma	92 (40%)
• Squamous	72 (31%)
• Other	23 (10%)
• NOS	44 (19%)
Stage	
• IIA	108 (47%)
• IIIB/C	114 (50%)
• III NOS	9 (4%)
Smoking	
• History of Smoking	205 (89%)
• No History of Smoking	19 (8%)
• Unknown/Missing	7 (3%)
Patients with VAF from LBx	205 (89%)
• MVAf, mean (SD)	3.2% (6.3%)
• Median (IQR)	0.9% (0.3% - 3.1%)

*Ages > 80 years were truncated to 80 years.

Test Methodology and Turnaround Time

- All (100%) of LBx and 91% of TBx were performed using NGS.
- Turnaround time was substantially shorter for LBx than for TBx (Figure 2).

Figure 2. Days from Specimen Collection to Results



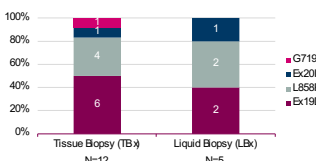
* Patients could have multiple eligible tests with different test dates per modality.

LBx is faster – with results in about a week.
TBx is slower – with results in about a month.

Actionable *EGFRm* Detection

- The actionable *EGFRm* mutation positivity rate was 5% (12/231) for TBx and 2% (5/231) for LBx; these rates were in the range of those in a parallel RWE study (Malapelle 2026).
- L858R and Ex19Del represented the majority of actionable *EGFRm* detected in both TBx and LBx results (Figure 3)

Figure 3. Distribution of Actionable *EGFRm* Results



Note: Actionable mutations include: Ex19Del, Ex20ins, L858R, T790M, G719C, S768I, L861Q; no co-mutations involving 2+ actionable mutations were detected.

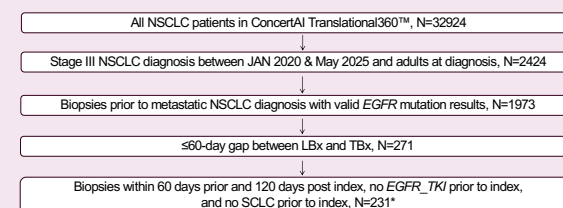
Key Takeaways

LBx can be used as a complementary tool for *EGFRm* detection in stage III NSCLC.

LBx can be used to initiate targeted treatment quickly if it identifies *EGFRm* given the fast turnaround time and high NPA.

When LBx does not identify *EGFRm*, waiting for TBx results is recommended, particularly if ctDNA levels are low.

Figure 1. Eligibility Criteria and Derivation of Eligible Sample



* Additional exclusion criteria included no prior *EGFR*-TKI exposure and no prior prophylactic cranial irradiation (SCLC); these criteria did not result in further patient exclusions.

Performance of LBx for *EGFR* Mutation Detection

- Overall concordance between LBx and TBx detection of actionable *EGFRm* was high: 97% (95% CI, 95%-99%). This is similar to that observed in the prior CONCORDANCE study (Malapelle 2026).
- NPV was high, reflecting the large proportion of patients without actionable *EGFR* mutations. PPV was 100% because no false-positive LBx results were observed.
- All discordant results in our study were false negative LBx results; we did not observe any false positive LBx results.

All positive LBx *EGFRm* results in our study were true positive results.

Performance of LBx for *EGFR* Mutation Detection by Patient Characteristics and ctDNA Levels

- No clear performance differences were observed across patient characteristics (Table 2); although subgroup interpretation is limited by small sample sizes and few mutation-positive cases.
- Among those with available VAF, there were no discordant results among persons with high MVAf ($\geq$ median 0.9%). In contrast, among patients with low MVAf ($<$ 0.9%), 4 of 6 *EGFRm*-positive cases detected by TBx were not detected by LBx (false negatives).

Figure 4. Performance of LBx vs TBx to Detect Actionable *EGFR* Mutations

		Tissue Biopsy	
		<i>EGFRm</i> Positive	<i>EGFRm</i> Negative
Liquid Biopsy	<i>EGFRm</i> Positive	5	0
	<i>EGFRm</i> Negative	7	219

Concordance (95% CI): 97% (95%, 99%)

Estimate (95% CI):
PPA: 42% (14%, 70%)
NPV: 100% (48%, 100%)

NPA: 100% (98%, 100%)
PPV: 97% (95%, 99%)

Table 2. Performance of LBx vs TBx to Detect Actionable *EGFR* Mutations by Select Patient Characteristics

	N	TP	TN	FP	FN	Concordance	PPA	NPA	PPV	NPV
Estimate (95% CI)										
Gender										
• Male	126	4	120	0	2	98% (94%, 99%)	67% (22%, 96%)	100% (97%, 100%)	100% (40%, 100%)	98% (94%, 100%)
• Female	105	1	99	0	5	95% (89%, 98%)	17% (0%, 64%)	100% (96%, 100%)	100% (3%, 100%)	95% (89%, 98%)
Smoking										
• History of smoking	205	1	202	0	2	99% (97%, 100%)	33% (1%, 91%)	100% (98%, 100%)	100% (3%, 100%)	99% (97%, 100%)
• No history of smoking	19	4	10	0	5	74% (49%, 91%)	44% (14%, 79%)	100% (69%, 100%)	100% (40%, 100%)	67% (38%, 88%)
Stage										
• IIA	108	3	100	0	5	95% (90%, 98%)	38% (9%, 76%)	100% (96%, 100%)	100% (29%, 100%)	95% (89%, 98%)
• IIIB/IIIC	114	2	110	0	2	98% (94%, 100%)	50% (7%, 93%)	100% (97%, 100%)	100% (16%, 100%)	98% (94%, 100%)
Histology										
• Adenocarcinoma	92	5	81	0	6	93% (86%, 98%)	45% (17%, 77%)	100% (96%, 100%)	100% (48%, 100%)	93% (86%, 97%)
MVAf based on LBx										
• Low (< median 0.9%)	99	2	93	0	4	96% (90%, 99%)	33% (4%, 78%)	100% (96%, 100%)	100% (16%, 100%)	96% (90%, 99%)
• High ($\geq$ median 0.9%)	106	3	103	0	0	100% (97%, 100%)	100% (29%, 100%)	100% (96%, 100%)	100% (29%, 100%)	100% (96%, 100%)

Note: TP = true positives, TN = true negatives, FP = false positives, FN = false negatives, PPA = positive percent agreement, NPA = negative percent agreement, PPV = positive predictive value, NPV = negative predictive value. Subgroup analyses limited to categories with sufficient N (e.g., unknown smoking status excluded from subgroup analyses).

Abbreviations

CI, confidence interval; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; Ex19Del, exon 19 deletion; Ex20ins, exon 20 insertion; FN, false negative; FP, false positive; IQR, interquartile range; LBx, liquid biopsy; MVAf, maximum variant allele frequency; NGS, next-generation sequencing; NOS, not otherwise specified; NPA, negative percent agreement; NPV, negative predictive value; NSCLC, non-small cell lung cancer; PPA, positive percent agreement; PPV, positive predictive value; QR, quick response; SCLC, small cell lung cancer; SD, standard deviation; TBx, tissue biopsy; TKI, tyrosine kinase inhibitor; TN, true negative; TP, true positive; VAF, variant allele frequency.

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References

- Malapelle U, et al. ESMO Open. 2026;11(1):106029.

Corresponding author email address: christian.rolfo@osumc.edu

Corresponding author Twitter handle: @ChristianRolfo

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