

The five most important developments of 2025 that transformed therapeutic strategies in non-small cell lung cancer

Abstract

Background: In 2025, multiple developments reshaped NSCLC therapeutic strategy. **Objectives:** Identify and integrate the five most impactful advances. **Methods:** Narrative expert review of 2025 clinical trials and guidelines. **Results:** Key breakthroughs included perioperative immunotherapy,¹⁻⁶ next-generation KRAS/HER2 inhibitors,⁷⁻¹⁵ postoperative ctDNA-guided therapy,¹⁶⁻¹⁸ AI-assisted pathology,¹⁹⁻²¹ and standardized biomarker testing.²²⁻²⁶ **Conclusions:** These advances established a unified precision oncology framework.

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Introduction

The therapeutic landscape of non-small cell lung cancer (NSCLC) underwent profound transformation in 2025. The maturation of perioperative immunotherapy data,¹⁻⁶ expansion of targeted therapies,⁷⁻¹⁵ clinical adoption of circulating tumor DNA (ctDNA) as a postoperative decision tool,¹⁶⁻¹⁸ implementation of artificial intelligence in diagnostic pathology,¹⁹⁻²¹ and establishment of global biomarker reflex testing guidelines²²⁻²⁶ collectively redefined modern thoracic oncology. Pathology became more central than ever, anchoring molecular precision and therapeutic direction.

Development of the topic

Perioperative immunotherapy

Landmark updates from KEYNOTE-671, AEGEAN and CheckMate-77T demonstrated that perioperative chemo-IO produces sustained improvements in event-free survival and pathologic complete response.¹⁻⁶ Standardized reporting of major pathologic response (MPR) became essential for outcome correlation and global surgical-pathology harmonization.

KRAS and HER2 targeted therapy

Second-generation KRAS G12C/G12X inhibitors and HER2-selective tyrosine kinase inhibitors achieved higher intracranial activity, improved tolerability, and superior response rates.⁷⁻¹⁵ These findings mandated expanded NGS testing, optimized HER2 IHC, and RNA-based variant confirmation.

ctDNA-guided postoperative therapy

Postoperative ctDNA became a validated biomarker of minimal residual disease, predicting recurrence with higher accuracy than clinical factors alone.¹⁶⁻¹⁸ Therapeutic escalation for ctDNA-positive patients and de-escalation for ctDNA-negative individuals reduced overtreatment and improved DFS.

AI-assisted digital pathology

Artificial intelligence algorithms for PD-L1 scoring, TIL quantification, and mixed histology detection proved superior in reproducibility and reduced interobserver variation.¹⁹⁻²¹ AI optimized

small-biopsy evaluation and improved biomarker consistency across centers.

Global biomarker consensus

International guidelines established reflex testing for EGFR, ALK, ROS1, KRAS, BRAF, HER2, RET, NTRK, MET exon 14, and PD-L1.²²⁻²⁶ Minimal tissue adequacy standards ensured efficient molecular workflows and faster access to targeted therapy.

Results

These five developments improved event-free survival, CNS disease control, diagnostic precision, treatment personalization, and workflow efficiency. Collectively they defined a unified global precision-oncology model for NSCLC (Table 1) (Figures 1&2).

(ASCII diagram)

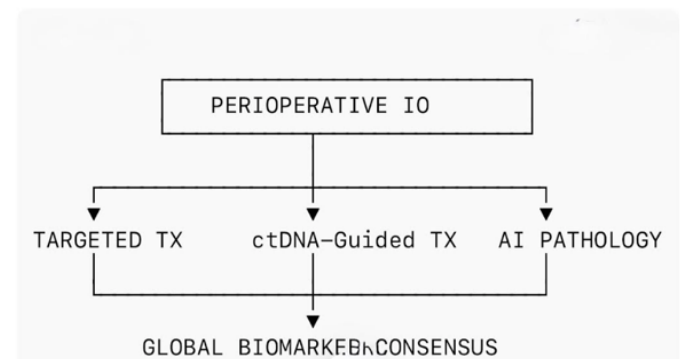


Figure 1 Conceptual Map of Breakthroughs.

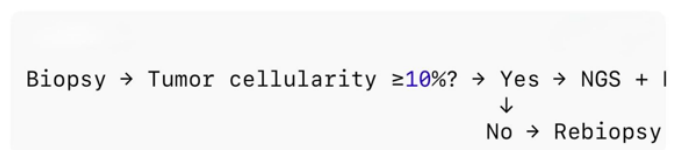


Figure 2 Reflex Biomarker Workflow.

Table 1 Key Advances in NSCLC Treatment in 2025

Breakthrough	Clinical Impact	Pathology Implications
Perioperative IO	↑EFS, ↑pCR	Standardized MPR reporting
KRAS/HER2 inhibitors	Improved CNS control	Expanded NGS & HER2 assays
ctDNA-guided therapy	Personalized adjuvant therapy	Tumor-informed sequencing
AI digital pathology	Reduced variability	Automated quantification
Biomarker consensus	Faster treatment initiation	Reflex testing protocols

Future perspectives

Emerging innovations include whole-exome and transcriptome sequencing, real-time ctDNA-adaptive therapy, expanded neoadjuvant targeted agents, and multimodal AI integration combining pathology, radiomics, and genomics. These trajectories will continue refining individualized lung cancer care.

Conclusions

In 2025, thoracic oncology entered a new era. Perioperative immunotherapy, next-generation targeted therapy, ctDNA-guided management, AI-augmented pathology, and standardized biomarker testing collectively reshaped clinical practice. Pathology now anchors precision oncology from diagnosis through treatment selection.

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