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TARGETED THERAPIES AND IMMUNOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER – CURRENT STANDARDS AND NEW DIRECTIONS

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ABSTRACT

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality, but advances in targeted therapies and immunotherapy have radically changed the prognosis of advanced disease. The introduction of tyrosine kinase inhibitors directed against alterations in EGFR, ALK, ROS1, BRAF, MET, RET, KRAS G12C, NTRK, HER2 and other genes has led to a shift away from uniform chemotherapy toward treatment based on precise molecular characterization of the tumor. In parallel, immune checkpoint–blocking antibodies, primarily targeting PD-1/PD-L1 and CTLA-4, have become the standard of care in first and subsequent lines of treatment for patients without oncogenic drivers, used both as monotherapy and in combination with chemotherapy and anti-angiogenic agents.

Despite substantial survival gains, most patients develop primary or acquired resistance to targeted therapy and immunotherapy, which represents a major clinical challenge. This article reviews current standards of care in advanced NSCLC, emphasizing the role of molecular testing and PD-L1 assessment in therapy selection, the place of combination regimens including immune checkpoint inhibitors, and emerging strategies to overcome resistance, such as next-generation inhibitors, bispecific antibodies, antibody–drug conjugates, neoantigen vaccines and cellular therapies. Particular attention is given to future perspectives for further personalization of treatment, the role of predictive biomarkers (including PD-L1, TMB and ctDNA), and ongoing and planned studies of combination approaches that may further improve outcomes for patients with advanced NSCLC.

KEYWORDS

Non-Small-Cell Lung Cancer, Targeted Therapy, Immunotherapy, Tyrosine Kinase Inhibitors, Checkpoint Inhibitors, Treatment Resistance

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Introduction

Lung cancer remains one of the most serious challenges in modern oncology, being globally the most common cause of death from malignant neoplasms. Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancer cases and is characterized by considerable biological and clinical heterogeneity (Wagner et al., 2020; Li et al., 2023). Despite advances in diagnostics, surgery, radiotherapy and chemotherapy, the prognosis of patients with advanced NSCLC has for many years remained unfavorable (Cho et al., 2023).

Traditionally, the backbone of systemic treatment was platinum-based chemotherapy, administered according to "one-size-fits-all" regimens, regardless of the molecular characteristics of the tumor. This approach was associated with limited efficacy and substantial toxicity. A breakthrough came with the identification of so-called driver mutations and the development of targeted therapies. The discovery of activating mutations in the EGFR gene, rearrangements in ALK and ROS1, and subsequently other alterations (BRAF, MET, RET, NTRK, HER2, KRAS G12C) enabled the development of tyrosine kinase inhibitors (TKIs), which in selected patient subgroups demonstrated a clear advantage over chemotherapy (Li & Shi, 2024; Cho et al., 2023).

In parallel, there has been a dynamic development of immuno-oncology. The introduction of immune checkpoint inhibitors (ICIs) directed against PD-1, PD-L1 and CTLA-4 has revolutionized the treatment of advanced NSCLC. Immunotherapy, used as monotherapy or in combination with chemotherapy, has allowed a subset of patients to achieve long-lasting responses and significantly prolonged survival.

As a result, a paradigm shift has occurred—from an empirical approach to a strategy based on the molecular characterization of the tumor and predictive biomarkers (driver mutations, gene fusions, PD-L1 expression, TMB, ctDNA). The development of NGS diagnostics, liquid biopsy, and "basket" and "umbrella" trials has further accelerated the implementation of new therapies (Liu et al., 2025; Zhang et al., 2024).

Despite this progress, most patients treated with targeted therapies develop acquired resistance, and the response to immunotherapy remains heterogeneous. Combined regimens are therefore gaining importance—integrating targeted agents, immunotherapy, chemotherapy and radiotherapy—as well as new classes of drugs such as bispecific antibodies and antibody–drug conjugates (ADCs) (Wagner et al., 2020; Li et al., 2023).

The aim of this article is to present current standards and the latest directions in the development of targeted therapies and immunotherapy in advanced NSCLC, with particular emphasis on the role of molecular diagnostics, mechanisms of resistance, and prospects for further personalization of treatment.

Methodology

A literature review was conducted using the PubMed, Scopus, and Web of Science databases. Combinations of English-language keywords and MeSH terms were applied, including: “non-small cell lung cancer,” “NSCLC,” “targeted therapy,” “tyrosine kinase inhibitor,” “EGFR,” “ALK,” “immunotherapy,” “immune checkpoint inhibitor,” “PD-1,” “PD-L1,” “CTLA-4,” “advanced,” and “metastatic.”

Publications from 2003–2025 were considered, with particular emphasis on literature from the last decade (2015–2025), encompassing meta-analyses, current scientific society guidelines, and phase II–III clinical trials concerning the treatment of advanced lung cancer.

Results of targeted therapies in advanced NSCLC

The introduction of targeted therapies has fundamentally changed the prognosis of patients with advanced non-small cell lung cancer (NSCLC) harboring specific molecular alterations, allowing survival to be prolonged and measured in years in selected subgroups of patients (Li et al., 2024; Gálffy et al., 2024; Rothe et al., 2025). Currently available targeted agents inhibit activating EGFR mutations, the BRAF V600E mutation, MET exon 14 skipping, as well as ALK, ROS1 and RET rearrangements and NTRK fusions (Li et al., 2024; Gálffy et al., 2024).

EGFR

In patients with classic activating EGFR mutations (exon 19 deletion, L858R), first- and second-generation EGFR tyrosine kinase inhibitors (TKIs; gefitinib, erlotinib, afatinib) yield response rates of approximately 60–70% and a median PFS of about 9–12 months, clearly outperforming platinum-based chemotherapy (Li et al., 2024; Guaitoli et al., 2023; Zhang & Sun, 2025). Third-generation TKIs, represented by osimertinib, further improve outcomes—meta-analyses and clinical trials indicate the highest efficacy of first-line osimertinib, with a favorable safety profile, prolongation of PFS to around 18 months and improvement in OS (Li et al., 2024; Guaitoli et al., 2023). Osimertinib also demonstrates significant intracranial activity, translating into better control of CNS metastases in patients with EGFR-dependent NSCLC (Bar et al., 2022; Guaitoli et al., 2023; Li & Shi, 2024). The efficacy of osimertinib has also been confirmed in the subgroup of patients with uncommon EGFR mutations, where response rates reach approximately 55–60% and median PFS about 9–10 months (Bar et al., 2022; Okuma et al., 2023).

ALK

In patients with ALK rearrangements, ALK inhibitors (crizotinib, alectinib, brigatinib, lorlatinib) significantly prolong PFS and improve OS compared with chemotherapy (Li et al., 2024; Gálffy et al., 2024). Newer-generation agents, such as alectinib and lorlatinib, achieve median PFS exceeding 25–30 months, high response rates (around 70–80%) and very good CNS disease control due to improved penetration into the central nervous system (Li et al., 2024; Gálffy et al., 2024; Li & Shi, 2024). Population-based data in patients with brain metastases indicate that the presence of ALK alterations is associated with longer OS and PFS compared with some other molecular subtypes (Li & Shi, 2024).

ROS1

ROS1 rearrangements represent a rare but readily identifiable patient population. Crizotinib and entrectinib demonstrate high response rates (60–70%) and median PFS of 15–20 months in patients with ROS1-positive NSCLC (Li et al., 2024; Gálffy et al., 2024; Rothe et al., 2025). Entrectinib, due to good CNS penetration, additionally provides effective control of brain metastases, which is particularly important given the relatively frequent CNS involvement in this group (Li et al., 2024; Cho et al., 2023).

BRAF V600E

BRAF mutations occur in approximately 3–5% of NSCLC cases, with the V600E subtype being the best characterized in the context of targeted therapy (Guaitoli et al., 2023; O’Leary et al., 2019). In phase II trials, the combination of dabrafenib and trametinib in patients with BRAF V600E-mutated NSCLC results in an ORR of around 60–70% and median PFS of approximately 9–11 months, clearly surpassing outcomes achieved with chemotherapy alone (Guaitoli et al., 2023; O’Leary et al., 2019; Telli et al., 2025). Real-world data confirm the superiority of first-line dabrafenib plus trametinib over chemotherapy in terms of ORR, DCR and PFS (Telli et al., 2025). For non-V600E mutations, the role of targeted therapy is less clear, and some analyses suggest greater benefit from immunotherapy or chemo-immunotherapy regimens (Guaitoli et al., 2023; Kropf-Sanchen et al., 2025).

METex14

MET exon 14 skipping (METex14) is a recognized oncogenic driver for which selective MET inhibitors such as capmatinib and tepotinib have been developed (Gálffy et al., 2024; Guaitoli et al., 2023). In clinical and observational studies, these agents achieve ORR in the range of 40–60% and median PFS of 8–12 months in patients with advanced NSCLC harboring METex14 alterations treated in various lines of therapy (Gálffy et al., 2024; Guaitoli et al., 2023; Zhao et al., 2024). Real-world data also suggest that patients with METex14 may achieve relatively good outcomes with chemo-immunotherapy regimens, particularly in the setting of high PD-L1 expression, although targeted therapy remains the preferred option when available (Shin et al., 2025; Tian et al., 2024).

RET

In patients with RET rearrangements, selective inhibitors such as selpercatinib and pralsetinib show ORR of approximately 60–70% and significant prolongation of PFS compared with chemotherapy or non-selective anti-RET approaches (Gálffy et al., 2024; Guaitoli et al., 2023). Clinical trials and real-world analyses suggest that the efficacy of immunotherapy in this group is limited and generally lower than in unselected populations, further supporting the priority of targeted therapy (Chen et al., 2024; Tian et al., 2024; Guisier et al., 2020).

NTRK

NTRK fusions are very rare (approx. 0.2% of NSCLC) but highly sensitive to TRK inhibitors, particularly larotrectinib and entrectinib (Gálffy et al., 2024; Guaitoli et al., 2023; Cho et al., 2023). Integrated analyses of phase I/II trials in NSCLC patients demonstrate ORR above 60%, median PFS of around 28 months and durable responses, including within the CNS (Cho et al., 2023). Entrectinib achieves an intracranial ORR of about 64% in patients with brain metastases, with very long-lasting responses (Cho et al., 2023).

Summary of targeted therapy outcomes

In molecularly selected subgroups of patients, the use of targeted therapies leads to a substantial increase in response rates and prolongation of PFS, and in many cases OS, compared with chemotherapy (Li et al., 2024; Gálffy et al., 2024; Guaitoli et al., 2023; Rothe et al., 2025). Particularly favorable outcomes are observed in EGFR-, ALK-, ROS1- and NTRK-positive groups, where median PFS with targeted treatment can exceed 18–30 months, with good CNS disease control thanks to newer-generation TKIs (Li et al., 2024; Bar et al., 2022; Gálffy et al., 2024; Li & Shi, 2024; Cho et al., 2023). Targeted therapies also generally have a more favorable toxicity profile, translating into improved quality of life (Li et al., 2024; Gálffy et al., 2024; Rothe et al., 2025). However, the magnitude of benefit remains strictly dependent on the presence of appropriate molecular aberrations and on the implementation of comprehensive biomarker testing at diagnosis (Li et al., 2024; Gálffy et al., 2024; Guaitoli et al., 2023).

Summary of the most important molecular targets and effects

Table 1. Comparison of major targeted therapies for NSCLC

Molecular target/drug	Typical outcomes (ORR, PFS)	Citations
EGFR – TKI 1./2. gen., ozymertynib	ORR ~60–70%, PFS 9–12.; ozymertynib: highest PFS, good activity in the CNS	(Li et al., 2024; Bar et al., 2022; Okuma et al., 2023; Guaitoli et al., 2023; Li & Shi, 2024)
ALK – alectynib, lorlatinib	ORR 70–80%, PFS >25–30, high effectiveness in the CNS	(Li et al., 2024; Gálffy et al., 2024; Li & Shi, 2024)
ROS1 – kryzotynib, entrektynib	ORR 60–70%, PFS 15–20., effectiveness in the CNS (entrektynib)	(Li et al., 2024; Gálffy et al., 2024; Cho et al., 2023)
BRAF V600E – dabrafenib+trametynib	ORR 60–70%, PFS ~9–11	(Guaitoli et al., 2023; O'Leary et al., 2019; Telli et al., 2025)
METex14 – capmatinib, tepotinib	ORR 40–60%, PFS 8–12	(Gálffy et al., 2024; Guaitoli et al., 2023; Zhao et al., 2024)
RET – selperkatynib, pralsetynib	ORR 60–70%, PFS prolongation vs. chemotherapy	(Gálffy et al., 2024; Guaitoli et al., 2023; Tian et al., 2024; Guisier et al., 2020)
NTRK – larotrektynib, entrektynib	ORR >60–70%, PFS ~28, strong activity in the CNS	(Gálffy et al., 2024; Guaitoli et al., 2023; Cho et al., 2023)

Results of immunotherapy in advanced NSCLC

Immunotherapy using immune checkpoint inhibitors (ICIs) has become one of the pillars of treatment for advanced non-small cell lung cancer (NSCLC) without driver gene alterations, both in the first and subsequent lines of therapy (Wagner et al., 2020; Dafni et al., 2019; Ellis et al., 2017; Berghmans et al., 2020). The use of anti–PD-1/PD-L1 antibodies, alone or in combination with chemotherapy, leads to a significant prolongation of overall survival (OS) and progression-free survival (PFS) compared with chemotherapy alone, with a more favorable or comparable toxicity profile (Wagner et al., 2020; Dafni et al., 2019; Ferrara et al., 2020; Wang et al., 2019).

First-line treatment

In first-line NSCLC treatment, immunotherapy can be used as monotherapy in patients with high PD-L1 expression (most often TPS ≥50%) or in combination with chemotherapy regardless of PD-L1 level (Wagner et al., 2020; Dafni et al., 2019; Ferrara et al., 2020; Wang et al., 2019).

Pembrolizumab monotherapy in patients with PD-L1 ≥50% significantly improves OS and PFS compared with chemotherapy, while simultaneously reducing the incidence of severe adverse events (Wagner et al., 2020; Dafni et al., 2019; Ferrara et al., 2020; Ellis et al., 2017). In meta-analyses, first-line pembrolizumab shows clearly better OS compared with chemotherapy, and in the PD-L1 ≥50% group it is considered the standard of care (Wagner et al., 2020; Dafni et al., 2019; Ferrara et al., 2020; Wang et al., 2019).

Adding ICIs to chemotherapy (e.g., pembrolizumab + platinum, atezolizumab + chemotherapy ± bevacizumab) leads to further improvement in OS and PFS compared with chemotherapy alone, in patients with high, intermediate, and low/negative PD-L1 expression (Wagner et al., 2020; Li et al., 2023; Dafni et al., 2019; Wang et al., 2019). Network meta-analyses indicate that pembrolizumab + chemotherapy and atezolizumab + bevacizumab + chemotherapy are among the most effective first-line strategies, providing the highest OS and PFS rates in the unselected population and in subgroups with PD-L1 <1% and 1–49% (Li et al., 2023; Dafni et al., 2019; Wang et al., 2019).

In some patients, favorable results are also achieved with dual immunotherapy (e.g., nivolumab + ipilimumab), especially in groups with high tumor mutational burden and in squamous histology, with a sustained OS and PFS benefit over chemotherapy (Lu et al., 2023; Alifu et al., 2023; Di Federico et al., 2025; Berghmans et al., 2020).

Subsequent lines of treatment

In the second and later lines of treatment, ICIs (nivolumab, pembrolizumab, atezolizumab) have shown superiority over docetaxel in terms of OS, with at least comparable PFS and lower toxicity (Wagner et al., 2020; Mencoboni et al., 2021; Ellis et al., 2017; Passiglia et al., 2018). A meta-analysis showed that second-line ICIs reduce the risk of death by about 30% compared with docetaxel (HR for OS ~0.69), with a more favorable safety profile (Wagner et al., 2020; Mencoboni et al., 2021; Ellis et al., 2017). Real-world data confirm that median OS reaches approximately 10–12 months, and the effectiveness and tolerability outcomes are similar to those of the registration trials (Mencoboni et al., 2021).

Significance of PD-L1 expression and other clinical factors

PD-L1 expression remains the main biomarker for selecting an immunotherapy strategy. ICI monotherapy provides the greatest benefit in the PD-L1 ≥50% group, whereas in groups with lower expression, optimal outcomes are achieved with combination therapy with chemotherapy (Wagner et al., 2020; Li et al., 2023; Dafni et al., 2019; Wang et al., 2019). In patients with PD-L1 <1%, adding ICIs to chemotherapy significantly improves OS and PFS compared with chemotherapy alone, whereas the effectiveness of monotherapy is limited (Zhang et al., 2024; Li et al., 2023; Gemelli et al., 2025; Ferrara et al., 2020).

Meta-analyses also indicate that the greatest benefits of chemo-immunotherapy are seen in patients without liver metastases, in those with brain metastases, and in patients with a history of smoking; the effect is less pronounced in never-smokers (Liu et al., 2025; Zhang et al., 2024; Wagner et al., 2020; Gemelli et al., 2025). In the elderly population (≥65 years), ICIs still clearly improve OS and PFS compared with chemotherapy, although in patients ≥75 years and with PD-L1 <1% the gains are smaller and require further confirmation (Yao et al., 2025).

Efficacy, safety, and long-term outcomes

Overall, immunotherapy (as monotherapy, in combination with chemotherapy, or in dual regimens) significantly prolongs OS and PFS and improves response rates and disease control compared with chemotherapy in advanced NSCLC, particularly in patients without driver alterations (Wagner et al., 2020; Yu et al., 2019; Dafni et al., 2019; Wang et al., 2019; Berghmans et al., 2020). These benefits apply to both adenocarcinoma and squamous carcinoma, though in squamous carcinoma the advantage of chemo-immunotherapy regimens and selected antibodies (e.g., cemiplimab, camrelizumab, tislelizumab) is particularly pronounced (Liu et al., 2025; Zhang et al., 2024).

The safety profile of ICIs is generally more favorable than that of chemotherapy, with a lower incidence of severe toxicities in monotherapy and slightly higher in combination regimens (especially dual immunotherapy), with an acceptable risk of adverse events (Wagner et al., 2020; Mencoboni et al., 2021; Alifu et al., 2023; Dafni et al., 2019). Long-term analyses show stabilization of survival curves and achievement of several-year survival in a significant proportion of patients, especially with optimal selection based on PD-L1, TMB, and other biomarkers (Goulart et al., 2024; Yu et al., 2019; Di Federico et al., 2025; Berghmans et al., 2020).

Summary of the main immunotherapy strategies for advanced NSCLC

Table 2. Main immunotherapy strategies and their outcomes in NSCLC

Treatment strategy	Key clinical outcomes (OS, PFS, ORR)	Citations
Monotherapy ICI (PD-L1 ≥50%)	Significantly prolonged OS and PFS vs. chemotherapy, lower toxicity	(Wagner et al., 2020; Dafni et al., 2019; Ferrara et al., 2020; Ellis et al., 2017; Berghmans et al., 2020)
ICI + chemotherapy	Highest gain in OS and PFS regardless of PD L1, high ORR	(Zhang et al., 2024; Wagner et al., 2020; Li et al., 2023; Dafni et al., 2019; Wang et al., 2019)
Dual immunotherapy (np. PD-1 + CTLA-4)	Improved OS/PFS vs. chemotherapy, especially PD L1 low/TMB high; higher toxicity	(Lu et al., 2023; Alifu et al., 2023; Yu et al., 2019; Di Federico et al., 2025)
ICI in the second and further lines	Improved OS vs. docetaxel, better tolerability; median OS ~10–12 months.	(Wagner et al., 2020; Mencoboni et al., 2021; Ellis et al., 2017; Passiglia et al., 2018)

Conclusions

The introduction of targeted therapies and immunotherapy has completely changed the prognosis of advanced non-small cell lung cancer, transforming treatment from homogeneous chemotherapy regimens into a multidimensional, individualized strategy based on tumor molecular profiling and immunologic biomarkers (Wang et al., 2025; Su et al., 2025; Cheng et al., 2021; Majeed et al., 2021; Li et al., 2023). In selected subgroups of patients with activating driver alterations (EGFR, ALK, ROS1, MET, RET, NTRK, BRAF, etc.), targeted therapies allow high response rates and survival measured in many months or even years, with a relatively favorable toxicity profile (Su et al., 2025; Cheng et al., 2021; Majeed et al., 2021; Rodak et al., 2021; Guo et al., 2022). In patients without driver alterations, checkpoint inhibitors have become standard in first and subsequent lines of therapy, significantly improving overall survival and progression-free survival, both as monotherapy and in combination with chemotherapy (Wang et al., 2025; Su et al., 2025; Mamdani et al., 2022; Zhou et al., 2025; Li et al., 2023; Miller & Hanna, 2021).

Current standards of care in advanced NSCLC are based on mandatory broad biomarker diagnostics – including a panel of oncogenic driver alterations and PD-L1 expression – which conditions optimal selection between targeted therapy, immunotherapy (mono- or polytherapy), chemoimmunotherapy, and sequential treatment (Su et al., 2025; Cheng et al., 2021; Meyer et al., 2024; Rodak et al., 2021; Guo et al., 2022). The development of genomic techniques and comprehensive tumor profiling enables increasingly precise patient stratification, but at the same time exposes the growing complexity of clinical decisions and the need for close collaboration within multidisciplinary teams (Cheng et al., 2021; Miao et al., 2023; Li et al., 2023; Guo et al., 2022).

Despite spectacular progress, advanced NSCLC remains largely incurable; almost all patients eventually develop resistance to targeted therapy or immunotherapy, and the benefits obtained are uneven across molecular subtypes and patient groups (Wang et al., 2021; Cheng et al., 2021; Chen et al., 2020; Meyer et al., 2024; Guo et al., 2022). Key challenges include: better understanding and overcoming resistance mechanisms, identifying reliable predictive biomarkers (also beyond PD-L1 and classic mutations), optimizing combinations and treatment sequences, as well as improving access to modern therapies and reducing their costs (Wang et al., 2021; Mamdani et al., 2022; Wolf et al., 2025; Meyer et al., 2024; Li et al., 2023; Guo et al., 2022; Leone et al., 2025).

The future direction of development is the integration of targeted therapies, immunotherapy, bispecific antibodies, antibody–drug conjugates (ADC), cell therapies, and cancer vaccines within personalized, adaptive treatment strategies based on multi-omic data and dynamic assessment of the tumor microenvironment (Wang et al., 2025; Su et al., 2025; Krawczyk et al., 2025; De Lucia et al., 2025; Wolf et al., 2025; Li et al., 2023; Garg et al., 2024). Only such an approach – combining advanced diagnostics, rational drug combinations, and close monitoring of response and toxicity – offers a real chance for further improvement of long-term outcomes in patients with advanced NSCLC.

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