

ATS 2026: Lung Cancer Management Advances in Targeted Therapy

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The management of lung cancer, particularly non-small cell lung cancer (NSCLC), continues to present a significant clinical challenge due to its heterogeneity and often late-stage diagnosis. The American Thoracic Society (ATS) International Conference 2026 provided updates on the integration of molecular profiling into routine practice and the expanding landscape of targeted therapeutic options, aiming to refine treatment strategies and improve survival rates.

KEY TAKEAWAYS

- **The Pivot:** Molecular profiling for actionable mutations is now standard, guiding first-line therapy decisions.
- **The Data:** Specific targeted therapies demonstrate superior progression-free survival (PFS) compared to chemotherapy in biomarker-selected populations.
- **The Action:** Clinicians must ensure comprehensive molecular testing for all newly diagnosed NSCLC patients to identify eligible candidates for targeted treatments.

Lung cancer remains a leading cause of cancer-related mortality globally, with NSCLC accounting for approximately 85% of all cases.¹ Historically, treatment relied on surgery, radiation, and cytotoxic chemotherapy. However, the understanding of lung cancer biology has evolved, revealing numerous oncogenic drivers that can be targeted therapeutically. This shift towards precision medicine has been a central theme in oncology, with significant progress presented at ATS 2026. The conference underscored the importance of identifying specific molecular alterations, such as mutations in EGFR, ALK rearrangements, ROS1 rearrangements, BRAF V600E mutations, and MET exon 14 skipping alterations, which dictate treatment selection and prognosis.²

Current State of Targeted Therapies in NSCLC

The ATS 2026 presentations reinforced the established role of targeted therapies in NSCLC. For patients with EGFR-mutated NSCLC, third-generation tyrosine kinase inhibitors (TKIs) like osimertinib have demonstrated superior efficacy. For instance, in the FLAURA trial, osimertinib showed a median progression-free survival (PFS) of 18.9 months compared to 10.2 months with standard EGFR-TKIs (HR 0.46, 95% CI 0.37-0.57, $p < 0.001$) in the first-line setting.³ This data supports its continued use as a preferred initial treatment for these patients. Similarly, for ALK-positive NSCLC, next-generation ALK inhibitors such as alectinib have shown improved outcomes. The ALEX trial reported a median PFS of 34.8 months for alectinib versus 10.9 months for crizotinib (HR 0.32, 95% CI 0.23-0.44, $p < 0.001$), establishing alectinib as a standard first-line option.⁴

Beyond these well-established targets, ATS 2026 highlighted advancements in therapies for less common but equally

critical alterations. For patients with ROS1-positive NSCLC, entrectinib and crizotinib remain viable options, with entrectinib demonstrating an objective response rate (ORR) of 77% (95% CI 62-88) and a median PFS of 19.0 months (95% CI 12.2-not estimable) in a pooled analysis of phase 1/2 trials.⁵ For BRAF V600E mutations, the combination of dabrafenib and trametinib has shown an ORR of 64% and a median PFS of 10.9 months.⁶

Emerging data presented at ATS 2026 also focused on MET exon 14 skipping mutations and KRAS G12C mutations. Capmatinib and tepotinib have received approval for MET exon 14 skipping NSCLC, with capmatinib showing an ORR of 68% in treatment-naïve patients and 41% in previously treated patients.⁷ For KRAS G12C mutations, sotorasib and adagrasib represent a new class of targeted agents. Sotorasib demonstrated an ORR of 36% and a median PFS of 6.8 months in previously treated patients with KRAS G12C-mutated NSCLC.⁸ These developments underscore the rapid expansion of actionable targets and available therapies.

The conference also addressed resistance mechanisms to targeted therapies and strategies to overcome them. Sequential use of different generations of TKIs, combination therapies, and the role of liquid biopsies for monitoring treatment response and detecting resistance mutations were discussed. The integration of immunotherapy with targeted therapy in specific contexts, particularly for patients with co-occurring driver mutations and high PD-L1 expression, was also a topic of interest, though definitive guidelines for such combinations are still evolving.⁹

The patient populations benefiting from these targeted therapies often present with advanced or metastatic NSCLC, where conventional chemotherapy offers limited survival benefits. Molecular testing, typically performed on tumor tissue biopsies or liquid biopsies, identifies the specific genetic alterations that drive tumor growth. This precision approach allows for the selection of therapies designed to inhibit the activity of these specific oncogenic drivers, leading to improved response rates and progression-free survival compared to non-targeted treatments. The mechanisms of action for these targeted agents vary but generally involve inhibiting key signaling pathways essential for cancer cell proliferation and survival. For instance, EGFR TKIs block the tyrosine kinase activity of the epidermal growth factor receptor, thereby disrupting downstream signaling. Similarly, ALK inhibitors target the anaplastic lymphoma kinase, preventing its aberrant activation in ALK-rearranged tumors.

Limitations in current practice include the accessibility and turnaround time of comprehensive molecular testing, which can delay initiation of optimal therapy. Furthermore, the cost-effectiveness of these advanced therapies remains a consideration for healthcare systems globally. Disparities in access to advanced molecular diagnostics and targeted therapies persist across different regions and socioeconomic groups, impacting patient outcomes. Future research is directed towards identifying novel targets, developing therapies for currently undruggable mutations, and understanding the optimal sequencing and combination of existing treatments to prolong patient survival and improve quality of life.

CLINICAL IMPLICATIONS

The ATS 2026 presentations on lung cancer management underscore a clear directive for clinicians: comprehensive molecular profiling is no longer an optional extra, but a mandatory first step for every newly diagnosed NSCLC patient. The era of empiric chemotherapy as a default first-line treatment is receding, replaced by a precision-guided approach that demonstrably improves progression-free survival. Failure to conduct broad panel testing for actionable mutations, including EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and KRAS G12C, risks denying patients access to therapies that offer superior outcomes compared

to traditional cytotoxic regimens.

The pharmaceutical industry's continued investment in targeted therapies for increasingly rare molecular subsets is evident. While this fragmentation of the market presents challenges for drug development and regulatory approval, it ultimately benefits patients by providing tailored treatment options. However, the economic implications of these highly specialized drugs, often priced at a premium, will continue to be a point of contention for healthcare payers and national health systems. Guideline bodies like NCCN and ESMO will need to rapidly integrate these new data points into their recommendations, providing clear algorithms for testing and treatment selection to ensure equitable access to these advances.

For patients, the message is one of hope, tempered by the complexity of their disease. The availability of targeted therapies means that a diagnosis of advanced NSCLC no longer automatically implies a uniformly poor prognosis. Instead, it opens the door to personalized treatment plans that can extend life and maintain quality. However, patients must be informed advocates, understanding the importance of molecular testing and discussing all available options with their oncologists. The rapid pace of discovery means that what is state-of-the-art today may be superseded tomorrow, necessitating continuous education for both clinicians and patients.

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